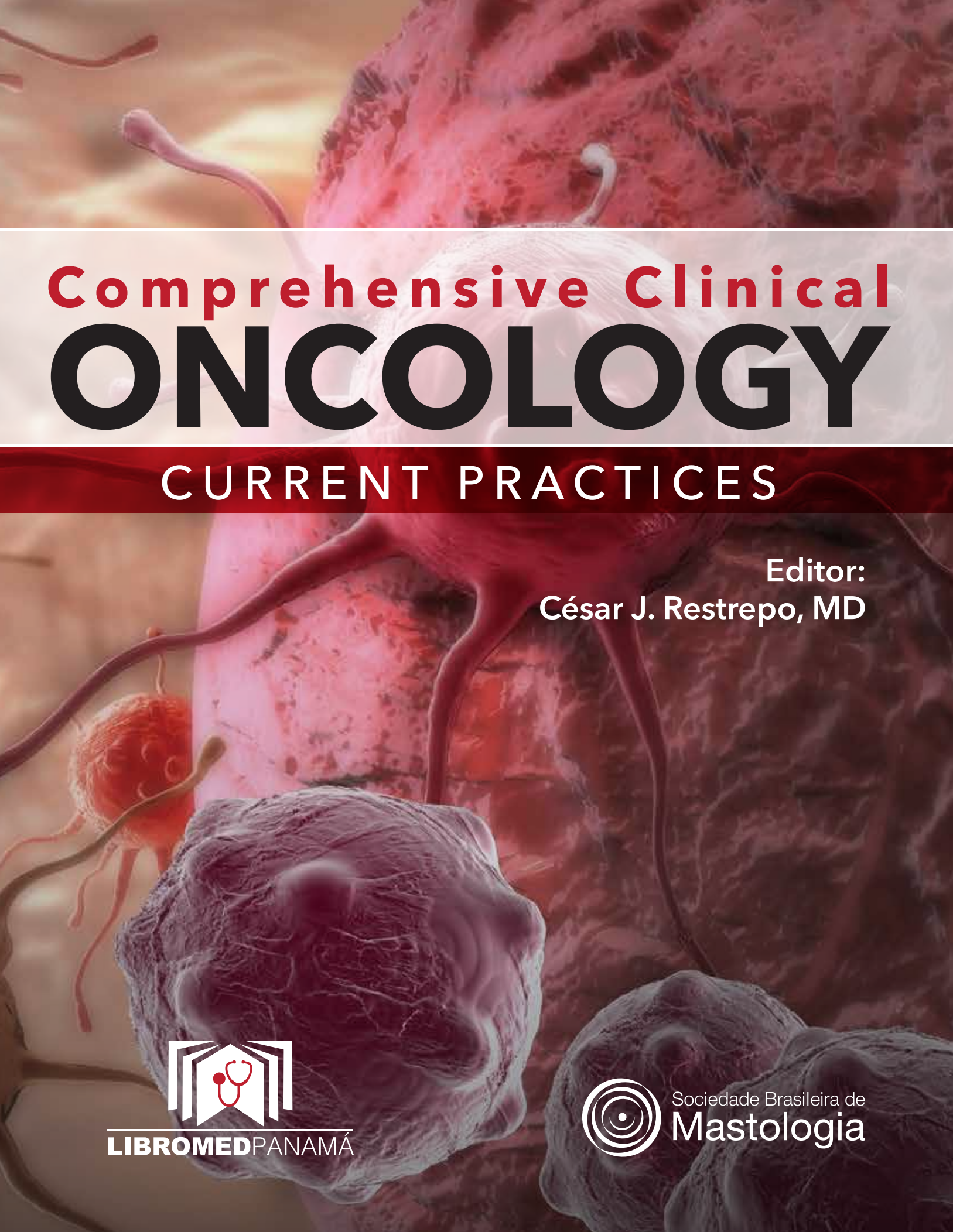




Comprehensive Clinical **ONCOLOGY**

CURRENT PRACTICES

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César J. Restrepo, MD



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DEDICATION

To my wife Itzel M.

*To my kids: Itzelita, César Jr., Marieangie,
Georgios Emmanuel, Adriana Sofía.*

To my Mentor and Friend Charles Balch,

To Raphael Pollock, more than a friend, a “Big Brother”.

*To all the family members, that fought the battle against this
dreadful disease named Cancer and finished with the head up.*

To the students of all ages.

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To the Authors of this book, to Srinivas Chaubey, Sheyla Marengo and Elektra McDermott. I hope it's not too late, I want to thank you for having trusted in this project.

I am not rich, but I am very lucky, I believe in God, I have a big family and some friends (a few, and you are one of them). We aspire to a lot, without appreciating the little, which is really what belongs to us.

I want to tell you: these last 20 years, especially the last 10 have been, extremely difficult, "from so much crying I learned to smile". Thanks for being in my life.

I hope that one day, I can thank you, all the time and in every place, the only one that is always, is God. In the good you will be surrounded by many, in the bad, you will find me. Thanks for your example, for your friendship.

PROLOGUE

This book is designed to serve an important gap in our clinical knowledge base, which is that there are no oncology texts describing the key elements of multidisciplinary cancer care focusing on malignant diseases of prevalence in Central and South America as well as the Caribbean. This is a vast and diverse catchment area in which cancer is emerging as a major health challenge on an individual and population-wide basis.

For practitioners who specialize in oncology as well as more general practitioners, medical students and residents in training, it is hoped that this small volume will help address this deficit in compiled oncology information.

The book is organized with a focus on individual diseases that are frequently as well as only occasionally encountered in the target geographic locations. The role of multi-disciplinary care, including the role of diagnostic physicians such as pathologists and radiologists as well as treating physicians, including medical, surgical, and radiation oncologists are concisely yet thoroughly discussed. How to care for specific cancer entities, including addressing oncology care priorities when resources may be scarce, are likewise developed in the context of specific diseases.

The key starting point of developing multi-disciplinary cancer planning conferences is critical, and this is a prospect that increasingly will be aided by teleconference mechanisms connecting physicians, patients, and experts elsewhere in an orchestrated and concerted effort to provide the highest quality care access to all patients burdened by malignant disease.

The format of each chapter is designed to provide immediate access to key information needed to establish an informed therapeutic relationship between caregivers and patients.

A brief list of pertinent and contemporary references is included in each chapter. It is hoped that this very focused volume will prove to be useful to you, and we would be delighted to hear from you with questions, comments, as well as direct feedback on whether or not we have hit our desired targets!

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PROLOGUE

Cancer is serious public health problem in countries of all resource levels. Although major advances in the detection and treatment of the disease have occurred in higher income settings, similar progress has been slow or scarce in most low- and middle- income countries (LMCs).

The poorer outcomes in LMCs may relate to the limited capability of their healthcare systems (HCS) to provide successful early detection, diagnosis, and treatment of cancer.

Impediments to better outcomes include insufficient numbers of appropriately trained healthcare workers, limited access to screening/treatment facilities, inadequate supplies of necessary drugs, and timeliness of treatment after diagnosis.

This initiative, facilitated by Cesar J. Restrepo, MD, and with the participation of prestigious oncologists from various countries around the world, reinforces the importance of the development and training of oncology specialists.

Soon, cancer will be the number one disease in many countries, and we need to prepare for it. Being one step ahead of cancer to help healthcare systems and public policies reduce mortality from cancer worldwide.

Enjoy reading this very elaborate book.

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INTRODUCTION

This Oncology Book is written, from “the battlefield”, there are extraordinary Oncology Books, well written, but none like this (as far as I know). This book fills a space with these other books and shows the reality of our situation.

Written by extraordinary and frequent writers, all Experts in their field, members of International Surgical Oncology Societies. It is designed in such a way that the Oncologist, as well as the profane, the scholar and the students will understand.

We do not need to prove, that our Cancer statistics are not good, they do not reflect our reality. When studying the current International Guidelines for Cancer, we cannot apply them in full, due to our “lack of resources, different culture and geographic location”, so we end up (“Tropicalizing”), making local adjustments. This is our Book spirit and Goal.

Cancer is a genetic disease, in addition to studying Cancer, it is necessary to understand those affected, patients and relatives; the society, the country. The incidence of Cancer is, and will, continue to increase, up to 75% in 2030. Low and middle-income countries will experience the greatest impact.

Lung cancer and those caused by infections will be those with the greatest increase. In the rich area of the planet, prostate, colon and breast cancer will continue to have the highest incidence. Developing countries will suffer the evils of tobacco, which generates 12 percent of their cancer cases, a percentage that continues to grow. Another 25 percent of cases find their origin in chronic diseases. Researchers estimate that by the year 2030, 1.7 million cancer cases will be diagnosed in Latin America and the Caribbean and more than one million deaths from cancer.

This Book has 55 chapters, the last tells the history of Oncology in Panama, linked to the History of Panama and the World. A small country with 4 million inhabitants, a “melting pot”, a genetic mixture.

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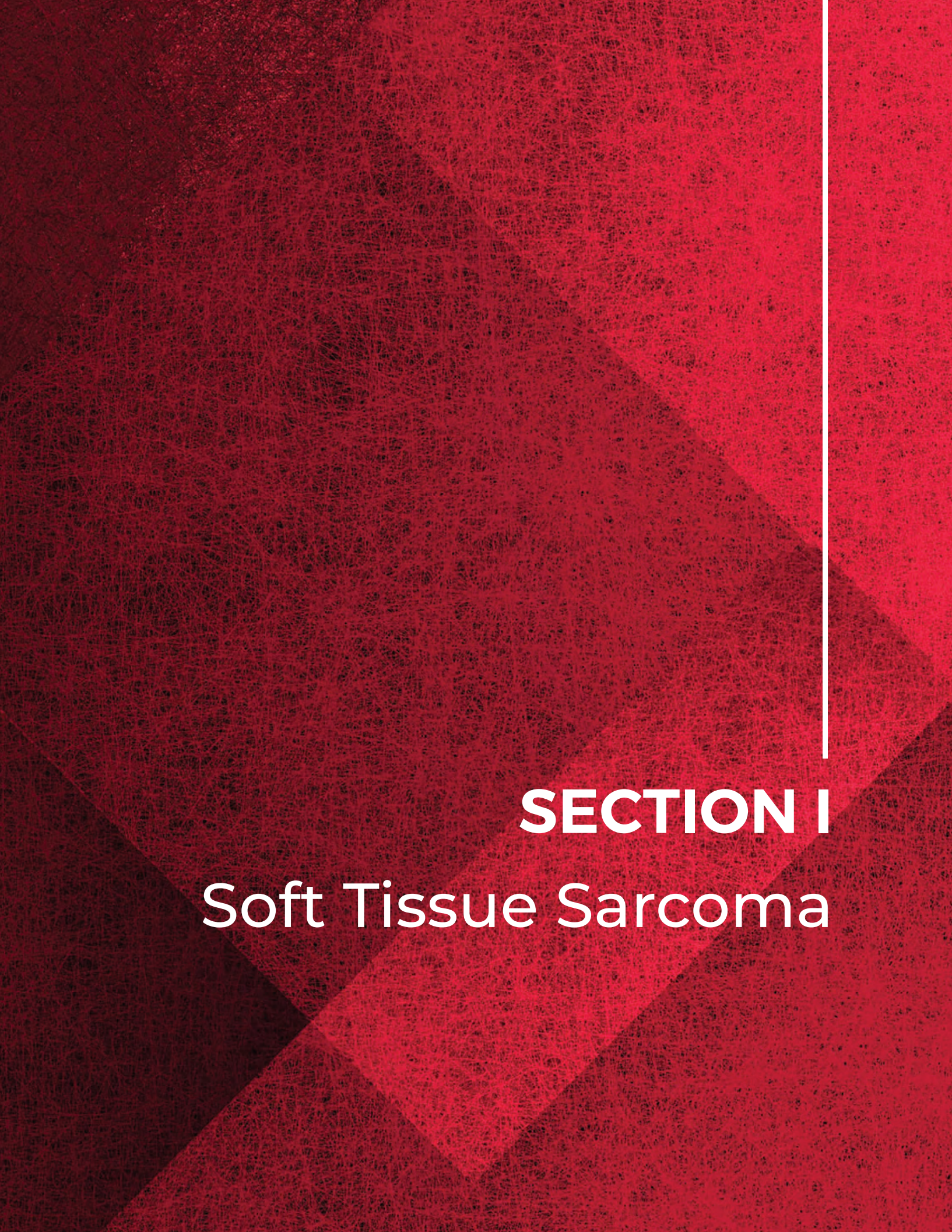
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SECTION I

Soft Tissue Sarcoma

Chapter 1

Soft Tissue Sarcoma

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Background

Soft tissue sarcomas (STS) are rare, nonepithelial, extra-skeletal, tumors of mesenchymal cell origin that make up approximately 1% of all new cancers with an annual incidence of 3.4 new cases per 100,000 persons.^(1,2) STS represent a heterogeneous group of soft tissue tumors with over 50 subtypes, each with their own histologic, cytogenic and clinicopathologic characteristics. Given the rarity and heterogeneity of STS, it is important to manage patients with STS within specialized multidisciplinary cancer teams in order to maximize patients' clinical outcomes. This chapter will provide an overview of STS pathogenesis, clinical presentation, prognostic factors, current staging system, and review of key features of some of the most common histologic subtypes. Finally, general treatment strategies and future directions in clinical care management will be summarized.

Pathogenesis

The majority of STS are spontaneous without an underlying clear pathogenesis. However, several predisposing factors have been identified. Although the exact mechanism is not understood, epidemiological studies have identified racial differences in the incidence of STS, with African Americans demonstrating the highest rates.⁽³⁾ Several inherited genetic disorders have also been associated with an increased risk of developing STS. These include Neurofibromatosis type 1 (*NF1* gene), Li-Fraumeni syndrome (*TP53* gene), Hereditary retinoblastoma (*RBI* gene), Werner syndrome, Carney-Stratakis syndrome (*SDH* gene), and Gardner syndrome (*APC* gene).⁽³⁻¹²⁾

In addition to the hereditary factors associated with STS, environmental and other exposures have been linked to the development of STS. Ionizing radiation, either through radiation therapy or atomic bomb exposures, has been identified as an independent risk factor for the development of STS.^(5,13-15) Radiation-induced sarcomas are most often seen after treatment for breast cancer or non-Hodgkin lymphoma and have a delayed presentation, with a mean of 10 years from the time of radiation exposure to the time of diagnosis.^(7,13,16,17) The most commonly associated histologic subtypes are angiosarcoma, undifferentiated pleomorphic sarcoma, undifferentiated spindle cell carcinoma, or leiomyosarcoma.^(5,7,18) Chronic lymphedema has been associated with the development of angiosarcoma or lymphangiosarcoma (Stewart-Treves syndrome).⁽¹⁹⁻²³⁾ Patients infected with the human herpes virus 8 (HHV8) and with acquired immunodeficiency syndrome (AIDS) due to human immunodeficiency virus (HIV) infection are known to have a 100,000-fold increased risk of developing Kaposi's sarcoma.^(3,4,24,25) Multiple studies have been conducted evaluating environmental/occupational exposures to the risk of STS with several studies describing an increased STS risk with exposure to phenoxyacetic acid herbicides, chlorophenols, dioxins, cutting oil, and vinyl chloride.⁽²⁶⁻³⁰⁾ While the majority of STS are spontaneous it is important to evaluate for these underlying conditions in the evaluation and management of the patient.

Clinical Presentation

The median age at diagnosis for all subtypes is 60 years of age with a slight 1.4:1 male predominance.⁽²⁾ STS tend to present as painless, enlarging, masses and depending on

their site of origin can be quite large before they become clinically evident. In the retroperitoneal/abdominal location, they most commonly present with nonspecific symptoms of an enlarging abdominal mass (pain, nausea or vomiting, weight loss, abdominal bloating/fullness, palpable abdominal mass, etc.). Incidental resection or delayed diagnosis is not uncommon, as they can initially be thought to be a lipoma or a spontaneous or posttraumatic hematoma. Delayed presentation of retroperitoneal STS is also quite common given their overall slow growth rate, tendency to displace surrounding structures (not invade), and the large retroperitoneal potential space. STS can be found in any part of the body, but the majority arise in the extremities (40%; 28% lower and 12% upper), followed by the viscera (22%), retroperitoneum (16%), trunk (10%), and then all other anatomic sites (12%).⁽³¹⁾ The most common STS subtypes are liposarcoma (LPS), leiomyosarcoma (LMS), undifferentiated pleomorphic sarcoma (UPS; previously named malignant fibrous histiocytoma), and gastrointestinal stromal tumor (GIST).^(2,31-33) However, distribution of the STS histologic subtypes varies based on the site of origin. For example, the thigh makes up 44% of all extremity STS and liposarcoma is the most common histologic subtype for all extremity STS.^(5,31) The most common visceral tumors are LMS and GIST, while the most common retroperitoneal tumors are LMS and LPS.⁽⁵⁾

Evaluation

An experienced multidisciplinary sarcoma oncology team should evaluate all patients suspected of having a STS. During physical examination, it is important to note if there is fixation of the tumor and if there is presence of any motor or sensory deficits. Dedicated cross-sectional imaging with and without contrast of the primary tumor should be performed to delineate tumor size, location, and contiguity to or involvement of adjacent structures (muscle, bone, viscera, etc.) and neurovascular bundles. The optimal imaging modality used is dependent on the location of the primary tumor, with magnetic resonance imaging (MRI) being the preferred modality for extremity and pelvic tumors and computed tomography (CT) for intra-abdominal or retroperitoneal tumors.

Tissue diagnosis with a pretreatment biopsy is important for developing a multidisciplinary treatment plan and should be performed in patients presenting with a soft tissue mass, especially if the mass is enlarging or is larger than 5 cm. For tumors less than 5 cm in size that can be completely excised without significant defect, surgical resection is

often diagnostic and therapeutic without affecting other treatment modalities or prognosis. Core-needle biopsy is the preferred method for most as it is accurate and minimally invasive.⁽³⁴⁻³⁶⁾

After tissue diagnosis is obtained, staging work-up should be performed evaluating for pulmonary metastatic disease with a chest x-ray or a chest CT without contrast, as this is the most common site of metastasis for all types of STS. Currently the choice between these modalities is based on risk of metastasis of the particular histologic type and primary tumor location, as neither has been proven to be more effective or cost-efficient. Certain histologic types require additional imaging based on metastatic patterns. For myxoid round cell liposarcoma, leiomyosarcoma, angiosarcoma, and epithelioid sarcoma of the extremity, an abdominal and pelvic CT scan should be performed. Additionally, in patients with myxoid round cell liposarcoma dedicated images of the spine should also be performed to evaluate for osseous metastatic disease. Given the risk of cerebral metastasis with alveolar soft part and angiosarcoma, brain MRI should also be considered in these patients. Positron emission tomography (PET)/CT may be useful in some circumstances to assess extent of disease or further evaluate concerning lesions identified on previous imaging but is not routinely used in STS staging workup.

Clinicopathologic Prognostic Factors

Grade, anatomic site and histopathologic subtype are all important factors in the treatment and prognosis of STS. Grade has been the most well described and until recently was the only factor in the American Joint Committee on Cancer (AJCC) staging system. The most commonly used grading systems are the French Federation of Cancer Centers (FNCLCC) and the National Cancer Institute (NCI) grading systems. In the FNCLCC system, tumor grade is determined by three histologic features (degree of tumor differentiation, mitotic activity, and extent of tumor necrosis).⁽³⁷⁻³⁹⁾ The NCI grading is based on both histologic subtype and histologic features with some histologic subtypes automatically classified as grade 1 or grade 3 secondary to their favorable or aggressive clinical behavior, respectively, and the remaining classified based on the extent of tumor necrosis.⁽⁴⁰⁾ A head-to-head comparison of the prognostic capability of the FNCLCC and the NCI staging systems was performed by Guillou *et al.* and on multivariate analysis found that both systems provided prognostic value for metastatic-free and OS.⁽⁴¹⁾ However, the FNCLCC system was slightly superior with better

correlation with metastatic-free and OS compared to the NCI grading system.⁽⁴¹⁾

Anatomic site of tumor origin plays a key role in tumor recurrence patterns and clinical outcomes.^(31,42,43) Brennan *et al.* evaluated the results of 10,000 patients with STS and found that visceral tumors had a local recurrence (LR) rate less than 20% and a disease-specific mortality (DSM) rate of approximately 35% at 10 years, extremity tumors had a LR rate of approximately 25% and a DSM rate of approximately 40% at 10 years, and retroperitoneal tumors had LR and DSM rates greater than 60% at 15 years.⁽³¹⁾ Others have demonstrated similar findings comparing extremity location versus retroperitoneal.⁽⁴²⁾ These results emphasize the fact that extremity and visceral STS tend to have low rates of LR and that distant recurrence is the key factor in DSM. While retroperitoneal tumors that tend to have high rates of LR, local progression is the key factor in DSM.

For extremity and truncal tumors, tumor depth is classified based on the tumor location in relation to the investing fascia of the musculature, superficial (above) or deep (below). Increased tumor size and deep tumor location have been repeatedly demonstrated to be independent predictors of STS clinical outcomes.^(31,38,43-45) Given that superficial tumors tend to be much smaller in size at time of presentation compared to deep tumors, tumor size and depth may not necessarily be two independent risk factors. Brennan *et al.* evaluated the influence of both tumor depth and tumor size on disease specific survival (DSS) and found that tumors ≤ 5 cm had a better DSS vs. tumors > 5 cm and that superficial tumors ≤ 5 cm had a better DSS vs. deep tumors ≤ 5 cm.⁽³¹⁾ However, for tumors > 5 cm tumor depth no longer influenced DSS and tumor size independently impacted DSS.⁽³¹⁾

Due to the rarity of this disease the effects of histopathologic subtype on clinical outcomes has been difficult to assess given the small number of patients and the vast number of histologic subtypes. However, several studies have demonstrated that clinical outcomes are driven by histology. Koea *et al.* evaluated the influence of histopathologic subtype as a prognostic factor in patients with primary extremity STS and demonstrated that MPNST subtype was an independent risk factor for LR, whereas the LMS subtype was an independent risk factor for distant metastasis (DM).⁽⁴⁶⁾ LPS and fibrosarcoma subtypes were associated with a decreased likelihood of DM.⁽⁴⁶⁾ Similarly, Tan *et al.* evaluated the influence of histopathologic subtype as a prognostic factor in patients with primary retroperitoneal STS. High rates of LR were seen for both high-grade and low-grade LPS.⁽⁴⁷⁾ Conversely, histologic subtypes that

demonstrated high rates of DM were LMS and solitary fibrous tumor (SFT).⁽⁴⁷⁾ A large study performed by the Multi-institutional Collaborative Retroperitoneal Sarcoma Working Group assessing the recurrence patterns of primary retroperitoneal sarcomas also demonstrated similar trends in the influence of the histologic subtype in the recurrence pattern and overall outcomes of patients.⁽⁴⁸⁾ It is important to understand the relationship between histopathologic subtype and clinical outcomes as the histologic subtype may influence the use of neoadjuvant/adjuvant treatment options and surgical approach.

Staging

The major clinicopathologic factors used to establish stage for STS are tumor grade, depth, anatomic site of origin, and size.⁽⁴⁹⁻⁵²⁾ The most commonly used system for STS is the AJCC TNM staging system. Staging of STS with this system is challenging given several inherent issues with this disease process: (i) heterogeneity in STS histologic subtypes; (ii) lack of standardization and reproducibility of tumor grading system; (iii) vast distribution of tumor anatomic sites with varying site-specific biological behaviors; (iv) lack of prognostic differentiation between large tumors given that two thirds of STS present with a mean tumor size of ≥ 5 cm and one third with mean tumor size of ≥ 10 cm;⁽³¹⁾ and (v) that only a handful of STS have a propensity to metastasize to lymph nodes (synovial sarcoma, clear cell sarcoma, angiosarcoma, rhabdomyosarcoma, and epithelioid sarcoma) the traditional N-stage evaluation of the TNM staging does not provide significant prognostic information. Subsequent editions of the AJCC Cancer Staging Guidelines have attempted to address these issues by incorporating histologic features into the tumor grade classification, and consolidation into a three-tiered grading system using the FNCLCC system for better reproducibility of histologic grade, and incorporation of tumor depth.⁽⁵³⁻⁵⁵⁾

The most recent eighth edition of the AJCC Cancer Staging Manual continues to address some of these major issues for STS with three major updates.⁽⁵⁶⁾ First, to incorporate the importance of site-specific biological behaviors, the new AJCC staging system now splits STS staging based on the anatomic site of tumor origin: head and neck, trunk and extremities, abdominal and thoracic visceral organs, GIST, and retroperitoneum. Second, given that previous studies have demonstrated that tumor size may independently impacts outcomes, regardless of tumor depth, tumor depth has been removed from the T-stage classification and the T-stage categories have been increased from two (T1 –

T2) to four (T1 - T4) categories in order to provide better diagnostic information for larger tumors. Finally, given that the majority of STS spread hematogenously and not through lymphatic spread, regional lymph node metastasis in extremity STS are now considered stage IV disease. A table summary of the eighth edition AJCC staging system is outlined in **Table 1-1**.

Common Histologic Subtypes

Key features of the common STS histologic subtypes outlined below are presented in **Table 1-2**.

Liposarcoma (LPS). Liposarcomas arise from adipose tissue and are one of the most common STS found in adults, accounting for up to 25% of all cases. ⁽⁵⁷⁻⁵⁹⁾ Liposarcomas are further subclassified based on distinct biologic, histologic, cytogenic, molecular, and clinicopathologic features. The four major LPS subtypes are atypical lipomatous tumor (ALT)/well-differentiated liposarcoma (WDL), dedifferentiated liposarcoma (DDL), myxoid/round cell liposarcoma (MRCL), and pleomorphic liposarcoma (PLS). ^(57,60) In order to choose the best management strategy for patients with LPS, it is important to understand the key differences between each of these subtypes.

ALT/WDL. ALT/WDL is the most common LPS subtype, accounting for roughly 40% of all LPS cases, and tends to present between the sixth and seventh decade of life. ⁽⁶⁰⁻⁶²⁾ The deep soft tissues of the extremities are the most common location for ALT/WDL (75% of cases), with the remainder of cases located in the retroperitoneum (20%) or other anatomic sites (5%). ⁽⁶³⁻⁶⁵⁾ Typical imaging characteristics of ALT/WDL include the presence of a large, multi-lobulated and well-demarcated fat density mass with fibrous septa. (**Figure 1-1.A**) ⁽⁶⁶⁻⁶⁸⁾ ALT/WDL is characterized by amplifications in segments of chromosome 12q13–15, containing several oncogenes. ^(62,66,69,70) Of these, *MDM2* and *CDK4* demonstrate the largest oncogenic role. ^(66,69) ALT/WDL are low-grade tumors without metastatic potential but do have the potential to be locally aggressive. ^(60,64,70-72) Patient outcomes are influenced by primary tumor location. Retroperitoneal tumors demonstrate higher LR rates (40-60% vs. 5-15%), higher rates of dedifferentiation (20% vs 5%), and higher rates of DSM (30% vs. 0%) compared to extremity tumors. ^(47,48,63,66,69,73,74) Given these differences, most authors advocate that the term WDL be used for retroperitoneal tumors and ALT be reserved only for extremity tumors. ^(62-65,70-72)

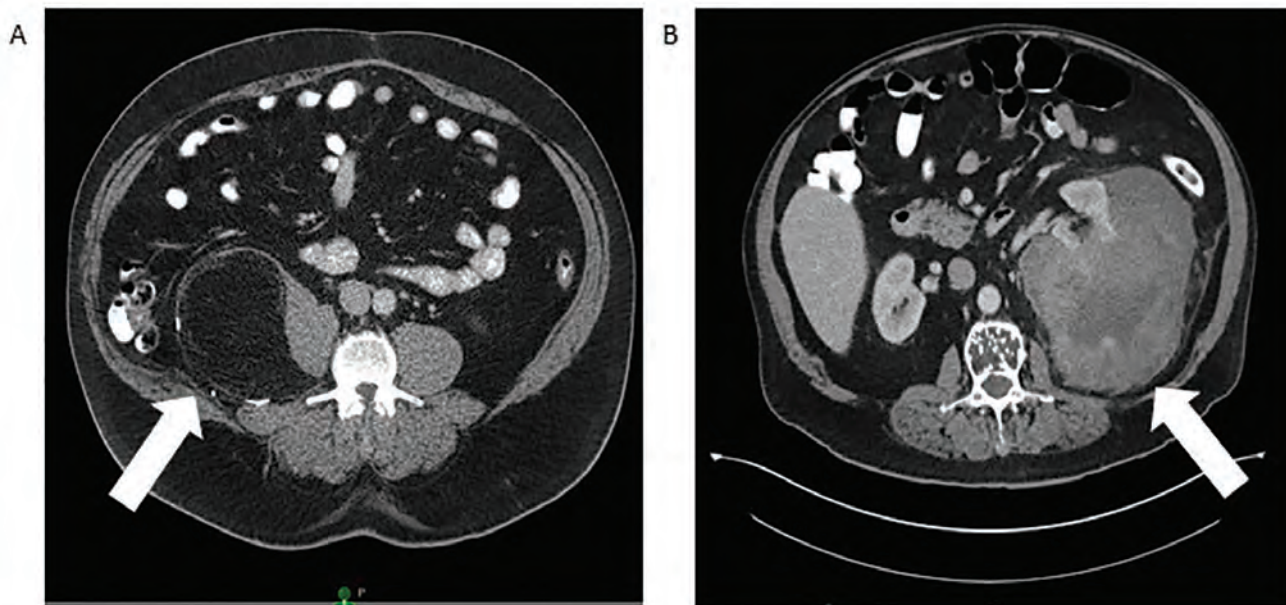


Figure 1-1. Liposarcomas of the retroperitoneum show the differences of the two most common subtypes.
A) Well-differentiated liposarcoma of the right psoas; these tumors are almost completely fatty with septa and a capsule that differentiates them from surrounding retroperitoneal fat.
B) Retroperitoneal dedifferentiated liposarcoma; these tumors have a solid, nonlipomatous, nodular regions. Careful review of the imaging for associated well-differentiated lipomatous component should be performed. Tumors are highlighted by the arrows.

Table 1-1. Soft Tissue Sarcoma American Joint Committee On Cancer Staging System, 8th Edition +

	Trunk & Extremities	Retroperitoneum	Head & Neck	Visceral Organs ^a	GIST
Primary Tumor (T) ⁺	TX Cannot be assessed	TX Cannot be assessed	TX Cannot be assessed	TX Cannot be assessed	TX Cannot be assessed
	T0 No evidence of tumor	T0 No evidence of tumor	T1 ≤ 2 cm	T1 Organ confined	T0 No evidence of tumor
	T1 ≤ 5 cm	T1 ≤ 5 cm	T2 > 2 cm and ≤ 4 cm	T2 Extension into tissue beyond organ	T1 ≤ 2 cm
	T2 > 5 cm and ≤ 10 cm	T2 > 5 cm and ≤ 10 cm	T3 > 4 cm	T2a- serosa or visceral peritoneum	T2 > 2 cm and ≤ 5 cm
	T3 > 10 cm and ≤ 15 cm	T3 > 10 cm and ≤ 15 cm	T4 Invades adjoining structures T4a- orbit, skull base/dura, central compartment viscera, facial skeleton, or pterygoid muscle	T2b- beyond serosa (mesentery)	T3 > 5 cm and ≤ 10 cm
	T4 > 15 cm	T4 > 15 cm	T4b- brain parenchyma or prevertebral muscles, carotid artery encasement, or CNS involvement via perineural spread	T3 Invades another organ	T4 > 10 cm
				T4 Multifocal involvement	
				T4a- 2 sites	
				T4b- 3-5 sites	
				T4c- > 5 sites	
Regional Lymph Nodes (N)		N0 No regional lymph node metastasis or unknown lymph node status			
		N1 Regional lymph node metastasis			
Distant Metastasis (M)		M0 No distant metastasis			
		M1 Distant metastasis			
Grade (G)		GX Grade cannot be assessed			Low ≤ 5 mitoses/5 mm ² or 50 HPF ^d
		G1 Total differentiation, mitotic count, and necrosis score of 2 or 3 ^c			High > 5 mitoses/5 mm ² or 50 HPF ^d
		G2 Total differentiation, mitotic count, and necrosis score of 4 or 5 ^c			
		G3 Total differentiation, mitotic count, and necrosis score of 6, 7, or 8 ^c			
Stage	IA	T1, N0, M0, G1/GX	IA	T1, N0, M0, G1/GX	Gastric^e IA T1-2, N0, M0, Low
	IB	T2-4, N0, M0, G1/GX	IB	T2-4, N0, M0, G1/GX	IB T3, N0, M0, Low
	II	T1, N0, M0, G2-3	II	T1, N0, M0, G2-3	II T1-2, N0, M0, High T4, N0, M0, Low
	IIIA	T2, N0, M0, G2-3	IIIA	T2, N0, M0, G2-3	IIIA T3, N0, M0, High
	IIIB	T3-4, N0, M0, G2-3	IIIB	T3-4, N0, M0, G2-3	IIIB T4, N0, M0, High
	IV	T1-4, N1, M0, G1-3	IV	T1-4, N1, M0, G1-3	IV T1-4, N1, M0, Low/High
		T1-4, N0-1, M1, G1-3	IV	T1-4, N0-1, M1, G1-3	T1-4, N0-1, M1, Low/High
				n/a	SB^f I T1-2, N0, M0, Low
					II T3, N0, M0, Low
					IIIA T1, N0, M0, High T4, N0, M0, Low
					IIIB T2-4, N0, M0, High
					IV T1-4, N1, M0, Low/High T1-4, N0-1, M1, Low/High

GIST, gastrointestinal stromal tumor; SB, small bowel, n/a, no recommended prognostic stage group definitions available at this time. ^a includes abdominal and thoracic visceral organs; ^b tumor size based on greatest dimension; ^c calculated based on the French Federation of Cancer Centers (FNCLCC) grading system; ^d grading of GIST is dependent on mitotic rate; ^e staging group definition also used for omental GIST; ^f staging group definition also used for esophageal, colorectal, mesenteric, and peritoneal GIST.

Table modified from AJCC Cancer Staging Manual, 8th edition, New York: Springer: 2017

Table 1-2. Features of soft tissue sarcomas presented in this chapter.

Common Subtypes	% of STS cases	Incidence Age	Male:Female ratio	Anatomic Location	Cytogenic Features	Rate of LR	Rate of DM	Rate of DSM
LPS								
ALT/WDL		6 th & 7 th decade	1:1	Ext: 75% RP: 20% Other: 5%	<i>MDM2</i> amp (100%) <i>CDK4</i> amp (90%)	Ext: 5-15% RP: 40-60%	0%	Ext: 0% RP: 30%
DDL	25%	6 th & 7 th decade	1:1	Ext: 55% RP: 25% Other: 20%	<i>MDM2</i> amp (100%) <i>CDK4</i> amp (90%) <i>1q23</i> co-amp <i>12q24</i> co-amp <i>1p32</i> or <i>6q23</i> co-amp	Ext: 30% RP: 40-62%	15-30%	Ext: 25-30% RP: 30-75%
MRCL		5 th decade	1:1	Ext: 75% Other: 25%	<i>t(12;16)(q13;p11) (>95%)</i> <i>t(12;22)(q13;p12) (<10%)</i> RET, IGF1R, or IGF2 overexpression	15-30%	20-45%	15-30%
PLS		5 th & 6 th decade	1.25:1	Ext: 60% Trunk: 15% RP: 5% Other: 20%	<i>13q14.2-q14.3 del (60%)</i> <i>17p13 del</i> <i>17q11.2 del</i>	20-45%	26-43%	28-35%
LMS	10-15%	7 th decade	1:1.5 RP 1:1.2 Ext	RP/Abdominal: 75% Other: 25%	Complex nonspecific alterations	10-25%	Ext: 34-45% RP: 50-58%	Ext: 40-51% RP: 60-80%
UPS	15%	6 th & 7 th decade	1.6:1	Ext: 70% RP/Abdominal: 15% Other: 15%	Complex nonspecific alterations	20-30%	30-40%	26-37%
GIST	10%	6 th decade	1:1	Stomach: 60% Small intestine: 30% Duodenum (5%), Rectum (3%) Colon (2%)	<i>KIT</i> mutation <i>PDGFR4</i> mutation	25-40%	3.6% ^a 12% ^b 55% ^c 86% ^d	10-20%

STS, soft tissue sarcoma; LR, local recurrence; DR, distant metastasis; DSM, disease-specific mortality; LPS, liposarcoma; ALT/WDL, atypical lipomatous tumor/well-differentiated liposarcoma; DDL, dedifferentiated liposarcoma; MRCL, myxoid/round cell liposarcoma; PLS, pleomorphic liposarcoma; LMS, leiomyosarcoma; UPS, undifferentiated pleomorphic sarcoma; GIST, gastrointestinal stromal tumor; SFT, solitary fibrous tumor; Ext, extremity; RP, retroperitoneum; CNS, central nervous system; ^a, tumor > 5 cm with ≤ 5 mitoses/50 HPF; ^b, tumor > 10 cm with ≤ 5 mitoses/50 HPF; ^c, tumor > 5 cm with > 5 mitoses/50 HPF; ^d, tumor > 10 cm with > 5 mitoses/50 HPF

DDL. DDL is the third most common LPS subtype and accounts for 18% of all cases. ⁽⁵⁹⁾ Approximately 10% of DDL tumors arise from dedifferentiation of ALT/WDL tumors, the others arise de novo. ^(59,66) Similar to the incidence age of ALT/WDL, DDL presents between the sixth and seventh decade. ⁽⁶⁶⁾ As opposed to ALT/WDL, the retroperitoneum is the most common location for DDL (55% of cases), followed by the deep soft tissues of the extremities (25%) and other anatomic sites (20%). ^(59,66) Typical imaging characteristics of DDL include the presence of a large, multinodular, deep-seated mass containing a mixture of both fat density and solid tumor components. (**Figure 1-1.B**) ⁽⁶⁶⁾ Similarly to ALT/WDL, DDL are characterized by amplified segments of chromosome 12q13–15. ^(62,69,70) Amplifications of *MDM2* and/or *CDK4* genes are seen in 90% of these tumors. ⁽⁶⁶⁾

DDL is a high-grade tumor and is associated with higher rates of DM and DSM when compared to ALT/WDL. ^(47,48) Outcomes for DDL are also influenced by tumor location and, similar to ALT/WDL, retroperitoneal tumors have higher rates of LR (40-60% vs 30%) and higher incidence of DSM (53% vs 25%) when compared to extremity tumors. ^(48,66,75,76) Unlike ALT/WDL, DDL does have the potential to metastasize. Similar rates of DM are seen between retroperitoneal and extremity DDL with rates of 15-30%, and metastasis to either the lung (76%) or liver (24%). ^(48,66,69,74-77) Overall reported DSM ranges from 30-75% with mortality most commonly due to advanced local-recurrent disease. ^(66,69,74-76)

MRCL. MRCL accounts for 30-35% of all LPS cases and is the second most common LPS subtype. ⁽⁶⁹⁾ MRCL tumors tend to present slightly earlier than ALT/WDL and DDL during the fifth decade of life. The deep soft tissues of the lower extremities within the popliteal space or medial thigh is the most common location for MRCL (75% of cases) with the remainder of cases located in other anatomic sites and less frequently in the retroperitoneum. ⁽⁵⁹⁾ Typical imaging characteristics of MRCL include the presence of a multinodular heterogeneous intramuscular tumor with less than 10% lipomatous content and intense post-contrast enhancement. ^(68,74,78-80) On cytogenic analysis MRCL is characterized by t(12;16)(q13;p11) which results in generation of fusion gene *FUD-DDIT3* and is seen in over 95% of cases. ^(69,81,82)

The clinical behavior of MRCL tumors can range from a low-grade tumor to a high-grade tumor based on the round cell component. ⁽⁸³⁻⁸⁷⁾ Clinicopathologic features associated with worse outcomes include increased percentage of round

cell dedifferentiation, increased tumor size, spontaneous tumor necrosis, and p53 overexpression. ^(84,85,87,88) The overall LR rates for MRCL range from 15-30%, DM rates range from 20-45%, and DSM rates range from 12-30%. ^(74,84,85,87-89) MRCL tumors have a unique metastatic pattern compared to other STS with metastases to bones and other soft tissues frequently seen (66%) and lung metastases less frequently seen (34%). ^(84,85,87,89,90)

PLS. PLS makes up about 5% of all LPS cases. ^(59,91) The extremities are the most common location for PLS (60% of cases) with the remainder of cases located in the truncal wall (15%), other anatomic sites (20%), and less frequently in the retroperitoneum (5%). ^(92,93) Unlike the other LPS subtypes, 25% of cases develop in the skin or superficial soft tissues. ⁽⁹³⁾ On cytogenic analyses, PLS demonstrates a large number of recurrent chromosomal imbalances secondary to complex genetic rearrangements, with deletion of 13q14.2-q14.3 (resulting in dysregulation of the *RBI* gene) being the most common alteration (60% of PLS tumors). ^(32,94-97) PLS arising from the skin or superficial soft tissues demonstrate less aggressive clinical behaviors with reported LR rates of about 10% and very low rates of DM. ⁽⁹⁸⁾ All other PLS demonstrate aggressive clinical behaviors associated with high-grade tumors and, aside from surgical resection, demonstrate resistance to most current treatment options. ⁽⁹⁹⁾ The overall reported rates for LR range from 20-45%, DM range from 26-43%, and DSM range from 28-35%. ^(74,92,93,99) The most common metastatic sites are to the lung (75%) and liver (25%). ⁽⁹²⁾ Clinicopathologic features associated with worse outcomes include deep tumor location, truncal anatomic location, large tumor size, high mitotic rate, and vascular invasion. ^(92,93)

LMS. Soft tissue LMS arise from smooth muscle tissue and are less common than visceral LMS (uterine, gastrointestinal, etc.) accounting for approximately 10-15% of adult STS. ^(31,100-102) These tumors tend to present in the seventh decade of life. ⁽¹⁰¹⁻¹⁰³⁾ Soft tissue LMS are most commonly found in retroperitoneum or abdominal cavity (75%) and less commonly in the extremities or trunk (25%). ^(100,101) Unlike LPS, retroperitoneal/abdominal LMS commonly involve adjacent structures through direct invasion. ⁽¹⁰⁰⁾ The majority of extremity/truncal LMS are found to arise from small vessels and are most commonly located on the lower extremities. ^(100,103) These tumors are much smaller than retroperitoneal/abdominal tumors and typically present as enlarging masses.

Soft tissue LMS tend to be aggressive tumors and outcomes are influenced by the grade and location of the tumor. The

rates of LR are similar for both retroperitoneal/abdominal and extremity/truncal tumors at 10-25%.^(46-48,101,102,104) However, the reported rates of DM and DSM differ based on tumor location. Extremity/truncal soft tissue LMS have reported DM rates of 34-45% while retroperitoneal/abdominal LMS have slightly higher reported DM rates of 50-58%.^(46-48,100,101,104) Similarly, the reported DSM rates for retroperitoneal/abdominal tumors are higher than the reported rate for extremity/truncal tumors, with rates of 60-80% and 40-51%, respectively.^(46,48,101,105)

UPS. UPS, formally known as malignant fibrous histiocytoma, accounts for approximately 15% of STS and tends to present between the sixth and seventh decade of life.^(31,106,107) UPS demonstrates a male predominance with a male:female ratio of 1.6:1.^(108,109) The extremities are the most common location for UPS (65-70% of cases) with the lower extremities, particularly the thigh, being the most common site.^(31,106,110-112) The retroperitoneum and abdominal cavity occur less frequently, accounting for less than 15% of cases.^(31,106,109,113)

Like most other STS, these tumors tend to present as painless enlarging mass. However, inflammatory UPS tumors (typically retroperitoneal) can induce the development of a paraneoplastic syndrome, which is thought to occur through tumor cytokine production.⁽¹¹⁴⁻¹¹⁶⁾ These patients can present with fevers, leukocytosis, and hypoglycemia. Paraneoplastic symptoms most often resolve after the tumor has been excised. Similar to other pleomorphic and high-grade tumors, UPS demonstrates a large number of complex and nonspecific chromosomal structural abnormalities and imbalances.⁽¹¹⁷⁾

Most UPS tumors present as high-grade lesions with LR rate of 20-30% and DM rate of 30-40%.^(46,107,109-113) The majority of LR and DM occur within the first two years of diagnosis.^(108,110,111) The lungs (80-90%) are the most common site of metastasis for these tumors, but unlike most other STS regional lymph node metastasis has been reported to occur in 3-7% of cases.^(106,107,109,111-113) Other sites of metastases include bone and liver.^(106,109,111,113) The overall reported DSM rate for these tumors ranges from 26-37% and is most commonly due to systemic disease.^(46,106,107,109-111)

GIST. GIST arises from the intestinal cells of Cajal and are the most common mesenchymal tumors of the gastrointestinal (GI) tract and account for 10% of all STSs.^(31,118) GIST have a peak incidence in the sixth decade of life.⁽¹¹⁹⁾ These tumors arise throughout the entire GI tract but are most commonly seen in the stomach (60% of cases),

followed by the small intestine (30%), duodenum (5%), rectum (3%) and colon (2%).^(5,120) Many times GIST are found incidentally on imaging for other indications, but can also present with chronic blood loss anemia, GI bleed, abdominal fullness, or symptoms from intraabdominal mass effect.⁽¹²¹⁾ Microscopically, GIST are found within the muscularis propria and can be subclassified as epithelioid, spindle cell, or mixed morphology.⁽¹²²⁾

An activating KIT mutation is seen in 70-80% of tumors on exon 9, 11, 13, or 17.⁽¹²³⁾ The most common is exon 11 (37% of cases) followed by exon 9 (10% of cases). Approximately 10-15% of cases have a *PDGFRA* mutation. The *PDGFRA* gene encodes for a receptor tyrosine kinase that is related to KIT.⁽¹¹⁹⁾ Those with *KIT* exon mutations involving exons 9 and 11 have a reported more aggressive disease biology, versus *PDGFRA* exon 18 mutation.^(124,125) GIST prognosis and treatment is determined by tumor size, anatomic primary tumor location, and mitotic rate.⁽¹²⁵⁾ GIST with low-risk features have 96% 5-year disease free survival, compared to those with intermediate- and high-risk features have a 54% and 20%, respectively, 5-year disease free survival.⁽¹²⁶⁾ Metastasis most commonly occurs to the liver or within the peritoneal cavity. In the rare occasions of extra-abdominal metastatic disease, it can occur in the lung, dermal and subcutaneous tissues, bone and brain.^(123,127,128)

Angiosarcoma. Angiosarcoma is a rare STS and represents less than 1% of all cases.⁽¹²⁹⁾ Angiosarcomas are vascular tumors that can arise anywhere in the body from small blood vessels. Unlike most other STSs, angiosarcomas tend to occur in the skin and superficial soft tissues. Although most cases are sporadic, they are associated with well-established risk factors (most importantly radiation and chronic lymphedema) and should be in the differential for cutaneous lesions in patients with these known risk factors.^(5,7,18-21) Primary angiosarcomas most commonly present in the sixth and seventh decade of life.⁽¹²⁹⁻¹³¹⁾ Radiation-induced angiosarcomas typically develop within 7-10 years from the time of treatment, however they can occur within five years in women who receive radiation treatments for breast cancer, and these account for approximately 25% of all angiosarcomas.^(129,131,132) Angiosarcomas in patients with chronic lymphedema typically develop > 10 years from onset of lymphedema.⁽¹²⁹⁾ Early tumors tend to present as ill-defined areas of ecchymosis or hematoma in patients without a history of trauma.⁽¹³⁰⁾ Patients with more advanced tumors can present with irregular palpable lesions with associated symptoms including pain, swelling, or occasional bleeding.^(130,131)

Angiosarcomas are aggressive tumors and are associated with poor clinical outcomes. These tumors have a reported LR rate ranging from 20-80% and a DM rate ranging from 36-60%.^(130,131,133,134) Like most other STSs, the most common site of metastasis is the lung.⁽¹³¹⁾ However, angiosarcomas are one of the few STS subtypes that can also metastasize to the bones, brain, and lymph nodes.^(130,131,134) Angiosarcomas have an overall reported DSM rate of 40-60%.^(130,131,134)

Management of STS

Given the rarity, heterogeneity and complexity of the disease, clinical management of STSs should be conducted under the guidance of a specialized multidisciplinary team. These teams should include pathologists, radiologists, medical oncologists, radiation oncologists, and surgeons with expertise in the management of STS. Studies have shown patients managed at specialized centers with multidisciplinary team have improved outcomes.⁽¹³⁵⁻¹³⁸⁾

Surgery

Surgery remains the mainstay of treatment for most STS. Surgical resection should be performed via radical or wide excision with appropriate negative margins. One-centimeter gross margins have been recommended by some consensus groups; however, a clear-cut number is not agreed upon and appropriate resection requires *en bloc* excision of the tumor with a rim of normal surrounding tissue. If uninvolved with tumor, the fascia, peritoneum and periosteum function as anatomic barriers and are often used to delineate the boundaries of excision. One major issue related to surgical treatment of this disease is the unplanned/incidental excision of a STS during an operation for a separate disease process or during removal of the lesion that was originally thought to be a benign process (i.e. lipoma). Marginal or intralesional incisions have been associated with high rates of LR and can lead to contamination of the surrounding tissues; requiring more extensive surgery, reconstruction, and need for further treatments, such as radiation.⁽¹³⁹⁻¹⁴³⁾ Therefore, it is important to get adequate pre-treatment imaging and core needle biopsy to provide a specific diagnosis of any mass larger than 5 cm or less than 5 cm that cannot be excised with appropriate negative margins at the initial operation. Surgical resections and incisional/excisional biopsies of trunk and extremity lesions should all be performed through an incision orientated along the

long axis to decrease the need for reconstruction or wider radiation fields should further treatment be necessary.

Extremity STS. Surgical management of extremity STSs evolved from radical amputation to limb-sparing in the 1980s when Rosenberg *et al.* published the results of a clinical trial comparing amputation to limb-sparing surgical resection plus radiation therapy in 43 adult patients with high-grade extremity STSs. They demonstrated no difference in survival between the two groups and a 15% LR rate in the limb-sparing group.⁽¹⁴⁴⁾ Since then, several other studies of STSs treated with limb-sparing surgery have also demonstrated low recurrence rates.⁽¹⁴⁵⁻¹⁴⁸⁾ Margin status after limb-sparing surgical resection of STS has been reported to be a strong prognostic indicator of local disease recurrence.⁽¹⁴⁸⁻¹⁵³⁾ However, an impact on the development of distant metastasis and OS has not been clearly defined.^(154,155) Therefore, limb-sparing surgical resection with complete tumor excision and preservation of critical structures, +/- neoadjuvant or adjuvant radiotherapy, is currently the primary treatment strategy for the majority of extremity STSs.^(154,156,157) Amputation may be considered in patients with localized disease who present with functional deficits from neurovascular tumor invasion or those with proximal high-grade tumors in which complete surgical resection cannot be performed without loss of limb function; as amputation will provide durable disease control and function has already been lost.^(158,159) In patients with metastatic disease, amputation should only be considered for palliation of symptoms.

Retroperitoneal and Intraabdominal STS. Similar to extremity and truncal tumors, complete surgical resection is the mainstay of treatment for retroperitoneal/intraabdominal STSs. Margin assessment is more difficult owing to the size and the fact that the majority of the retroperitoneum and abdominal cavity does not provide a true anatomic barrier to assess tumor extension. Therefore, most centers define complete resection of retroperitoneal/intraabdominal STSs as the removal of all macroscopic disease.⁽¹⁶⁰⁻¹⁶²⁾ Incomplete resection, in which all macroscopic disease is not removed, is associated with poor outcomes and no survival benefit in this patient population.⁽¹⁶²⁻¹⁶⁷⁾ Tumor location, and not size, is the major determinant of retroperitoneal/intraabdominal STS resectability. Highlighting this point, **Figure 1-2** demonstrates three different patients with an inferior vena cava (IVC) LMS. The probability of obtaining complete gross tumor resection along with associated risk of complications and impact on quality of life must be evaluated.

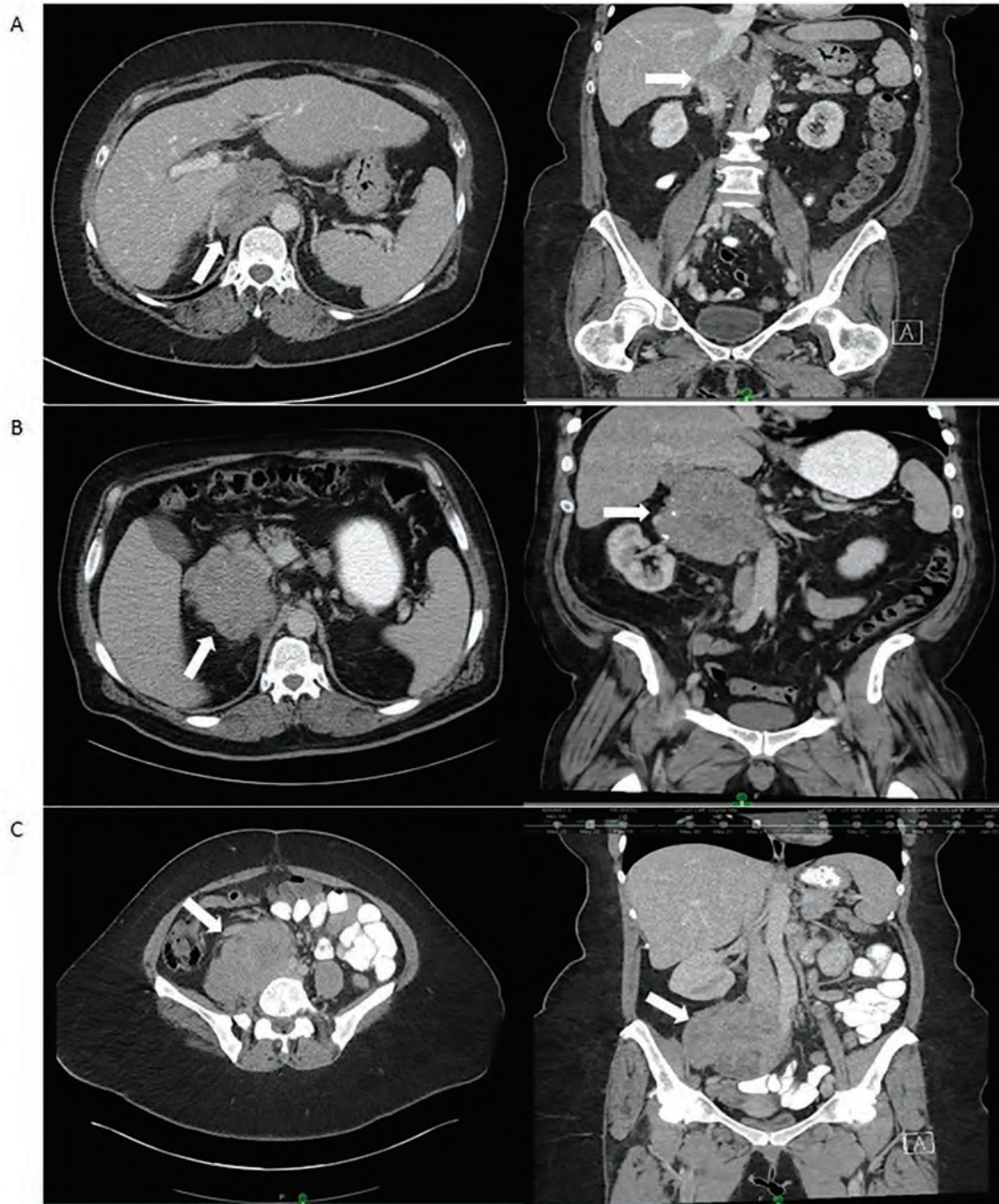


Figure 1-2. Leiomyosarcoma of the inferior vena cava (IVC) demonstrate the importance of location in determining resectability and operative planning.

- A) Leiomyosarcoma of the retrohepatic IVC. In this location, removal can require bypass and explantation of the liver to remove the tumor.
- B) Leiomyosarcoma of the para-renal IVC. This is a more favorable location; however, it can require nephrectomy even when the tumor does not directly invade the kidney.
- C) Leiomyosarcoma of the infrarenal IVC. This tumor is the favorable for resection based on its location, even though it is the largest tumor. Tumors are highlighted by the arrows.

Due to the high LR rates of STS in this anatomic location, several groups have evaluated clinicopathologic factors associated with recurrence rates. Microscopically positive margins have borne out as a significant prognostic factor in several studies, despite the limitations of assessment.⁽¹⁶⁸⁻¹⁷¹⁾ Therefore, in an effort to improve rates of margin negative resection extended compartmental resection was proposed vs. gross total excision with organ preservation for retroperitoneal STS. Two recent retrospective studies have reported their experiences with extended surgical resection, they showed a decrease in LR rates from 50% to 10-28% when comparing patients based on time period of resection (before and after shift to extended resection).⁽¹⁷²⁾ In subgroup analysis the effect on improved LR was only significant in the liposarcoma subtypes, calling into question if the importance of extended resection is dependent on histology.^(172,173) In a follow-up, several European centers combined their data and again demonstrated that extended compartmental resection had lowest rates of LR compared to simple resection, resection of only contiguously involved organs or re-excision.⁽¹³⁵⁾ However, extended compartmental resection was also found to have an associated overall complication rate of 18%, postoperative mortality rate of 3%, a 12% reoperation rate for postoperative morbidity, and increased morbidity associated with resection of more than three organs.⁽¹³⁵⁾ None of these studies demonstrated an improvement in OS with extended resection.^(135,172,173) Although the results of these studies are promising, these studies are limited by their retrospective nature and the combination of multiple histologic subtypes. It will be important to see the long-term follow up of these patients to assess the durability of these results.

Radiation Therapy

Radiation therapy (RT) in conjunction with surgical resection is the standard for intermediate and high-grade localized STS. It is also used as primary treatment for advanced STSs or for palliation of symptoms. Radiation therapy is typically delivered via external beam radiation (EBRT), other methods of delivery have been developed to help improve outcomes and decrease toxicities from radiation treatments. These systems include brachytherapy (BRT), intensity-modulated radiation therapy (IMRT), and intraoperative radiotherapy (IORT).

Extremity and Truncal STS. The first major push for the use of multimodality treatment for STSs was in 1982 where Rosenberg *et al.* first published on the successful

use of limb-sparing surgery plus adjuvant radiation for the treatment of extremity STSs, as described above.⁽¹⁴⁴⁾ Since then, several trials have examined the use of radiation with limb-sparing surgery for local treatment of extremity STSs. Yang *et al.* evaluated the impact adjuvant EBRT on LR and OS after limb-sparing resection in 141 patients randomized to surgery vs. surgery plus EBRT. A significant decrease in probability of LR with adjuvant EBRT was seen, but no difference in DM or OS.⁽¹⁷⁴⁾ Similarly, the use of adjuvant BRT demonstrated a significant decrease in LR in patients with high-grade tumors, however this was not seen in patients with low-grade tumors and no difference in DM and DSM in patients with low- or high-grade tumors.⁽¹⁷⁵⁾ The results of these two hallmark randomized studies support the use of RT in conjunction with surgical resection as the standard multimodality treatment for localized extremity and truncal STSs. However, these studies also suggest that in patients with low-grade tumors and low risk of LR, RT can be omitted.

Since the establishment of the benefit of RT for STS for LR and limb-sparing the main area of study is timing of radiation in relation to surgery. Preoperative RT is able to utilize a lower radiation dose, smaller radiation field and thereby lower radiation toxicity risks to normal surrounding tissues, due to the intact tumor and blood supply.⁽¹⁷⁶⁾ However, it is associated with a higher risk of wound complications. Postoperative RT minimizes surgical delays and allows selection of patients that are at greatest risk of LR based on complete pathologic diagnosis (including histologic subtype, tumor grade, and margin status) and to identify patients where radiation therapy may not be needed. However, postoperative radiation requires a larger radiation field and potential higher radiation dose, thereby increasing the risk of radiation toxicity to normal surrounding tissues and associated long-term complications (fibrosis, edema, joint contractures, etc.).⁽¹⁷⁶⁾

Although multiple studies have evaluated the risks and benefits of neoadjuvant or adjuvant radiation therapy, only one randomized clinical trial has been performed comparing these two approaches.⁽¹⁷⁷⁾ The NCI of Canada/Canadian Sarcoma Group SR2 clinical trial evaluated the impact of timing of EBRT on wound complications and disease outcomes. A total of 190 patients were stratified based on tumor size and randomized to neoadjuvant RT (50 Gy) vs. adjuvant RT (66 Gy). This study demonstrated significantly higher wound complication rates with neoadjuvant RT vs. adjuvant RT (35% vs 13%) but higher rates of late radiation morbidity and worse quality of life scores with adjuvant

RT vs. neoadjuvant RT.^(177,178) No difference in LR or DM was identified, and although a slight improvement in OS was initially observed with neoadjuvant RT, there was no significant differences in OS on longer follow up.⁽¹⁷⁹⁾ As a result of improved function, temporary acute toxicity and equivalent disease control demonstrated in the SR2 clinical trial, neoadjuvant RT is favored. However, there are some situations when adjuvant RT is indicated, including when prompt surgical palliation is needed and when diagnosis is in question.

Retroperitoneal and Intraabdominal STS. Radiation therapy for retroperitoneal and intraabdominal STSs remains controversial and lacks any randomized, prospective clinical data to support its use. When used for retroperitoneal/intraabdominal tumors, RT is typically delivered via EBRT as primary treatment for unresectable tumors or as a neoadjuvant multimodality treatment. Adjuvant RT and adjuvant radiation boosts are not recommended, except for in highly selected cases, given the high risk of radiation related toxicities to the adjacent visceral organs. Several retrospective institutional studies have evaluated the risks and oncologic benefits of RT for retroperitoneal/intraabdominal STSs and have demonstrated mixed results.^(163,172,173,180-184) While some studies did report a benefit in LR or disease-free survival with RT,^(163,172,180,185-189) others did not.^(173,181,183,184,190) Additionally, only two studies have been able to demonstrate an association with the use of RT and an improved OS.^(187,189) Two recent analyses of the National Cancer Data Base (NCDB) demonstrated improved OS with the use of either preoperative or postoperative RT compared with surgery alone, however when pre-operative RT was evaluated alone it did not demonstrate a survival benefit.^(191,192)

The rarity of this disease has limited the ability to performing randomized clinical trials to assess the use of perioperative RT in the management of retroperitoneal/intraabdominal STSs. In fact, ACOSOG Z90312 (NCT00091351) has been the only randomized controlled trial performed in the USA, but it closed early due to insufficient patient accrual. Currently, the results of an ongoing international cooperative group trial (STRASS; NCT01344018) evaluating neoadjuvant RT and surgery vs surgery alone in retroperitoneal STSs are awaited. The use of IORT and BRT have not been proven to be of significant value as a multimodality therapy for retroperitoneal/intraabdominal STSs.⁽¹⁹³⁾ Based on the available data, the use of neoadjuvant RT may be considered in a select group of patients after careful evaluation by a STS specialized multidisciplinary cancer team.

Chemotherapy

The role of chemotherapy in the management of STS has been limited to the metastatic or unresectable locally advanced disease setting. A doxorubicin-based regimen is the standard and response rates are low at approximately 20%. It has limited use in downsizing borderline resectable to potentially resectable STSs and as neoadjuvant or adjuvant treatment of chemo-sensitive histologic subtypes. Chemo-sensitive histologic subtypes that have demonstrated benefit from perioperative chemotherapy include GIST, synovial sarcomas and rhabdomyosarcomas.^(194,195) The use of adjuvant or neoadjuvant chemotherapy in all other settings remains an area of debate.

Neoadjuvant Chemotherapy. Several studies have evaluated the benefit of neoadjuvant chemotherapy in STSs, with mixed results and they have failed to consistently show an improvement in RFS or OS.⁽¹⁹⁶⁻²⁰⁰⁾ Included in these studies is a phase II study of 134 patients randomized to either surgery alone or three cycles of neoadjuvant doxorubicin and ifosfamide plus surgery.⁽¹⁹⁶⁾ This study failed to demonstrate any difference RFS (52% vs. 56%, $p=0.4$) or OS (64% vs 65%, $p=0.2$) at a median follow-up of 7.3 years. Although this study did not establish any oncologic benefit, it did demonstrate that neoadjuvant doxorubicin and ifosfamide was relatively well tolerated and did not interfere with planned surgical resection or subsequent treatments.⁽¹⁹⁶⁾ Others have shown some benefit from the combination of neoadjuvant chemotherapy and radiotherapy for large and high-grade extremity STSs.^(197,201,202) This information has led to the general consensus that neoadjuvant therapy be considered for large and/or high-grade STSs, especially when a decrease in tumor size may provide a surgical advantage.

Adjuvant Chemotherapy. Doxorubicin-based chemotherapy has long been the adjuvant treatment for resectable STSs. However, randomized control trials to prove its efficacy have been plagued by limited sample size and discrepant results. To try to provide a consensus on the use of adjuvant chemotherapy for localized STSs, Pervaiz *et al.* conducted a meta-analysis in 2008 evaluating the available randomized control trials.⁽²⁰³⁾ This meta-analysis demonstrated a small, but significant, benefit for LR, DM, recurrence free survival (RFS) and OS for patients who received adjuvant doxorubicin-based chemotherapy vs. observation. Additionally, when the combination of doxorubicin plus ifosfamide was compared to doxorubicin alone the risk reduction for mortality only supported the combination regimen; however, these differences were small

and controversy remained. ⁽²⁰³⁾ A randomized controlled clinical trial (EORTC 62931) was then performed to evaluate the use of adjuvant doxorubicin, ifosfamide, and lenograstin with macroscopically resected STSs and demonstrated no benefit in RFS or OS with the use of adjuvant chemotherapy.

⁽²⁰⁴⁾ A subsequent retrospective analysis by the French Sarcoma Group, evaluating the predictive value of grade for benefit from adjuvant chemotherapy, found a significant benefit in 5-year metastasis-free survival (58% vs. 49%, $p=0.01$) and 5-year OS (58% vs. 45%, $p=0.001$) for grade 3 tumors. This information has led to the general consensus that adjuvant therapy be considered for resected high-grade STS.

Chemotherapy for Unresectable or Metastatic Disease.

Doxorubicin alone or doxorubicin plus ifosfamide remains the first-line chemotherapeutic regimen for most STSs. Doxorubicin has been associated with response rates of approximately 20% and OS of 12-16 months. A randomized controlled trial was performed comparing the use of doxorubicin alone to intensified doxorubicin plus ifosfamide as first-line therapy for advanced or metastatic STSs. Although the addition of ifosfamide did demonstrate a higher overall response rate (26% vs 14%, $p<0.001$) and a benefit in progression free survival (7.4 months vs. 4.6 months, $p=0.003$), it failed to demonstrate any benefit in OS (14.3 months vs. 12.8 months, $p=0.08$) and was associated with significantly higher rates of grade 3-4 toxicities. ⁽²⁰⁵⁾ Given these findings, doxorubicin plus ifosfamide should only be considered when treatment response is necessary or if tumor shrinkage will aid in symptom palliation, otherwise sequential therapy starting with single chemotherapeutic agent is recommended.

Chemotherapy Stratification Based on STS Histologic Subtype.

Given the STS heterogeneity and the unique characteristics of each histologic subtype, several studies have attempted to identify histologies with improved response to particular regimens that have been more broadly applied. For example, ifosfamide-based chemotherapy has demonstrated a survival benefit in synovial sarcomas. ⁽¹⁹⁴⁾ LMS have demonstrated improved survival with combination treatments, including gemcitabine plus dacarbazine or gemcitabine plus docetaxel. ^(206,207) Combination treatment with gemcitabine plus docetaxel has also demonstrated improved survival in patients with UPS. ⁽²⁰⁸⁾ Trabectedin has been associated with cytotoxic activity in patients with myxoid liposarcomas and LMS. ⁽²⁰⁹⁻²¹¹⁾ The use of etoposide plus ifosfamide has demonstrated some promising responses in patients with MPNST. ⁽²¹²⁾ Paclitaxel has shown improved efficacy for treatment of angiosarcomas.

⁽²¹³⁾ While the majority of these studies have been conducted in patients with metastatic or unresectable disease, they do provide some promise for potential histologic subtype specific guidance in selection of neoadjuvant or adjuvant chemotherapeutic treatment regimens. However, its true applicability is still not completely defined. The ISG-STS 1001 phase 3, multicenter, clinical trial comparing the outcomes of histotype-tailored neoadjuvant chemotherapy to standard chemotherapy in patients with high-risk STSs sought to answer this question. Patients were randomized to standard neoadjuvant chemotherapy (epirubicin plus ifosfamide) or histotype-tailored chemotherapy. However, histotype-tailored neoadjuvant chemotherapy failed to show any survival benefit. ⁽²¹⁴⁾

Targeted Therapies. As the knowledge of cytogenic and molecular properties of STSs improves, targeted therapies have been developed. Imatinib, for the treatment of GIST, is the flagship for targeted therapies. Imatinib is a selective a tyrosine kinase inhibitor of the KIT protein and is FDA approved for the treatment of *KIT*-positive GIST. Imatinib has demonstrated significant rates of overall treatment response (>50%) and durable disease control and has revolutionized the management of GIST. ^(215,216) **Figure 1-3** depicts the response that can be seen with imatinib for GIST. The top two panels demonstrate a patient who presented with extensive disease (**Figure 1-3.A**) and just after 8 weeks of imatinib significant decrease in tumor size is appreciated. (**Figure 1-3.B**) The bottom panels are representative images of a patient who initially presented with bleeding from a gastric GIST. (**Figure 1-3.C**) This patient was treated with neoadjuvant imatinib and on his restaging scans demonstrated significant decrease in tumor size. (**Figure 1-3.D**) This second patient was ultimately found to have a complete pathologic response on final surgical specimen.

Imatinib is now the mainstay of systemic treatment of GIST and can be administered as primary therapy for unresectable of metastatic disease, neoadjuvantly if shrinkage of the tumor would minimize surgical morbidity, or adjuvantly in patients with intermediate or high risk of recurrence. ⁽²¹⁷⁻²²¹⁾

Other targeted therapies have also shown improved efficacy in the treatment of STS specific histologies. Pazopanib is a multitargeted tyrosine kinase inhibitor that has demonstrated improved progression free survival as second line therapy in non-adipocytic tumors. ^(222,223) Cyclin-dependent kinase (CDK) inhibitors targeting CDK4 and CDK6 have demonstrated promise in the systemic treatment of liposarcomas. ⁽²²⁴⁾

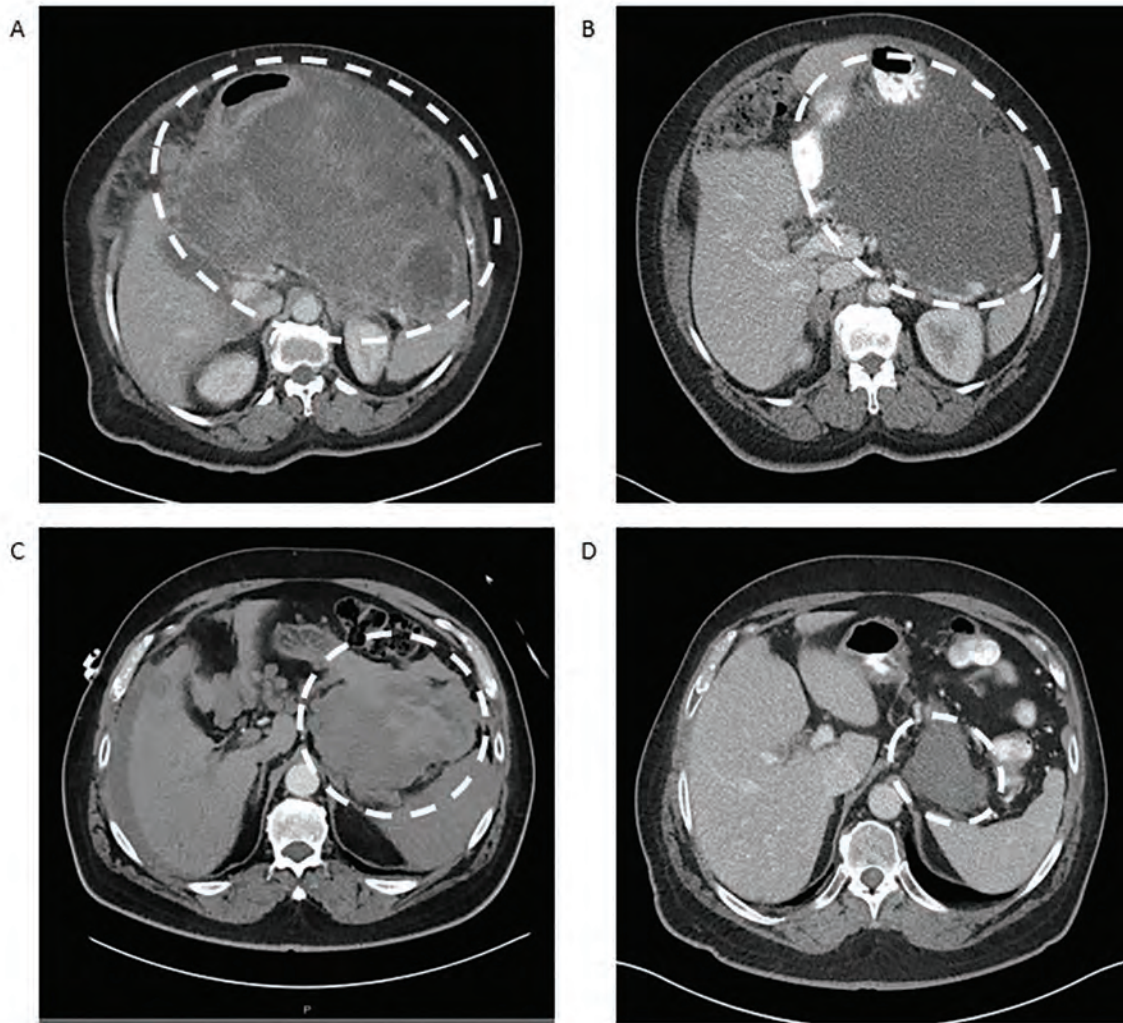


Figure 1-3. Imatinib treatment response in patients with gastrointestinal stromal tumors (GIST). Patient A, depicted in panels A and B, presented with extensive disease at time of diagnosis.

A) Representative cross-sectional image of the locally advanced GIST taking up the majority of his upper abdomen and compressing the porta hepatis at initial presentation.

B) Significant decrease in tumor size after 8 weeks of imatinib therapy. Patient B, depicted in panels C and D, presented with bleeding from a gastric GIST.

C) Representative cross-sectional image of a large gastric GIST at initial presentation.

D) Significant decrease in tumor size on restaging scans after completion of neoadjuvant imatinib. Tumors are outlined in dashed white lines.

Future Directions

Given the rarity and heterogeneity of this disease, continued characterization of the histologic subtypes and thereby specific treatments for the management of STSs is crucial. This will only continue to grow with continued multiinstitutional collaborations and patient enrollment into cooperative group clinical trials. Identification of molecular diagnostic markers for improved risk stratification and identification of tumor chemosensitivity for STSs is needed. Better understanding of major cytogenetic and molecular genetic alterations of each histologic subtype will allow us to develop targeted, and more effective, treatments.

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SECTION II
Head and Neck Cancer

Chapter 2

Introduction to Head and Neck Cancer

Efrain Cambronero M., MD

Introduction

Cancer arising in the mucosa of head and neck (H&N) is a complex and heterogeneous disease that required a multidisciplinary approach from the beginning.

The anatomy and functionality of H&N structures add complexity to the treatment decision making process as quality of life is a paramount aspect that may be severely impacted by treatment whether it is radical surgery, radiation and/or chemotherapy.

Head and neck cancers comprise tumors originating in the lip mucosa, oral cavity, oropharynx, hypopharynx, larynx, paranasal sinuses, salivary glands and mucosal melanoma.

By and large these tumors are biologically aggressive and the majority are advanced at initial diagnoses. About 30% to 40 % of H&N malignancies are diagnosed as early disease, stages I and II, with no regional lymph node involvement. The remaining 60% to 70% are loco-regionally advanced, stage III and IV tumors. Distant metastatic disease is uncommon at diagnosis but when do occur have grave implications as disease becomes incurable.

Although our knowledge on squamous cell carcinoma biology and genetics, surgical and radiation techniques has advanced significantly in the last 3 decades this has not been translated into a significant survival improvement.

Anatomy Overview

Head and neck anatomy is complex, composes of several anatomical regions with their own lymphatic drainage that have a great influence in the clinical features of cancers arising from the mucosa of these sites.

In general, the head and neck is divided for academic purposes in skin, lip and oral cavity, oropharynx, larynx, hypopharynx and salivary glands which in turn are subdivide in multiples sites.

Likewise, the rich lymphatic network of some of these areas drain in neck lymph nodes that have also been divided in anatomic levels, namely I to V. Although there are levels VI and VII lymph nodes, these pertain more to the thyroid gland lymphatic drainage which is being reviewed in a different chapter of this book. Having said that, levels VI and VII are also first lymphatic echelon for larynx and hypopharynx.

Knowledge of this anatomic lymphatic system helps to predict which echelons are most commonly afflicted by a primary tumor and vice versa, when the patient first presents with afflicted neck nodes their anatomic location helps to search for an occult primary. For instance, cancer of the lip, oral cavity and facial skin spread initially to level I lymph nodes while pharyngeal cancers tend to do so to levels II, III and IV and nasopharyngeal cancer and the posterior scalp to level V.

The abundance or lack of lymphatic vessels of a given head and neck mucosal site is also known. There are no lymphatics in the mucosa of the true vocal cords, tumors must invade beyond the lamina propria before acquiring the ability to metastasize.

One can predict the richness of the lymphatic network in head and neck by the incidence of metastatic disease associated to an anatomical site. The nasopharynx, oropharynx and hypopharynx have the most abundance lymphatic network of the head and neck. Contrary to paranasal sinuses, hard palate, laryngeal glottis, sites with few or no lymphatic capillaries.

Nasal Cavity (NC) and Paranasal Sinuses (PNS)

The nasal cavity (**Figure 2-1.A**) begins with the vestibule, its entrance, a pear-shaped with three-wall cavity lined with skin that contains hair follicles and sebaceous glands. It measures about 1.5cm and continuous posteriorly with the limen nasi, a mucous ridge between the nasal vestibule and the nasal cavity proper. The vestibule's anterolateral and medial walls are composed of alar cartilage and the columella. The latter formed by the medial wing of the alar cartilage and the anterior portion of the cartilaginous septum. Its floor is the maxilla.

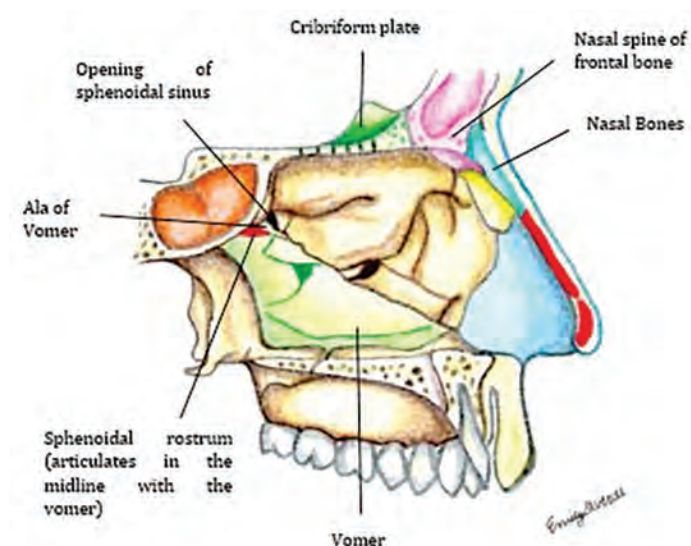


Figure 2-1.A. Nasal Cavity.

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The nasal cavity proper starts at the limen nasi and extends posteriorly to the posterior choanae that open onto the nasopharynx. The lateral walls feature the turbinates, superior, middle and inferior, thin bony folds that project themselves into the nasal cavity. The nasolacrimal duct opens underneath the inferior turbinate and the frontal and ethmoid sinuses drain into the NC under the middle turbinate. The sphenoid sinus communicates with the NC by way of an opening on its anterior wall.

The roof of the NC is made by the cribriform plate of the anterior skull base a thin egg-shell bony lamina perforated by several (about 20) small nerve fibers that form the olfactory nerve (II C.N.) and are distributed on the upper third of the septum and superior turbinate. The upper half of

the nasal cavity contains a non-ciliated columnar epithelium while the lower half is covered by respiratory epithelium with lymphoid tissue and mucous glands.

Paranasal Sinuses. (**Figures 2-1.B and 2-1.C**) The maxillary sinus, two single triangular spaces, like the other sinuses, is filled with air. Its shared middle wall is the lateral wall of the nasal cavity, it contains one or two communicating opening in the middle meatus under the medial turbinate at the semilunar hiatus where the frontal and ethmoid sinus

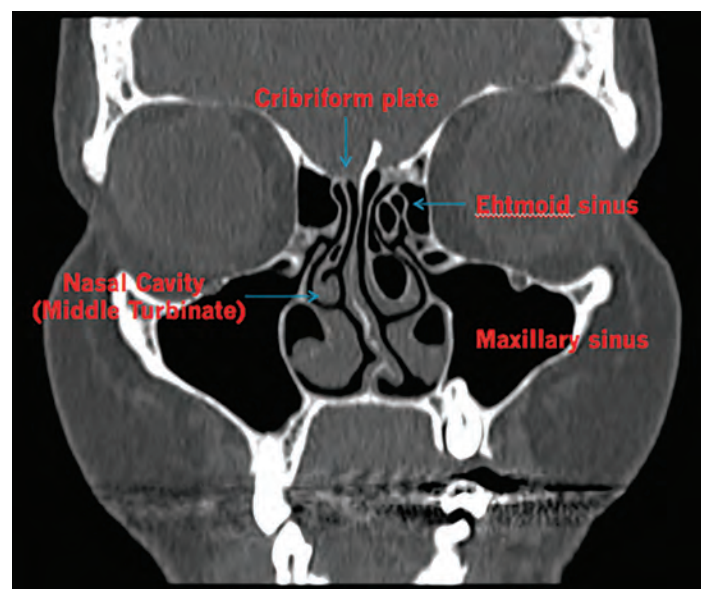


Figure 2-1.B. Paranasal Sinuses.

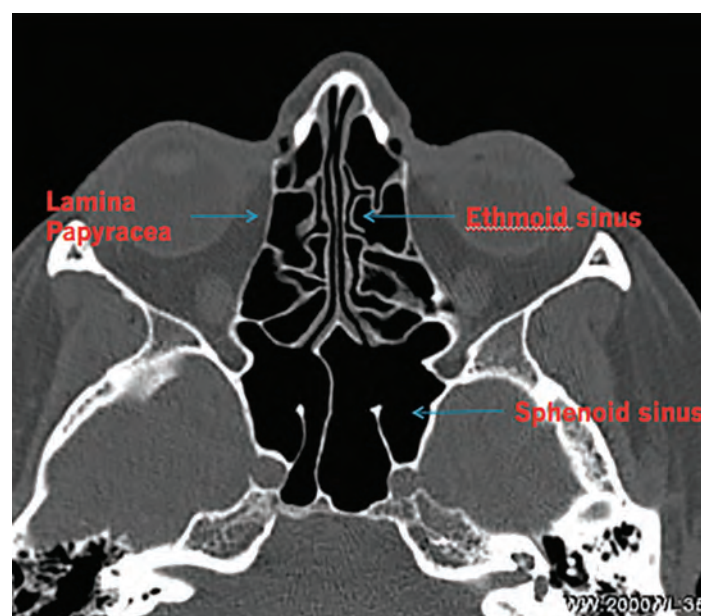


Figure 2-1.C. Paranasal Sinuses.

also communicate. The inferior wall or floor is the hard palate, its posterolateral wall is related to the zygomatic process and the pterygomaxillary space and the roof or superior wall is the floor of the orbital cavity.

The frontal sinuses are also two irregular shaped spaces divided by a fragile bony septum. It communicates with the nasal cavity by the frontonasal duct that drains in the middle meatus and is separated from the anterior ethmoid cells by a thin bony wall. Posterior to it a rather thick bony wall separates it from the anterior cranial fossa.

The ethmoid sinuses are composed of several air cells that lie between the medial orbital and lateral walls of the nasal cavity. The lateral wall of the ethmoid is the lamina papyracea of the medial orbital wall, a thin, porous bony layer. Medially the ethmoid cells buldge into the lateral wall of the nasal cavity. Anteriorly, the lacrimal bone covers the lateral aspect of the anterior ethmoid cells. Although the cells are divided for academic purposes, as there are no anatomic divisions, in anterior, medial and posterior cells, there is a perpendicular midline plane that separates the right from the left ethmoid cells.

The sphenoid sinus is a small midline space in the sphenoid bone. It has important anatomic relationships such as the cavernous sinuses laterally, hypophysis above, the clivus and brainstem lie posteriorly. It has communications with the nasal cavity and the ethmoid in front and the nasopharynx beneath. The right and left sphenoid sinuses are sometimes separated by an incomplete bony septum.

The mucosa of the nasal cavity and paranasal sinuses in general, has very sparsely lymphatics with negligible drainage.

The nasal vestibule lymph drains into level Ib lymph nodes and sometime into facial nodes just behind the labial commissure.

The lymphatic network of the nasal cavity is divided into two separated regions with no communications between them. That of the olfactory region that runs posteriorly and drains into the jugular chain at the skull base in the parapharyngeal space. It connects with the subarachnoid space.

The lymphatics of the respiratory region of the nasal cavity runs laterally into the retropharyngeal nodes and level II neck nodes.

Oral Cavity

The oral cavity (OC) (**Figure 2-2**) consists of the lips, floor of mouth, anterior oral tongue, buccal mucosa, upper and lower alveolar ridge, hard palate and retromolar triangle. It is separated from the oropharynx by the anterior tonsillar pillar anteriorly, soft and hard palate superiorly and the circumvalate papilla inferiorly.

The lips are composed of the orbicularis oris muscle with skin on the external surface and mucosa on the internal one, the transition from skin to mucosa is called vermillion.

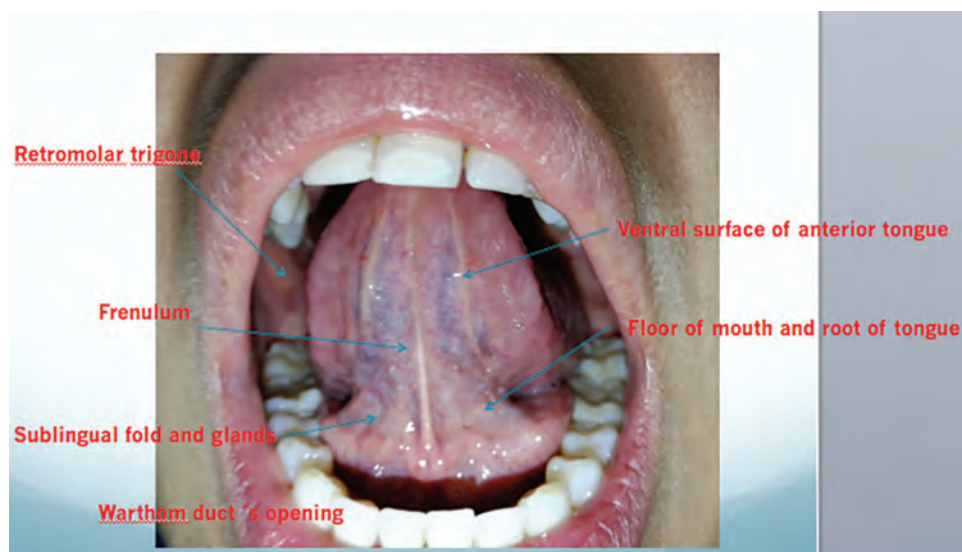


Figure 2-2. Oral Cavity.

The blood supply to the lips comes from the labial artery branch of the facial artery. The motor nerves for all the muscle facial expression are branches of the facial nerve (VII cranial nerve). Sensation to the lips depends on the infraorbital nerve, branch of the trigeminal nerve (V2) for the upper lip and the mental nerve (V3) for the lower lip.

Floor of Mouth

The floor of mouth (FOM) is the area limited by the lower gum and the anterior tongue laterally and medially. Its posterior boundary is the anterior tonsillar pillar. The sublingual glands lie immediately under the mucous membrane separated by the genioglossus and geniohyoid muscles which point of insertion are the genial tubercle, a bony protuberance found on the inner aspect of the symphysis of the mandible.

An additional muscle that forms part of the FOM is the mylohyoid which arises from the mylohyoid ridge of the mandible and extends posteriorly at about the level of the third molars. On its external surface lies the submandibular gland between the mandible and the insertion of the mylohyoid on the hyoid bone. Warthon's duct of the submandibular gland, a near 5cm long duct, courses between the sublingual gland and the genioglossus muscle and its exit opening is found in the anterior FOM at each side of the frenulum linguae at the midline (sublingual papilla) in relation to a small bilateral ridge, the sublingual folds which is raised by the sublingual glands and where it opens into the mouth through several openings.

Oral Tongue

The oral or anterior tongue is separated from the tongue base, part of the oropharynx by the circumvallate papillae. There are two groups of tongue muscles:

- **Intrinsic:** These muscles are confined to the tongue itself with no bone insertion. Its fibers are composed of several longitudinal, transverse and vertical fascicles.
- **Extrinsic:** These muscles originated from bony structures that give their name and are inserted in the tongue. They are genioglossus, hyoglossus, styloglossus and palatoglossus.

These muscles confer great mobility and plasticity to the oral tongue enable it to perform essential functions related to breathing, swallowing and phonation. Both, intrinsic

and extrinsic musculature motor nerve supply is giving by the hypoglossal (XII C.N.) except the palatoglossus that is innervated by the vagus nerve (X C.N.). The sensation is provided by the lingual nerve branch of the 3rd division of the trigeminal (V C.N.). Blood supply to the tongue comes from the lingual arteries branches of the external carotid artery.

Buccal Mucosa

The buccal mucosa (BM) is the mucous membrane of the inner surface of the cheek and lips, limits above and below with the alveolous ridge or gingiva, this slit-shaped area is known as vestibule. Posteriorly the BM limits with the retromolar trigone. Underneath the mucosa rests the buccinator muscle and at the level of the second upper molar is located its more visible feature the Stenon's duct opening that pierces the muscle and brings saliva from the parotid gland into the mouth. Its sensory nerve supply is given by the buccal nerve, that branches off the mandibular division of the V C.N. The motor innervation and blood supply depend on branches of the facial nerve (VII C.N.) and facial artery, branch of the external carotid artery.

Gingiva, Hard Palate and Retromolar Trigone

The lower gingiva or inferior alveolar ridge includes the keratinized mucosa covering the mandible from the gingivobuccal gutter or vestibule to the origin of the nonkeratinized lining mucosa covering the floor of the mouth. There are no minor salivary glands in the mucosa covering the alveolar ridge.

The hard palate forms the roof of the mouth and the floor of the nasal cavity and it is composed of the palatine processes of the maxilla and is completed posteriorly by the horizontal processes of the palatine bones.

The retromolar trigone, a triangled-shape area that lies behind the third molar and superiorly is contiguous with the maxillary tuberosity. The retromolar trigone is associated with the pterygomandibular raphe which is a tendinous structure attached to the hamulus of the pterygoid and the posterior aspect of the mylohyoid raphe of the mandible and function as insertion point of the following muscles: buccinator, orbicular oris and superior pharyngeal constrictor.

Posterior to the pterygomandibular raphe, between the medial pterygoid muscle and the ascending ramus of the

mandible is the pterygomandibular space containing the lingual nerve, nerves to the teeth and the deep lobe of the parotid gland. It is part of the parapharyngeal space, **(Figure 2-3)** an inverted-pyramid shaped-area localized between the masticator muscles and the oropharynx and muscles of deglutition that contains important structures like the trigeminal nerve, internal carotid, internal jugular vein, internal maxillary and ascending pharyngeal arteries and the pterygoid venous plexus.

Nasopharynx

The nasopharynx (NP) **(Figure 2-4)** is a small space of about 2-3cm sited behind the choanas of the nasal cavity and inferiorly is separated of the oropharynx by the soft palate, which serves as its incomplete floor. Laterally, it is related with the middle ear via the Eustachian tubes, the torus tubarius and fossa of Rosenmuller, all of which are prominent features of the lateral wall. The roof and posterior wall, part of the skull base are covered by an irregular

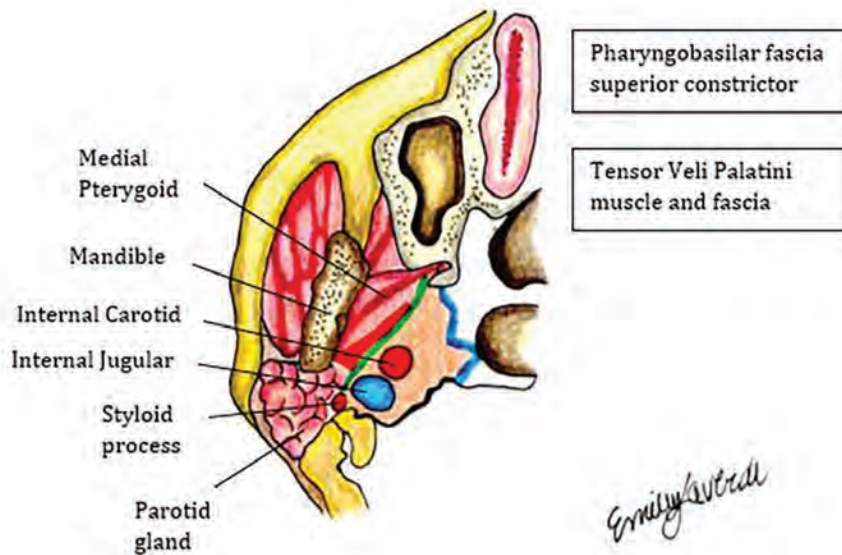


Figure 2-3. Parapharyngeal space, axial view.
Medical Illustrator: Ms. Emily Laverde

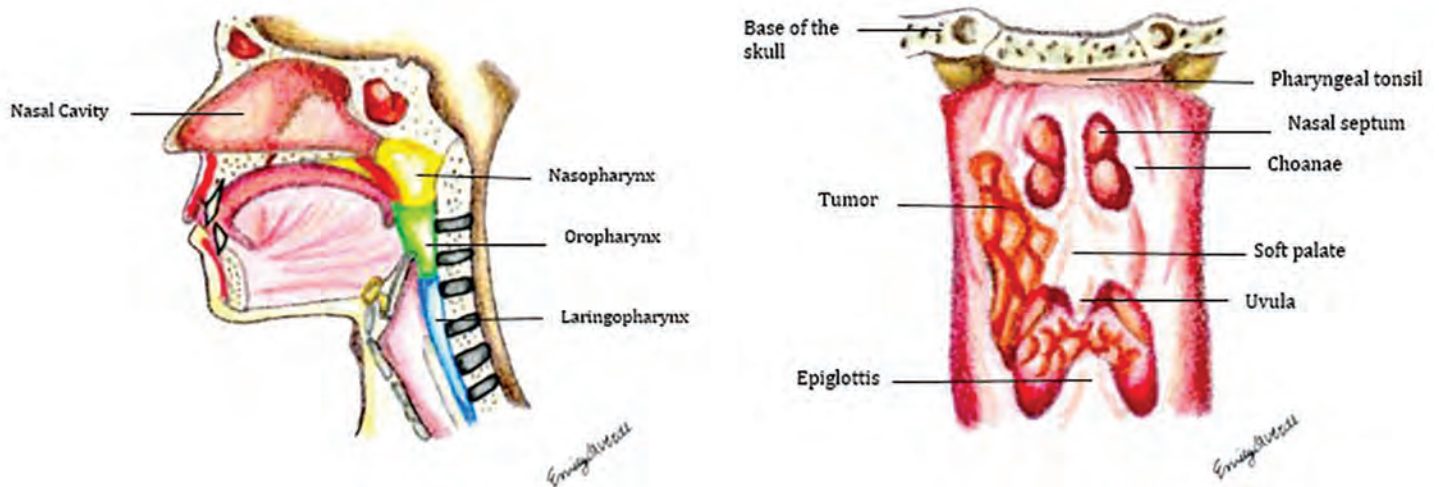


Figure 2-4. Nasopharynx. Lateral and Anterior views.
Medical Illustrator: Ms. Emily Laverde

mucosa because of the presence of lymphoid tissue that tends to diminish and becomes smooth with age.

The NP has an extensive lymphatic capillary network that drains to spinal accessory nerve, jugular vein and retropharyngeal lymph node stations. The latter lie in the retropharyngeal space medial to the carotid artery just anterior to the C1 and C2 vertebral bodies.

Oropharynx

The oropharynx (OP) (**Figure 2-5**) is a complex anatomical area composed of the anterior and posterior tonsillar pillars, tonsils, the tongue base, vallecula, the soft palate and the posterior pharyngeal wall.

The musculature of the base of the tongue (BOT) is continuous with that of the anterior tongue, anteriorly it limits with the circumvallate papilla that separates it from the oral tongue, laterally limits with the glossotonsillar sulcus and posteriorly extends to the vallecula a smooth strip of mucosa that limits with the epiglottis.

The tonsillar fossa a space where the tonsils lie, is bounded by the anterior and posterior tonsillar pillars which is made by the palatoglossus and palatopharyngeal muscles respectively. Its inferior limit is the glossotonsillar sulcus and the pharyngoepiglottic fold, in fact the glossotonsillar sulcus extends from the anterior tonsillar pillar down the

pharyngoepiglottic fold. Laterally the tonsillar fossa is bounded by the superior constrictor muscle and its fascia, the angle and ascending ramus of the mandible and the parapharyngeal space.

The tonsillar fossa is separated from the BOT by the glossotonsillar sulcus underneath of which lies the styloglossus muscle and the stylohyoid ligament.

The soft palate is a thin, mobile and soft muscle (the tensor veli palatine muscle) suspended from the posterior border of the hard palate, sloping down and back between the oral and nasal part of the pharynx. It is a thick fold of mucosa enclosing an aponeurosis, muscular tissue, vessels, nerves, lymphoid tissue and mucous glands. Its oral surface is covered with squamous epithelium and the nasal aspect of it is covered by respiratory epithelium.

The mucosa of the posterior pharyngeal wall corresponds to the anterior face of the bodies of the second and upper half of the third cervical vertebrae.

Larynx

The larynx (**Figure 2-6**) is another anatomically and functionally complex and specialized area, it is composed of several cartilages, ligaments and muscles especially designed to help breathing, with phonation and with deglutition. It is divided into three parts: supraglottis, glottis and subglottis.

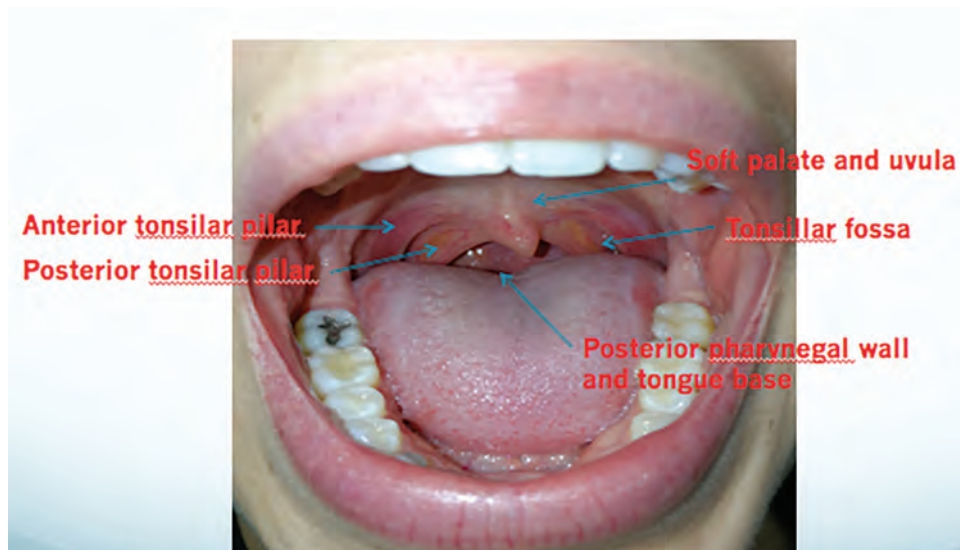


Figure 2-5. Oropharynx.

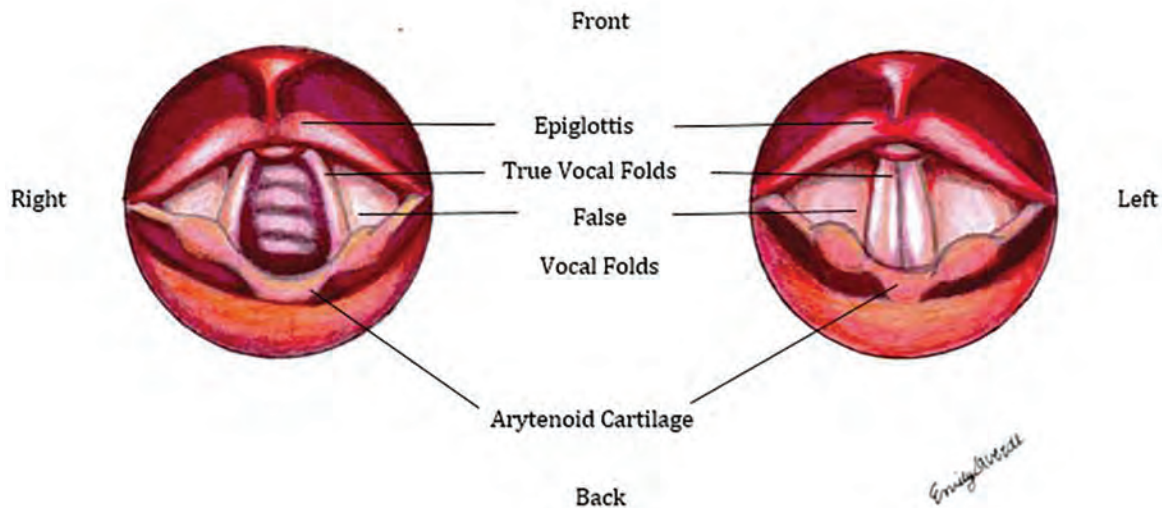


Figure 2-6. Larynx. Superior view.
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The supraglottis includes the laryngeal aspect of the epiglottis, aryepiglottic folds, false vocal cords, the ventricles of Morgagni and the arytenoid cartilages.

The glottis consists of the true vocal cords, the anterior and posterior commissures.

The subglottis extends from the undersurface of the true vocal cords to about 2cm down to the inferior edge of the cricoid cartilage, a ring-like cartilage, narrow anteriorly and broad posteriorly, that joints with the trachea and on top of which the arytenoid cartilages are articulated. On the arytenoid cartilages insert the intrinsic laryngeal muscles (posterior and lateral cricoarytenoids, transverse arytenoid, cricothyroid, thyroarytenoid and oblique arytenoid), all of them innervated by the recurrent laryngeal nerve except for the cricothyroid muscle whose innervation is provided by the external branch of the superior laryngeal nerve.

The pre-epiglottis space is an important anatomical area where glottic cancer involving the anterior commissure frequently extends to. It is located immediately underneath the vallecula and hyoepiglottic ligament, its posterior limit is the epiglottis and anterolaterally is bounded by the thyroid cartilage and the thyrohyoid membrane. It is a fat-filled space rich with lymphatics that continues with the paraglottis space bilaterally.

The supraglottis has a rich lymphatic drainage that pass through the pre-epiglottic space and the thyrohyoid membrane to level II, III and IV lymph nodes. The glottis

is almost deprived of lymphatic vessels, therefore lymph node metastasis is only found at advance stages of glottic cancers when they have invaded the supraglottis or the subglottis.

The subglottis has moderate lymphatic capillaries that pass through the cricothyroid membrane anteriorly and drain into the prelaryngeal or Delphian lymph nodes and into level IV, also pierce posteriorly the cricotracheal membrane and drain into levels VI and VII lymph nodes.

Hypopharynx

The squamous mucosa lining the hypopharynx (**Figure 2-7**) is a continuum with that of the oropharynx and nasopharynx.

There are three areas composing the hypopharynx: the pyriform sinus, posterolateral pharyngeal wall and postcricoid area a transitional zone, 3-4 cm in length, inferiorly located where the hypopharynx continues with the esophageal inlet at C4 level. The lateral walls of the hypopharynx are about 4-5cm in width and 6-7 cm in height and superiorly extends from the pharyngoepiglottic fold down to the esophageal inlet at the level of the superior and inferior borders of the cricoid cartilage. Constitutes also the lateral wall of the pyriform sinus. The medial wall is represented by the aryepiglottic folds. Therefore, the pyriform sinus is an inverted-funnel -pyramid-shaped structure with three walls: anterior, lateral and medial, that

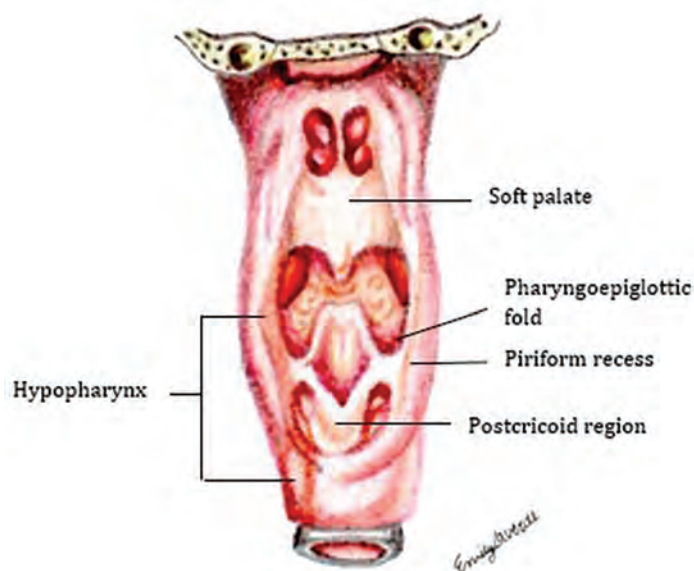


Figure 2-7. Hypopharynx. Posterior view.
Medical Illustrator: Ms. Emily Laverde

functions as food receptacle and brings the bolus into the esophagus. There is no posterior wall. The external anatomy to the pyriform sinus is given superiorly by the hyoid bone and the thyrohyoid membrane and inferiorly by the thyroid cartilage, cricothyroid membrane and the cricoid cartilage.

The anterior wall of the postcricoid pharynx is represented by the cricoid cartilage which in turn is the posterior and lower wall of the larynx. It begins just below the arytenoid cartilages.

The sensory innervation to the hypopharynx, just like the supraglottic larynx is given by the internal branch of the superior laryngeal nerve, branch of the vagus (X C.N.).

The recurrent laryngeal nerve, (**Figure 2-8**) branches also of the vagus, courses in or close the tracheoesophageal groove and enters the larynx at the level of the cricopharyngeus muscle, just posterior to the cricothyroid articulation, adjacent to the junction of the hypopharynx and the esophagus.

Neck Lymph Node Anatomy

The lymphatic drainage of the head and neck is unique. Its remarkably well-delineated and characterized anatomic subgroups are closely associated with draining anatomic structure, these, in turn, are related to different malignant

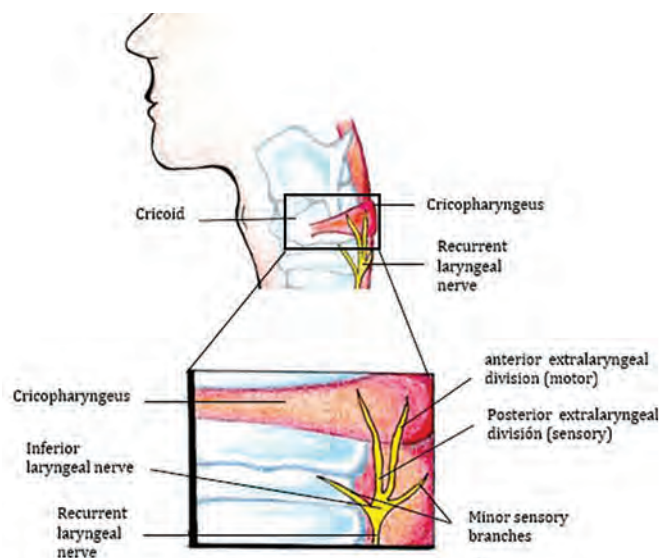


Figure 2-8. Recurrent laryngeal nerve and its branches.

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neoplasms arising from them. Intimate knowledge of this network allows the surgeon to complete an oncologically-sound dissection. It also helps the radiation oncologist appropriately treat elective nodal levels to reduce recurrence, and the primary care physician to guide the path to the necessary diagnostic work up.

The enlargement of neck lymph nodes is associated with multiple pathologic conditions such as acute and chronic infection, autoimmune disease, and malignancy.

The lymphatic drainage of the neck is fairly well defined and commonly affected nodal groups are indicators of a specific-diseased area of the head and neck. These anatomic relations have important clinical implications in terms of diagnosis and treatment of head and neck cancer. ^(1,2,3)

There is an estimation of 300 lymph nodes in the neck distributed in 10 levels. The lymphatic channels that connect the lymph node groups tend to proceed from superior to inferior and fairly lateral, meaning that there is little crossover except for lymphatics draining midline structures: nasopharynx, base of tongue, soft palate, posterior pharyngeal wall and supraglottic larynx.

These channels arise at the skull base descend toward the internal jugular and spinal accessory nerve chains. From there, tend to proceed to the supraclavicular area. Here, on the left side, they drain either directly into the jugulo-subclavian venous confluence or directly into the thoracic duct. On the right side, they flow directly into lymphatic ducts.

Lymph Node Levels (Figure 2-9)

LEVEL I

Two groups of lymph nodes constitute level I: Submental (Ia) and Submandibular (Ib).

Level Ia

This level, also called submental triangle, contains the submental lymph nodes that drain capillaries from the lower lip, skin of the chin, anterior floor of mouth and anterior part of oral tongue. Tumors arising in these anatomic regions tend to metastasize to these lymph nodes.

The boundaries of level Ia are: superior the symphysis of the mandible, inferior the hyoid bone, lateral the anterior belly of the digastric, medial the midline, posterior the mylohyoid muscle and anterior the platysma.

Level Ib

Also called, the submandibular triangle, these nodes receive lymph from level Ia, the upper and lower lips, the skin and soft

tissue the cheek and midface, oral cavity, the soft palate, lower or anterior nasal cavity and the submandibular gland.

The limits are: lateral the mandible, medial the digastric muscle, anterior the symphysis menti, posterior the posterior border of the submandibular gland, superior the mylohyoid and inferior the hyoid bone.

LEVEL II

Contains lymph nodes from the upper third of the internal jugular vein (IJV) and spinal accessory nerve (XI C.N.) and it's the most frequently involved level from head and neck malignancies.

Level II receives lymphatic vessels from the oral cavity, submandibular and parotid glands, larynx, the entire pharyngeal mucosa (nasopharynx, oropharynx and hypopharynx), levels I and retropharyngeal lymph nodes, external auditory canal and skin of the face.

Level II boundaries are: lateral, medial surface of the sternocleidomastoid muscle (SCM), medial the scalenus muscle and internal carotid artery, superior the insertion of

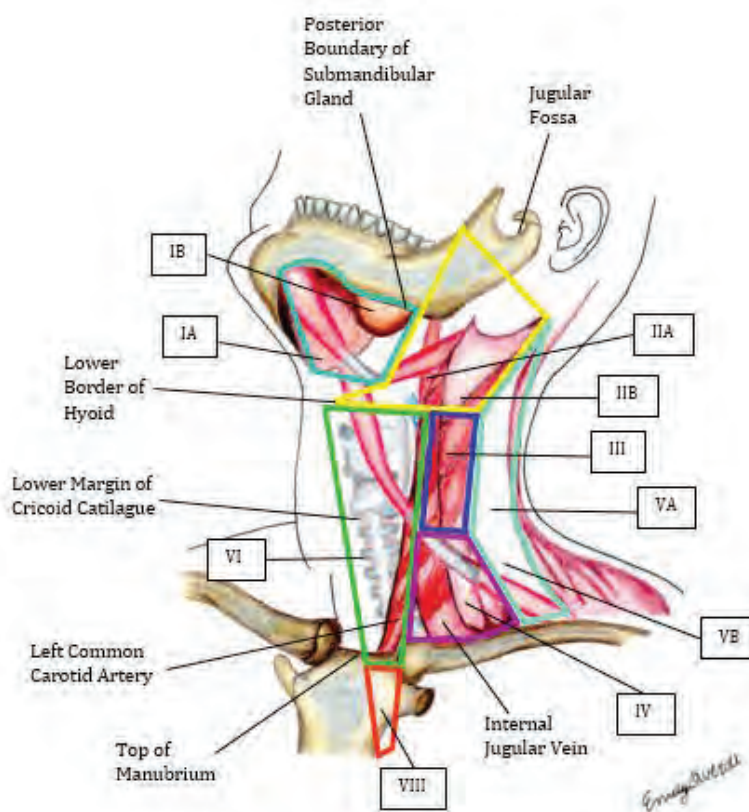


Figure 2-9. Neck Lymph node Levels.
Medical Illustrator: Ms. Emily Laverde

the posterior belly of the digastric into the mastoid, inferior the lower edge of the hyoid bone or the surgical landmark of the carotid bifurcation, anterior is the posterior edge of the submandibular gland and posterior, the posterior border of the SCM muscle.

LEVEL III

Corresponds to the lymph nodes found adjacent to the middle third of the IJV. These nodes drain efferent lymphatics from level II, V, retropharyngeal, pretracheal and paratracheal nodes. Also, from the oropharynx, larynx, hypopharynx and thyroid gland.

Its limits are given by: the caudal edge of the hyoid bone as superior, the caudal edge of the cricoid as inferior, surgical landmarks are the carotid bifurcation superior and inferior at the point where the homohyoid muscle crosses over the IJV respectively. Lateral the medial aspect of the SCM, medial the carotid artery and the scalenus muscle. Anterior the posterior edge of the thyrohyoid muscle and its posterior limit is the posterior edge of the SCM.

LEVEL IV

Level IV is divided in two subgroups: the lower jugular group and the medial supraclavicular group. It contains the lymph nodes of the lower third of the internal jugular vein and drain lymph from lymph nodes of level III and V, pretracheal, paratracheal and retropharyngeal lymph nodes, larynx, hypopharynx, cervical esophagus and thyroid gland.

Its limits are given by the caudal border of the cricoid cartilage superiorly, this landmark corresponds surgically to the homohyoid muscle. Its inferior border is the clavicle, posteriorly the posterior border of the SCM and medially is bordered by the common carotid artery, thyroid gland and scalenus muscle.

LEVEL V

Corresponds to lymph nodes from the posterior triangle group that lie posterior to the SCM and along the spinal accessory nerve (C.N. XI), the transverse cervical artery and supraclavicular region. Its boundaries are the trapezius muscle posteriorly, the posterior border of the SCM anteriorly and the clavicle inferiorly. A virtual line at the caudal margin of the cricoid cartilage divides the level in Va (superior) and Vb (inferior). This level drains lymphatics from the occipital and parietal scalp, suboccipital and retroauricular lymph nodes, skin from the lateral neck and nasopharynx.

LEVEL VI

Also known as anterior compartment, localized in the anterior neck, contains superficial lymph nodes anterior to the infrahyoid or strap muscles and deep to it. Includes the prelaryngeal or Delphian, pretracheal, paratracheal or recurrent laryngeal nodes. Its limits are composed of the hyoid bone superiorly, sternal manubrium inferiorly and carotid sheath laterally.

These lymph nodes drain lymphatics from the thyroid gland, larynx, hypopharynx and cervical esophagus. ^(4,5)

LEVEL VII

Lymph nodes at the upper and anterior mediastinum posterior to the manubrium and above the aortic arch and medial to the carotid artery on the right and innominate artery on the left.

Additional Lymph Nodes Groups of Clinical Relevance

a. Retropharyngeal group: Lymph nodes located in a virtual space that extends from the superior border of C1 or the hard palate to the hyoid bone. Laterally the internal carotid artery is located on both sides. These lymph nodes are posterior to the superior and middle pharyngeal constrictor muscles and anterior to the longus capitis and longus colli muscles and they are subdivided into medial lateral groups. They drain lymphatics from the pharyngeal mucosa, oropharynx and nasopharynx.

b. Retrostyloid group: These are among the deepest lymph nodes of the neck, they lie above level II. Its limits are: superior, the skull base at the jugular foramen, inferior, the inferior edge of the lateral process of C1, anterior: the prestyloid parapharyngeal space, lateral: the styloid process and deep lobe of the parotid gland and medially the internal carotid artery. They drain lymphatics from the nasopharynx.

c. Parotid Group: Includes pre-auricular, superficial and deep parotid and subparotid lymph nodes. There are about 20 lymph nodes within the parotid gland. This group is confined by the zygomatic arch and external auditory canal superiorly, the angle of the mandible inferiorly. Anteriorly by the ascending ramus of the mandible, medially by the medial pterygoid muscle and laterally by the masseter muscle. They drain lymphatics from the frontal, temporal, midface and eyelid skin, the external auditory canal, the parotid gland and nasopharynx. ⁽⁶⁾

d. Buccofacial group: This group is composed of the malar and the buccofacial or facial lymph nodes which are located along the facial vessels. They are limited superiorly by the inferior border of the orbit, inferiorly by the mandible and lie on the external surface of the buccinator muscle. They drain the skin the the nose and eyelid, buccal mucosa and soft tissue of the cheek.

e. Retroauricular and Subauricular Nodes: This group includes nodes that lie within a fatty pad over the mastoid process, splenius capitis muscle and behind the auricle. They are limited by the external auditory canal superiorly and by the mastoid tip inferiorly and drain efferents from the skin of the posterior scalp, auricle, retroauricular and the external auditory canal.

f. Occipital Nodes: These nodes are located inferior to the external occipital protuberance are connected to the retroauricular and subauricular lymph nodes. They lie over the splenius capitis muscle and are limited anteriorly by the posterior border of the SCM insertion on the mastoid and posteriorly by the trapezius muscle. They drain the posterior scalp skin. ⁽⁷⁾

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Chapter 3

Immunotherapy in Head and Neck Cancer

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The immune system could potentially control head and neck cancer development. There is evidence involving cellular mediated immune response. ⁽¹⁾ According to Badoual *et al.*, the infiltration of head and neck tumors with T lymphocytes and/or natural killer cells correlated with both better locoregional control and a longer survival rate of head and neck cancer patients. ⁽¹⁾ It has also been reported that regression of head and neck squamous cell carcinoma in mice can be induced by activated T lymphocytes. ⁽²⁾ In addition, spontaneous regression of head and neck tumors was observed in humans ⁽³⁾ evidencing participation of an immune-mediated process.

According to Farias *et al.* the antigens already well studied in squamous cell carcinoma of the head and neck are the P53 protein, cyclin D1, epidermal growth receptor (EGFR), the family of Bcl2 proteins, Ki-67 (MIB-1), cell proliferation nuclear antigen (PCNA), cathepsin D, CD31, CD44, P16 protein, among others. These molecules are suggested by mutations and modulations of the immune system causing cancer. ⁽⁴⁾

Cancer immunotherapy is based on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. The immune system plays a key role in the development, establishment, and progression of head and neck squamous cell carcinoma. ⁽⁵⁾ A greater understanding of the dysregulation and evasion of the immune system in the evolution and progression of head and neck squamous cell carcinoma provides the basis for improved therapies and outcomes for patients. Head and neck squamous cell carcinoma cells evade the host immune system through manipulation of their own immunogenicity, production of immunosuppressive mediators, and promotion of

immunomodulatory cell types. Through the tumor's influence on the microenvironment, the immune system can be exploited to promote metastasis, angiogenesis, and growth. ⁽⁶⁾

The genesis of cancer can be explained by derangements in the immune system or alterations in the transformed cells may allow immune escape. Tumors themselves produce cytokines, such as transforming growth factor- β (TGF- β), interleukin (IL)-6, and IL-10, which suppress cell-mediated antitumor immunity while activating STAT1 (signal transducer and activator of transcription 1) suppression. ⁽⁷⁾ Inflammatory transcription factors, such as NF- κ B (nuclear factor κ -light chain-enhancer of activated B cells) and STAT3, are aberrantly activated in tumor cells and are intensively studied as possible targets for therapeutic intervention. ⁽⁸⁾

Tumor progression depends on acquisition of traits that allow cancer cells to evade immune surveillance and an effective immune response. Head and neck squamous cell carcinoma is an immunosuppressive disease, with lower absolute lymphocyte counts than those found in healthy subjects. ⁽⁹⁾ Impaired natural killer (NK) – cell activity ⁽¹⁰⁾ and poor antigen-presenting function. ⁽¹¹⁾ Impairment of tumor-infiltrating T lymphocytes has also been reported in head and neck squamous cell carcinoma and other cancers, ⁽¹²⁾ with a strong impact on clinical outcome. ⁽¹³⁾ In addition, suppressive regulatory T cells (Tregs) have been linked to head and neck squamous cell carcinoma tumor progression. Tregs secrete suppressive cytokines such as TGF- β and IL-10, express cytotoxic T lymphocyte-associated protein 4 (CTLA-4), and correlate with tumor progression. ⁽¹⁴⁾ Disruption of this T-cell response, whether by immunosuppression or various tumor immune evasion

mechanisms, may play an integral role in the progression of head and neck squamous cell carcinoma. ⁽⁵⁾

Immunomodulatory therapies that overcome immune suppressive signals in patients with head and neck squamous cell carcinoma are a therapeutic promise. These include cancer vaccines using tumor peptide antigens, or viral, bacterial, and DNA-based vectors – as well as tumor antigen-specific monoclonal antibodies (moAbs). Antibody-based cancer immunotherapy became a reality after the development of techniques which made possible production large quantities of antigen specific antibodies (Abs). ⁽¹⁵⁾ The basic premise of Abs-based immunotherapy is that tumor cells express on their surface antigens that distinguish them from normal cells. Abs can specifically bind to tumor antigens, triggering multiple immune responses that result in tumor cell lysis. Cell-transfer therapy relies on expanding autologous tumor-reactive killer CD8⁺ T lymphocyte populations *in vitro* to large cell numbers for injection back into the patient. CD8⁺ T lymphocytes are routinely expanded in the presence of anti-CD3 monoclonal antibodies, which act as surrogate antigens, and IL-2, a T-cell growth factor. The target tumor antigen for this method of immunotherapy should be a processed protein presented by human leukocyte antigen, also known as major histocompatibility complex (MHC) protein. In contrast to Abs that react only with antigen expressed on the tumor cell surface, T lymphocytes can recognize processed antigen expressed inside or on the surface of tumor cells. ⁽¹⁶⁾

Some moAbs targeting immune checkpoint receptors, including anti CTLA-4 and anti-programmed death-1 (anti PD-1) was recent clinical efficacy of Food and Drug Administration (FDA) approved. ⁽¹⁷⁾ These medicines promise for patient benefit from immunomodulatory therapies as positive clinical data emerge. ⁽¹⁷⁾

Blockade of immune checkpoints, which regulate the duration and extent of immune responses, is an approach by which antitumor T-cell immunity may be activated. Immune checkpoints serve to modulate physiologic immune responses in order to prevent excessive inflammatory responses or the development of autoimmunity. For instance, interaction between PD-1 and its ligands PD-L1 and PD-L2 has been shown to downregulate T-cell activation in both mouse models and human systems and has been implicated in tumor immune evasion in head and neck squamous cell carcinoma. ⁽¹⁸⁾ PD-1 is a member of the CD28 family of T-cell costimulatory receptors that is expressed on activated T-cells, B-cells, and myeloid cells. Overexpression of PD-L1 by tumor cells, or immune infiltration by PD-1 + T-lymphocytes, can result in immune evasion. PD-L1 is

overexpressed in > 50%-60% of head and neck squamous cell carcinoma. ⁽¹⁹⁾ It has been reported that among head and neck cancer patients, there is higher expression of immune checkpoint inhibitors such as CTLA-4 and PD-1 in intratumoral regulatory T-cells compared to peripheral blood samples. ⁽²⁰⁾ This finding may reflect a previous immune response against tumor that might be reactivated by PD-1/PD-L1 blockade. ⁽²¹⁾

The application of anti PD-1 (**Figure 3-1**) therapies for recurrent or metastatic head and neck squamous cell carcinoma has found promising results. This has led to interest in combining immunotherapy with radiotherapy for the primary treatment of locally advanced head and neck squamous cell carcinoma. RT with concurrent cetuximab is an option for patients who are medically unfit to receive cisplatin. Ongoing trials are evaluating the use of anti PD-1 and anti PD-L1 therapies in the upfront setting for newly diagnosed high-risk, locally advanced head and neck squamous cell carcinoma, in an effort to improve disease control. ⁽²¹⁾

The anti PD-1 monoclonal antibodies nivolumab and pembrolizumab have been shown to improve progression-free survival and overall survival in advanced melanoma, non-small cell lung cancer, and urothelial cancer, compared to standard systemic therapy. ^(23,24) Utilization of these agents has also been investigated in head and neck squamous cell carcinoma. The recently published KEYNOTE-012 trial was the first to demonstrate the efficacy of immune checkpoint inhibition in head and neck squamous cell carcinoma. ⁽²⁵⁾ This was a Phase Ib trial aimed at evaluating the clinical efficacy and safety of pembrolizumab for advanced solid tumors, including recurrent or metastatic head and neck squamous cell carcinoma. ⁽²⁶⁾ In the initial cohort of 60 head and neck squamous cell carcinoma patients, all of whom had at least 1% PD-L1 expression in tumor and stromal cells, patients received pembrolizumab at 10mg/kg IV once every 2 weeks. ⁽²⁷⁾ The objective response rate was 21% by clinician review, the median duration progression-free survival was 2 months, and overall survival was 13 months. ⁽²⁸⁾

In a subsequent expansion cohort, 132 additional patients with head and neck squamous cell carcinoma were enrolled regardless of PD-L1 expression status, and a less frequent dosing schedule of 200mg IV once every 3 weeks was used. ⁽²⁹⁾ The overall response rate was 18% by central imaging review, at the cost of grade 3 drug-related adverse events in 9% of patients. The 6-months progression-free survival was 23%. ⁽²⁹⁾ The degree of PD-L1 expression was found to be strongly predictive of best overall response,

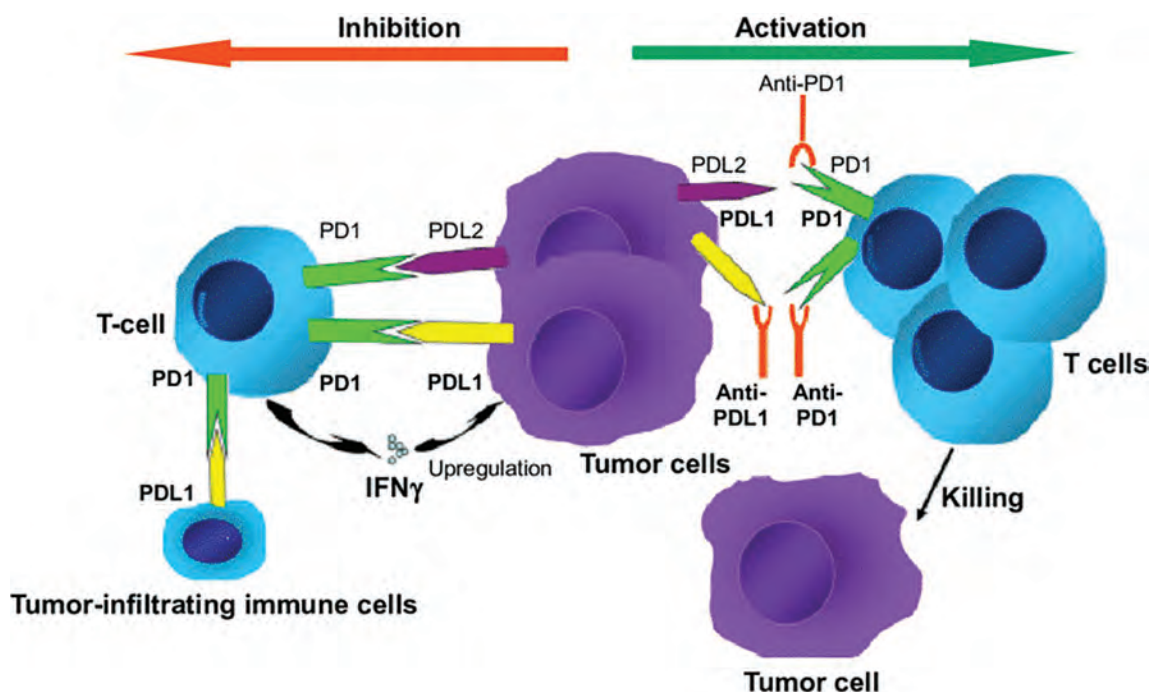


Figure 3-1. Anti PD-1 action: PD1 is expressed by T cells. PDL1 is expressed in tumor cells and tumor-infiltrating immune cells. Inhibiting the interaction of PD1 and its ligands can significantly enhance T-cell function, resulting in antitumor activity (green arrow).⁽²²⁾

progression-free survival, and overall survival. The overall response rate was 22% for patients who were PD-L1 positive ($\geq 1\%$), compared to 4% for patients who were PD-L1 negative ($< 1\%$) ($P = 0.021$). In addition, patients with HPV-associated disease had a higher overall response rate of 32%, compared to 14% for those with HPV-negative disease.⁽³⁰⁾

Based on the early results of KEYNOTE-012, the FDA granted accelerated approval of pembrolizumab for recurrent and metastatic head and neck squamous cell carcinoma in August 2016.⁽³¹⁾ The utility of pembrolizumab for recurrent or metastatic head and neck squamous cell carcinoma is to be confirmed in a randomized Phase III study, KEYNOTE-040, which assigns patients to pembrolizumab or standard single-agent methotrexate, docetaxel, or cetuximab. This study is ongoing, but closed to recruitment, with results eagerly awaited.⁽³¹⁾ These promising survival data suggest that future studies investigating pembrolizumab as a first-line therapy are indicated.⁽³¹⁾

NRG-HN003 is a Phase I trial that seeks to determine the optimal dosing of pembrolizumab when given in combination with cisplatin and radiotherapy in the

adjuvant setting for high-risk, stage III-IV head and neck squamous cell carcinoma. The primary outcome is dose-limiting toxicities up to 4 weeks posttreatment.⁽³²⁾ Secondary outcome measures include change in expression of peripheral immune inflammatory biomarkers, levels of PD-L1, and disease control and survival outcomes at 1 year. Inclusion criteria include pathologically confirmed diagnosis of stage III-IV head and neck squamous cell carcinoma involving the oral cavity, oropharynx p16 negative, larynx, or hypopharynx, status post definitive gross total surgical resection, with at least one high-risk pathologic feature, defined as extracapsular nodal extension or positive margins. This trial is currently on hold nationally for scheduled interim monitoring.⁽³²⁾

The recently published Checkmate-141 randomized Phase III trial assigned 361 patients with recurrent head and neck squamous cell carcinoma who had progressed within 6 months after platinum-based chemotherapy to nivolumab at 3mg/kg once every 2 weeks, or standard second-line single-agent systemic therapy consisting of either docetaxel, methotrexate, or cetuximab, as per investigator choice.⁽³³⁾ This study demonstrated that compared to standard therapy, nivolumab significantly improved overall

survival from a median of 5.1 to 7.5 months, with the 1-year overall survival rate nearly doubled for those treated with nivolumab (16.6% vs 36.0%). The response rate was 13.3% for nivolumab, compared to 5.8% for standard therapy. Exploratory biomarker analysis showed that the overall survival benefit remained, regardless of PD-L1 expression or p16 status, although those with PD-L1 positive or HPV-associated disease benefited the most. Among patients receiving nivolumab, overall response rates were 17% vs 12.3% if PD-L1 positive ($\geq 1\%$) vs PD-L1 negative ($< 1\%$), and 15.9% vs 8.0% if p16 positive vs p16 negative. ⁽³³⁾

Patients treated with nivolumab did not worsen the quality of life as an adverse effector, showed slight improvements in compared with other drugs like cetuximab and chemotherapy, ⁽³⁴⁾ besides having better overall survival ⁽³⁵⁾ and should be considered the new standard for patient with disease progression. ⁽³⁶⁾

RTOG 3504 is an ongoing trial for newly diagnosed, locoregionally advanced head and neck squamous cell carcinoma, seeking to integrate nivolumab with standard definitive concurrent chemoradiotherapy. ⁽³⁵⁾ The Phase I, dose-finding portion of the trial includes 3 randomized arms: nivolumab (240mg q 14 days x 10, starting on day 14) with weekly cisplatin (40mg/m² x 7) – based chemoradiotherapy, nivolumab (240mg on day - 14 followed by 360 mg q 21 days x 7) with high-dose cisplatin (100mg/m² IV on days 1, 22, and 43) – based chemoradiotherapy, or nivolumab (240mg q 14 days x 10) with weekly cetuximab and radiotherapy. ⁽³⁷⁾

Although epidermal growth factor receptor (EGFR) overexpression is present in the majority of head and neck squamous cell carcinoma, the efficacy of cetuximab is limited. There is increasing evidence that cetuximab induces not only tumor antigen-specific cytotoxic T lymphocyte responses, but also immunosuppressive regulatory T-cells that express CTLA-4, thus limiting the efficacy of cytotoxic T lymphocytes. ⁽³⁸⁾ Blockade of CTLA-4 could prevent activation of this inhibitory pathway and potentially enhance the efficacy of cetuximab. UPCI 12-084 was a Phase I dose-escalation trial that integrated ipilimumab, an anti – CTLA-4 monoclonal antibody, into a standard regimen of cetuximab plus radiotherapy in patients with previously untreated, locally advanced head and neck squamous cell carcinoma. Eligible patients had stage III-IVb of the larynx or pharynx. Ipilimumab was delivered at weeks 5, 8, 11, and 14. Preliminary results were presented at ESMO 2016. Among 18 enrolled patients, 6 patients were in cohort 1 and received ipilimumab at 3mg/kg. Two of these 6 patients developed grade 3 immune-related dermatologic dose-limiting toxicities unique to ipilimumab, consisting

of perforating folliculitis and autoimmune dermatitis. No patients in cohort 1 ($n = 12$), who received ipilimumab 1mg/kg, experienced any dose-limiting toxicities. Therefore, the recommended Phase II dose for ipilimumab is 1mg/kg. ⁽³⁹⁾

Avelumab is a human IgG1 monoclonal antibody against PD-L1. Unlike anti – PD-1 antibodies, which target T-cells, thus affecting both the PD-L1 and PD-L2 pathways, avelumab selectively targets PD-L1 on tumor cells. Therefore, avelumab may be associated with a lower risk of immune-related adverse events, as the PD-L2/PD-1 pathway is left intact to promote peripheral self-tolerance. ⁽⁴⁰⁾ The JAVELIN trial is a Phase III randomized, double-blind, international multicenter trial aiming to demonstrate that the combination of avelumab with standard of care chemoradiotherapy offers superior progression-free survival compared to chemoradiotherapy alone for the definitive treatment for patients with high-risk, locally advanced head and neck squamous cell carcinoma. ⁽⁴⁰⁾

Conclusion

Faced with several studies on the subject, it is conceivable that the immune system could potentially control head and neck cancer development, and immunotherapy may be effective for the treatment of patients with head and neck squamous cell carcinoma. Cellular-based therapies provide unique tumor specificity, the ability to detect and destroy micrometastases, and the potential to develop prolonged antitumor memory. Investigation on the mechanistic basis of the immune system has led to the development of breakthrough immunotherapies, mainly through checkpoint inhibition. Immune checkpoints, such as CTLA-4 and PD-1, are normal immunoregulatory pathways that have a major role in maintaining self-tolerance and modulating immune response in normal human peripheral tissues. Anti CTLA-4 and anti PD-1 antibodies have demonstrated substantial clinical activity in a variety of cancer types, including head and neck squamous cell carcinoma.

Approved since 2016 by Food and Drug Administration, nivolumab stands out as being the only drug approved in European Commission as monotherapy for the treatment squamous cell carcinoma of the head and neck (SCCHN) in adults with disease progression on or after platinum-based therapy. Nivolumab is the first and only immuno-oncology that has demonstrated significant improvement in overall survival for these patients in a phase III trial setting.

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Chapter 4

Advances in Radiotherapy and Chemotherapy as Organ Preservation in Head and Neck Cancer

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Introduction

Head and neck (oral cavity, oropharynx, hypopharynx, and larynx) squamous cell carcinomas occur frequently with over 500,000 new cases diagnosed worldwide each year.⁽¹⁾ The conventional treatment of patients with locally advanced (Stage III or IV) squamous carcinoma of the head and neck consisted of complete surgical resection of the tumor (if possible) combined with postoperative radiotherapy; or exclusive radiotherapy when unresectable.⁽²⁾

The surgical procedure usually involves physical, functional, social, and psychological sequelae that negatively affect the patient's quality of life by determining deformities in appearance, loss of the natural voice, definitive tracheotomy or tracheostoma, difficulty in chewing and swallowing, respiratory distress, decreased visual acuity and smell; causing loss of self-esteem and relationship problems.^(3,4)

In selected patients with moderately advanced cancer (T3N0), partial laryngeal resections that spare vocal function^(5,6) or primary radiation therapy^(7,8) achieve survival rates comparable to those obtained with total laryngectomy, permitting preservation of the larynx in 40-70% of these patients. The addition of chemotherapy before surgery or radiation in patients with advanced cancer of the head and neck^(9,10) has resulted in high rates of complete tumor regression that are associated with prolonged survival^(11,12,13,14) and that predict a favorable response to subsequent radiotherapy.^(15,16)

Several pilot studies have indicated the feasibility of avoiding surgical resection in selected patients who have complete tumor regression after induction chemotherapy and who then receive definitive radiotherapy.^(17,18) With such an approach, prolonged survival with organ preservation

has been reported for patients with cancer of the larynx or hypopharynx.^(19,20)

In 1985, the Cooperative Studies Program of the Department of Veterans Affairs performed a prospective, randomized study in patients with previously untreated advanced (Stage III or IV) laryngeal squamous carcinoma to compare the results of induction chemotherapy followed by definitive radiotherapy with those of conventional total laryngectomy and postoperative radiation. In this study, 332 eligible patients were enrolled and were assigned in equal numbers to introduction chemotherapy and radiation therapy (The Chemotherapy group) or surgery and radiation therapy (The surgery group). There are no significant differences between the treatment groups with respect to age, sex, or known prognostic factors, including performance status, T class, N class, tumor stage, tumor site, tumor grade, cartilage involvement, or vocal cord fixation. (**Table 4-1**)

Ninety percent (90%) used tobacco, and 85% consumed alcohol. Twenty patients had toxicity that necessitated the discontinuation of the chemotherapy.⁽²¹⁾

Induction chemotherapy consisted of cisplatin 100mg/m² given as a rapid intravenous infusion, followed by a continuous 24-hour intravenous infusion of fluorouracil 1000mg/m²/d for 5 days. Chemotherapy was repeated on days 22 and 43. The response of the primary tumor determined the patient's eligibility to proceed with radiation. Patients with at least a partial response at the primary tumor site (defined as a 50% reduction in the sum of the product of the longest dimension and its perpendicular, as compared with the initial tumor dimensions) and no progression of any neck adenopathy received a third cycle of chemotherapy and definitive radiation.⁽²¹⁾

Table 4-1. Characteristics of the Patients According to treatment Assignment. ⁽²¹⁾

Characteristic	Surgery	Chemotherapy
No. of patients	166	166
Stage		
III	95	93
IV	71	73
Tumor class		
T1,2	15	16
T3	109	107
T4	42	43
Node class		
N0	94	86
N1	26	34
N2	21	16
N3	25	30
Site		
Glottic	63	61
Supraglottic	103	105
Cartilage invasion	13	17
Fixed vocal cords	98	90
Performance status (Karnofsky score)		
<80	40	39
≥80	126	127

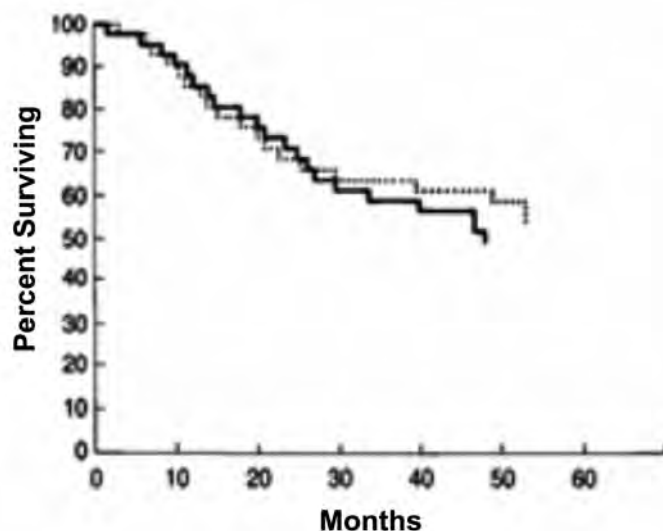


Figure 4-1. Overall survival of 332 patients Randomly Assigned to Induction Chemotherapy and Radiation Therapy (Solid Line) or Conventional Laryngectomy and Postoperative. Survival rates at two years were 68 percent for both groups. The median follow-up was 33-months. ⁽²¹⁾

Patients without at least a partial response in the larynx and those with any evidence of disease progression underwent immediate surgical resection and postoperative radiotherapy. Definitive radiation therapy consisted of 6600 to 7600 cGy to the primary tumor site. The doses to the nodes varied according to the initial nodal size: 5000 cGy for nodes with no involvement (N0), 6600 cGy for nodes measuring less than 2 cm in diameter, 7000 cGy for nodes 2 to 4 cm in diameter, and 7500 cGy for nodes more than 4 cm in diameter. The dose to the spinal cord was kept below 4500 cGy. Five daily fractions of 180 to 200 cGy per field were used for all fields. ⁽²¹⁾

The estimated two-year survival was 68% for the surgery group and 68% for the chemotherapy group. (**Figure 4-1**) Survival rates were similar for the patients who responded to chemotherapy and those who did not, and when these two groups were compared with the patients assigned to primary surgery. Of the surviving patients from the chemotherapy group treated successfully, 64% retained a functioning larynx. These results suggested a role for chemotherapy

in patients with advanced laryngeal cancer and indicated that a treatment strategy involving induction chemotherapy and definitive radiotherapy could be effective in preserving the larynx in a high percentage of patients, without compromising overall survival. ⁽²¹⁾

No significant differences in actuarial survival were found between treatments when the patients were grouped according to tumor stage or site. Survival rates were similar in the patients who responded to chemotherapy and those who did not and when these two groups were compared with patients assigned to primary surgery. The survival curve for the patients who had a histological confirmed complete response after three cycles of chemotherapy did not differ significantly from the curve for the surgery group. ⁽²¹⁾

In 1996, the European Organization for the Advent of the Cisplatin and 5-fluorouracil (CF) regimen in the early 80s shifted many paradigms in the management of head and neck squamous cell carcinoma (SCC), especially for advanced laryngopharyngeal SCC. Research and Treatment of

Cancer (EORTC) Head and Neck Cancer Group conducted a randomized controlled trial in patients with respectable stage III/IV hypopharynx cancer, comparing induction chemotherapy with cisplatin plus fluorouracil followed by radiotherapy, or surgery (total laryngectomy with partial pharyngectomy) and postoperative radiotherapy. Five-year survival rates were 38% and 33% for the induction chemotherapy group and surgery group, respectively. ⁽²²⁾

In 2012, this group presented 10-year results of EORTC trial 24891 and concluded that this strategy did not compromise disease control or survival (that remained poor) and allowed more than half of the survivors to retain their larynx. Larynx preservation based on a selection of patients with induction chemotherapy appeared safe and efficient in this trial. ⁽²³⁾ More recently, a randomized trial of patients who would have required total laryngectomy for laryngeal or hypopharyngeal squamous cell carcinoma compared two induction chemotherapy regimens before radiation in order to preserve the larynx.

To improve upon induction chemotherapy with cisplatin/fluorouracil, randomized controlled trials of newly diagnosed patients receiving non-surgical curative therapy evaluated the addition to taxane to the standard cisplatin/fluorouracil doublet (docetaxel 75mg/m², cisplatin 75mg/m², fluorouracil 750mg/m²/d continuous intravenous infusion for 5 days). Three phase III trials demonstrated superior efficacy for the 3-drug regimen, and less toxicity was exhibited with this combination. ^(24,25) Docetaxel/cisplatin/fluorouracil has now been established as an induction chemotherapy regimen that yields better response rates and a milder toxicity profile than earlier induction regimens, including cisplatin/fluorouracil. ⁽²⁶⁾

Chemotherapy can be administrated before, at the same time or after locoregional treatment corresponding to induction, concomitant or adjuvant chemotherapy. A meta-analysis of randomized trials showed that chemotherapy improved survival in non-metastatic head and neck squamous cell carcinomas treated by surgery and/or radiotherapy with an overall 4% benefit at 5 years, from 32% to 36%. This meta-analysis pooled the data from trials performed between 1965 and 1993. However, five trials which represented about 7% of the data explained a heterogeneity and when they were excluded the higher benefit of concomitant chemotherapy disappeared. ⁽²⁷⁾

MACH-NC group decided to confirm the results by updating its database with the inclusion of the randomized trials performed between 1994 and 2000. In this study Pignon made an update on 93 randomized trials and

17,346 patients were studied. There was an absolute benefit for chemotherapy of 4.5% at 5 years, and a significant interaction between chemotherapy timing (adjuvant, induction or concomitant) and treatment. Both direct and indirect comparisons showed a more pronounced benefit of the concomitant chemotherapy as compared to induction chemotherapy. For the 50 concomitant trials, the absolute benefit was 6.5% at 5 years. ⁽²⁸⁾

With advances in molecular biology and immunohistochemistry, there has been an increase in the number of factors regarding prognosis in patients with head and neck cancer. Farias et. al. evaluated 22 factors and the expression of proteins p53, Bcl2, Ki67, and PCNA as predictive factors in response to chemoradiotherapy in patients with laryngeal and oropharyngeal squamous cell carcinoma. ⁽²⁹⁾

Patients older than 18 years were selected and enrolled in the Brazilian National Cancer Institute in the period of January 2000 to August 2003 with a diagnosis of carcinoma, locally advanced laryngeal squamous cell or oropharynx (stages III or IV) and without distant metastases. All the patients should have clinical performance between 0 and 1.

The 22 factors studied were:

1. Anatomical site;
2. Presence of second primary tumor;
3. Chemotherapy delay;
4. Patients who received less than three cycles of cisplatin chemotherapy;
5. Patients who had one cycle, two cycles or three cycles of chemotherapy, were compared individually;
6. Hypernutrition through nasoesophageal tube before and during treatment;
7. Stages (III, IVa and IVb);
8. Alcoholism;
9. Histological grade;
10. Age;
11. Presence of cervical metastases;
12. Staging of cervical metastases (N1, N2 or N3);
13. Weight loss over 10%;

14. Performance status;
15. Dose of radiotherapy;
16. Gender;
17. Tumor size (T1, T2, T3 or T4);
18. Smoking;
19. Presence of skin toxicity;
20. Presence of gastrointestinal toxicity;
21. Presence of hematological toxicity; and
22. Presence of tracheostomy prior to treatment.

Among the 22 predictive factors, only the lack of hypernutrition through nasoesophageal tube ($P = 0.0006$), tumor size ($P = 0.009$) and the lack of tracheostomy were predictive of a better response to the treatment (univariate analysis). Nevertheless, when a multivariate analysis was made, only the lack of previous tracheostomy to treatment ($P = 0.0056$) and the lack of hypernutrition through nasoesophageal tube ($P = 0.002$) were predictive factors for a better result.

In an isolated way (univariate analysis), the non-expression immunohistochemistry of Bcl2 in the normal mucosal tumor or in both were predictive factors of a good response to radiotherapy and chemotherapy in patients with laryngeal and oropharyngeal SCC, with a probability of response of 3.64, 5.29 and 7.68 times (respectively) higher when compared with patients which positively expressed Bcl2. ⁽²⁹⁾

Patients with recurrent head and neck tumors (recurrences or new primaries) were inoperable and occurred in a previously irradiated area. Chemotherapy is palliative and response rates are around 20% with a median survival of 5–9 months. ^(30, 31) In the EXTREME protocol for patients with recurrent or metastatic squamous-cell carcinoma of the head and neck, adding cetuximab to platinum-based chemotherapy with fluorouracil (platinum-fluorouracil) significantly prolonged the median overall survival from 7.4 months in the chemotherapy-alone group to 10.1 months in the group that received chemotherapy plus cetuximab ($P = 0.04$). Cetuximab (Erbix, developed by Merck [Darmstadt], under license from ImClone) is an IgG1 monoclonal antibody that inhibits ligand binding to the EGFR5-7 and stimulates antibody dependent cell-mediated cytotoxicity.

It also enhances the activity of a number of chemotherapeutic agents, including cisplatin. Cetuximab is effective in recurrent or metastatic squamous-cell carcinoma of the head and neck that progresses despite platinum-containing therapy. ^(32,33)

In first-line therapy, adding cetuximab to cisplatin improves the response rate as compared with cisplatin alone. ⁽³⁴⁾ A combination of platinum, fluorouracil, and cetuximab is also active in first-line treatment. ⁽³⁵⁾ Stereotactic radiotherapy appears to be potentially feasible for head and neck reirradiation. ^(36,37) The addition of cetuximab prolonged the median progression-free survival time from 3.3 to 5.6 months ($P < 0.001$) and increased the response rate from 20% to 36% ($P < 0.001$). As compared with platinum-based chemotherapy plus fluorouracil alone, cetuximab plus platinum–fluorouracil chemotherapy improved overall survival when given as first-line treatment

Conclusion

There is a trend of chemoradiotherapy to be the standard treatment for locally advanced squamous cell carcinoma of the head and neck when there is intention to organ preservation. There are predictive factors, such as tumor size, presence of tracheostomy and hypernutrition through nasoesophageal tube, that define a low response to treatment. The most widely therapeutic regimen used is concomitant cisplatin and radiation, but there are several studies that associated taxol and fluorouracil with good results.

On the other hand, patients with recurrent head and neck tumors (recurrences or new primaries) were usually inoperable and occurred in a previously irradiated area. Chemotherapy is palliative and response rates are around 20% with a median survival of 5–9 months. In the extreme protocol for patients with recurrent or metastatic squamous-cell carcinoma of the head and neck, adding cetuximab to platinum-based chemotherapy with fluorouracil (platinum-fluorouracil) significantly prolonged the median overall survival.

The addition of cetuximab prolonged the median progression-free survival time and increased the response rate. As compared with platinum-based chemotherapy plus fluorouracil alone, cetuximab plus platinum–fluorouracil chemotherapy improved overall survival when given as first-line treatment.

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Chapter 5

Molecular Biology in Head and Neck Cancer

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Introduction

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common malignancy in the world, with an annual world-wide incidence of over 600,000 cases per year and 350,000 deaths per year. ⁽¹⁾ Cancers in the head and neck can originate from a variety of subsites including the lip, oral cavity, nasopharynx, oropharynx, and larynx.

The most common causes of head and neck cancers are tobacco and alcohol, which work synergistically, and are responsible for 70–75% of cases. ^(2,3) In parts of Asia, betel-quid chewing also plays a significant role in the development of malignancy. ⁽⁴⁾ On a molecular level, these cancers often have p53 mutations and many display chromosomal instability. ⁽⁵⁾

The past decade has seen an unprecedented increase in our understanding of the biology and etiology of head and neck squamous cell carcinomas (HNSCC). Genome-wide sequencing projects have identified a number of recurrently mutated genes, including unexpected alterations in the NOTCH pathway and chromatin related genes.

More recently, the human papilloma virus (HPV) has been shown to promote HNSCC and primarily cause oropharyngeal cancers (a sub-site in the head and neck). ⁽⁶⁾ Researchers have found significant differences in the pathogenesis and prognosis of HPV-related malignancies and HPV-negative malignancies and have tended to classify HPV associated malignancies as a separate biologic entity. Unlike HPV-negative cancers, HPV-related oropharyngeal malignancies are not as strongly associated with tobacco and alcohol exposure. They are, instead, related to sexual behavior, which is a conduit to transmit HPV. ^(7,8) Relative

to HPV-negative malignancies, HPV-positive cancers are associated with a more favorable prognosis. ^(7,9) The incidence of HPV-positive cancer is rising, while incidence of HPV-negative cancers is decreasing.

Treatment of HNSCC is made challenging due to the diversity of the anatomic sites in the head and neck and the critical normal structures that may be near a particular tumor site. Treatment options for HNSCC can consist of definitive surgical resection, definitive chemo-radiation, or a combination of surgery and chemo-radiation. Despite the availability of aggressive treatments, the 5-year survival rate for head and neck malignancies remains relatively poor at 65%, with only modest gains in the past few years. ⁽¹⁰⁾

An understanding of the molecular and genetic abnormalities leading to oncogenesis in head and neck malignancies has dramatically increased in the past decade. Initial attempts to understand the genetic etiology of head and neck cancers focused on cytogenetic studies. The development of microarray technology enabled the classification of HNSCC into distinct types based on gene expression.

More recently, next-generation sequencing technologies have allowed multiple groups of researchers to sequence a large number of tumors to identify novel mutated tumor suppressor genes and oncogenes. An underlying rationale for these genomic profiling studies was to gain a more thorough understanding of the molecular abnormalities in head and neck cancer to help guide the development of new therapeutics. Before reviewing the major discoveries of each of these profiling techniques, we will briefly discuss genetic factors that may pre-dispose individuals to develop HNSCC.

Genetic Predisposition of HNSCC

Although most cases of HNSCC are induced by carcinogens or viral infection, a small fraction of cases are familial in nature. The syndromic etiology with the clearest link of an increased risk of HNSCC is Fanconi anemia, an autosomal recessive genomic-instability syndrome associated with bone marrow failure, leukemia, congenital defects, and sensitivity to cross-linking agents. Treatment of these patients requires care as they are sensitive to common chemotherapeutics used in HNSCC and may be sensitive to radiotherapy as well, although this latter point is controversial. ⁽¹¹⁾ Rare clusters of HNSCC have also been reported in families with germ-line mutations in CDKN2A and ATR. ^(12,13)

In non-syndromic families, initial case-control studies demonstrated a genetic predisposition, with first-degree relatives having a 3.5 fold increased risk of HNSCC. Subsequent pooled analysis, however, led to an odds ratio of 1.7. ⁽¹⁴⁻¹⁷⁾ It has been hypothesized that genetic differences in pathways such as DNA repair, carcinogen metabolism, and cell cycle control may increase the risk of carcinogenesis from exposure to tobacco or alcohol. ⁽¹⁸⁾ Phenotypic differences in these processes in lymphocytes from HNSCC patients and controls have been identified. ^(19,20) Candidate gene-based studies have generated mixed results, with the notable exception of a nearly 9000 patient series that identified SNPs in multiple alcohol dehydrogenase (ADH) genes associated with a decreased risk of an upper aerodigestive malignancy. ⁽²¹⁻²⁴⁾ Subsequently, a genome-wide association study in upper aerodigestive malignancies validated the ADH SNPs and also identified a SNP in HELQ (a DNA repair gene) as being associated with risk of malignancy. Cumulatively, these SNPs only accounted for 4% of the familial risk. ⁽²⁵⁾

Expression Profiling

One of the first attempts to genomically profile HNSCC was with mRNA profiling. Unsupervised hierarchical clustering of the transcriptome of 60 HNSCC patients ⁽²⁶⁾ identified 4 subtypes: basal, atypical, mesenchymal type, and classical subtype; which have subsequently been verified by other investigators. ⁽²⁶⁾ Classical tumors exhibit alterations in expression of genes involved in oxidative stress, such as KEAP/NFEL2. The atypical cluster is enriched with HPV-positive tumors (discussed further below). Mesenchymal tumors demonstrate an elevation in expression of genes associated with epithelial-to-mesenchymal transition

(EMT). The basal subtype has an expression pattern similar to basal epithelial cells in airways and is named for its similarity to the basal type in squamous cell carcinoma of the lung.

The four subtypes do not show a significant correlation with age or smoking status but do appear to be related to site of origin. ⁽²⁶⁾ Still, each anatomic subsite, except for hypopharyngeal cancer, is present to some extent in each cluster, suggesting that expression-based subtypes reflect a biology that, at least in part, transcends anatomic sub-site. Of significant interest is that there is a strong correlation between each of these subtypes and their corresponding expression-based subtypes in squamous cell carcinoma of the lung. ⁽²⁶⁾

Mutational Analysis and Alterations in Specific Genes and Pathways in HNSCC

The first two large-scale sequencing efforts in HNSCC identified a number of recurrently mutated genes. The majority of these were in tumor suppressor genes rather than oncogenes. ^(27,28)

Stransky *et al.* performed whole exome-sequencing on 74 tumor/normal pairs, with 150-fold mean coverage, while Agrawal *et al.* sequenced 32 tumor/normal pairs, with a mean coverage of 77-fold and performed targeted follow-up sequencing in an additional 88 patients. For HPV-negative tumors, Stransky *et al.* found a mutation rate of 4.83 per Mb while Agrawal *et al.* found a mutation rate of 20.6 per Mb. The large discrepancy between the two groups may have arisen from differences in bioinformatics techniques of mutation calling or differences in coverage of sequencing. Since these initial studies, two other groups have looked at mutations specifically in oral cavity cancers ^(29,30) for study details.

In a pan-cancer analysis, Stratton and colleagues identified HNSCC as possessing the 9th highest average mutational load out of 30 tumor types studied, with patients having a range of mutations from less than 1 mutation per Mb to over 100 mutations per Mb. ⁽³¹⁾ They identified several active mutational processes in HNSCC, including mutations due to tobacco exposure, aging, UV light, and alterations in the apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like (APOBEC) enzymes. Multiple groups have found signatures of tobacco exposure in HNSCC, which often include guanosine-to-thymidine transversions. ^(32,33)

In HPV-negative tumors, the predominant finding from these sequencing efforts was that a large number of tumor suppressor genes were mutated. The Broad group identified 39 genes with recurrent mutations ($q \leq 0.1$), whereas the JHU group identified 6 genes with mutations in more than 4% of their study. Mutations and other genomic alterations in individual genes and key pathways are reviewed individually below. Of the non-coding mutations, an interesting one occurs in the promoter of TERT in nearly 20% of HNSCC, resulting in increased expression of telomerase. ⁽³²⁾

TP53

TP53 is a tumor suppressor gene that functions primarily as a transcription factor and regulates the expression of hundreds of downstream target genes in response to a variety of cellular stresses. ^(34,35) Mutations in TP53 appear to be acquired early in the pathogenesis of HNSCC and are present in pre-malignant lesions, suggesting an important role in early oncogenesis. ^(33,36) Most of the missense mutations in TP53 cluster in the DNA binding domain (DBD) whereas frame-shift and nonsense mutations are more equally distributed throughout the gene. One third of the mutations in the DBD occurs within 6 hotspot residues and result in preventing binding to DNA. Besides mutation, p53 may be inactivated in other ways such as via MDM2 over-expression or amplification (MDM2 is a negative regulator of p53) or deletion of CDKN2A (negatively regulates MDM2). ⁽³⁷⁾ Inactivation of p53 also occurs in HPV-positive tumors and is discussed in more detail below.

As p53 plays an integral role in handling genotoxic stress, multiple groups found that TP53 mutation results in worse outcomes in patients uniformly treated with either definitive radiotherapy or post-operative radiotherapy. ⁽³⁸⁻⁴⁰⁾

However, as TP53 mutations also are prognostic in patients treated with surgery alone, it is unclear if mutational status is a true predictive marker. Further, the mechanism by which p53 promotes radio-resistance remains unclear. ⁽⁴¹⁾ In cell types susceptible to p53-mediated apoptosis, loss-of-function would theoretically induce radio-resistance. p53-mediated apoptosis, however, does not appear to be the dominant mode of cell death in epithelial tumors. ⁽⁴¹⁾ Recent *in vitro* work with HNSCC cell lines has suggested that a subset of p53 mutations may have a gain-of-function phenotype that promotes senescence and subsequent radio-resistance. ⁽⁴⁰⁾ Future investigation and more accurate models will be needed to sort out this controversy.

Cell cycle alterations: CDKN2A, CCND1, and RB1

There is homozygous deletion of CDKN2A in nearly 30% of HNSCC and the gene is mutated in another 10–20% of samples and is frequently subject to LOH. ⁽⁴¹⁻⁴³⁾ The majority of mutations are inactivating and includes frame shifts, nonsense mutations, and splice site changes. Additional epigenetic alterations may lead to this gene being inactivated in up to 80% of tumors. ⁽⁴⁴⁾ One possible strategy to target this alteration would be to inhibit CDK4/CDK6. Recently, Palbociclib, a CDK4/6 inhibitor, increased progression free survival in a cohort of breast cancer patients, suggesting such an approach may be efficacious. ⁽⁴⁵⁾

The next most commonly altered cell cycle gene in HNSCC is CCND1, which is amplified in over 20% of tumors. ⁽⁴³⁾ CCND1 encodes cyclin D1, which serves as a cofactor for CDK4 and CDK6 to phosphorylate Rb. ⁽⁴⁶⁾ Again, CDK4/6 inhibitor could serve as a method to target these tumors, and both p16 loss and CCND1 amplification are being investigated as biomarkers in the Palbociclib trial. In the TCGA data, genetic alteration of one of either CCND1 or CDKN2A occurs in nearly 60% of cases and in the study by Pickering *et al.*, it was 94%. ⁽²⁹⁾ RB1, the retinoblastoma gene, also appears to be either mutated or deleted in approximately 5% of patients.

EGFR

When activated by binding its ligand, EGFR homodimerizes or heterodimerizes with other members of the ErbB family, stimulating its tyrosine kinase activity and leading to autophosphorylation of tyrosine residues in its cytoplasmic tail. ⁽⁴⁶⁾ This can lead to activation of downstream signaling cascades including RAS/RAF/MAPK, PI3K/AKT/mTOR and/or JAK/STAT. These pathways are important regulators of proliferation, invasion, angiogenesis and metastasis. Cetuximab, a chimeric murine/human monoclonal antibody against EGFR, has improved overall survival compared to standard treatment in the locally advanced and metastatic settings, although adoption in the locally advanced setting remains controversial. ⁽⁴⁷⁻⁵⁰⁾

Although EGFR is expressed on the surface of the majority of HNSCC tumors and the degree of over expression is associated with a worse prognosis, the muddled picture from therapeutic interventions in the pathway has led to uncertainty on exactly how this pathway is activated in HNSCC. ⁽⁵¹⁻⁵⁴⁾

The molecular and clinical trial results suggest that perhaps cetuximab's efficacy is mediated more by its antibody-dependent cell-mediated cytotoxicity than blockade of the EGFR pathway. ^(55,56) Alternatively, resistance to EGFR inhibition may occur quickly by up-regulation of other erbB receptors, such as ERBB2 (HER2/NEU). ⁽⁵⁷⁾ Strategies addressing both these possibilities are being actively pursued clinically with the development of pan-erbB inhibitors and monoclonal antibodies as well as the pairing of cetuximab with various immune check-point inhibitors in development.

PI3K/AKT/mTOR

PIK3CA is the 2nd most commonly mutated gene across human cancers and alterations in this pathway are thought to play an important role in cancer cell growth, survival, and metabolism. ⁽⁵⁸⁾ The PI3K family of kinases consists of three classes, with class IA being most frequently involved in cancer. Activation of PI3K leads to phosphorylation of phosphatidylinositols (PIP₂, a second messenger) and subsequent activation of AKT, one of the main effectors of PI3K signaling. ⁽⁵⁹⁾ Activated forms of AKT have been found in the majority of HNSCC tumors analyzed by tissue microarrays. AKT further activates mTOR, which is also responsible for integrating cellular signals regarding nutrient levels, cellular energy stores, and stress. One mechanism of PI3K activation in HNSCC is by receptor-tyrosine kinases, such as EGFR. Although EGFR cannot directly activate PI3K, if EGFR heterodimerizes with ERBB3 it can subsequently activate PI3K signaling. ⁽⁶⁰⁾

Another mechanism of activation of PI3K pathway in HNSCC involves mutation, with mutations occurring in PI3K catalytic subunit, p110 α (encoded by PIK3CA gene). Approximately 20% of tumors have mutations in PIK3CA, however these mutations occur much more commonly in HPV-positive tumors compared to HPV-negative tumors. ⁽⁴³⁾

Further, initial experience with dual PI3K-mTOR agents appear to be limited by toxicity. To-date, however, experience in HNSCC remains limited and trials are presently on-going. ⁽⁴³⁾

NOTCH1/p63/FBXW7

Notch1 is a transmembrane receptor that plays a role in cell differentiation and embryonic development. ^(61,62) Signaling

is thought to be mediated by cell-to-cell contact, enabling binding of Notch to one of five known ligands. After receptor activation by ligand binding, a cascade of proteolytic cleavages take place that result in the release of Notch1's intracellular domain (NICD). Notch1 mutations are oncogenic in T-cell acute lymphoblastic leukemia and cause ligand-independent cleavage of Notch1, ultimately leading to constitutive activation. ⁽⁶³⁾ Notch's oncogenic functions are thought to be mediated by prompting cell cycle progression and inhibition of apoptosis. ⁽⁶²⁾

Oxidative Stress Response: NRF2/KEAP1/CUL3

Genes involved in oxidative stress are altered by mutation or copy number change in nearly 20% of HNSCC, and by IHC, NRF2 is overexpressed in 90% of tumors. ^(43,64) NRF2 (encoded by the NFE2L2 locus) is a transcription factor that activates the cellular antioxidant response. ⁽⁶⁵⁾

It is typically constitutively expressed under basal conditions and kept in the cytoplasm and degraded by KEAP1 and CUL3. CUL3 is a core component of an E3 ubiquitin ligase complex, which relies on KEAP1, a substrate specific adaptor, to successfully ubiquitinate NRF2 and promote its degradation. The interaction between NRF2 and KEAP1 is mediated by NRF2's Neh2 domain and KEAP1's Kelch/DGR domain. In the presence of oxidative stress, the interaction between KEAP1 and NRF2 is inhibited, leading to the accumulation of NRF2 in the cytoplasm, subsequent translocation to the nucleus, and thereafter transcriptional activation of its target. Increased activation of NRF2 may promote cancer cell growth and protect against cytotoxic therapies. ⁽⁶⁵⁾

The majority of mutations are missense mutations and they occur both in domains involved with binding to NRF2 and those responsible for binding to CUL3. These also presumably lead to increased cytoplasmic NRF2, and subsequent activation of the pathway. Lastly, CUL3 is mutated or deleted in approximately 6% of patients.

Chromatin Related Genes: MLL2, NSD1, EP300, and Other Epigenetic Changes

The discovery of recurrent mutations in chromatin modifying genes was one of the major discoveries of cancer sequencing projects in general. Chromatin modifying genes can covalently modify histone proteins, which alters the

structure of the nucleosome or alternatively alter DNA. ⁽⁶⁶⁾ These modifications play a critical role in regulating DNA-based processes, such as transcription and DNA repair. MLL2 (aka KMTD2) is a histone methyltransferase that is mutated in 19% of HNSCC. MLL2 can methylate several lysine residues on histones, including H3K4, which is often associated with positive gene regulation. In leukemia's, MLL translocations are quite common and their role in carcinogenesis is much better understood than the role of the more recently discovered MLL2 point mutations. ^(67,68) NSD1 is another histone methyltransferase that is mutated in 10% of patients, with, again, a strong bias towards truncating and nonsense mutations.

EP300 is histone acetyltransferase that is mutated in 7% of HNSCC. EP300 can also directly interact with a wide range of transcription factors, pro-proliferation proteins, and tumor suppressors directly, including c-MYC, c-MYB, CREB, c-JUN, c-FOS, p53, STAT1, BRCA1, and SMAD homologous proteins. Given its cooperation with such a wide variety of proteins, it can promote opposing cellular processes depending on cell type and context.

FAT1/CASP8

FAT1 and CAPS8 mutations may define a distinct subtype of HNSCC. FAT1 is mutated in 23% of tumors, with a predominance of nonsense and frame-shift mutations, suggesting a tumor suppressor function. FAT1 is thought to suppress cancer cell growth by playing a role in Wnt signaling by binding to β -catenin and limiting its ability to translocate to the nucleus. ⁽⁶⁹⁾ Truncating mutations would inhibit this functionality and promote tumor cell growth. CASP8 is specifically involved in the extrinsic pathway of apoptosis signaling and is activated by membrane bound receptors such as Fas and TNF. ⁽⁷⁰⁾ Upon activation, Casp-8 triggers the execution phase of apoptosis.

Chromosomal Instability and Copy Number Alterations

Among HPV-negative HNSCC, 80% display significant chromosomal instability and over 40% of tumors have undergone whole genome duplication. ⁽⁷⁰⁾ The amount of chromosomal instability is known to vary between gene-expression defined molecular subtypes. On average, an individual tumor will have 7.3 arm-level alterations and 16 focal alterations. TCGA and others have identified a

large number of recurrent alterations, including 12 arm-level amplification events, 14 arm-level deletions, 26 focal amplifications, and 49 focal deletions. Some of the most commonly lost regions include 3p, 4p, and 9p, whereas those commonly gained include 3q, 7p, and 8q. ^(71,72)

Increasing levels of chromosomal instability in pre-malignant lesions have been associated with an increased risk of progression to malignant disease in multiple retrospective studies. ⁽⁷³⁻⁷⁵⁾ Across a variety of malignancies, once cancer has already developed, increasing chromosomal instability also appears to be associated with worse outcome. ⁽⁷⁶⁾ Similarly, in head and neck cancer, increasing chromosomal instability has been associated with a worse outcome and a more severe malignant phenotype in multiple studies, including worse overall survival and higher risk of lymph node metastasis. ⁽⁷⁷⁻⁷⁹⁾ In terms of predicting response to treatment, one small case control study compared the copy number profile of tumors sensitive to chemoradiotherapy vs. those that were resistant and found a difference in the patterns of gains and losses. ⁽⁸⁰⁾

HPV

Human Papillomavirus (HPV) family of viruses are double-stranded DNA viruses with a propensity to infect squamous epithelium. ^(80,81) The HPV family is composed of both low and high-risk strains, which is determined by a strain's ability to lead to malignant progression. Definitive evidence linking HPV as a causative agent in oropharyngeal cancer didn't emerge until the turn of the century. Since then, it has become clear that HPV-related oropharyngeal cancers are a distinct entity with a better prognosis compared to traditional smoking and alcohol related head and neck cancers. HPV16 is the main subtype associated with HNSCC, although a number of other subtypes have also been reported. ^(81,82)

The role of HPV in the pathogenesis of non-oropharyngeal head and neck cancers remains unclear at present and is an area of active investigation. The HPV genome consist of 8000 base pairs and is divided into 3 segments, an early coding region (E), a late coding region (L), and a long control region (LCR). In cancer, the HPV genome can exist either in an episomal form or integrated into the host genome. The viral load and transcription of HPV-related genes in tumors can vary on the order of several magnitudes between different tumors. ^(81, 82)

Integration into the host genome was thought to favor common fragile sites but can occur randomly. Recent

work has suggested recurrent insertions in RAD51 and ERBB2. Integration is also thought to promote oncogenesis. HPV contains two oncogenes, E6 and E7, that inactivate p53 and Rb respectively and are thought to be important mediators in producing a malignant phenotype. E6 can also promote transcription of hTERT, facilitating immortalization of cells. E7 inhibits Rb by facilitating ubiquitination and degradation of the protein.⁽⁸³⁾ Although the E7 protein from low-risk HPV serotypes is also able to bind to Rb, E7 from high-risk HPV serotypes is much more efficient. Both E6 and E7 also interact with a variety of other host proteins that may also play a role in oncogenesis.

As HPV-positive tumors have a better prognosis, a number of clinical trials are underway investigating various ways of de-escalating treatment to reduce morbidity of treatment. The molecular differences between HPV-positive and negative tumors clearly play a role in their prognosis and will also help guide de-escalation trial design. For instance, some have found an inverse relationship between HPV and the presence of EGFR by IHC staining.⁽⁸³⁻⁸⁵⁾ However, at present there is no definitive clinical data to suggest a difference in efficacy for anti-EGFR therapy in HPV-positive compared to HPV-negative patients.⁽⁸⁶⁾

Conclusion

Sequencing efforts and integrative genomics have revealed a great deal about the molecular abnormalities that underlie HNSCC. Unfortunately, they have also demonstrated marked heterogeneity, which will make optimizing therapeutic intervention difficult. In HNSCC, oncogenic mutations are rare and mutations in tumor suppressor genes dominate. Restoring function of a tumor suppressor pharmacologically is difficult. Targeting these alterations may require exploring synthetic lethal approaches. Although any individual tumors may still have some targetable alterations (i.e. amplification or mutation in a known oncogene), it is unclear in many cases if these are passengers or driving events.

Furthermore, oncogenic pathways can be activated by non-genetic mechanisms, which would not have been detected by genomic efforts. Now that a genetic blueprint for HNSCC has been completed, the challenge moving forward will be to identify ways to use this information to develop improved diagnostic and therapeutic modalities.⁽⁸⁶⁾

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Chapter 6

Molecular Targeted Therapies in the Treatment of Head and Neck Cancer

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Despite the development of standard therapies, including surgery, radiotherapy and chemotherapy, survival rates for head and neck squamous cell carcinoma (HNSCC) have not changed significantly over the past three decades. ⁽¹⁾

Complete recovery is achieved in <50% of patients. The treatment of advanced HNSCC frequently requires multimodality therapy and involves significant toxicity. The promising, novel treatment option for patients with HNSCC is molecular targeted therapies. ⁽¹⁾

The best known targeted therapies include: Epidermal growth factor receptor (EGFR) monoclonal antibodies (cetuximab, panitumumab, zalutumumab and nimotuzumab), EGFR tyrosine kinase inhibitors (gefitinib, erlotinib, lapatinib, afatinib and dacomitinib), vascular endothelial growth factor (VEGF) inhibitor (bevacizumab) or vascular endothelial growth factor receptor (VEGFR) inhibitors (sorafenib, sunitinib and vandetanib) and inhibitors of phosphatidylinositol 3-kinase / serine / threonine - specific protein kinase/mammalian target of rapamycin. ⁽¹⁾

Among head and neck cancers (HNC), the majority, $\leq 90\%$, comprise of mutations originating in the squamous epithelium of the upper aerodigestive tract. ⁽²⁾ Standard therapies used for treatment of HNSCC have achieved a consistent five-year survival rate ranging from 40–50% in the past three decades. ⁽²⁾

Treatment for the early stage of this disease is a single therapeutic method, including surgery or radiotherapy. ⁽³⁾ Cure rates of >90 and 70% have been achieved for stage I and II, respectively. ⁽⁴⁾ The radical treatment of patients with locally advanced cancer in stage III or IV requires multimodality therapy. At these stages, a surgical treatment is complemented with radiotherapy or chemoradiotherapy,

depending on the risk factors for a relapse including: dubious margin of healthy tissue; poorly differentiated (G3) cancer; and feature pT4 (advanced local disease) or metastases in the regional lymph nodes. ⁽⁵⁾

In stage III and IV it is also possible to apply an organ conserving therapy, such as chemo-radiotherapy or targeted therapy using monoclonal antibodies in combination with radiotherapy; ⁽⁵⁾ however, the treatment effects are not as satisfactory, compared with the early stages of the disease. ⁽⁵⁾

Unsatisfactory outcomes of the HNC treatment using standard methods with high toxicity warrant a search for novel therapeutic options considering the overall toxicity of chemotherapy and radiotherapy together or alone. ⁽⁶⁾ Molecular target therapy for squamous cell involves several mechanisms of action such as Epidermal growth factor receptor (EGFR) monoclonal antibodies, EGFR tyrosine kinase inhibitors, Vascular endothelial growth factor (VEGF) inhibitors, VEGFR inhibitors, PI3K/AKT/mTOR pathway inhibitors and Anti-PD-1 antibodies. **Table 6-1** shows some examples of molecular-targeted therapies in the treatment of head and neck squamous cell carcinoma. ⁽¹⁾

EGFR is a transmembrane protein that belongs to the activity of the ErbB / HER family of receptor tyrosine kinase (RTK). ⁽⁷⁾ The extracellular signals, which are transduced, are altered in intracellular responses, influencing cell proliferation, apoptosis, angiogenesis and the ability of metastatic tumor cells. ⁽⁷⁾ The monoclonal anti-EGFR antibody binds to the extracellular domain of EGFR, preventing connections between ligands and thus interferes with the transmission of signals into the cell ⁽⁸⁾ and the EGFR tyrosine kinase inhibitors (TKIs), bind to the cytoplasmic region of EGFR by competing with adenosine-5'-triphosphate, and thereby inhibit the autophosphorylation

Table 6-1. Examples of molecular-targeted therapies in the treatment of head and neck squamous cell carcinoma ⁽¹⁾

Mechanism of Action	Molecular Targeted Therapy
EGFR monoclonal antibodies	Cetuximab, panitumumab, zalutumumab and nimotuzumab
EGFR tyrosine kinase inhibitors	Gefitinib, erlotinib, lapatinib, afatinib and dacomitinib
VEGF inhibitors	Bevacizumab
VEGFR inhibitors	Sorafenib, sunitinib and vandetanib
PI3K/AKT/mTOR pathway inhibitors	Rapamycin, temsirolimus, everolimus, torin1, PP242 and PP30
Anti-PD-1 antibodies	Pembrolizumab and nivolumab

Paulina Kozakiewicz; Ludmila Grzybowska Szatkowska. *Application of molecular targeted therapies in the treatment of head and neck squamous cell carcinoma. March 20, 2018. Volume 15 Issue 5; 7497-7505.* ⁽¹⁾

of EGFR and signal transmission to the lower levels of the intracellular route. ⁽⁹⁾ (**Figure 6-1**)

VEGF is a signaling protein produced by cells that stimulate angiogenesis. ⁽¹¹⁾ The overexpression of VEGF is present in the majority of HNSCC, consequently favoring tumor growth by changing the microvessel density in the vicinity of cells, cell migration and the formation of distant metastases. ⁽¹²⁾ There are several strategies aimed at VEGF, which are being evaluated in clinical trials and mediate the inhibition of angiogenesis. ⁽¹³⁾ The most common molecules used in targeted therapies are: Bevacizumab, cetuximab, sorafenib, sunitinib and vandetanib. ⁽¹³⁾

The PI3K/AKT/mTOR pathway is an intracellular signaling pathway. ⁽¹⁴⁾ The first signal of this pathway, that is PI3K can be activated in several ways. This is conducted by EGFR or insulin-like growth factor 1 receptor and by the adhesion of molecules, including integrins, G protein-coupled receptors (GPCRs) and by oncogenes, including RAS. ⁽¹⁴⁾ Its function is to regulate the cell cycle, cell survival and proliferation by monitoring the availability of nutrients, cellular energy level, cellular oxygenation and mitogenic signals. ⁽¹⁵⁾ PI3K/AKT/mTOR pathway inhibitors are molecules that prevent cell proliferation, are divided into first and second generation.

PD-1 is an immunoreactor and a negative regulator of the immune response. ⁽¹⁶⁾ It is inductively expressed on T and B lymphocytes, as well as on dendritic cells and monocytes. The receptor is activated by binding to one of its ligands: PD-ligand 1 (PD-L1) or PD-L2. ⁽¹⁵⁾ The production of cytokines and proteins promoting cell survival decreases, and synthesis of the interleukin-10 cytokines increases, contributing to the suppression of the inflammatory response. ⁽¹⁷⁾ The clinical potential of anti-PD-1 and anti-PD-L1 antibodies have been successfully. Pembrolizumab was granted accelerated approval by the FDA for patients with recurrent or metastatic HNSCC after platinum-containing chemotherapy. ⁽¹⁸⁾ Nivolumab is another anti-PD-L1 is a new and potent drug that has obtained excellent results concomitant with chemotherapy. ⁽¹⁹⁾

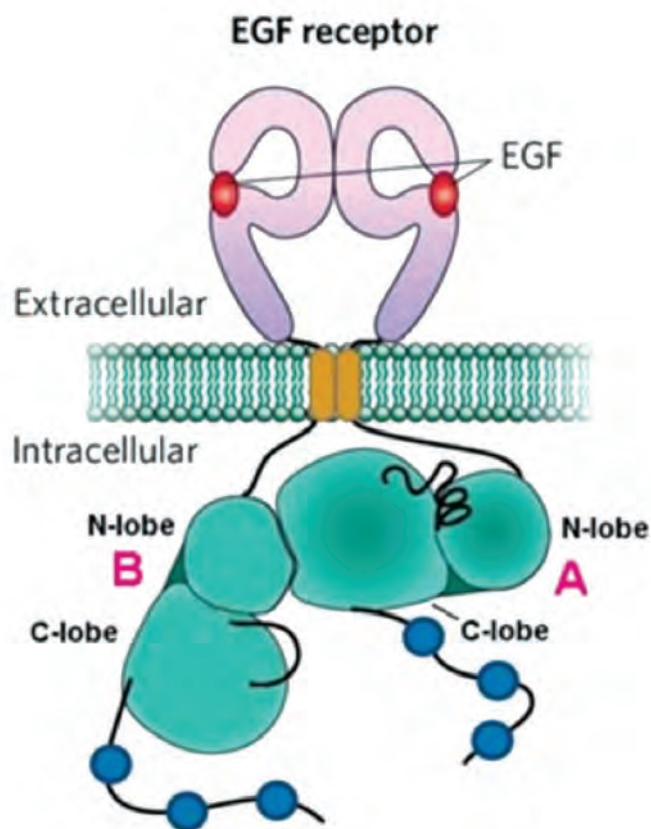


Figure 6-1. ⁽¹⁰⁾ EGFR is a transmembrane protein that belongs to the activity of the ErbB / HER family of receptor tyrosine kinase (RTK) generating extracellular signals, which are transduced, are altered in intracellular responses, influencing cell proliferation, apoptosis, angiogenesis and the ability of metastatic tumor cells ⁽⁷⁾

Other types of tumors less prevalent than squamous cell carcinoma also possess molecular targeted like for basocellular carcinoma with inhibition of Hedgehog signaling, for exemple the Vismodegib for advanced cases. ⁽²⁰⁾ Besides that, the discovery of BRAF mutations in melanoma led to the development of BRAF inhibitors for the treatment of advanced melanoma, for example Dadrafenib and Vemurafenib. ⁽²¹⁾

Cetuximab is the only drug approved by the FDA on treatment of head and neck. ⁽²²⁾ It's effective in platinum-resistant recurrent or metastatic squamous-cell carcinoma of the head and neck. As compared with platinum-based chemotherapy plus fluorouracil alone, cetuximab plus platinum-fluorouracil chemotherapy improved overall survival when given as first-line treatment in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck. ⁽²³⁾ Besides that, adding cetuximab to cisplatin improves the response rate as compared with cisplatin alone. ⁽²⁴⁾ A combination of platinum, fluorouracil, and cetuximab is active in first-line treatment. In an Indian study show that the addition of a platinum chemotherapy regimen to cetuximab in patients with disease that progresses on platinum seems to confer no further benefit over cetuximab alone, either in terms of response rate (RR) or survival. ⁽²⁵⁾

Conclusion

Molecular target therapy has been showing promising results. It is a broad area of research where new drugs will emerge. With the improvement of molecular diagnosis and the use of personalized treatment, a great improvement in survival is expected.

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Chapter 7

Neoplasms of the Anterior Cranial Fossa and Paranasal Sinuses

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Paranasal Sinuses and Skull Base Tumor

Paranasal sinuses and nasal cavity carcinoma account for 0.2-0.8% of all human malignant neoplasms. Among them, sinonasal squamous cell carcinoma is one of the rarest epithelial neoplasms and represents about 3% of all malignancies of the head and neck region. It predominantly occurs within the maxillary sinus (60-70%) and less frequently in the nasal cavity (12-25%), ethmoid (10-15%) and sphenoid/frontal sinus (1%).⁽¹⁾

There are four paired paranasal sinuses: the maxillary, ethmoid, sphenoid, and frontal. In health, each is filled with air and communicates with the nasal lumen through an ostium. The bony ostium is slightly larger than the opening in the mucous membrane. Each sinus is lined by a relatively thin, ciliated mucous membrane whose cilia beat the overlying blanket of mucus toward the sinus ostium to join the mucous blanket in the nose. The cilia in the sinal mucous membrane become more numerous as the ostium is approached. For clinical purposes, the sinuses are divided into two groups, anterior and posterior, depending on their location in reference to the line of attachment of the middle turbinate to the lateral wall of the nose. The anterior group consisting of the frontal, maxillary, and anterior ethmoid cells open into or near the infundibulum. The posterior group, made up of the posterior ethmoid cells and the sphenoid sinuses, opens above the middle turbinate.⁽²⁾

The poor prognosis for patients with nasal and paranasal sinus malignancy has led many investigators to focus their attention on it. Unfortunately, no true consensus has been reached regarding many aspects of treatment for these disease entities. This stems from the wide variety of tumors found in the area, the relatively short clinical course of patients afflicted with these neoplasms, and the rarity with which the

tumors occur. However, with recent developments in fiber optics, radiographic imaging, and a growing consensus on staging and nomenclature, a vast amount of clinical information is now becoming available.⁽³⁾ Despite the rarity of nasal and paranasal sinus neoplasms, many histologically diverse types are described in the literature. The following discussion focuses on the most common pathology seen in this area. Whereas most sinus neoplasms are malignant, in the nasal cavity, there is a fairly even distribution between benign and malignant disease.⁽³⁾

The majority of these benign lesions are papillomas that may be subdivided into three categories: fungiform (50%), inverted (45%), and cylindrical cell (5%). The benign neoplasms are divided into epithelial and nonepithelial tumors.⁽⁴⁾ (Table 7-1)

The malignant tumors are also divided into epithelial and non-epithelial ones as shown in the Table 7-2.

Table 7-1. Benign Neoplasms of the Nose and Paranasal Sinuses

Epithelial Tumors	Non-epithelial Tumors
Papillomas	Osteomas
Adenomas	Fibromas
	Chondromas
	Hemangiomas
	Nerve sheath tumors

Mortignoni G al. Assessment of patients with suspected sinonasal neoplasm. In: Kraus DH, Levine HL, editors. Nasal neoplasia. New York: Thieme; 1997. p. 21-42⁽⁴⁾

Table 7-2. Malignant Neoplasms of the Nose and Paranasal Sinuses

Epithelial Tumors	Non-epithelial Tumors
Squamous cell carcinomas	Rhabdomyosarcomas
Adenomas	• Neurogenic sarcomas
Adenoid cystic carcinomas	• Leiomyosarcomas
Mucoepidermoid carcinomas	• Fibrosarcomas
Melanomas	• Angiosarcomas
Esthesioneuroblastomas	Hemangiopericytomas
• Teratomas	• Osteogenic sarcomas
• Teratocarcinomas	• Chondrosarcomas
	• Lymphomas

Mortignoni G *al.* Assessment of patients with suspected sinonasal neoplasm. In: Kraus DH, Levine HL, editors. Nasal neoplasia. New York: Thieme; 1997. p. 21–42 ⁽⁴⁾

Malignant epithelial neoplasms constitute the majority of sinonasal tumors, representing 45 to 80% of all sinus neoplasia and the squamous cell carcinoma is the most common. ⁽⁵⁾ As in other areas of the head and neck, the tumor may present with varying degrees of differentiation. Glandular carcinomas are the next most common tumors, comprising 4 to 15% of all sinus neoplasms. Of these, adenocarcinomas are the most common, representing 5 to 19% of nasal and paranasal sinus tumors. ⁽⁶⁾ Mucoepidermoid carcinoma is an extremely rare form of glandular carcinoma. It is composed of a combination of squamous cells and glandular, mucus-producing, basal cells. They are notable for their propensity toward distant metastases. ⁽⁷⁾

As would be expected from such a broad group of tumors, treatment largely depends on the nature of the lesion. The development of endoscopic endonasal surgery has provided a natural orifice surgical option that appears to have similar oncologic outcomes and lower relative morbidity in the hands of high-volume surgeons, but a lot of cases will need to traditional transfacial (**Figure 7-1. Degloving approach in child**) and open resections (**Figure 7-2. Maxillectomy and Facial Translocation approach**). Surgery is the treatment of choice in almost all circumstances for benign lesions and most commonly is the primary treatment for malignancies as well. ⁽⁸⁾

Exceptions to this include certain sarcomas treated with neoadjuvant radiation, lymphomas treated entirely by local radiation and chemotherapy, and certain biologically aggressive or initially unresectable lesions such as squamous cell carcinoma, sinonasal undifferentiated carcinoma,

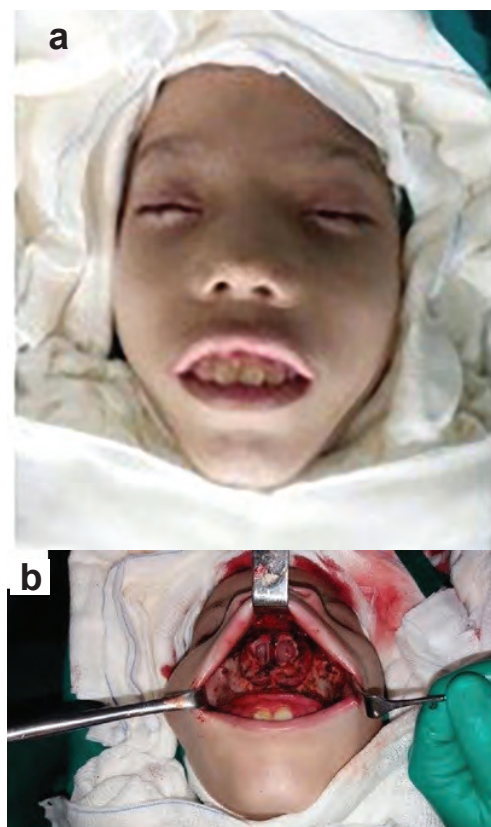


Figure 7-1. A) Child with Nasoangiofibroma Tumor. B) Degloving Approach

small-cell neuroendocrine carcinoma that may be treated with neoadjuvant chemotherapy or chemoradiation. For advanced lesions invading the orbit, surrounding bony structures, or skin of the face, surgery may imply a partial or total rhinectomy, partial or total maxillectomy and adjacent sinuses (ethmoid and frontal), and orbital exenteration. ⁽⁹⁾

Lesions involving the skull base with or without intracranial extension require collaboration with neurosurgery through endoscopic or craniofacial resection. Prognosis largely depends on the type and stage of the cancer, with most experts agreeing that survival is improved with multimodal therapy including surgery, radiation, and sometimes chemotherapy. Five-year overall survival approaches 60% for all types, is best for olfactory neuroblastoma (>70%), and worst for undifferentiated carcinoma (20% to 40%) and mucosal melanoma (10% to 30%). ⁽⁹⁾

Anterior Cranial Fossa

The anterior fossa is composed of the frontal bone anteriorly and laterally, the cribriform plate of the ethmoid bone

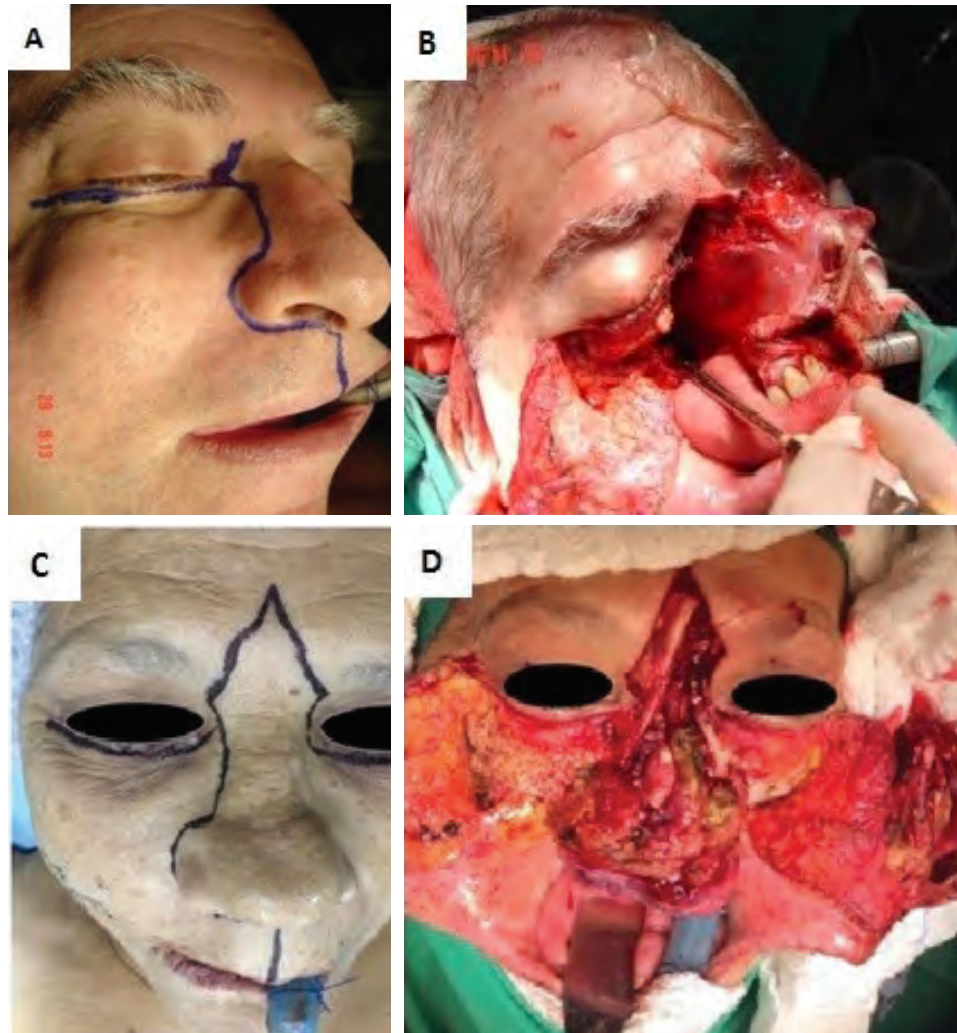


Figure 7-2. A) Weber Ferguson Dienffebach Incision. B) Total Maxillectomy. C) Facial Translocation Incision. D) Facial Translocation Approach.

centrally, and the body and lesser wing of the sphenoid bone posteriorly and centrally. Immediately anterior to the cribriform plate is the foramen cecum, through which an emissary vein passes to the nasal cavity. The perforated cribriform plate allows passage of the olfactory nerve fibers traveling from the olfactory epithelium of the superior part of the nasal cavity to the olfactory bulb. The optic chiasm rests anterior and superior to the pituitary in the chiasmic groove. The cavernous sinus lies lateral to the pituitary gland and *sella turcica*.⁽¹⁰⁾

The differential diagnosis of skull base (Table 7-3) lesions are glomus tumors, meningiomas, neural tumors, neurilemmoma, carcinomas (primary squamous cell carcinoma, basal cell carcinoma, metastatic,

Table 7-3. Differential Diagnosis of Skull Base Lesions

Glomus tumors	Neurilemmoma (Neuro fibroma, Chordoma)
Meningiomas	Metastatic (Squamous cell carcinoma and adenocarcinoma)
Neural tumors Primary cholesteatomas Rare lesions	Carcinomas (Primary, Squamous cell carcinoma, Basal cell carcinoma, Metastatic, Adenocarcinoma)
Petrositis	

Sekhar S. Tumors of the cranial base. Diagnosis and treatment. Mount Kisco (NY): Futura Publishing; 1987.⁽¹²⁾

adenocarcinoma), nasopharyngeal angiofibromas and rare lesions (rhabdomyosarcoma, plasmacytoma, melanoma, giant cell tumor, osteoblastoma, lipoma, chondrosarcoma, teratoma Histiocytosis Hemangiopericytoma).⁽¹¹⁾ Some mass lesions may be unique to specific areas of the anterior cranial fossa. Include benign fibro-osseous lesions and osseous lesions as well as malignant entities such as sinonasal tumors and esthesioneuroblastoma.

Fibro-osseous lesions, fibrous dysplasia and ossifying fibroma, are common benign lesions of the anterior part of the skull base. Another common lesion is an osteoma tumor. Osteomas frequently arise in the frontal and ethmoid sinuses and involve the anterior part of the skull base secondarily. Pathologic differentiation among these lesions is sometimes difficult. Treatment of these lesions is necessary only when functional problems arise, or cosmetic deformity occurs.⁽¹²⁾

Two malignant lesions that can involve the anterior part of the skull base are paranasal sinus carcinoma and esthesioneuroblastoma. Ethmoid and, less commonly, frontal sinus tumors (most of which are squamous cell carcinomas) involve the anterior part of the skull base through direct extension. Wide surgical removal, usually in combination with radiation or chemotherapy, is necessary when treatment for cure is planned. Esthesioneuroblastomas are of neural crest origin and represent about 2% of all malignant nasal neoplasms. The cribriform plate is involved early as this lesion arises from the olfactory epithelium.⁽¹²⁾ Total gross removal may require craniofacial resection as well as orbital exenteration in addition to sinus resection.

Craniofacial Approach

Because of the complexity of the skull base and the diversity of the possible abnormalities, many surgical approaches have been developed. They are continually being modified, and new ones are being described. For lesions that involve the roof of the ethmoid sinuses or the superior nasal vault (cribriform area), visualization from above (cranially) and below (facially) can be obtained through a craniofacial approach. The most common lesions include olfactory neuroblastoma and ethmoid sinus cancer.⁽¹³⁾ The approach from above is initiated with a bicoronal incision originating anterior and superior to the auricles bilaterally followed by flap elevation over the forehead. (**Figure 7-3**)

An anterior craniotomy exposes the frontal sinus, which is completely removed, and the frontal lobes that are gently elevated, necessitating transection of the olfactory nerves. This allows visualization of the floor of the anterior cranial



Figure 7-3. A) Bicoronal Incision. B) Pericraniogaleal flap.

fossa, including the roofs of the orbits and cribriform plate area. Visualization can be obtained back to the area over the anterior portion of a fully pneumatized sphenoid sinus. The cribriform plate and various amounts of bone can be resected. Ideally, the tumors are extradural, although dura (and even brain parenchyma) can be resected.⁽¹⁴⁾

The approach from below is more variable but generally involves at least an ethmoidectomy. Most commonly, a lateral rhinotomy incision is used to allow a generous view of the

nasal vault and associated paranasal sinuses. If necessary, the ethmoidectomy can be combined with maxillectomy or orbital exenteration or the resection performed. ⁽¹⁵⁾

At the completion of the procedure, dural repair can be accomplished with temporalis fascia, fascia lata, or a local pericranial flap. In the most limited resections, the anterior cranial bone flap is replaced, and the upper and lower incisions are closed primarily. For more extensive resections, local or distant flaps may be required to reconstruct the defect, and/or surgical prostheses may be necessary. ⁽¹⁶⁾

There is an intimate anatomical proximity between neoplasms of the anterior fossa of the skull and paranasal sinuses. Thus, both structures can be considered as the epicenter of the primary site in locally advanced tumors. In addition, surgical treatment involves global knowledge of any craniofacial structure. Skin tumors when located in the inner and outer corners of the eyes, nasal wing base and external auditory canal are more aggressive and can reach the base of the skull, producing the three-dimensional defect of the face and skull that is characterized by loss of anatomical contour normal with destruction of anatomical structures, such as skin, subcutaneous tissue, muscles, bones and dura mater. ⁽⁸⁾ Such locally advanced lesions constitute a serious reality because of the precarious conditions of the health system and the socioeconomic situation of population.

The combined access facial skull for the resection of advanced tumors invading the anterior cranial fossa, cribriform plateau and paranasal sinuses and the multiprofessional performance involving head and neck surgery, neurosurgery and microsurgery became a therapeutic alternative allowing the treatment of previously considered cases inoperable. ⁽⁸⁾

The vast majority of tumors involving the paranasal sinuses and skull base show advanced stage tumors demonstrating a high potential for local aggression, allying or not with metastatic potential, justifying the radicality of the resections. Endoscopic resections are not good options for these cases. Combined craniofacial access and monobloc resection of these tumors is the treatment of choice for advanced tumors affecting the anterior cranial fossa, fulfilling the criteria for oncological cure. A multicenter study found the high prevalence of atypical facial accesses due to locally advanced skin tumors. In this study, the most commonly employed facial approach was atypical, tailored to encompass all compromised skin and underlying tissues, in 55.5% of cases, followed by the Weber-Ferguson approach, with all its variations (e.g., nasal swing) in 17.8%, lateral rhinotomy in 12.2%, facial translocation in 3.8%, and other techniques in 7.7%. ⁽¹⁷⁾ **(Figure 7-4)**

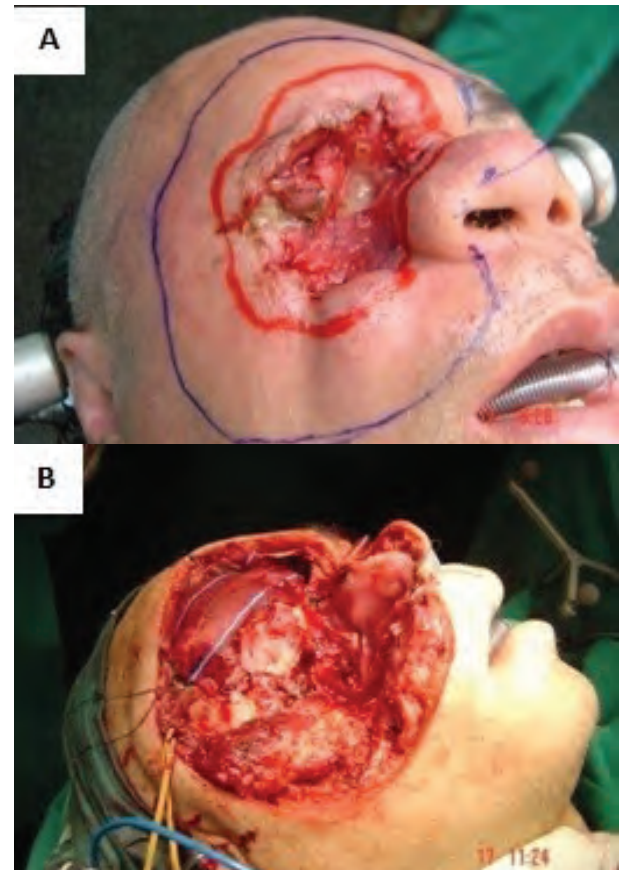


Figure 7-4. Atypical Facial Access. A) Frontal view; B) After craniofacial in block resection of the tumor.

The method for repairing the defects resulting from these resections was, until the development of microsurgery, a limiting factor for the resection of these tumors. The advantages of the microsurgery flaps, which are highlighted below, have provided the diminishing use of the pedicled local or myocutaneous flaps. The characteristics of size, volume, arc of rotation, safety, post-radiotherapy effects make many of the local flaps no longer useful for extensive cranial reconstructions. For reconstructions above the zygomatic arch, pedicled myocutaneous flaps are less secure, have higher rates of partial necrosis, and are volume deficient. ⁽¹⁸⁾

Microsurgery came to offer a highly vascularized tissue of adequate dimensions, favoring a better repair of the defects, a better fight against infection and a better esthetic effect than the reconstructions with local flaps. For these reasons, microsurgical reconstruction is the first-choice method for the repair of extensive defects affecting the base of the skull. Some of the most commonly used flaps include the free flap of the rectus abdominis muscle. **(Figure 7-5)** In a study described by Galvão *et al.* ⁽¹³⁾ This flap corresponded to 93.6% of reconstructions. In extreme cases, like showed

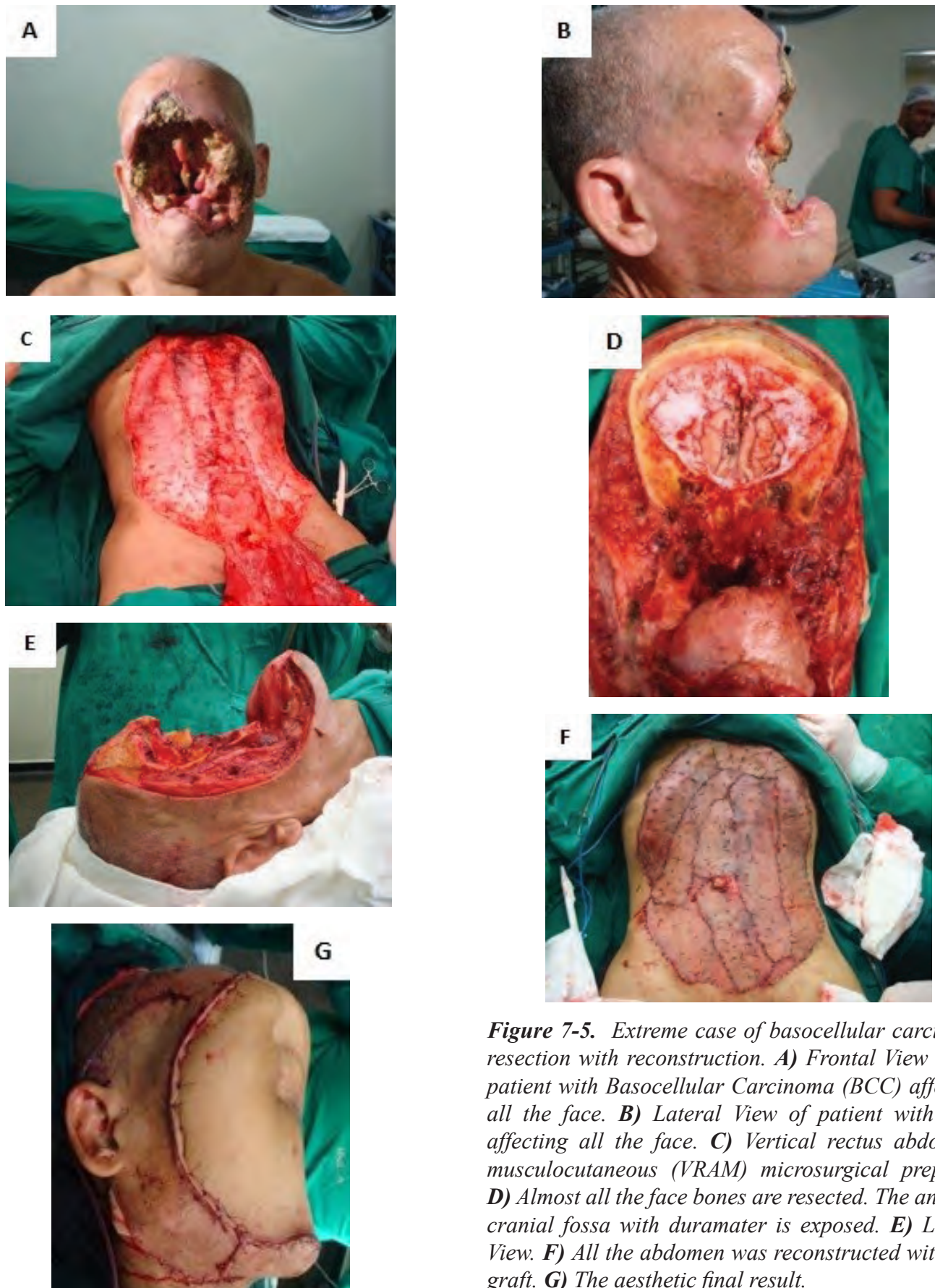


Figure 7-5. Extreme case of basocellular carcinoma resection with reconstruction. **A)** Frontal View of the patient with Basocellular Carcinoma (BCC) affecting all the face. **B)** Lateral View of patient with BCC affecting all the face. **C)** Vertical rectus abdominis musculocutaneous (VRAM) microvascular prepared. **D)** Almost all the face bones are resected. The anterior cranial fossa with duramater is exposed. **E)** Lateral View. **F)** All the abdomen was reconstructed with skin graft. **G)** The aesthetic final result.

in Figure 7-5, a bilateral microsurgery vertical rectus abdominis musculocutaneous (VRAM) flap is used to cover all the face (**Figure 7-5**. Microsurgery reconstruction for an extreme case). Chang *et al.* also confirm the preference for this type of reconstruction. ⁽¹⁹⁾

By involving components of the visceral skull, craniofacial management becomes a potentially contaminated surgery making local infections as the most common complication.

Resection of tumors that exposes the dura mater and, in some cases, the subdural space or the encephalon, has as main complications infections of the central nervous system, which in most cases are consequent to the cystic fistulas and ascending infections from the upper airways. ⁽²⁰⁾

Classic craniofacial surgery resulted from the impossibility of resection of tumors of the skull base due to unique surgical access. (**Figure 7-6**)

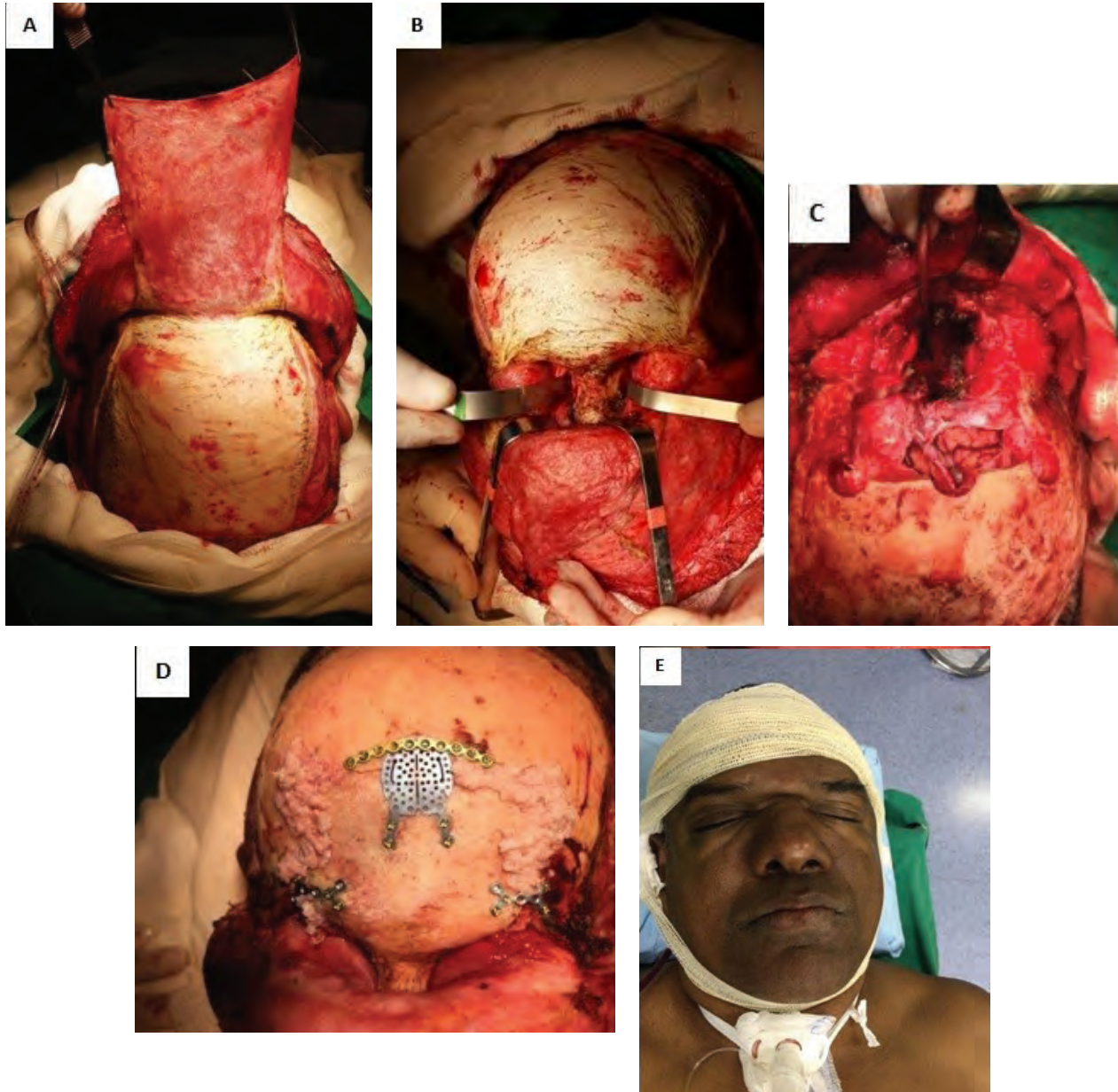


Figure 7-6. Classic craniofacial surgery. **A)** Big pericraniogaleal flap to reconstruction the skull base after the surgery; **B)** Preparation for removal of almost all frontal bone for access to the skull base; **C)** Classical craniofacial surgery. Observe that almost all the frontal bone has been removed for access. Part of the meningeal was resected due to tumor involvement; **D)** Frontal bone fixed with miniplates at the end of surgery; **E)** Final aesthetic result. Tracheostomy was done to prevent pneumoencephalus.

The success of the procedure required a wide surgical field, direct visualization of the tumor and intracranial components, making tumor removal oncologically effective according to Ketcham and Van Buren *et al.* ⁽²¹⁾ The combination of intra- and extra-cranial accesses facilitates a wide communication between the anterior fossa and the sinonasal tract, which increases the risk bone necrosis, meningitis and even liquoric fistula due to a large bifrontal osteotomy with bone resection and laceration of dura mater. Raveh in 1978 developed extended subcranial access to the base of the anterior skull to reduce complications (**Figure 7-7**. Raveh's Craniofacial Approach). This trans frontal technique allows wide access to the orbit and sinus as well as nasal fossa and paranasal sinuses. ⁽²²⁾

Farias *et al.* developed the minimally invasive subcranial

approach. (**Figure 7-8**) This technique uses only a craniotomy above the upper limit of the frontal sinus with a triangular-shaped osteotomy towards the orbit and removal of the frontonasal bone segment. ⁽²³⁾

The monobloc resection of the cribriform plateau and dissection of the dura mater is done using a surgical microscope. Pericraniogaleal flap is used for reconstruction with or without fibrin glue. ⁽²³⁾ In comparison to the classical craniofacial approach, the minimally invasive approach stands out for notable benefits such as reduction of neurological and general complications; tendency to reduce surgical time; low blood transfusion rate; shorter hospital and intensive care hospital stay; feasibility for facial tumors affecting cribriform plateau or discrete invasion of the anterior cranial fossa. ⁽²³⁾

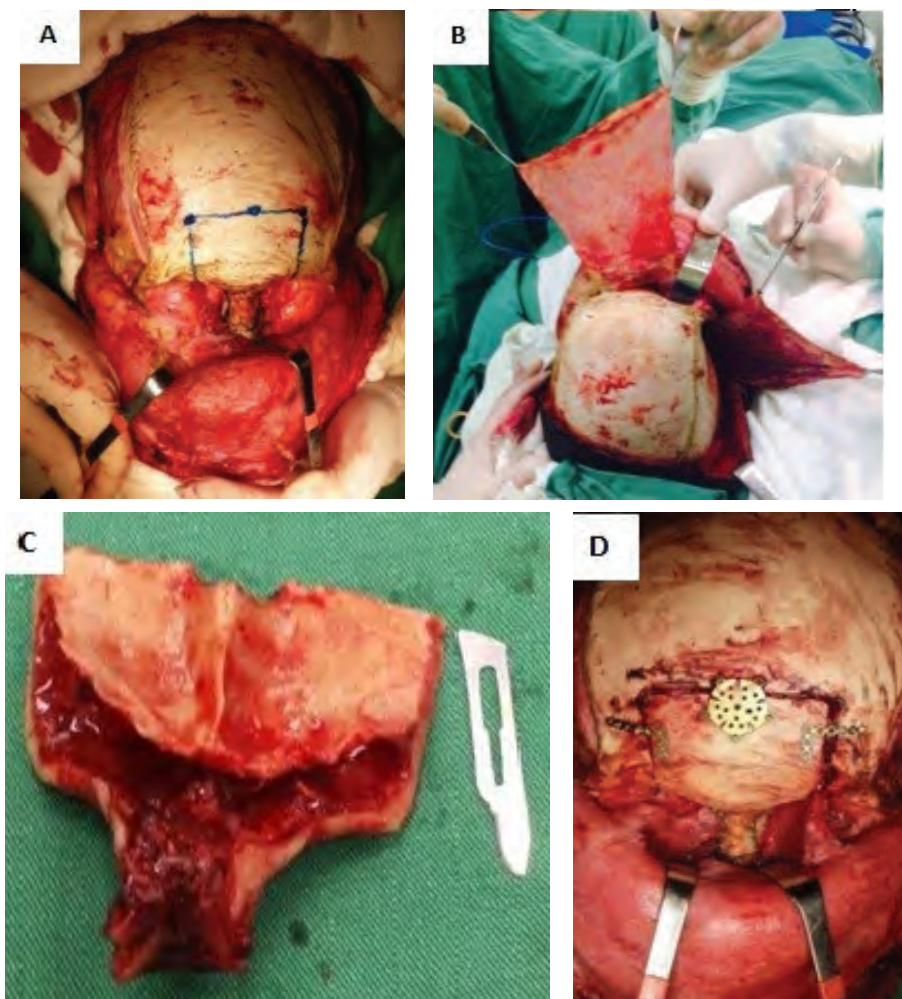


Figure 7-7. Raveh's Craniofacial Approach. **A)** Raveh craniofacial approach beginning with a bicoronal incision, exposing both orbits; **B)** Pericraniogaleal flap is necessary to make the reconstruction of the skull base after tumor remove; **C)** A minimal subfrontal approach with a resection of a fronto nasal bone flap; **D)** The fronto-nasal flap fixed with titanium microplates at the end of surgery case from Dr. Terence Farias.

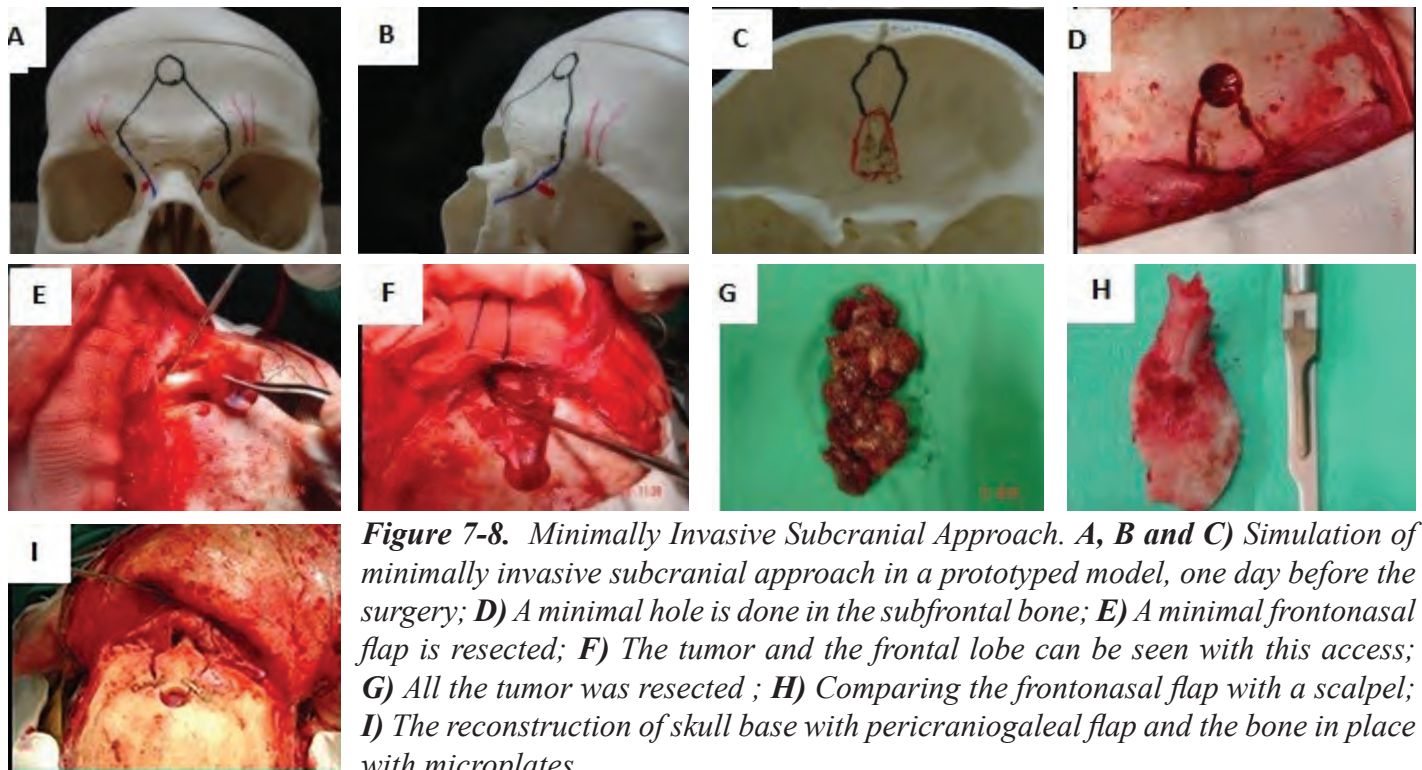


Figure 7-8. Minimally Invasive Subcranial Approach. **A, B and C)** Simulation of minimally invasive subcranial approach in a prototyped model, one day before the surgery; **D)** A minimal hole is done in the subfrontal bone; **E)** A minimal frontonasal flap is resected; **F)** The tumor and the frontal lobe can be seen with this access; **G)** All the tumor was resected ; **H)** Comparing the frontonasal flap with a scalpel; **I)** The reconstruction of skull base with pericraniogaleal flap and the bone in place with microplates.

Dias *et al.* in a study done at the National Cancer Institute of Brazil highlights several complications of craniofacial approaches and divides them into early and late complications as the **table 4** below in descending order of occurrence. ⁽²⁰⁾

Table 7-4. Distribution of Postoperative Major Complications According to Time of Occurrence	
Early complication (<14 days)	Late (> 14 days)
Cerebrospinal fluids leaks	Bone-flap failures
Alteration of neurologic status	Meningitis
Free-flap failures	Cerebral abscess
Local-flap failures	Cerebrospinal fluid leaks
Sub dural hemorrhage	Pneumonia
Pneumocephalus/ Hydrocephalus	Gastrointestinal hemorrhage
Pneumonia	
Meningitis	

Dias FL, Sá GM, Kligerman J *et al.* Complications of Anterior Craniofacial Resection. *Head & Neck*, Jan. 1999. ⁽²⁰⁾

Another study by Dias *et al.* emphasizes that staging and age were occurred of poor prognostic factors and are directly related to complications in craniofacial surgeries. Infection processes with a 50% of complication and extravasation of cerebrospinal fluid in association with meningoencephalitis was the main cause of postoperative mortality. The high incidence of dural resections with subdural space of extensive exposure may explain the main complication. ⁽²⁴⁾

Conclusion

Sinus cancer of the face has a poor prognosis. The treatment should be radical and most often multimodal associated with or not radiotherapy with or without chemotherapy is necessary. In the early stages and for small tumors endoscopic resection may be indicated. However, monoblock resection often with craniofacial access with a multidisciplinary team and elaborate reconstruction, is the gold standard of a curative treatment.

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Chapter 8

Nasopharynx Cancer

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Introduction

Nasopharyngeal cancer (NPC) is a distinct form of cancer of the upper respiratory or digestive tract in which the epidemiologic features, origin histopathology types, treatment, and prognosis are different from those associated with other malignant neoplasm of this anatomical area. It is prevalent among populations originating from southern China and their descendants who have emigrated to other parts of the world. ⁽¹⁾ Its epidemiologic features, origin histopathological types, presentation, treatment, and prognosis differ from those of malignant neoplasm occurring in other sites of the aerodigestive tract. ^(2,3) Contemporary major challenges in the treatment of NPC, particularly in its advanced stages, are how to improve locoregional control and prevent the development of distant metastases. ^(4,5)

Etiopathogenesis

Although tobacco and alcohol consumption remain the most important etiologic factors, viral exposure (e.g., Epstein-Barr virus [EBV]) is associated to NPC tumors and have a unique histopathological composition; they are undifferentiated carcinomas with a prominent lymphocytic infiltrate. The interaction between cancer cells and lymphocytes is thought to contribute to the propagation of malignancy. ⁽⁶⁾

Epstein-Barr virus (EBV) has been implicated as a causative agent in multiple cancers, including nasopharyngeal cancer. EBV infection is acquired subclinically in most people. The virus is found in the tumor cells of the nasopharynx. The exact role of EBV in cancer causation is not clearly

understood, but recent evidence points to the carcinogenic properties of herpes viruses. ⁽⁷⁾ EBV-related peptides are capable of inducing malignant transformation *in vitro* cell lines. Preliminary data suggest that the latent membrane protein expression in EBV-infected cells might protect the cells from apoptosis. Familial clustering of cases indicates the potential role for genetic factors. ⁽⁸⁾ Major histocompatibility complex H2 locus antigen, BW46 (Singapore antigen), and B17 have been implicated. The role of environmental factors (especially dietary habits) has been suggested. The DNA adducts of nitrosamines in salted fish have been shown to be carcinogenic. ⁽⁸⁾ In addition, the possible roles of occupational exposure to wood and wood dust have been implicated. Exposure to formaldehyde vapors also was suggested as etiologic in some studies. ⁽⁸⁾

The workup for NPC may include EBV testing of both the tumor itself and the blood, particularly in the presence of nonkeratinizing and undifferentiated histology. ⁽⁹⁻¹¹⁾ Testing methods for detection of EBV in the tumor include *in situ* hybridization for EBV-encoded RN and immunohistochemical staining for LMP1 (latent membrane protein 1). The former tends to be a more sensitive testing method for carcinomas, relative to LMP1 immunohistochemical staining. ⁽¹²⁾ PCR may be used to evaluate EBV DNA load in plasma. Sensitivity and specificity values range from 53% to 96% and 88% to 100%, respectively ⁽¹³⁾ testing for plasma EBV DNA has been used in select centers as a means of residual disease monitoring. For patients with locoregional disease, studies have shown that high initial levels of plasma EBV DNA, or persistently elevated levels near or at the end of radiotherapy (RT), are associated with a significantly poorer outcome following RT or chemoradiotherapy (CRT). ⁽¹⁴⁾

Diagnosis

In addition, because of the rich lymphatic network of the nasopharynx, regional lymph node metastases occur early and often, and a neck mass may be the presenting symptom in many patients.

As with the nasopharynx, regional lymph node metastases are quite common and may be the first manifestation of the disease. Nodal metastases occur in a predictable and sequential manner, with lymph nodes in the anterior triangle of the neck (levels I to IV) being at highest risk. ⁽¹⁵⁾

Patients with lesions of the nasopharynx present with symptoms of nasal obstruction, epistaxis, otalgia, unilateral or bilateral middle ear effusion, or cranial neuropathy as a result of the location and extent of the primary tumor. On the other hand, cervical lymph node metastases may be the first and only clinical manifestation in patients with squamous cell carcinoma of the nasopharynx. Clinical diagnosis requires adequate evaluation of the primary tumor through flexible or rigid nasal endoscopy and examination of the nasopharynx through the oral cavity with a 30-degree and 70-degree rigid telescope if the nasopharynx is obstructed. Tissue diagnosis of exophytic mucosal lesions can be established easily by a transnasal or peroral biopsy under topical anesthesia. ⁽¹⁶⁾

Computed tomography (CT) and magnetic resonance imaging (MRI) is essential for accurate assessment of the extent of the lesion and staging of malignant tumors. Radiographic imaging is crucial for delineating the third dimension of the tumor, whereas clinical examination is more reliable for assessment of its surface extent. Although MRI is superior for assessment of the soft tissue extent of the tumor, its utility is limited by motion artifact if the patient cannot control swallowing during the examination. ⁽¹⁷⁾

Pathological

Nasopharyngeal squamous cell carcinoma is classified by the World Health Organization into basaloid, keratinizing, and nonkeratinizing types. ⁽¹⁸⁾ Nonkeratinizing carcinoma is further subclassified into differentiated and undifferentiated subtypes. The undifferentiated subtype of nonkeratinizing carcinoma is particularly common in Southeast Asia, where it represents 15% to 20% of all cancers and is thought to be associated with EBV infection. EBV can be detected in the tumor cells and B lymphocytes of 75% to 100% of the undifferentiated type of nonkeratinizing carcinoma but

rarely in keratinizing NPC. Moreover, 85% of patients with undifferentiated nonkeratinizing NPC also have antibodies to EBV and serum immunoglobulin A anti-EBV. ⁽¹⁸⁾

Staging

Nasopharyngeal carcinoma often presents with early lymphatic spread. The retropharyngeal nodes and the cervical nodes (both jugular and spinal accessory chains) are involved, often bilaterally. The lymphatic spread in NPC follows a predictable and orderly pattern from upper to lower neck; “skip” metastasis is rare. ^(19,20)

Staging for primary tumors of the nasopharynx depends on local extension to the adjacent soft tissues (parapharyngeal space) and bone (skull base). In clinical evaluation, the maximum dimension (in any direction) of the nodal mass, the laterality, and the lowest level of neck involvement should be assessed. Midline nodes are considered ipsilateral nodes. Nodal size larger than 6 cm in greatest dimension and/or extension below the caudal border of the cricoid cartilage is associated with the worst prognosis. Nasopharyngeal carcinoma is notorious for a high risk of distant metastasis. The most common sites include lung, bone, liver and distant lymph nodes. Involvement of lymph nodes below the clavicle (including mediastinum, infraclavicular region, axilla, or groin) is considered as distant metastases. ⁽²¹⁾

A large majority of nasopharyngeal cancers are positive for Epstein-Barr virus (EBV) by Epstein-Barr-encoded RNA (EBER). ⁽²²⁾ Consequently, in the proper clinical context, demonstrating the presence of either EBV establish an anatomic site of origin. ⁽²²⁾

In the 8th Edition there are two changes in T classifications relating to anatomic markers rather than depth of invasion (DOI). The previous T4 criteria “masticator space” and “infratemporal fossa” were used as synonyms, but their anatomic descriptions differ, sowing confusion among clinicians. These terms will now be replaced by specific description of soft-tissue involvement to avoid ambiguity. And, adjacent muscle involvement (including medial pterygoid, lateral pterygoid, and prevertebral muscles) will now be “down-staged” to T2 based on a recent analysis, showing then to have a more favorable outcome using current treatment. ⁽²¹⁾ In addition, neck classification of nasopharynx changed too. The iconic, traditional description of the supraclavicular fossa that was unique to this will be replaced by contemporary definitions used for other head and neck sites and more suited to axial cross-sectional imaging. In addition, low neck involvement and >6cm size

will be merged into a single N3 designation (formerly N3a and N3b), and T4 and N3 will both designate IVa (formerly IVa and IVb) in stage grouping. ⁽²¹⁾

Treatment

Nasopharyngeal squamous cell carcinomas, by virtue of their anatomic location and relative inaccessibility for a curative surgical resection, generally are not managed initially by surgical intervention. In addition, these tumors are highly responsive to radiotherapy and chemotherapy. Thus, at this time a combination of chemotherapy and radiotherapy remains the choice of initial treatment. ⁽²⁴⁾ This highly treatable disease has shown an excellent response to radiotherapy (RT) and chemotherapy.

The optimum treatment approach depends on the stage of the disease. T1 and T2 stages of the disease are treated with radiotherapy; local control rates range from 80% to 90%. ^(23,24) (The radiotherapy can be delivered via external beam or through a combination of external beam and intracavitary sources. For locally advanced nasopharyngeal carcinoma (i.e., T3, T4, or node-positive disease), radiotherapy alone is not adequate.

A combination of chemotherapy with radiation is the optimal way to treat these high-risk patients. ⁽²⁴⁾ Cisplatin-based chemotherapy should be used. Concurrent chemoradiotherapy followed by adjuvant chemotherapy is the current standard of care. In patients with recurrent and/or metastatic disease, adequate chemotherapy and other palliative treatments result in 15% to 20% long-term survival and may be curative. Al Sarraf *et al.* reported the first randomized trial to demonstrate an overall survival benefit with the use of concurrent chemoradiotherapy followed by adjuvant chemotherapy as compared with radiotherapy alone. ⁽²⁴⁾ The use of concurrent high-dose cisplatin and full-dose radiotherapy has produced improved results in patients with advanced nasopharyngeal cancers and other unresectable head and neck cancers ^(25,26) without a substantial increase in local toxicity. Al Sarraf clearly demonstrates that in patients with advanced nasopharyngeal cancers, the addition of high-dose cisplatin to radiotherapy simultaneously is of benefit. Due to the high incidence of late systemic recurrences in these patients, additional effective chemotherapy is needed to improve further results of the combined modality treatment in advanced nasopharyngeal cancer. ⁽²⁷⁾

While brachytherapy has been the most common procedure for dose boosting to the primary tumor site during the 2-dimensional radiation therapy, but in the 3-dimensional radiation therapy era, the modern IMRT technique may use the simultaneous integrated boost technique to serve a similar purpose. Intranasal insertion, i.e. intracavitary brachytherapy, is the main brachytherapy approach because it is relatively easy to use. ^(28,29) Unfortunately, intracavitary brachytherapy is not as effective for treatment of deeply infiltrating tumors such as those of T4 disease with intracranial extension because of the rapid dose fall-off as distance from the radioactive source increases. ^(30,31)

Since IMRT has become the standard treatment for NPC and can achieve excellent local control of the primary tumor, intracavitary brachytherapy as a boost treatment following external-beam irradiation has dramatically declined. ⁽³²⁻³⁴⁾

Re-irradiation, either as adjuvant treatment for patients with high-risk features (positive margins and/or extracapsular extension) at the time of salvage surgery, or definitive re-irradiation often combined with concurrent chemotherapy is a reasonable salvage option for unresectable locoregional recurrence. IMRT remains one of the most effective and common methods used for salvaging recurrences by providing dose coverage of the recurrent tumor while sparing surrounding previously irradiated tissues. ⁽³⁵⁾ The time interval since prior irradiation is an important prognostic factor of re-irradiation failure. In RTOG 9610, the 1-year survival rate for patients re-irradiated within 3 years of prior RT was only 35%. However, it was 48% for patients re-irradiated more than 3 years later from prior RT. ⁽³⁶⁻³⁹⁾

Surgery has a minimal role in the management of residual disease that persists after radiation and chemotherapy. The role of newer agents, new combinations, and radiosensitizing chemotherapeutic agents must be defined in future trials. ⁽³⁷⁾ Surgical intervention may be considered in a select group of patients for whom previous chemoradiation therapy has failed and who have a localized, well-defined, residual or recurrent cancer. ⁽³⁷⁾ Similarly, neck dissection for regional metastases is considered only in the setting of residual or recurrent nodal metastases that are not responsive to nonsurgical treatment. ⁽³⁸⁾ Surgery is the preferable treatment option for regional lymph node failure in patients treated primarily with combined chemoradiation. ⁽³⁹⁾ Its use in local recurrences of the nasopharynx itself often needs demanding procedures. Surgery is especially challenging in

locally advanced lesions because of the difficult exposure of this region and flawed with a high risk of functional deficits. ⁽⁴⁰⁾ An approach to expose the nasopharynx was described by William Wei in 1991. The maxilla, severed from its bony connections, is swung laterally to provide exposure of the nasopharynx. ⁽⁴¹⁾

Farias *et al.* reported 173 cases with newly diagnosed NPC were treated at Brazilian National Cancer Institute. ⁽⁴²⁾ Clinical records and radiographic studies of the patients were retrospectively reviewed. Documented data of the initial resenting symptoms, head and neck examination, radiotherapy protocols, chemotherapy (CT) treatment regimens, and surgical techniques and approaches were analyzed. There were 136 male (78.6%) and 37 female (21.4%) patients median age, 49 years most (71.1%) of them were of white race. Eighty-seven (50.3%) of these patients had a history of tobacco consumption, and 77 (44.5%) had a history of alcohol consumption.

One hundred twenty-nine patients (74.6%) were treated with RT and 44 underwent CCRT (Cisplatina plus 5-fluoracil). 57 patients (33%) had local residual disease or recurrence of their tumors, and 27 (15.6%) had regional nodal residual disease or recurrence of their metastases. Distant metastasis was observed in 34 patients (Bone > Lung > Brain). The five year disease specific survival rate for the 173 patients was 32.3%, and the five year disease specific survival rates for the groups of patients according to their stages were 100% for stage I, 85.7% for stage IIa, 54.5% for stage IIb, 30.4% for stage III, 25% for stage IVa, and 25% for stage IVb. The prognostic association of stage with the outcome of patients in our study was statistically significant. ⁽⁴²⁾ The prognostic factors associated with an adverse effect on locoregional control of disease and on disease-specific survival included advanced stage, invasion of surrounding bony structures, and age older than 40 years.

To assess the prognostic association of each therapeutic modality (RT x CCRT) with outcome, we compared the groups according to their 5-year disease specific survival rates. The prognostic factors associated with an adverse effect on locoregional control of disease and on disease-specific survival included advanced stage, invasion of surrounding bony structures, and age older than 40 years. The difference was statistically significant (RT group, 2.5% and CCRT group, 61.4%). A comparison between the therapeutic groups is shown in **Figure 8-1**. ⁽⁴²⁾

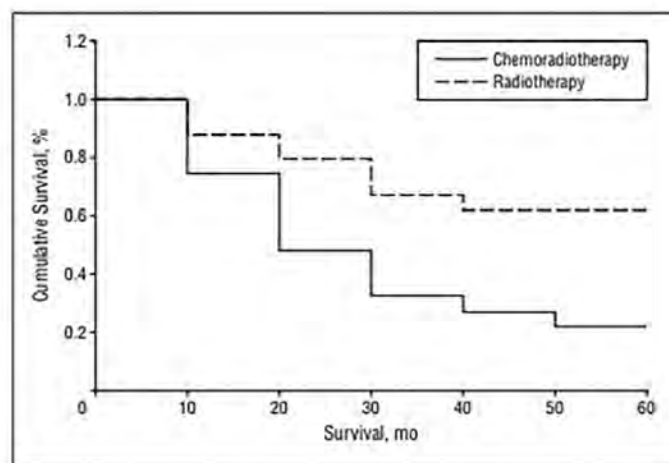


Figure 8-1. Comparison of 5-years disease specific survival between the therapeutic groups in Brazilian NCI (National Cancer Institute).

Conclusion

Nasopharyngeal carcinoma usually runs asymptotically for long periods. In most cases, the diagnosis is made based on locoregional advanced disease symptoms, such as cranial nerve involvement or cervical nodes metastasis. Nasopharyngeal carcinomas are sensitive to RT and CT. The RT and CT sensitivity of these tumors and the difficulties and complexity of current surgical approaches have led to the conservative management of NPC, with surgical therapy left for salvage of residual or recurrent locoregional disease. Concurrent chemoradiotherapy followed by adjuvant chemotherapy is the current standard of care. The prognostic factors associated with an adverse effect on locoregional control of disease and on disease-specific survival included advanced stage, invasion of surrounding bony structures, and age older than 40 years.

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Chapter 9

Oropharynx Cancer

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Oropharynx Cancer

Since 1990, the incidence of cancers of the tonsil and tongue base associated with HR-HPV has risen at an alarming 5% per year in the United States and elsewhere. ^(1,2) HPV types 16 and 18 are the most commonly detected, transcriptionally active HR-HPV types in head and neck cancer. ⁽²⁾

Demographically, HR-HPV-associated oropharyngeal squamous cell carcinoma (OSCC) represents a novel disease that occurs more often in younger, healthier individuals with little or no tobacco exposure. ⁽¹⁾ The entity is highly responsive to treatment and carries an excellent prognosis. Therefore, a new staging system was needed for HR-HPV OSCC. Immunohistochemistry for overexpression of the tumor suppressor protein p16 (cyclin-dependent kinase 2A) is an established, robust biomarker for HPV-mediated carcinogenesis; it is also an independent positive prognosticator in the context of OPC. ^(3,4) Specifically, the cutoff point for p16 overexpression is diffuse ($\geq 75\%$) tumor expression, with at least moderate (12/3) staining intensity. This coincides with the usual staining pattern seen in HR-HPV-associated OSCC. ⁽⁵⁾

T categories in both p16-positive, HR-HPV-associated OSCC and p16-negative, non-HR-HPV-associated OSCC were equally valid from a prognostic standpoint and thus remain the same with 2 exceptions: the p16-positive classification includes no carcinoma *in situ* (Tis) (because of the nonaggressive pattern of invasive of p16-positive OSCC and the lack of a distinct basement membrane in the epithelium of Waldeyer ring), and the T4b category has been removed from p16-positive OSCC (because the curves of the T4a and T4b categories proved indistinguishable). 2A variety of treatment approaches for p16-positive, HR-

HPV-associated OSCC are currently used. The National Comprehensive Cancer Network Guidelines consider radiation-based or surgically based treatment equally acceptable as first line therapy. ⁽⁶⁾

Clinically involved lymph nodes, whether one or multiple, as long as they were ipsilateral and less than 6 cm in size, had similar impact on survival (similar hazard consistency) and thus are included in the same N category: N1. Survival with clinically palpable and/or radiographically evident, bilateral or contralateral lymph nodes was distinguishable with a worse outcome than N1. Therefore, contralateral or bilateral lymph nodes are classified as N2. Lymph nodes greater than 6 cm foretold the worst survival from regional disease and thus warranted the highest N category: N3. This represents a significant change from the non-HR-HPV-associated (p16-negative) OPC N category. ⁽⁷⁾

The status of the regional lymph nodes in head and neck cancer has tremendous prognostic significance, so the cervical lymph nodes must be assessed for each patient. ENE has been added as a prognostic variable for regional lymph node metastases in addition to the number and size of metastatic lymph nodes. ⁽⁷⁾ Evidence has existed for decades that extranodal extension ENE profoundly affects prognosis for head and neck cancers, with the recently recognized exception of p16-positive, HR-HPV-associated OSCC. ⁽⁸⁻¹⁰⁾

Radiological evidence alone may be supportive but is not sufficient. Therefore, for clinical staging, only unambiguous ENE, as determined by physical examination (invasion of skin, infiltration of musculature/dense tethering to adjacent structures, or dysfunction of a cranial nerve, the brachial plexus, the sympathetic trunk, or the phrenic nerve) and

supported by radiological evidence, should be present to assign a status of ENE-positive. ⁽¹¹⁾

Pathological ENE is defined as extension of metastatic carcinoma from within a lymph node through the fibrous capsule and into the surrounding connective tissue, regardless of the presence of stromal reaction. ⁽¹¹⁾

This is an important trend clinically as HPV positive is associated with a better prognosis and treatment outcome. ^(12,13) In the past, the management of OSCC has largely been guided by treatments that minimized functional morbidities. Radiation/chemoradiation (RT/CRT) was often preferred because historically, surgical intervention involved open *en bloc* resection of the tumor with free flap reconstruction, resulting in significant compromise of surrounding structures and ultimately function. However, RT/CRT has been associated with significant acute and long term toxicities and decreased quality of life. ^(14,15)

Despite these limitations, transoral laser microsurgery (TLM) offers potential advantages over open surgery including shorter recovery time, fewer complications and better functional outcomes. ^(16,17) Similarly, preliminary studies have demonstrated TLM to have improved functional outcomes compared to RT/CRT, particularly with respect to swallowing function. ^(18,19) Increasing evidence supports the use of transoral surgery as an effective, minimally invasive strategy for the treatment of OSCC. Currently, two transoral treatment modalities exist, TLM and transoral robotic surgery (TORS). Both transoral approaches have demonstrated excellent local control and overall survival for the treatment of primary OSCC, while minimizing functional compromise. ⁽²⁰⁻²²⁾

Recent studies have also demonstrated TLM and TORS to be effective as salvage therapy for recurrences in previous RT/CRT failures. ^(23,24) This current study adds to the growing body of evidence, demonstrating TLM to have high rates of local control and overall survival for both primary and recurrent oropharyngeal cancers with excellent functional outcomes. There was no recurrence in patients with stage I/II primary disease who received TLM monotherapy. Although it is difficult to draw conclusions from small numbers, this study provides further evidence for the benefit of TLM as a single treatment modality for early disease and the potential benefit of postoperative adjuvant therapy in select patients with advanced disease. Previous studies have demonstrated HPV positive OSCCs to have a better prognosis and treatment outcome compared to HPV negative disease. ^(12,13)

The optimal treatment strategy for oropharyngeal carcinoma is highly debated. However, growing evidence supports the use of TLM as a safe and effective first-line treatment modality for OSCCs. ⁽²⁵⁾

Transoral surgery for oropharyngeal carcinoma is not a new procedure. Holsinger and Laccourreye pointed out that Huet had described a transoral procedure in the French literature in 1951 for tonsil cancer, and they reported on 191 patients who had undergone this procedure during the period from 1980 to 2000. ⁽²⁶⁾ As the location of the tumor proceeds distally in the oropharynx to the base of tongue (BOT). For centuries, successful surgery has depended on the fundamentals of wide exposure and control of bleeding with hand-held instruments. This is why BOT tumors were treated surgically with mandibulotomy; the mandible precluded the surgeon from seeing the BOT directly through the mouth, and most surgeons could not get their hand in the mouth to manipulate the tumor and to control the bleeding during removal. ⁽²⁷⁾ (**Figure 9-1**)

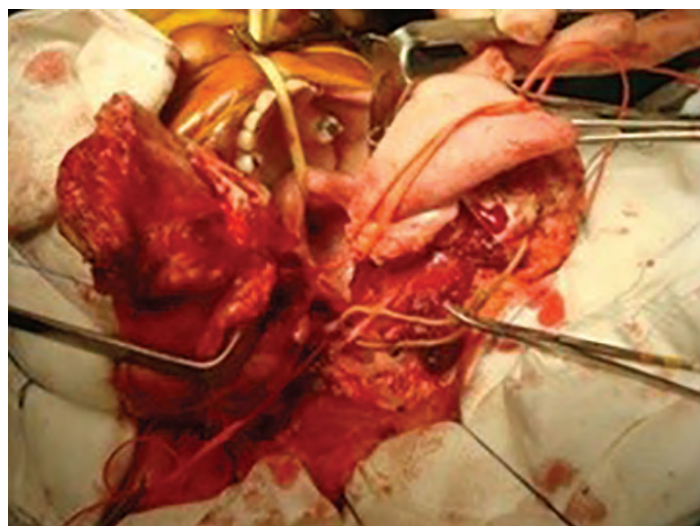


Figure 9-1. Mandibulotomy to treat BOT tumor.

While the majority of the world was dealing with this anatomical challenge by discarding mandibulotomy as overly morbid and transitioning to primary chemoradiation therapy (CRT) for BOT SCCA, Wolfgang Steiner in Goettingen, Germany, is credited with adopting an alternative approach transoral laser microsurgery (TLM). ⁽²⁷⁾ Sometimes, the surgery needs to split and swirls the repartible to take access of BOT.

These challenges were the inspiration for adopting robotic surgery to transoral surgery of the OP. Surgical robots were designed with diverse goals of enabling remote telesurgery and elimination of human factors such as tremor, but the DaVinci surgical robot gained its strongest foothold primarily in the minimal access surgical market. ^(28,29) (Figures 9-2 and 9-3)



Figure 9-2. TORS to treat BOT tumor.



Figure 9-3. Surgeon on robotic console.

In 2005, Neil Hockstein, then an otolaryngology resident at the University of Pennsylvania, took on this challenge of adapting the configuration of the robot to “fit” the transoral approach. He described the feasibility of transoral robotic surgery using the camera and two of the instrument arms of the DaVinci robot first in a robot, then in a cadaver, and finally in an animal model. ^(30,31) The field was set for clinical trials of transoral robotic surgery, and they followed quickly.

Greg Weinstein and Bert O’Malley from the University of Pennsylvania published the earliest series of transoral robotic surgery outcomes. ^(32,33) Tumors of the oropharynx, particularly the BOT, are the leading targets of TORS, primarily for anatomic reasons. The dimensions of the robotic arms require that the mouth be held open and the tumor exposed through with sizeable retractors. (Figure 9-2)

Tumors of the tonsil are easy to see, but they are directly in the line of sight of the surgeon through the open mouth, so they do not necessarily benefit from the angled telescope and the wristed instrument of the robot. Tumors of the larynx and hypopharynx are prime candidates for transoral surgery, but they are so far inferior to the oral opening and around the curvature of the tongue base that access with the currently available robot can be difficult or impossible. The base of the tongue and supraglottis can nearly always be accessed with the robot, and the angled telescopes, wide field of view, and wristed instruments do confer a surgical advantage in this area. ^(32,33)

In 2009, the Food and Drug Administration granted approval for TORS for select malignant tumors of the “throat and voice box.” Since this approval, the number of TORS procedures for OP SCCA has steadily increased, and most major centers treating head-and-neck cancer have surgeons performing TORS. ⁽²⁸⁾

Both multi-institutional series and series evaluating long-term and functional results of TORS appear now in the literature. ^(34,35) The results of the major transoral laser microsurgery and TORS studies that report data on 2-year and longer survival are shown in **Table 9-1.** ⁽²⁸⁾ The functional results of these studies are shown in **Table 9-2.** ⁽²⁸⁾

These studies follow the similar treatment pattern of TLMS: transoral removal of the primary with negative margins; unilateral or bilateral neck dissection as indicated; and adjuvant radiation therapy or CRT as indicated by neck disease.

Table 9-1. Oncologic results of TLMS and TORS

Authors (reference)	Method	Patients, N (% HPV+)	T3/T4 (%)	Stage 3,4 (%)	Postop RT/CRT (%)	LC	OC	OS	DSS
Steiner <i>et al</i> ⁽⁶⁾	TLMS, BOT	48 (?)	73%	94%	23 (48%)	85%	73%	52%	73%
Haughey <i>et al</i> ⁽⁹⁾	TLMS, OP	204 (74-90%)	34%	100%	74%	93%	87%	78%	84%
Grant <i>et al</i> ⁽¹⁰⁾	TLMS, OP	69 (?)	20%	64%	0 %	94%	82%	86%	86%
Moore <i>et al</i> ⁽¹⁷⁾	TORS, OP	66 (89%)	18%	88%	83%	97%	94%	92%	95%
White <i>et al</i> ⁽¹⁶⁾	TORS	89 (?)	20%	73%	63%	97%	91%	86%	86%
Weinstein <i>et al</i> ⁽²³⁾	TORS, OP	47 (74%)	23%	100%	89%	98%	85%	85%	90%

Abbreviations: CRT = chemoradiation therapy; DSS = disease-specific survival; LC = local control; OC = overall control; OP = oropharyngeal; OS = overall survival; RT = radiation therapy; TLMS = transoral laser microsurgery; TORS = transoral robotic surgery. The advanced T stage and overall stage and the percentage of the patient series that was HPV+ is shown (if reported).

Table 9-2. Functional results of TLMS and TORS

Authors (reference)	Method	Patients, N (% HPV+)	T3/T4 (%)	Stage 3,4 (%)	Normalcy of Diet (%)	PEG tube at 1 year (%)
Steiner <i>et al</i> ⁽⁶⁾	TLMS, BOT	48 (?)	73%	94%	85%	6%
Haughey <i>et al</i> ⁽⁹⁾	TLMS, OP	204 (74-90%)	34%	100%	87%	19%
Grant <i>et al</i> ⁽¹⁰⁾	TLMS, OP	69 (?)	20%	64%	100 %	0%
Moore <i>et al</i> ⁽¹⁷⁾	TORS, OP	66 (89%)	18%	88%	97%	3%
White <i>et al</i> ⁽¹⁶⁾	TORS	89 (?)	20%	73%	100%	0%
Weinstein <i>et al</i> ⁽²³⁾	TORS, OP	47 (74%)	22%	86%	97%	2.4%

Abbreviations: BOT = base of tongue; OP = oropharyngeal; TLMS = transoral laser microsurgery; TORS = transoral robotic surgery.

Moore *et al.* demonstrated a 3-year local control rate of 97% and a disease-specific survival rate of 95% in 66 patients with advanced-stage OP SCCA with TORS in this fashion. ⁽³⁵⁾ The indications for TORS for OP SCCA have been delineated, and, more importantly the absolute and relative contraindications (inability to expose the tumor, tumor invasion of the mandible or base of skull, deep extrinsic tongue muscle and lateral neck structures, and tumor involvement of greater than 50% of the tongue or significant laryngeal invasion) have been elucidated. The local control (97%), regional control (94%), long-term gastrostomy tube dependence (4.5%) and tracheostomy tube dependence (1.5%) and functional results are indistinguishable from those associated with other transoral surgery modalities. ⁽³⁵⁾ TORS for salvage surgery after previous nonoperative therapy can be performed in selected patients, but the local control and survival are not as good as in primary treatment. Finally, HPV status is playing a critical role in treatment outcomes. ⁽²⁸⁾

Gomes Neto *et al.*, studied at the Brazilian National Cancer Institute - Rio de Janeiro (INCA), 109 patients altogether. Among these, 65 (59.63%) underwent TORS as their first-line treatment; on the other hand, 44 (40.37%) presented recurring tumors and the surgery was a salvage procedure. ⁽³⁶⁾

The patients submitted to transoral robotic surgery as first-line treatment presented overall survival of 86.2% in 24 months, and of 74.2% in 36 months with a mean survival estimate of 48.9 months. The progression-free survival for the same period was 88.5% in 24 months and 86.0% in 36 months, with a mean progression-free survival of 48.1 months. We have also assessed specific survival, which was 91.5% in 24 months and 83.1% in 36 months, with a mean survival estimate of 48.6 months for these patients. Considering patients submitted to robotic surgery as salvage treatment, we found an overall survival of 68.4% in 24 months and 23.9% in 36 years, with the mean estimate of overall survival of 28.2 months. Disease-free survival in 24

months was of 49.2%, and in 36 months, of 32.1% with an estimate of disease-free survival of 23.9 months. ⁽³⁶⁾

The characteristics of patients submitted to TORS at INCA in this period are similar to the ones found in the literature, such as male patients with average age of 61 years old, at stages T1 and T2, with tumors located in the oropharyngeal cavity, especially at the tonsil and base of tongue. ⁽³⁷⁾ The vast majority of histopathological tumor types was squamous cell carcinoma, at a proportion comparable to the literatures. ⁽³⁸⁾

Transoral robotic surgery by means of the da Vinci system is oncologically safe, and it is possible to safely obtain clean margins both for treatment of oropharyngeal and supraglottal larynx tumors. All patients submitted to transoral robotic surgery had the speech and swallowing abilities rehabilitated in the long term, which, added to the low rate of relevant complications in our study, indicates low morbidity of the procedure. The absence of reportable deaths associated with the surgery is also relevant, as well as the absence of significant bleeding not clinically controllable. ⁽³⁶⁾

To definitively answer the question of which therapy and how much ideally treats patients with OP SCCA, we need to enroll patients in phase III clinical trials. These trials need to compare a transoral surgery arm with and without RT to a primary nonoperative therapy with RT or chemoradiotherapy with surgical salvage. We need to analyze not only locoregional recurrence and survival but long-term swallowing, quality of life, morbidity, and cost of therapy.

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Chapter 10

Oral Cavity Cancer

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Introduction

Oral cavity cancer is the sixth leading cause of cancer worldwide. In the United States alone, there are over 21,500 oral carcinomas diagnosed each year, and 6,000 Americans die of oral cancer each year. Ninety percent of oral malignancies are squamous cell carcinomas. However, the treatment of some other oral malignancies, like sarcoma and minor salivary gland carcinoma, is also primarily surgical excision, and the surgical principles are applicable to the treatment of these other tumors as well. ⁽¹⁾

Etiopatogenic

The etiology of oral cancer is exposure to carcinogens in tobacco and the tumor-promoting effects of alcohol. Tobacco smoke and alcohol are synergistic in their carcinogenic effects in the oral cavity. ⁽²⁾

The relative risk of oral cancer for heavy smokers is 7 times that of nonsmokers. The risk for heavy drinkers is 6 times that of nondrinkers. Tobacco is the most important factor, and more than 90% of patients have a history of smoking. Tobacco contains many carcinogenic molecules such as polycyclic hydrocarbons and nitrosamines. A clear dose-response relationship has been demonstrated between tobacco exposure and oral cancer. Other possible mechanisms include the ability of alcohol to impair macrophage activity and reduce T lymphocyte numbers. Alcohol may also reduce the activity of DNA repair enzymes, resulting in increased chromosomal damage. ⁽²⁾

Diagnosis

The diagnostic evaluation of a patient with oral carcinoma consists of the history and the physical examination, histopathologic tissue diagnosis, and imaging when indicated. The clinical history begins with the present illness and includes the duration and location of symptoms such as non-healing ulcer, mass in the oral cavity or neck, pain, bleeding, and any symptoms of cranial nerve deficits. The social history impacts strongly on the patient's ability to comply with and tolerate treatment and rehabilitation programs, and these issues are resolved during the treatment planning phase. The family history reflects any familial tendencies toward malignant disease and completes the historical data. A complete examination of the head and neck is performed to assess the precise location and extent of the primary tumor, **(Figure 10-1)** identify regionally metastatic disease and to rule out multiple primary malignancies. Grossly, the earliest cancers may present as nonulcerous white or red patches. ⁽³⁾

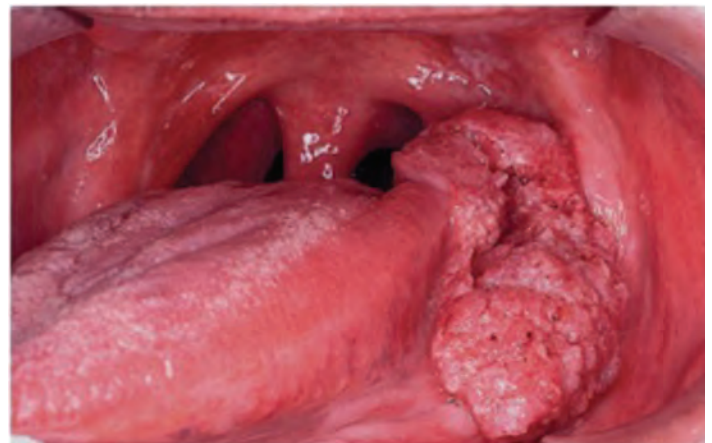


Figure 10-1. Extent of the tumor in the retromolar gingival.

Trismus suggests ominous pterygoid and masticator space involvement. The condition of dentition should be noted as tumors may, as the first sign, displace or loosen teeth. ⁽⁴⁾ **(Figure 10-2)**



Figure 10-2. *A deeply invasive endophytic squamous cell carcinoma of the tongue and poor dentition condition.*

The distance from the tumor to the mandible and the mobility of the lesion in relation to the mandible are critical elements in determining the management of perimandibular cancers. ⁽⁵⁾ **(Figure 10-3)**



Figure 10-3. *A verrucous carcinoma of the tongue close to mandible.*

A complete examination of the cranial nerves is performed, highlighting sensation over the chin for mandibular nerve deficit, tongue mobility for hypoglossal nerve deficit, facial nerve function, palatal elevation and gag reflex, and function of the accessory nerve. The neck should be thoroughly palpated for metastatic disease in the nodal groups at risk, and for abnormalities of the great vessels and

the thyroid gland which might impact treatment. Masses of the neck should be measured in centimeters, characterized for site (level), mobility, consistency, skin involvement, and proximity to vital structures. Computed tomography (CT) is the most common modality employed to assess the extent of oral cancers. **(Figure 10-4)**



Figure 10-4. *Computed Tomography showing bilateral mandible tumor.*

Advantages of CT include good soft-tissue discrimination and vessel identification and excellent definition of bone soft-tissue interfaces. CT scans are readily available and affordable. Cortical destruction and tumor in the alveolar canal and the bone marrow can be seen on CT. ⁽⁶⁾

Compared to CT scanning, magnetic resonance imaging (MRI) offers enhanced soft-tissue discrimination, excellent skull base and central nervous system (CNS) assessment, Sagittal views and no radiation exposure. Disadvantages are that the examination takes longer, is more expensive, is poorly tolerated by some, and the black signal of bone makes cortical bone abnormalities difficult to see. Positron emission tomography (PET) is a nuclear medicine study that demonstrates the difference in metabolism of radiolabeled glucose molecules between normal and malignant tissues. The clinical usage of this modality is currently not well-defined, but will likely aid in the diagnosis of recurrent and metastatic lesions. ⁽⁶⁾

Staging

Clinical staging for Lip and Oral Cavity cancers is predicated most strongly upon the history and physical examination. Biopsy is necessary to confirm diagnosis and is typically done of the primary. Nodal biopsy is done by fine needle aspiration when indicated. Results from diagnostic biopsy of the primary tumor, regional nodes, and distant metastases can be included in clinical classification. ⁽⁷⁾

Inspection of the lip and oral cavity typically reveals the greatest diameter of a cancer, though palpation is essential to assess depth of invasion (DOI) and submucosal extension. The mucosal extent of the cancer usually reflects its true linear dimension. ⁽⁷⁾ Induration surrounding a cancer typically is due to peritumoral inflammation. DOI should be distinguished from tumor thickness, and its determination is predicated on invasion beneath the plane defined by surrounding normal mucosa. Thick lesions often are defined by computed tomography (CT) or magnetic resonance (MR) imaging, but the difference between thickness and DOI must be observed.

Lesions located near the midline more often involve the contralateral side of the neck than well-lateralized cancers. Inability to move the node at all (without moving the head) is worrisome for extranodal extension (ENE), though the suspicion should be tempered for smaller nodes with limited mobility in level II. ⁽⁷⁾ Cross-sectional imaging of the oral cavity may be performed with either CT or MR imaging, depending on availability, patient imaging tolerance, contrast allergies, and cost. ⁽⁷⁾

As small but clinically evident mucosal tumors may be subtle on imaging, it is important to review the imaging exam with knowledge of the tumor site. T1, T2, and T3 tumors are distinguished only by size and depth of invasion. T4 disease entails deep tissue invasion, which varies according to the specific subsite of the oral cavity. Resected positive lymph nodes require examination for the presence and extent of ENE. Macroscopic ENE (ENema) is defined as either extranodal extension apparent to the naked eye at the time of dissection or extension > 2 mm beyond the lymph node capsule microscopically. Only ENema is used to define pathological ENE(+) nodal status. So Tis characterized by carcinoma *in situ*; T1 is Tumor 2 cm or smaller in greatest dimension without extraparenchymal extension; T2 is Tumor larger than 2 cm but not larger than 4 cm in greatest dimension without extraparenchymal extension; T3 Tumor larger than 4 cm and/or tumor having extraparenchymal extension; T4a Moderately advanced disease.

Tumor invades skin, mandible, ear canal, and/or facial nerve; T4b Very advanced disease. Tumor invades skull base and/or pterygoid plates and/or encases carotid artery. N1 Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE (-). N2a Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE (-). N2b Metastasis in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE (-). N2c Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE (-). N3a Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(-). N3b Metastasis in any node(s) with clinically overt ENE (+). M0 no distant metastasis; M1 distant metastasis. ⁽⁸⁾

The T Category for oral cavity cancer (OCC) acknowledges the different biological behavior of deeply invasive small tumors and incorporates depth of invasion (DOI). It has been recognized for decades that prognosis of OCC worsens when the tumor is thicker. ⁽⁹⁾ More recent data suggest that DOI is a better predictive parameter than tumor thickness. Starting in the eighth edition of the staging manual, DOI has been recorded and is available for analysis. ⁽⁹⁾

Kligerman and Dias, in two papers ^(10,11) report that patient with stage I and II cancer and >4mm tumor thickness, neck dissection remains mandatory in the early stage of oral cancer. ^(10,11) They reported that 49% patients were treating with Resection alone (RA) and 51% treated with RSOND. There was recurrence in 42% patients of Resection alone, and 24% patients of the RSOND group. The diseases-free survival rates at 3.5 years for RA and RSOND patients were 49%, and 72%, respectively. (Table 10-1)

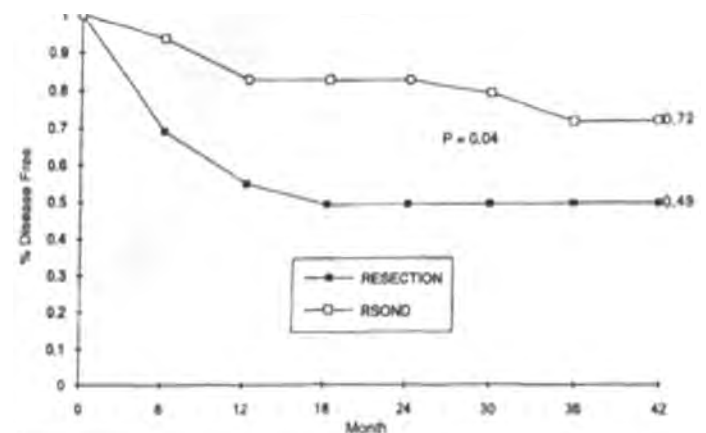


Table 10-1. Impact of types of treatment, resection only, or resection plus elective supraomohyoid neck dissection. (RSOND) on diseases-free survival in 67 patients with T1 and T2 N0 squamous cell carcinoma of the oral cavity. ⁽¹¹⁾

Therefore, neck dissection remains mandatory in the early stage of oral cavity cancer, because of better survival rates compared to RA and the poor salvage rate. In particular, patients with tumor thickness > 4mm treated with RSOND had significant benefit on disease-free on disease-free survival.⁽¹¹⁾

Assessing DOI by clinical examination requires palpation and attention to detail. Clinicians will need to distinguish a thick, exophytic, but less invasive tumor from one that is ulcerated and deeply invasive through careful palpation supplemented by radiographic assessment. Clinicians have been using physical examination to reflect subtle differences in size and extension of tumors, so distinguishing less invasive lesions (≤ 5 mm), from those of moderate depth (from >5 to ≤ 10 mm) or deeply invasive cancer (> 10 mm) should not be problematic. DOI will affect T category, accentuating the distinction between superficial or exophytic tumors and those that are more invasive.

Because data reported from a large in international collaborative study of OCC demonstrated a significant distinction in outcomes between T1 tumors with more than 5mm DOI and T1 through T4 tumors with greater than 10mm DOI, the T category for OCC is being modified in the eighth edition to improve hazard discrimination. Therefore, for every 5mm increase in DOI, both cT and pT categories will increase one level according to the following: ≤ 5 mm, > 5 mm but ≤ 10 mm, and > 10 mm. Pathologically, DOI is measured from the level of the basement membrane of the closest adjacent normal mucosa. A “plumb line” is dropped from this plane to the deepest point of tumor invasion.⁽¹²⁾

Tumor thickness underestimates aggressive potential; DOI is superior to tumor thickness. Generous preoperative biopsies of small tumors may interfere with DOI determination; therefore, it is important that, when pathologists examine the original biopsies, attention should be directed to DOI to incorporate all available information and to arrive at the most accurate DOI. Extrinsic muscle infiltration is no longer a staging criterion for T4 designation in OCC, because DOI supersedes it, and limited extrinsic muscle invasion is difficult to assess (either clinically or pathologically). DOI has been shown to have a 6.0 fold higher risk of local recurrence and lymph node metastasis on multivariate analysis.⁽¹²⁾

Treatment

Treatment of squamous carcinoma of the oral cavity is in general either by surgery or by radiation alone or in

combination. Chemotherapy and new immunologically based treatment protocols are at the moment reserved for patients with what is considered to be incurable disease in normal terms or for those patients in whom conventional treatment has failed.⁽¹³⁾

Treatment choices are best made after considering tumor factors, patient factors and resources factors. Tumor factors include subsite, T stage, N stage, histologic characteristics, endophytic vs. exophytic morphology, and proximity to bone. **(Figure 10-5)**

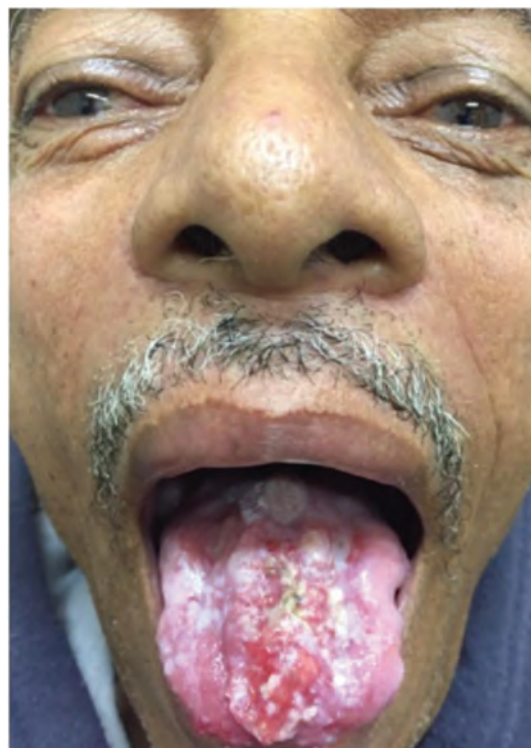


Figure 10-5. *Exophytic Squamous Cell carcinoma (SCC) involving all the tongue.*

Patient factors include the patient's age, co-morbidities, convenience, rehabilitation potential, and the patient's wishes. Resource factors include the availability of a well-trained surgeon or radiotherapist with a dedicated interest in head and neck cancer, availability of advanced hardware for the planning and delivery of radiation, and the availability of funds to pay for the treatment. The mainstay of treatment of early oral cancer is surgery. External beam radiation therapy alone can be effective for some early superficial lesions of the tongue or floor of mouth but sequelae of xerostomia and mandible irradiation, and long duration and expense of treatment make radiation a poor choice.⁽¹⁴⁾

Also, bone involvement by oral cancer limits the effectiveness of external beam radiation, so lesions of the gingiva and hard palate are best treated with surgery due to the close proximity of bone and the high incidence of bone invasion. Advanced T3 and T4 lesions are best treated with a combination of surgery and radiation therapy.⁽¹³⁾ Improvement in locoregional control of advanced oral cancer is attributable to the addition of postoperative radiation. Brachytherapy can sometimes be employed for oral cancers (especially tumors of the tongue) utilizing after-loading catheters. However, resection of small lesions is usually simpler and less morbid, and surgery followed by radiation is more appropriate for treating the large volume T3 or T4 lesion. Close proximity of the tumor to the mandible, complex surface anatomy, and uncertainty of the tumor margins are tumor factors that also limit use of brachytherapy for oral cavity cancers.⁽¹⁵⁾

The most important prognostic factor in oral cavity cancer is the lymph node stage.⁽¹⁶⁾ If there is presence of lymph node metastasis, its survival in five years decreases between 20% and 50%. However, most authors advocate elective treatment of the neck in cases where large cervical metastases are occult ($> 20\%$).⁽¹⁶⁾ The major lymph node chains at risk are I, II and III, and the lymphatic vascular network of this region is extremely rich.⁽¹⁶⁾

The most used imaging tests for N0 patient investigation are ultrasonography, computed tomography and magnetic resonance imaging.

Sentinel lymph node (SLN) research with the identification of the first tumor drainage chain is another weapon in the propaedeutics and cervical staging of these patients, with a medical sensitivity of 90%.⁽¹⁶⁾ The patients underwent a preoperative lymph node mapping through lymphocintigraphy in the morning of the day of surgery or one day before the surgery. (**Figure 10-6**)

The parameters then used to find the LNS were the patent blue lymph node uptake and the capture by the probe. (**Figure 10-7**)

Figure 10-8 shows capture of radiation emitted during the surgery. The major argument for the use of this technique is the lower aggressiveness of the procedure when compared to elective neck dissection subsequent gain in the quality of life of these patients.⁽¹⁶⁾

The effectiveness of sentinel lymph was reported by Farias *et al.* The test had a sensitivity of 100%, and a negative predictive value of 100% (true negatives). There was no false negative result.⁽¹⁶⁾



Figure 10-6. Multiple sentinel lymph nodes. Observe the cervical incision for radioguided surgery.

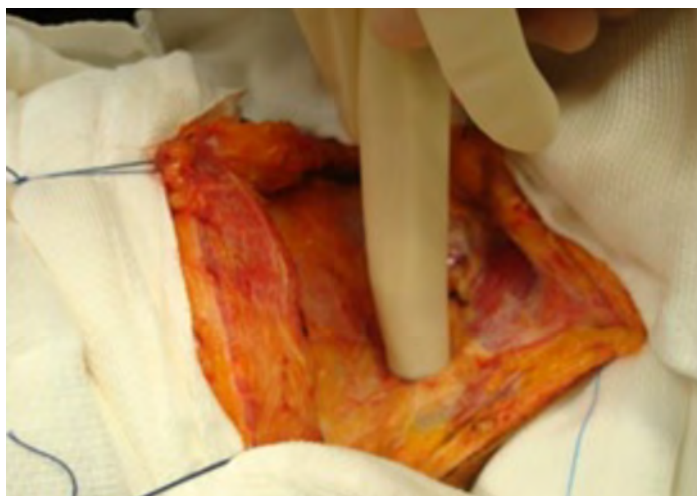


Figure 10-7. Detection of the sentinel lymph node with the neck open, intraoperatively with a gamma probe.



Figure 10-8. Capture of radiation emitted during the surgery.

Surgical Treatment

It is easy to underestimate the deep extension of tongue tumors and great care should be exercised to take more than 1 cm cuff of normal tongue musculature as the margin of surgical resection. For many T2 and T3 oral tongue tumors, and for any sized tumor in the posterior portion of the tongue or floor of mouth, the mandibulotomy approach provides the exposure required to perform an oncologically sound resection.⁽¹⁷⁾ At the present time it has been little used due to transoral robotic surgery.

In addition, the majority of these patients benefit from staging elective supraomohyoid neck dissection.⁽¹⁶⁾

Recent studies in patients with previously untreated T1 and T2 squamous cell carcinoma (SCC) of the tongue and floor of the mouth have shown a relationship between tumor thickness, neck metastasis, and survival.⁽¹⁷⁾ Several studies revealed that the presence of stage II tumor, tumor thickness > 2mm, positive cervical margin, and perineural and vascular invasion were significantly associated with recurrence.⁽¹⁷⁾

Because of the frequent involvement of the mandible by tumors of the floor of the mouth management of the mandible is an important aspect of planning resections in this case. Management of the mandible depends on the lesion's proximity to the mandible, whether the mandible is dentate or edentulous, the degree of atrophy of the alveolar ridge, whether the mandible has been irradiated, and whether there is mandible invasion.^(18,19) The key clinical question is: does the mandible require resection, and if so, how much the periosteum, a marginal mandibular resection or a segmental resection. A detailed and meticulous examination, often under anesthetic, must be undertaken before deciding the choice of surgical approach.⁽¹⁹⁾ Premalignant lesions and small, superficial tumors of the anterior floor of mouth, alveolus, and tongue may be resected through the open mouth. (Transoral excision). (Figure 10-9)



Figure 10-9. Transoral Excision of partial tongue.

Tumors of the posterior oral cavity are not easily accessible transorally, and a cheek flap may give more adequate exposure in appropriate cases. Larger tumors of the lateral border of the tongue or those involving or extending onto the floor of the mouth may occasionally be resected transorally with a separate neck dissection approach, but some require a lip-splitting mandibulotomy approach. Similarly, adequate surgical exposure of tumors located in the posterior oral cavity may be obtained using a mandibulotomy.⁽¹⁹⁾ The understanding of tumor invasion into mandible enables the use of marginal resection of bone based on the observation that the cortical part of the bone containing the mandibular canal lies inferior to the dental roots, remains relatively uninvolved in early stage disease, and can be safely spared.⁽¹⁹⁾

The management of the neck is a crucial and integral part of overall management of the patient with oral cancer. As described earlier, metastasis to the neck from an oral primary generally occurs in an orderly and predictable manner, most often involving levels I through III. In a patient with a clinically N0, the risk of metastasis to levels IV and V is very small and a supraomohyoid neck dissection (SOHND) would therefore adequately address the neck in these patients.⁽¹⁹⁾ (Figure 10-10)

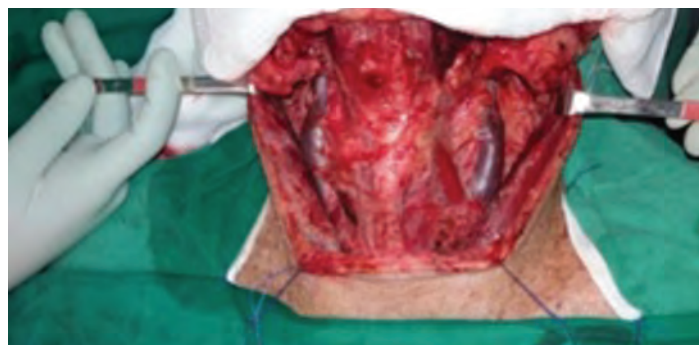


Figure 10-10. Elective supraomohyoid bilateral neck dissection (RSOND) for SCC of tongue.

Reconstruction

The reconstructive technique chosen can include multiple modalities, but the reconstructive ladder that applies to all defects is also applied in the oral cavity.⁽²⁰⁾

Reconstruction of the floor of the mouth requires thin pliable tissue. The extent of the defect will determine which technique is most appropriate. Very small defects can be allowed to granulate and remucosalize or may be covered with a split-thickness skin graft.⁽²⁰⁾ Local flaps may be used effectively in moderate-sized defects and include the facial

artery musculomucosal flap, tongue flaps, palatal flaps, and nasolabial flaps. For larger defects, the radial forearm flap has become the workhorse within the oral cavity. ⁽²⁰⁾ (Figures 10-11, 10-12 and 10-13)

The tongue is a unique muscular organ that fills the oral cavity and without which normal oral function cannot occur. The priorities for tongue reconstruction include restoration



Figure 10-11. Radial forearm flap designed.



Figure 10-13. Final result. The radial forearm flap used for tongue reconstruction.

of swallowing, articulation, and airway protection. The capability to rehabilitate oral function is largely dependent on the volume of native tongue and preservation of the hypoglossal and lingual nerves. Regional flaps such as the major pectorals (Figures 10-14, 10-15 and 10-16) provide good initial results but do not stand the test of time. Functioning muscle flaps have been advocated in order to obliterate the space between floor of mouth and palate during swallowing, but the results have been disappointing. ⁽²¹⁾

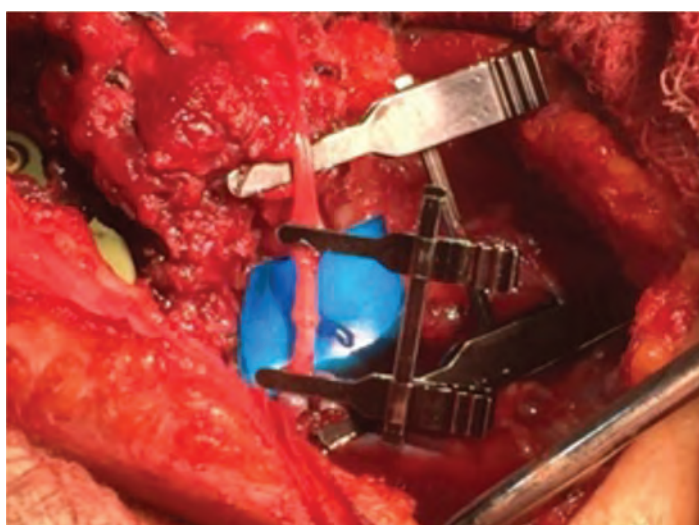


Figure 10-12. Microsurgical anastomosis.



Figure 10-14. Major pectorals preparation.



Figure 10-15. Major pectorals flap in position. A titanium plate was used to connect the gap of two cut of central arc of mandible.



Figure 10-16. Final result. The major pectorals in place.

The oropharynx is frequently involved in oral malignancies and as with areas within the oral cavity, it demands thin pliable cover. Again, in our practice, the radial forearm flap is the workhorse for this area. Other thin flaps, such as ulnar artery flap, the lateral arm, and anterolateral thigh flap have been used successfully and the selection, again, will be dictated by the size of the defect. ⁽²¹⁾

Mandibular reconstruction has evolved over the past two decades from a complex and often unsuccessful to a very reliable but still complex technique. The main reason for this advance has been the incorporation of microsurgical techniques and the development of reliable flaps for the reconstruction. ⁽²²⁾ Repair of a mandibular defect frequently includes bone and soft tissue, which are needed to replace intraoral lining, external skin, or both. Although microsurgery has revolutionized mandible reconstruction, there is still also a place for more traditional techniques.

Smaller defects can sometimes be repaired with reconstruction plates alone, and in certain circumstances the use of non-vascularized bone is still a reasonable approach. The choice of flap is determined by the characteristics of the defect. While rib metatarsal bone, humerus, and clavicle have all been used in mandible repair, the most widely used current donor sites include the fibula, (Figures 10-17 and 10-18) iliac crest, scapula, and radius. Of these, the fibula is the workhorse flap in these situations. ⁽²²⁾

The radial forearm flap provides excellent quality, thin, pliable skin, and has a reliable long vascular pedicle making it an ideal choice for intraoral reconstruction. The flap is designed on the volar aspect of the forearm based on the radial artery, which is identified with its concomitant venous system running within a condensation of fascia referred to as the lateral intermuscular septum that separates the flexor carpi radialis and the brachioradialis. (Figures 10-11, 10-12 and 10-13) The anterolateral thigh flap has recently been used more frequently for reconstruction of the oral cavity in those cases that require only soft tissue reconstruction.



Figure 10-17. Fibular osteotomys to create a new central arc.

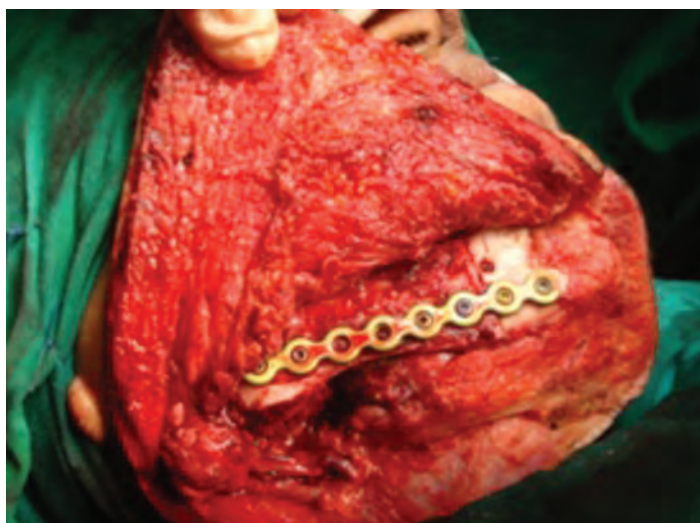


Figure 10-18. Fibula micro reconstruction of the mandible.

This flap can provide a large amount of soft tissue, which can include skin, muscle, and fascia if required. In many cases, the donor site can be closed primarily with no skin graft and thus minimize donor site morbidity. This flap is elevated from the lateral thigh and may extend from the greater trochanter to 3 cm proximal to the patella. ⁽²²⁾

The fibula can provide up to 25 cm of uniformly shaped bicortical bone and because of the profuse periosteal blood supply, it can tolerate multiple osteotomies. The skin island, based on the Septocutaneous blood supply is adequate in size and reliable in more than 90% of patients. **(Figures 10-17 and 10-18)** ⁽²²⁾

The first applications of prototyping in maxillofacial surgery were documented by Brix *et al.* and Mankovich *et al.*, in 1990. In 1994, Anderl *et al.* reported the use of a stereolithographic model in corrective surgery for a great cleft palate in a child at the University of Innsbruck. In 1995, Bill *et al.* reported the use of prototyping to facilitate the reconstruction of a complex cranial defect in a patient with sequelae of infection after exision of a meningioma. ⁽²³⁾

Major resections of head and neck tumors, owing to their small dimensions and their proximity to the organs in this region, cause important functional and aesthetic problems the significantly compromise patients' quality of life. ⁽²⁴⁾ Therefore, therapeutic planning should always extend beyond the resection to include functional and aesthetic reconstruction, preferably immediately. ⁽²⁴⁾

With progress in technological process to acquire medical images, including CT and MRI, high-quality 3D images

that permit the visualization, manipulation, and analysis of anatomic structures are, possible to generate. These technological advances, used in conjunction with new computerized analysis techniques, yield clinically relevant information from the original image. ⁽²⁵⁾

Microsurgical reconstruction represents a significant advance but has not yet been perfected. Using prototyping sought better aesthetic and functional outcomes or surgical reconstruction and attempted to reduce surgical risk. ⁽²⁵⁾

Farias *et al.* in his study with rapid prototyping produces biomodels (prototypes) that are identical to the patient's face and the donor area of the microsurgery bone flap (iliac crest of fibula) and helps surgeons to do the following: reduce the operative time with a better understating of the anatomic and tumor area before the molding of titanium plates in the biomodel, modeling of the bone flap in the prototype, and the choice of screws. Secondary to reducing the operative time, the biomodels would help decrease the morbidity of the donor bone flap (through accurate removal of bone without waste). ⁽²⁶⁾ **(Figures 10-19 and 10-20)**

A rapid prototyping is a constructive, additive process used to obtain physical prototypes from a digital 3 dimensional (3D) model. The downsides to prototypes arise from the need to reduce the probability of defects in the final products and to reduce the development time for new products. ⁽²⁶⁾

In this study, the biomodels was used for mock operations 1 day before the patient's actual surgery. The mean duration of surgery using the biomodels was 115 minutes, ranging from 40 to 155 minutes. At this time, the plates were molded



Figure 10-19. Patient with a mandible tumor in preoperative. The use of prototyping technique was of fundamental importance in this case.



Figure 10-20. Surgery in the prototype one day before the real surgery.



Figure 10-22. The figure shows that are identical: surgical specimens and tumor prototype.



Figure 10-21. Making surgery in the prototype, choosing the plates screws and modeling and bending the titanium plates one day before the real surgery.

according to the defect induced in the biomodel, and the bone flap was made, fractured, and adapted according to best practices. The appropriate screws for the bone thickness were selected. The prototypes were important for selecting the appropriate screws. ⁽²⁶⁾ **(Figure 10-21)**

Some advantages for the use of rapid prototyping in the medical field include the following: surgical simulation; make surgical guides on the bone; reduce surgical risk; reduce time and hospital costs; make personalized prostheses; use the opposite side to establish symmetry; planning with the patient at a distance; and aiding in documentation. Biomodels help to facilitate the surgery, improve outcomes, and reduce risks, complications, surgical time, and the overall cost of treatment. ⁽²⁶⁾

The use of prototyping tended to reduce the surgical time because the premolded plates and previous selection of screws facilitated the surgery, reducing the operating time. There was a tendency to reduce size of the bone flap harvest for reconstruction, decreasing morbidity at the donor area of the bone flap, and we observed better aesthetic results in the patients who underwent operations that used prototyping technique. ⁽²⁶⁾ **(Figures 10-21 and 10-22)**

Farias *et al.* published a series of 14 cases with mandible reconstruction using customizes titanium prosthesis. ⁽²⁷⁾

In **Figures 10-23, 10-24 and 10-25** we can observe a custom titanium mandible prosthesis and the final aesthetic effect with this use.

Prognosis

The single most important factor that affects long-term results following treatment for carcinoma of the oral cavity is the stage of disease at the time of presentation. For early-

staged tumors, excellent cure rates are anticipated. However, once regional lymph node metastases become apparent, a significant drop in cure rates is to be expected. ⁽²⁸⁾ (Table 10-2)



Figure 10-23. Mandible Titanium customized prosthesis.

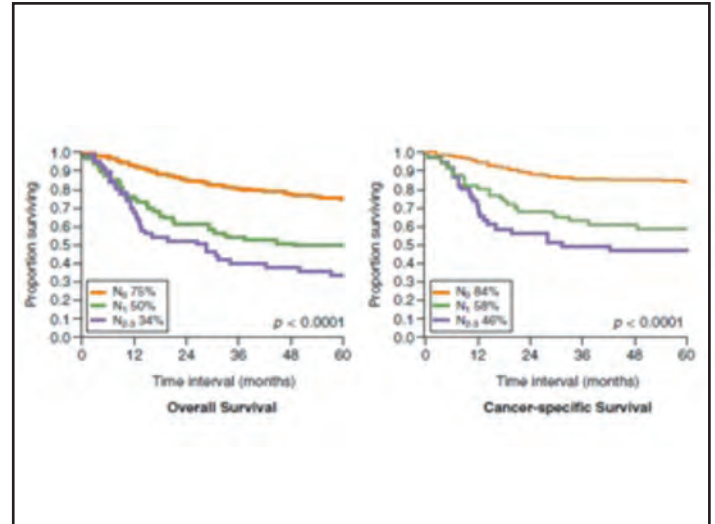


Table 10-2. Survival is significantly reduced by the presence of lymph node metastases. (Memorial Sloan-Kettering Cancer Center data, 1986-1995). ⁽²⁸⁾



Figure 10-24. Final aesthetic result with mandible titanium customized prosthesis (front view).



Figure 10-25. Final aesthetic result (lateral view).

Conclusion

Oral cavity cancer is one of the most frequent in head and neck surgery; the treatment of the neck is of fundamental importance for initial tumors, T1 and T2 with negative neck, can be treated using sentinel lymph node techniques or supraomohyoid cervical neck dissection. For T3 and T4 tumors, surgery with selective or radical neck dissection should be associated with radiotherapy. Techniques of immunotherapy and molecular target therapy are being reported with good results. The reconstruction is fundamental to rehabilitate the patient, with local or microsurgical flaps with or without the use of prototyping techniques.

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Chapter 11

Hypopharynx Cancer

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Hypopharynx Cancer

Malignancies arising in the hypopharynx represent approximately 7% of all cancers of the upper aerodigestive tract.⁽¹⁾ Over 95% of all cancers arising in the hypopharynx are squamous cell carcinomas. Hypopharyngeal squamous cell carcinoma is highly associated with tobacco and alcohol use. The most common signs and symptoms are dysphagia, presence of cervical mass, weight loss and gastroesophageal reflux. A correlation was observed with squamous cell carcinoma of the cervical esophagus. It may present a direct extension compromising the retrochoid area and the cervical esophagus, with similar etiological factors.⁽²⁻⁴⁾

Other factors proposed as important to the development of this disease include nutritional deficiency, exposure to oncogenic viruses, and underlying genetic defects in DNA repair mechanisms.⁽⁵⁾ Chronic irritation of the pharynx from gastroesophageal reflux has also received attention as another possible etiology for the development of hypopharyngeal cancer.⁽⁵⁾ The prognosis for patients with squamous cell carcinoma of the hypopharynx is among the worst for epithelial malignancies of the head and neck.^(1,2) Five-year survival has been reported as ranging from 11% to 47%.⁽⁶⁾

The main reason for the aggressive clinical behavior is submucosal dissemination, even in small lesions and multifocal involvement of the mucosa, justified by the cancerization field, which is frequent in malignant neoplasms of the upper aerodigestive tract.^(7,8)

Surgery, when possible, is the treatment that offers a better chance of cure and better local control of disease and may be followed by chemo-radiotherapy. Among the surgically treated patients, in the majority of cases a total



Figure 11-1. Pharyngolaryngectomy with esophagectomy.

pharyngolaryngectomy is performed and associated or not with esophagectomy. **(Figure 11-1)**

A radical procedure involving the creation of a definitive end tracheostomy and a continuity solution between the oral cavity and the thoracic esophagus must be done.^(9,10)

Bilateral neck dissection of levels II, III, IV and VI and lymph nodes of the anterosuperior mediastinum should also be performed during cervical time in cases not previously irradiated. Because of the possibility of microscopic disease and / or direct tumor extension, total thyroidectomy should be performed and, where possible, parathyroid glands should be preserved.⁽⁶⁾

The restoration of the continuity of the digestive tract and, consequently of the oral route, has a profound impact on



Figure 11-2. Tracheotomy, esophagostomy and pharyngostomy, after radical pharyngolaryngectomy.

the quality of life of these patients, avoiding a situation of orocervical fistula with constant sialorrhea and the deprivation of taste. ⁽¹¹⁾ **(Figure 11-2)**

Among the various techniques for reconstruction of the cervical esophagus are gastric pull-up, **(Figure 11-3)** transposition of the colon, **(Figure 11-4)** tubing of regional flaps, **(Figure 11-5)** tubing of free flaps, or jejunum-free flap, **(Figure 11-6)** with microsurgical vascular anastomosis. ^(11,12)

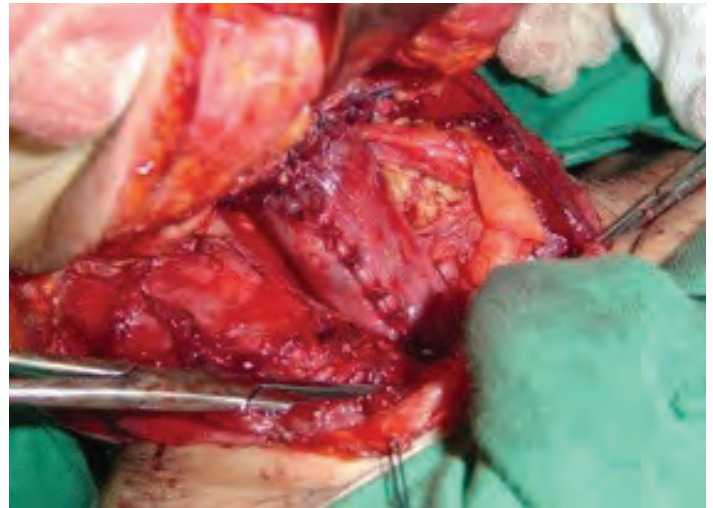


Figure 11-3. Reconstruction of the cervical esophagus with gastric pull-up.



Figure 11-4. Reconstruction of the cervical esophagus with transposition of the colon.

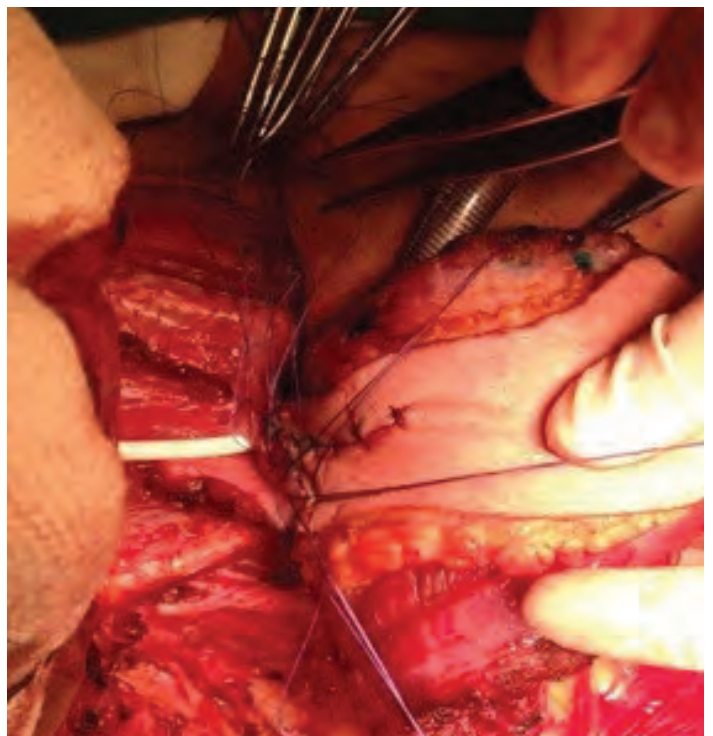


Figure 11-5. Reconstruction of the cervical esophagus with a major tubulized pectoralis flap.



Figure 11-6. Reconstruction of the cervical esophagus with jejunum-free flap.

Since 1960, when Ong and Lee first described pharyngectomy with gastric interposition and single-time pharyngo-gastric anastomosis, this has been the surgery of choice for the treatment of cervical esophagus and lower hypopharynx cancer. ^(7,8) Reconstruction with a microsurgical jejunal anastomosis is contraindicated when there is intrathoracic extension of cervical esophagus tumors. ⁽¹³⁾

The options of surgical approach with gastric interposition include:

- Three fields in open surgery, that is, laparotomy associated with right thoracotomy and cervicotomy, where the specimen is removed and gastric tube anastomosis performed.
- Trans-hiatal esophagectomy with cervicotomy and laparotomy (without thoracotomy).
- Minimally invasive esophagectomy (laparoscopy with thoracoscopy and cervicotomy). ^(3,7)

The only absolute contraindication for surgery is infiltration of the carotid artery and mediastinal vessels. ⁽⁵⁾ Another therapeutic option includes the preservation of organs with chemotherapy and concomitant radiotherapy, reserving surgery for rescue in the failure of local control. ⁽³⁾

Postoperative complications occur in approximately 50% of the patients and include pneumonia and pleural effusion, mainly. Chylous fistula, salivary fistula, and gastric tube necrosis may also occur. ⁽⁸⁾ Radical surgery with free margins is the most important prognostic factor.

⁽⁷⁾ The sequelae and complications associated with gastric transposition (extensive abdominal dissection, thoracic narrowing and force of gravity exerting tension under the anastomosis, which may have been done under previously irradiated tissue and early postoperative satiety due to loss of gastric filling capacity) restrictions. On the other hand, reconstruction with colon should be reserved for patients with previous gastric resection, since the surgical morbidity is higher, especially in the case of fistulas in the anastomosis when the cervical, thoracic and abdominal compartments are placed in contact with the colonic bacterial flora. ^(7,8)

In a Farias *et al.* study, they describe gastric automation prior to pharyngolaryngectomy for interposition. About 30 days before the esophagectomy, the patient performed gastric tube autonomization. The surgery consisted of a laparoscopic evaluation of the abdominal cavity, biopsies of suspected lymph nodes, ligation of the left gastric artery and ligation of the short gastric vessels, in order to optimize the gastric vascularization by the right gastric and right gastroepiploic artery pedicles, which may have improved the distal irrigation of the gastric tube and avoided fistulas. With this technique laparoscopic surgery was used. ⁽¹⁴⁾

The technique using jejunal free flap has been highly recommended, with good results reported by several authors. ⁽⁹⁻¹²⁾

This technique was initially proposed by Seidenberg *et al.* in 1959. At that time, techniques and materials of microvascular surgery were poorly developed, which prevented the achievement of good results. ⁽¹²⁾ Since then, multiple-stage procedures have been used for this purpose, such as fasciocutaneous (deltopectoral), myocutaneous (major pectoralis) (**Figure 11-5**) and posterior interposition of viscera. With the development of microsurgery from the mid-1970s, jejunal free flap became an accessible and effective method to reconstruct the continuity between the pharynx and the cervical esophagus. It is worth mentioning that the recognition of the advantages of microsurgical flaps for pharyngoesophageal reconstruction has stimulated the development of other alternatives, such as the free anterior tubular flap. ⁽¹²⁾

After pharyngolaryngectomy associated with cervical esophagectomy, it isolates the pharyngeal and esophageal stumps. Simultaneously the patient is submitted to laparotomy, a segment of about 20cm of jejunal loop being isolated approximately 30-40cm from the angle of Treitz, after verification by transillumination of the vascular arches and identification of the donor pedicle. ⁽¹¹⁾

The proximal and distal ends of this segment are then sectioned with mechanical suture, leaving it perfused by its pedicle. Next, the jejunal segment is transplanted to the neck after previous ligation of the mesenteric vessels in the abdomen, the flap being positioned in an isoperistaltic position. With the use of a surgical microscope, the vascular anastomosis is performed with 8-0 to 10-0 nylon wires, depending on the vascular caliber. ⁽¹¹⁾

The next step consists of the pharyngeal anastomosis, performed with separate, seromuscular stitches of 3-0 polyglactin yarn, in a single plane, with posterior inclusion of the pre-vertebral fascia for greater support of the flap. At that time, a nasoenteral catheter is passed through the flap. ⁽¹¹⁾

In a series described by Galvão *et al.*, he pointed out that complications were more frequent in patients submitted to previous radiotherapy. In these cases, both surgical access and microsurgical vascular anastomosis presented

greater technical difficulty. Because of that, we indicate whenever possible immediate reconstruction, complaints of significant dysphagia, justified by stenosis at the level of the proximal anastomosis and experience with the operated cases suggested that early rehabilitation associated with the relatively low rates of complications confirm the effectiveness of the flap free of jejunum that remains as procedure of first choice. ⁽¹¹⁾

After resection of advanced tumors, especially after laryngopharyngectomy associated with esophagectomy, and after resection of tracheostomy recurrence, there may be a need for a procedure to restore the alternate airway, a mediastinal tracheostomy (MT), which is the construction of a stoma in the anterior thorax, using the intrathoracic trachea with the need to remove the superior sternum, the medial third of the clavicles and, eventually, the proximal third of the first and second ribs, which gives access to the intrathoracic trachea. ^(15,16) **(Figures 11-7 and 11-8)**

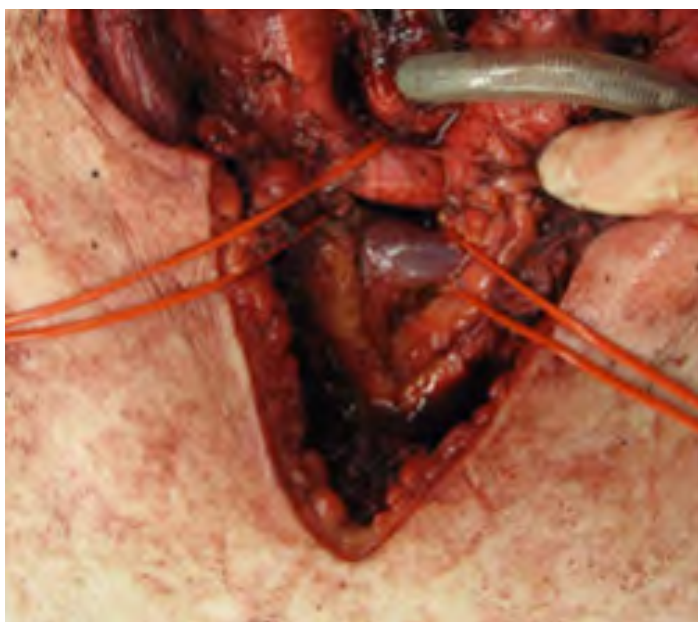


Figure 11-7. Mediastinal tracheostomy.



Figure 11-8. Mediastinal tracheostomy final aspect.

In 1962, Sisson *et al.* (1962) resected a large portion of skin along with the tumor and removed the notch and the heads of both clavicles in a surgery for recurrence of laryngeal carcinoma in stoma. Skin flaps were mobilized to the superior closure of the stoma and the lower failure was covered with skin grafts. ⁽¹⁶⁾

In 1966, Grillo (1966) confectioned a large bipediced total thickness flap from the skin of the anterior chest region through two main horizontal incisions in an effort to eliminate the tension in the tracheocutaneous anastomosis responsible for the poor healing and the threat of bleeding from the innominate artery. This flap found the terminal stump of the trachea in the mediastinum, which was accessed by removing the notch and sternal portions of both clavicles and the first and second costal cartilages. The stoma emerged at the center of the flaps, requiring only a simple suture. ⁽¹⁷⁾

According to Conti *et al.* (2010), the main indications for mediastinal tracheostomy are malignant neoplasms of the subglottic region extending to the proximal trachea, a recurrence in stoma after laryngectomy. ⁽¹⁸⁾

According to Maipang *et al.* (1996), the main contraindications for mediastinal tracheostomy are the invasion or involvement of the great vessels, distal trachea invasion of 3.0 to 4.0 cm above the carina, column or prevertebral fascia invasion, and the presence of disease in the bronchial lumen. ⁽¹⁹⁾

Siebra *et al.* described a successful case and concluded that TM is an exceptional procedure due to the morbidity and risks that it represents and should only be performed in patients with excellent general condition. It may also be indicated as palliative treatment in selected cases. This report shows the viability of its use in association with laryngopharyngoesophagectomy for a locally advanced tumor and transposition of the colon. ⁽²⁰⁾ The squamous cell carcinoma of the hypopharynx is aggressive and with a reserved prognosis. The surgeon should be aware of the possibility of esophagectomy, with various types of gastrointestinal transit reconstruction.

All these surgical techniques have high morbidity, with high complication rates. Selected cases should be operated. For other patients, radiotherapy alone or associated with chemotherapy should be considered as first-line treatment.

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Chapter 12

Larynx Cancer

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Etiology and Epidemiology

Laryngeal carcinoma is the eleventh-most common form of cancer among men worldwide and is the second-most common malignancy of the head and neck. ⁽¹⁾ Worldwide, there are an estimated 130,000 new laryngeal cancer cases and 82,000 deaths annually. ⁽²⁾ In the United States, laryngeal cancer accounts for about one-fourth of the 53,000 cases of head and neck cancer diagnosed annually. ⁽²⁾

Laryngeal cancer is diagnosed predominantly in men, which at least in part reflects in the effects of tobacco and alcohol use. Laryngeal cancer may also be due to infection with high-risk HPV infection in some cases. ⁽³⁾

The larynx consists of three main subsites, the supraglottis, glottis, and subglottis, each with its own distinct anatomic features and embryologic origins. The laryngeal skeleton is composed of a group of cartilages interconnected through ligaments, membranes and muscles. ⁽⁴⁾ The cartilages are the epiglottis, the cricoid, the thyroid cartilage, the arytenoids, the cuneiform and the corniculate. These in turn explain differences in the clinical behavior of cancers that can occur in each subsite. The supraglottis is composed of the epiglottis, aryepiglottic folds, arytenoid cartilage, false vocal cords, and the upper half of the laryngeal ventricle. The supraglottis has rich lymphatic drainage, which in part explains the more aggressive behavior of cancers in this area, particularly those arising in the “marginal zone” (the suprahyoid epiglottis and aryepiglottic folds). ^(5,6)

The glottis includes the lower half of the ventricle, the vocal cords including the anterior and posterior commissure, and the area extending 1 cm below the apex of the ventricle. The vocal cords (or folds) are comprised of several layers: epithelium, a gelatinous superficial layer, and more dense

intermediate and deep layers (called the vocal ligament). The conus elasticus extends from the superior edge of the cricoid cartilage to the inferior surface of the vocal cord to merge with the vocal ligament. This structure is a strong barrier to lateral extension of cancer from the glottis and subglottis and also accounts for the relative paucity of lymphatic drainage in the area. Lastly, the subglottis extends from the inferior margin of the glottis to the inferior border of the cricoid. ⁽⁷⁾

Laryngeal carcinomas are prevalent in heavy smokers, tend to have a relatively early presentation and with the exception of supraglottic malignancies, are less likely to metastasize early to the adjacent lymph nodes. Because of the shortened time from symptom evolution to diagnosis, tumors confined to the laryngeal framework have a substantially better prognosis. Certain occupational exposures are also known to be risk factors including wood and cement dust, asbestos, and certain fuels or industrial solvents. ⁽⁸⁾ Early detection relates to the effectiveness of the American Cancer Society’s campaign regarding early warning signs for malignancy which include persistent hoarseness and the ease of in-office endoscopic examination. ⁽⁹⁾

Early recognition of malignancies of larynx is crucial. Any patient with hoarseness lasting longer than 4 weeks should be evaluated by an otolaryngologist and/or a head and neck surgeon. Other symptoms of laryngeal carcinoma are hemoptysis, halitosis, and the so-called hot potato voice. A thorough laryngeal examination is essential. Cancers of the supraglottic larynx generally present later due to a paucity of early symptoms. Dysphagia, otalgia, and odynophagia should raise suspicion. Airway obstruction with no apparent voice change may represent the indicating sign of a large supraglottic or subglottic lesion. ⁽¹⁰⁾

Staging

Squamous cell carcinoma can be invasive or non-invasive. The term carcinoma *in situ* is used for non-invasive squamous cell carcinoma. ⁽¹¹⁾ From the histological point of view, invasive carcinoma can be well differentiated, moderately differentiated, little differentiated or undifferentiated. Tumor graduation is recommended using the classification proposed by Broder in 1927: G1: well differentiated; G2: moderately differentiated; G3: little differentiated and G4: undifferentiated (anaplastic). ⁽¹²⁾

The classification of TNM staging is constantly evolving. Farias T *et al.* in 2004 showed in a research that patients with T4 N0 M0 tumors, with minimal cartilage invasion, without any extra laryngeal spread have similar biological behavior when compared to patients with T3 N0 M0 tumors. ⁽¹³⁾ This had a bearing on the actual staging when considering that invasions only of the internal cortical of the cartilage are considered T3 and not T4 as the old classification. Thus, below follows the current classification according to the Joint American Committee on Cancer – AJCC eighth edition. ⁽¹⁴⁾ (**Table 12-1**)

The correct staging is very important for predicting the biological behavior of the disease and prognosis, as well as helping in the proper definition of conduct.

Diagnostic

The early diagnosis and prevention of laryngeal carcinoma is the most effective means for maximizing cure rates and preserving function. Fortunately, glottic laryngeal carcinoma, the most common laryngeal tumor, tends to be detected at an earlier stage than tumors located at other subsites of the head and neck. Nevertheless, the symptoms of laryngeal carcinoma can also be nonspecific and may result in a delay of diagnosis. In general, hoarseness lasting longer than 3 weeks or odynophagia or dysphagia lasting longer than 6 weeks should warrant a referral to a specialist for patients older than 50 years with an extensive smoking or drinking history. Associated otalgia, stridor, and weight loss should also be red flags to completely rule out a malignant process. ⁽¹⁵⁾

An office video endoscopic laryngeal assessment is an outpatient state of the art. With good topical anesthesia, outpatient endoscopic biopsies are easily obtained. (**Figure 12-1**) Imaging studies are of paramount importance in the management of laryngeal malignancies as they may aid in the selection of the most appropriate therapeutic modality.

Table 12-1. Larynx Staging – AJCC Eight edition

Supraglottis Staging	
T1	Tumor limited to one supraglottic subsite
T2	Tumor involving more than one supraglottic subsite or adjacent glottis sites, with normal vocal cord mobility
T3	Tumor limited to the larynx but with vocal cord fixation and/or invasions of the postcricoid area, paraglottic space, pre-epiglottic space, and/or inner cortex of thyroid cartilage.
T4a	Tumor extending through the thyroid cartilage or invading tissues beyond the larynx (trachea, strap muscle, thyroid, esophagus or oropharynx).
T4b	Tumor invading prevertebral space, encasing carotid artery, or invading mediastinal structures.
Glottis	
T1a	Tumor limited to one vocal cord.
T1b	Tumor involving both vocal cords.
T2	Tumor extension to supraglottis and/or subglottis and/or with impaired vocal cord mobility.
Subglottis	
T1	Tumor limited to subglottis.
T2	Tumor extending to glottis, normal vocal cord function.
T3	Tumor limited to larynx with vocal cord fixation.
T4a	Tumor invading cricoids/thyroid cartilage and/or invading tissues beyond the larynx (trachea, strap muscles, thyroid, esophagus, or oropharynx).
T4b	Same as supraglottis and glottis.
AJCC – American Joint Committee on Cancer. Cancer Staging Manual. Eighth Edition; 2017. ⁽¹⁴⁾	

⁽¹⁶⁾ Critical factors in the evaluation of laryngeal images include tumor volume, cartilaginous invasion, spread across supraglottic-glottic-subglottic boundaries, infiltration of preepiglottic, paraglottic, and pharyngeal planes, and nodal disease. Computed tomography and magnetic resonance imaging modalities are complementary and should be used judiciously in the preoperative planning. (**Figure 12-2**) Lastly, radiologic evaluation of the chest helps to rule out metastasis or second primary malignancies. ⁽¹⁶⁾

Over 90% of laryngeal cancer are of the squamous cell carcinoma type. Important tumor parameters include mobility

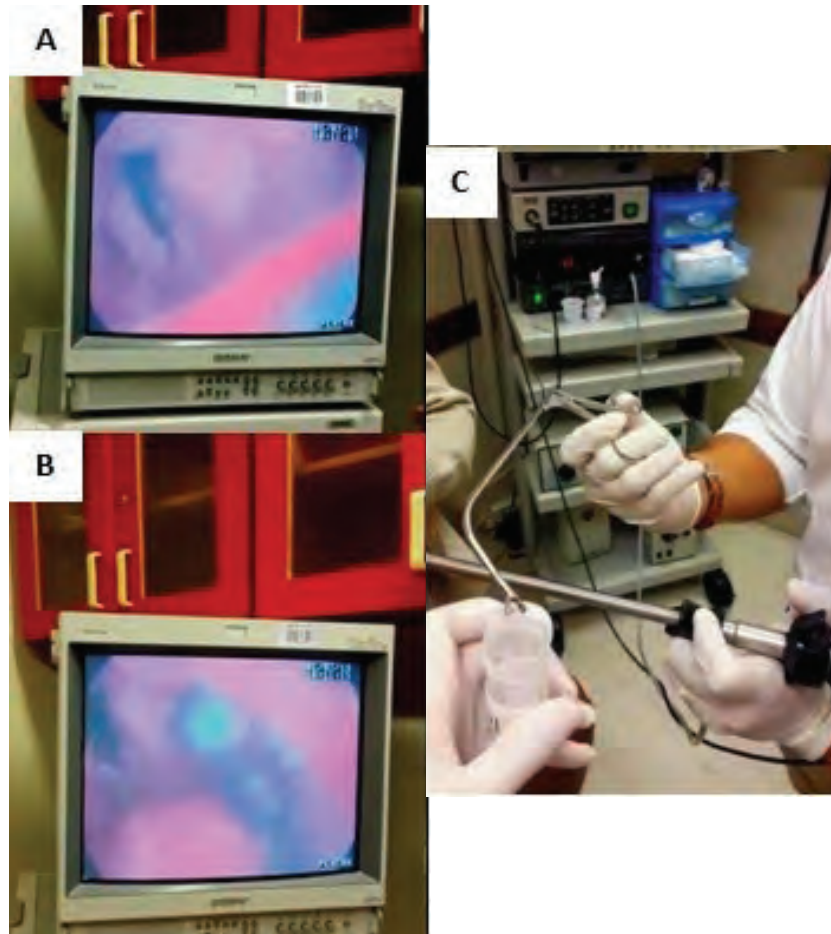


Figure 12-1. A) Left vocal fold lesion; B) Incisional lesion biopsy, and C) Forwarded fragment for pathological analysis in formalin.

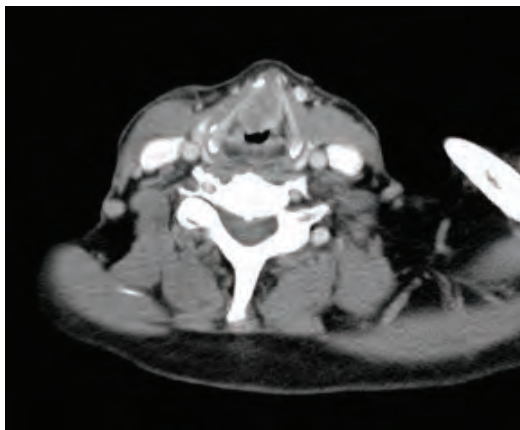


Figure 12-2. Computed tomography showing laryngeal cancer with cartilage and paraglottic invasion.

of the vocal cords, anterior commissure involvement, depth of cord invasion, T classification, and tumor location. Exophytic tumors tend to respond better to radiation than endophytic tumors and have a more favorable prognosis.⁽¹⁷⁾ The degree of differentiation has been correlated with metastatic potential, poorly differentiated tumors being more aggressive. Farias T *et al.* evaluated 22 factors and the expression of proteins p53, Bcl2, Ki67, and PCNA as predictive factors in response to chemoradiotherapy in patients with laryngeal and oropharyngeal squamous cell carcinoma.

Among the 22 predictive factors, only the lack of hypernutrition through nasoenteral tube ($P = 0.0006$), tumor size ($P = 0.009$) and the lack of tracheostomy were predictive of a better response to the treatment (univariate analysis).⁽¹⁸⁾ Nevertheless, when a multivariate analysis was made, only the lack of previous tracheostomy to treatment ($P = 0.0056$) and the lack of hypernutrition through nasoenteral tube ($P = 0.002$) were predictive factors for a better result.⁽¹⁸⁾

Occupational exposures that appear to be relevant include diesel vapors, mists containing sulfuric acid, coal dust and machining fluids. However, molecular analyses and immunohistochemistry evidenced the role of human papillomavirus (HPV) as a causative agent in laryngeal cancer by changing the epidemiology and way of facing the disease. ⁽¹⁹⁾

Molecular analysis is helping not only as a diagnostic marker but also predicts information on prognosis and treatment of laryngeal cancer in the last two decades. ⁽²⁰⁾ The most important molecular changes or mutations are protein p53, cyclin-dependent kinases and their inhibitors, marker of proliferation Ki-67 (MKI67), proliferating cell nuclear antigen (PCNA), BCL2 family members, epidermal growth factor receptor (EGFR) family members, vascular endothelial (CDHV), cathepsins and their endogenous inhibitors, e-cadherin (ECAD; Cadherin 1, Type 1; CDH1), prostaglandin-endoperoxide synthase 2 (VEGF), subfamily members and their receptors, secreted phosphoprotein 1 (SPP1) (PTK2), carbonic anhydrase IX (CA9), Parkinson's protein 7 (PARK7), telomerase reverse transcriptase (TERT), L-DOPA decarboxylase (DDC), kallikrein-related peptidase 11 (KLK11), microRNAs (miRNAs), antisense HOX transcript RNA (HOTAIR). ⁽²¹⁾

There is provocative evidence supporting a strong role for EGFR expression (and, to a lower extent, for its ligand, tumor growth factor α TGF α) in predicting prognosis of LSCC, as it adversely influences both overall, relapse-free and, in particular, regional metastasis free, survival in LSCC 1. Such a strong predictive value is retained by EGFR independently of treatment (surgery, chemotherapy and radiation) and EGFR the reliable prognostic molecular marker. ^(21,22) P53 gene mutation has been hypothesized to be more reliable than IHC over expression for characterization and it has been reported to predict the response to radiotherapy in LSCC patients. ⁽²³⁾

This is consistent with the biological role of p53, which mediates apoptosis associated with DNA damage. Nevertheless, evidence of a correlation with overall, and most of all, regional metastasis-free survival is still lacking. ⁽²³⁾ The biomarkers can also predict the potential risk of laryngeal cancer. According to Nankivell P *et al.* biomarkers such as p53, cortactin, cyclin D1 and ki67 may be indicators of dysplasia or neoplasia. ⁽²⁴⁾

Treatment

Treatment of laryngeal cancer often involves mutilation and loss of organ function, such as in total laryngectomy where

the entire organ of the larynx is resected, with loss of speech and natural way of breathing. Studies show that the patients' adaptability to the new lifestyle resulting from treatment sequelae is good, and depends on an integrated multidisciplinary team (doctors, nurses, speech therapists, psychologists and others). ⁽²⁵⁾ In view of the difficulty in finding a treatment that significantly increases survival, the paradigm is based on multimodal therapies that preserve the function of the organ without, however, harming the patient's survival. Chemotherapy, radiotherapy and partial surgeries have been implemented as viable options for the preservation of all or part of the larynx, improving the patient's quality of life and socialization. ⁽²⁶⁾

Treatment of laryngeal neoplasia will depend on the tumor and lymph node stage, and early stage tumors (stages I and II of the TNM classification) are treated with a therapeutic modality, whereas advanced stage tumors need multimodal therapy combining different forms of surgery, radiotherapy or chemotherapy. ⁽²⁷⁾ There is a need to treat lymphatic drainage of the larynx prophylactically or radically. Surgery followed by radiotherapy is used if there are positive margins, invasion of cartilage, neural or perivascular invasion, locally disseminated disease, multiple (more than one) compromised lymph nodes, lymph node greater than 3cm, contralateral lymph node or extracapsular lymph node extension. ⁽²⁷⁾

Radiotherapy with or without chemotherapy may be used in patients with advanced lymph node disease, followed by planned cervical emptying. It has already been shown that it is possible to find positive lymph nodes in salvage laryngectomy. ⁽²⁸⁾ Advanced locoregional disease is currently being treated with chemoradiotherapy and rescue surgery, achieving disease control, comparable to primary surgical treatment, but with higher preservation rates compared to exclusive radiotherapy. ⁽²⁹⁾

The treatment for advanced laryngeal cancer has undergone a considerable evolution over the past 20 years. The goal of many of the changes has been to achieve control of the disease, as well as the preservation of organ function. Before 1991, the conventional surgical treatment for these cases consisted of total laryngectomy with or without postoperative radiotherapy. ^(30,31) Because of the loss of function and a high degree of morbidity, organ preservation protocols with chemoradiotherapy have been proposed, in order to preserve laryngeal functionality. ^(32,33)

The Veterans Administration (VA) laryngeal cancer study, published in 1991, compared patients treated with induction chemotherapy and radiation therapy with patients treated

with total laryngectomy and adjuvant therapy.⁽³²⁾ Patients in the nonsurgical arm showed no decrease in survival and increased laryngeal preservation, leading to the adoption of nonsurgical therapy of patients requiring primary total laryngectomy.⁽³²⁾ This was one of the pioneering studies in organ preservation treatment.

The RTOG 91-11 study, the follow-up to the VA study, was a three-arm randomized trial comparing radiotherapy alone versus sequential chemotherapy and radiotherapy versus concurrent chemotherapy, completely eliminating primary total laryngectomy for the treatment of advanced laryngeal cancer.⁽³⁴⁾ This study has supported the routine use of concurrent chemotherapy and radiation therapy as a first line treatment for many advanced laryngeal cancers and has led many to abandon primary total laryngectomy.⁽³⁵⁾

Unfortunately, radiotherapy and chemotherapy carry significant early and late toxicities, which can result in swallowing and speech dysfunction, gastrostomy tube, tracheostomy dependence, and impaired quality of life.⁽³⁶⁾ To avoid this morbidity, transoral minimally invasive organ preserving procedures have been developed.⁽³⁷⁻³⁹⁾

Coincident with the shift toward nonsurgical treatment of patients with advanced larynx cancer are the considerable advances in surgical options for early, and select advanced, laryngeal cancers.⁽⁴⁰⁾ Transoral laser microsurgery (TLM) of early larynx cancer, as pioneered by Strong and Jako in America⁽³⁸⁾ and popularized in Europe, showed outstanding results and offered decreased morbidity when compared to open procedures. TLM resection techniques have been applied to pharyngeal and laryngeal tumors and have demonstrated comparable rates of tumor control to open and nonsurgical treatments. These procedures have the advantage of being minimally invasive approaches with improved functional outcomes when compared to standard open surgery. **(Figure 12-3)** TLM has limitations in its application to advanced laryngeal tumors, owing to access issues and the inability to suture tissues closed. In addition, surgical manipulation of the tissues is limited, as one hand is used for retraction and the other for manipulation of the laser. Despite these limitations, the techniques have proven successful, particularly for laryngeal cancer.⁽⁴⁰⁾

In 2000 the European Laryngological Society proposed a classification of different laryngeal endoscopic cordectomies. The classification comprises eight types of cordectomies: a subepithelial cordectomy (type I), which is resection of the epithelium; a subligamentary cordectomy (type II), which is a resection of the epithelium, Reinke's space and vocal ligament; transmuscular cordectomy (type III),

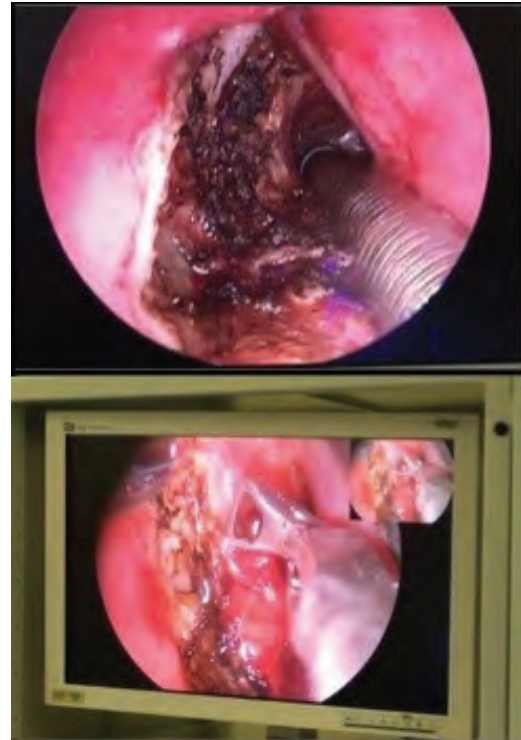


Figure 12-3. *Transoral laser microsurgery. Ventricular band, ventricle of Morgagni, and the vocal cord to the anterior commissure were resected with free margins.*

which proceeds through the vocalis muscle; total cordectomy (type IV); extended cordectomy, which encompasses the contralateral vocal fold and the anterior commissure (type Va); extended cordectomy, which includes the arytenoid (type Vb); extended cordectomy, which encompasses the subglottis (type Vc); and extended cordectomy, which includes the ventricle (type Vd).⁽⁴¹⁾

Peretti *et al.* reported their TLM experience in 595 patients with Tis to T3 glottic carcinoma and had a 5-year disease-specific survival of 100% with a laryngeal preservation rate of 72.7% in their T3 patients.⁽⁴²⁾ An important component of surgery is complete resection of the cancer and the achievement of negative margins. Therefore, techniques to enhance exposure and provide adequate margins would be expected to result in improved survival.⁽⁴⁰⁾

Transoral robotic surgery (TORS), utilizing the DaVinci robotic surgery system has begun to play a larger role in the surgery of the upper aerodigestive tract. TORS has proven to be safe, feasible, and minimally invasive^(43,44) within the oropharynx and has also proven feasible for sites outside of the oropharynx, including the supraglottic larynx, base of skull, parapharyngeal space, and thyroid and cervical lymph



Figure 12-4. The instrumentation articulates at the distal end of the robotic arm, providing complete freedom of motion with scissors, clamps, and cautery. ⁽⁵⁰⁾

nodes. ⁽⁴⁵⁻⁴⁹⁾ The use of TORS can extend the indications of transoral surgery through improved visualization and intra-pharyngeal suturing, among other advantages. In addition, when compared to TLM, the instrumentation articulates at the distal end of the robotic arm, providing complete freedom of motion with scissors, clamps, and cautery. **(Figure 12-4)** These characteristics allow a greater degree of tissue manipulation and dissection. ⁽⁵⁰⁾

The most recent advance in this area has been the application of TORS to perform supraglottic laryngectomy (SGL). ⁽⁵¹⁻⁵⁴⁾ TORS-SGL allows the surgeon to perform an oncologically sound resection without external incisions. The supraglottic laryngectomy resected with a laser may reduce complications of surgical morbidity of traditional partial laryngectomy, such as length of hospital stay and fistula. ⁽⁵³⁾ **(Figure 12-5)** It provides exceptional access with unparalleled views of the larynx, allowing the surgeon to make incisions around the tumor, achieve negative margins, and preserve as much normal tissue as possible. Early results show excellent functional outcomes and quality of life. ⁽⁵⁵⁾

The recommended criteria for TORS-SGL include ability to achieve adequate transoral exposure of the tumor and its margins; T1 or T2 supraglottic carcinoma; selected T3 supraglottic carcinoma, as pre-epiglottic space invasion, ability to preserve 50% of the tongue base with an oncological resection, or mobile vocal cords; and minimal piriform



Figure 12-5. Endoscopic laser surgery for supraglottic cancer. ⁽⁵³⁾

sinus involvement. ⁽⁵¹⁻⁵⁴⁾ TORS-SGL is not an appropriate operation in situations that may jeopardize oncological resection, would violate both cricoarytenoid units, or leave the patient with airway compromise. The contraindications to TORS-SGL include vocal cord fixation; bilateral arytenoid cartilage involvement; thyroid or cricoid cartilage invasion; anterior or posterior commissure involvement; or poor pulmonary reserve (FEV1/FVC < 50%). ⁽⁵⁵⁾

In the larynx, TORS was first used to perform supraglottic laryngectomy and then total laryngectomy. ⁽⁵⁵⁾ Surgical salvage laryngectomy is performed in a hostile local tissue environment and partial laryngectomy is often impractical and salvage total laryngectomy is common. ⁽⁵⁶⁾ Salvage total laryngectomy has a high incidence of perioperative complications, including fistulae and its sequelae. ^(57,58) Therefore, to minimize this risk, the routine use of flap closure is recommended. Even with flap reconstruction, however, wound complications can occur, incurring additional morbidity to the patient.

TORS total laryngectomy in a salvage setting may provide improved healing with a decreased need for routine flap use in salvage open laryngectomy. Furthermore, TORS total laryngectomy has been used to treat patients with subglottic chondrosarcoma, laryngeal chondronecrosis, bilateral vocal cord paralysis, subglottic stenosis due to prolonged intubation, chronic aspiration due to neurological disease, and subglottic adenoid cystic carcinoma. ^(59,60) The exact indica-

tions and limitations of this procedure are not yet defined; but patients with a narrow mandibular arch, anteriorly displaced larynges, or intact dentition will be poor candidates for TORS total laryngectomy using the current instrumentation and mouth retractors. In addition, neck dissection should not be performed simultaneously. ⁽⁵⁵⁾

Another therapeutic option for T1 and T2 laryngeal tumors and some T3 and T4 selected cases is supracricoid laryngectomy (SCL), once its results are found to be satisfactory for both, the laryngeal preservation and functions, when compared to total laryngectomy. ⁽⁶¹⁻⁶⁵⁾ Several literature reports show local control, low recurrence rate and survival rates similar to total laryngectomy, ^(61,62) besides allowing the nonuse of permanent tracheostomy, which enables the oral feeding, voice preservation and social functions, providing a better quality of life. ⁽⁶⁴⁻⁶⁷⁾

SCL includes resection of the true and false vocal folds, both paraglottic spaces, and the thyroid cartilage. It optionally includes up to 1 arytenoid cartilage, a portion or all of the epiglottis, and the preepiglottic space. ⁽⁶⁸⁾ For supraglottic and transglottic cancer, SCL involves resection of the entire epiglottis and preepiglottic space, and the reconstruction is a cricohyoidopexy (CHP). **(Figure 12-6)** For glottic cancer, SCL may preserve the epiglottis, and the reconstruction technique is a cricohyoidoepiglottopexy (CHEP). ⁽⁶⁸⁾ **(Figure 12-7)**

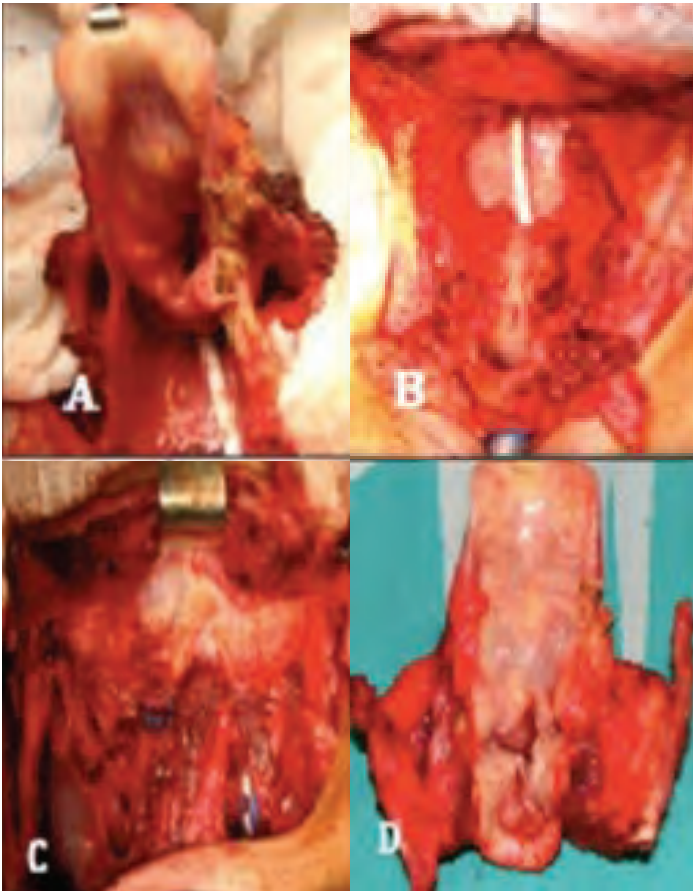


Figure 12-6. Supracricoid laryngectomy with cricohyoidopexy. A) Freeing up the larynx. B) After resection of the surgical specimen; observe the gap between the larynx (cricoid) and the base of the tongue (without epiglottis). C) Cricohyoidopexy. D) Surgical specimen.



Figure 12-7. Supracricoid laryngectomy with cricohyoidoepiglottopexy. A) Freeing up the larynx. B) After resection of the surgical specimen; observe the gap between the larynx (cricoid) and the base of the tongue (with epiglottis). C) Cricohyoidoepiglottopexy.

As with any technique, the key to successful outcome following SCL is careful patient selection. The tumor must be contained within the limits of the *en bloc* resection area. T1B and T2 primary glottic tumors are the ideal and most common indication for SCL. A T3 tumor with vocal cord fixation (which implies paraglottic space invasion) is a candidate for the SCL as long as the arytenoid is mobile. ⁽⁶⁸⁾ A fixed arytenoid indicates tumor invasion of the cricoarytenoid joint, and it is not a candidate for the SCL. Clear contraindications include a fixed arytenoid, subglottic extension to the level of the cricoid, hyoid invasion, and extralaryngeal spread. Maintenance of laryngeal function requires the preservation of at least 1 cricoarytenoid unit (arytenoid cartilage, cricoid cartilage, posterior and lateral cricoarytenoid muscles, and superior and recurrent laryngeal nerves). ⁽⁶⁸⁾

In 1990, Laccourreye *et al.* published the oncologic and functional outcomes of SCL with CHEP for glottic cancer performed in 36 patients. In 34 cases, both arytenoids were preserved, but in one patient the cricoarytenoid joint was disarticulated with resection of one arytenoid, and in the other was performed resection of the antero-lateral portion of the cricoid cartilage with tracheocricohyoidoepiglottomy (TCHEP). ⁽⁶⁹⁾ No complications occurred in these 2 patients, both were decannulated at 7 and 3 days, respectively. The 3-year survival rate was 86.5% and local and regional recurrences rates were 5.6% and 8.4%, respectively. All the patients were decannulated (mean time of 7 days, 3 - 57 days), recovered the swallowing and withdrew enteral tube (mean time of 15 days, 9 - 30 days), and presented vocal quality that allowed social interaction. ⁽⁶⁹⁾

In another publication, the same authors described the oncologic and functional outcomes of SCL with CHP performed in 68 patients for supraglottic/transglottic tumors. A 3-year survival rate was 71.4% with no local recurrence, but with a regional recurrence rate of 5.8% and a distant metastasis of 8.8%. ⁽⁷⁰⁾ All patients were decannulated (mean time of 7 days, 3 - 51 days), 74.6% had normal swallowing and withdrew the enteral tube (mean time of 15 days, 13 - 70 days) and all patients presented phonation that allowed social interaction. One patient died on the 3rd postoperative day due to rupture of the abdominal aortic aneurysm and another died in the 5th month due to recurrent aspiration pneumonia. ⁽⁷⁰⁾

Piquet and Chevalier reported a 5-year overall survival rate of 75%, withdrawn of the enteral tube within 45 postoperative days in 100% of the cases, and decannulation in up to 28 days of 81.5% of the cases in 104 patients undergoing SCL with CHEP in the period between 1972 and 1985. ⁽⁷¹⁾

In the study by Lima *et al.*, in which the functional and oncologic results of 43 patients with T3/T4 glottic cancer treated with SCL with CHEP were evaluated, the 5-year disease-specific survival and disease-free survival were 78% and 83%, respectively. The laryngeal preservation rate was 83.7%. In a previous study by the same authors, 2 of 27 patients undergoing SCL with CHEP for T2/T3 glottic cancer needed total laryngectomy (1 patient for repetitive aspiration pneumonia and 1 patient for rupture of pexy). ^(30, 72)

In 1997, another study published by Laccourreye *et al.* described the cases of rupture of pexy after SCL. In a period of 22 years (1974 - 1996), the incidence of this complication was 0.8% (3/371). In these situations, one can choose to total laryngectomy or to review the pexy with resection of the anterior arch of the cricoid and reconstruction with TCHEP. ⁽⁷³⁾

However, despite the good results of this technique, a significant number of patients may not be treated safely by SCL when there is, for example, subglottic extension greater than 1 cm, or the lesion. (STL) has been described as a surgical procedure designed to spare laryngeal function (breathing, phonation and swallowing), without impairing locoregional control, for glottic or supraglottic cancers with subglottic extension and/or involvement of the cricoarytenoid joint. ⁽⁷⁴⁾ The clinical feature most often characterizing these tumors is unilateral vocal cord and arytenoid fixation with cricoarytenoid joint and cricothyroid space involvement, combined with arytenoid and/or cricoid sclerosis. The choice of SCL in these cases would result in greater risk of positive margins. ⁽⁷⁵⁾

Indications for STL are glottic tumors with anterior and / or lateral subglottic extension, reaching the cricoid ring (T2-T3); glottic and / or supraglottic tumors spreading within the paraglottic space and involvement of only one cricoarytenoid joint, characterized by arytenoid fixation (T3); and locally advanced laryngeal tumors with anterior extension through the thyroid cartilage and minimal extralaryngeal extension (T4a). Local contraindications are tumors reaching both arytenoid cartilages, posterior commissure, base of tongue, hypopharynx and / or trachea; lesions with gross invasion of the preepiglottic space involving the hyoid bone, as well as lesions with large extralaryngeal spread of cancer. ^(74, 76-78)

In 2014 the European Laryngological Society proposed a systematic classification of open partial horizontal laryngectomies identifying three types of surgical procedures based on the lower limit of resection: type I, SGL; type II, SCL; and type III, STL. For types II and III, the suffix "a"

means that the suprahyoid epiglottis has been spared and performed CHEP (type IIa) or tracheohyoidoepiglottopexy - THEP (type IIIa), while the suffix “b” indicates its removal, and performed CHP IIb) or tracheohyoidopexy-THP (type IIIb).

Moreover, each type of laryngectomy may be extended to adjacent structures. Thus, the extent of surgical removal is indicated by abbreviations as follows: + ARY, when the resection involves one arytenoid; + BOT, when it involves the base of tongue; + PIR, for resection of one piriform sinus; + CAU, when it involves one cricoarytenoid unit composed of arytenoid, cricoarytenoid joint, and underlying hemicricoid plate.⁽⁷⁹⁾

The first STL with THEP was performed by Serafini in 1972. This procedure involved the preservation of the suprahyoid epiglottis and pexy between the hyoid bone, the remaining epiglottis, and the first tracheal ring, but this technique removed the two arytenoids, with a poor functional result. Therefore, it was abandoned in the early 1980s.⁽⁸⁰⁾

Succo *et al.* published the results of the largest series in the international literature, with 142 patients undergoing STL in a multi-institutional study in Italy. Of the cases in this series, 21.1% developed recurrence; 70% of these being local and 30% being regional. The 5-year overall survival, disease-specific survival, disease-free survival, and total laryngectomy-free survival were, respectively, 78.7%, 90.4%, 69.1%, and 85.4%.⁽⁸¹⁾

A study by Rizzotto *et al.* evaluated 469 patients undergoing SCL (399) and STL (70) over a period of more than 10 years, comparing the oncologic and functional outcomes. Overall survival and disease-free survival at 5 years and preservation of laryngeal function after 2 years of surgery were, respectively, 95.6%, 90.9%, and 95.7% for SCL, and 80%, 72.9%, and 80% for STL.⁽⁸²⁾ The total laryngectomy rate among all patients in this series was 4.4%. Withdrawn of the nasointestinal tube or gastrostomy occurred in 99.4% of patients (mean time of 16 days, 4 - 161 days) and decannulation occurred in 98.3% of the cases (mean time of 73 days, 16 - 852 days). Both types of laryngectomies present survival rates superior to those obtained through larynx preservation protocols, based on chemoradiotherapy.⁽⁸²⁾

Since 1981, Pearson *et al.* at the Mayo Clinic have reported using near-total laryngectomy (NTL) for the treatment of large tumors in the larynx, preserving the voice but keeping the tracheostoma as the airway.⁽⁸³⁾ (**Figure 12-8**) NTL is an operation for lateralized cord-fixing laryngeal and pharyngeal cancers, in which the entire larynx is resected, except for a narrow vertical posterolateral strip from the opposite

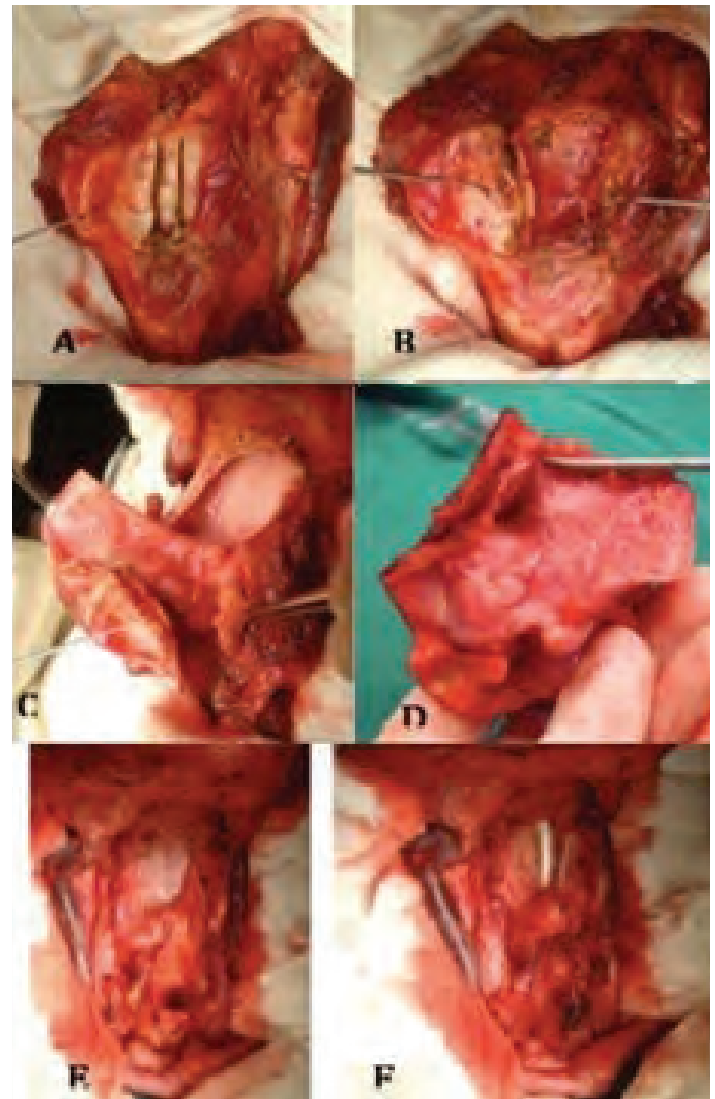


Figure 12-8. Near total laryngectomy. **A)** Incision on the side of the larynx. **B)** Entering the larynx in the paraglottic space. **C)** Freeing up the larynx for near total laryngectomy. **D)** Surgical specimen: $\frac{3}{4}$ of the resected larynx. **E)** After resection of the surgical specimen. **F)** Confection of the phonatory shunt.

side. The strip maintains mucosal continuity between the trachea and the pharynx to serve as the basis of a biological speaking shunt. When everything is healed, pulmonary air can be transmitted from the lungs to the pharynx for voice. It is automatically set into vibration from its passage through the shunt, and the voice thus produced can be articulated into speech by the tongue, lips, and palate as related by Lima.⁽⁸⁴⁾

Total laryngectomy is generally done for advanced cancers of the larynx and hypopharynx, recurrence following (chemo) radiation, and occasionally for intractable aspiration

and advanced thyroid cancer invading the larynx.⁽⁸⁵⁾ (**Figure 12-9**) Although it is an excellent oncologic procedure and secures good swallowing without aspiration, it has disadvantages such as having a permanent tracheostomy; the verbal communication is dependent on oesophageal speech, and/or tracheo-oesophageal fistula speech or an electrolarynx; hyposmia; and the psychological and financial implications. Even in the best centers, about 20% of patients do not acquire useful verbal communication.⁽⁸⁵⁾

Regarding the treatment of negative neck in T3/T4 transglottic and supraglottic squamous carcinoma, Dias F. and Kligerman in two reports advocate that the management of

these patients requires laryngectomy, elective lateral neck dissection (levels II-IV), either ipsilateral (glottic carcinoma) or bilateral (supraglottic, medial wall of pyriform fossa, bilateral glottic carcinoma) with conversion to modified neck dissection if cervical metastases are found intraoperatively. Level VI is included in subglottic and pyriform fossa carcinoma to clear the paratracheal nodes.^(86,87)

Prognostic

The prognosis is related to tumor factors as well as patient factors. In patients with early tumors, these factors are important for the choice of protocol (with or without organ preservation) and the best surgery (total or partial).^(88,89)

In early tumors, specific tumor factors such as vocal cord mobility, involvement of the anterior commissure, depth of invasion, extension in the vocal cord, and proximity to supraglottic swelling may be specific for surgery extension. Exophytic tumors tend to respond better to radiotherapy and have a better prognosis.⁽⁹⁰⁾ Endophytic cartilage invasive tumors involving soft neck tissues, or causing airway obstruction, usually present aggressive clinical evolution and poor response to treatment. Surgical or non-surgical treatment should be better studied. Aggressive surgical treatment is even more important for some cases, although it has been reported as an alternative to disease control. Small differential tumors have higher rates of metastasis than well-differentiated tumors, and aggressive protocols with adjuvant radiotherapy⁽⁹¹⁾ should be followed. There is an estimated survival rate for each disease stage.

Factors related to the patient that may affect the prognosis as a profession, intellectual capacity, general state of health and availability for daily modality. In relation to the general medical measure, the main factor that can influence in the direction is a pulmonary function.⁽⁹¹⁾ Patients who present some type of lung disease caused by smoking may contraindicate a partial clinical procedure, since partial laryngectomies patients have some postoperative aspiration and need a good lung search to perform sputum maneuvers.⁽⁹¹⁾

Survival rates in five years disease-free depend on the location of the primary site and the ability to distant metastasis. Tumors of glottic localization have a better prognosis than supraglottic localization, for example. Thus, tumor staging is directly related to prognosis and patient survival.⁽⁹²⁾ According to the American Cancer Society, 5-year relative survival rates for glottis at the localized stage is 83%, for stage with regional spread is 50% and for distant metastasis is 42%. Considering the supraglottic region the numbers are



Figure 12-9. Total laryngectomy for advanced cancer of larynx. A) Surgical specimen. B) After resection of the surgical specimen. C) Tracheostoma.

60%, 47% and 30% respectively for localized stage, regional spread and distant metastasis. The subglottic region has similar rates than the supraglottic region. ⁽⁹²⁾

Conclusion

In conclusion, squamous cell carcinoma of the larynx is one of the most common tumors of the head and neck. Predictive factors, such as tumor size, presence of tracheostomy, affected areas, invasion of cartilage, will dictate the treatment. Early-stage tumors can be treated with radiotherapy, transoral laser microsurgery, and partial laryngectomy. Advanced tumors can be treated with subtotal and total laryngectomies, or organ preservation with chemoradiotherapy in selected patients.

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Chapter 13

Malignant Tumors of the Parotid Gland

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Introduction

Parotid cancers are a histologically and biologically diverse group of neoplasms that are relatively uncommon, representing only a small percentage (3% to 6%) of all head and neck cancers and 0.3% of all cancers. ⁽¹⁾

Considering all variations in histological subtypes and anatomic sites, it is comprehensible to glimpse how difficult it is to set a line of protocols based on experience, since oncologists usually accumulate limited know-how with specific types. ⁽²⁾

The behaviors of some subtypes are indolent and need long follow up, making it harder to draw and line up conclusions about treatments. ⁽²⁾

Anatomy

The parotid gland is a major salivary gland located deep into superficial fascia of the face that appears in pairs overlying the angle of the mandible, below and in front of the ear canal, draining a mainly serous salivary secretions to the vestibule of the mouth through the parotid duct. ⁽³⁾

It is closely related to the cartilage of the ear canal posteriorly, the zygoma superiorly, the parapharyngeal space medially, and the sternomastoid and posterior digastric muscles inferiorly. ⁽⁴⁾

The facial nerve exits the stylomastoid foramen and runs through the substance of the parotid gland, splitting into its five main branches in the process, that are quite variable.

The virtual plane established by the nerve determines the superficial and deep lobe. ⁽⁴⁾

The parotid duct runs superficial to the masseter muscle, pierces the buccinator muscle and opens into the inner surface of the jugal mucosa as the parotid papilla, facing the maxillary second molar. ⁽⁴⁾

Blood supply comes from external carotid artery and its terminal branches (superficial temporal and the maxillary artery). The venous drainage returns to the retromandibular veins. ⁽⁴⁾ The lymphatic drainage is mainly to the preauricular or parotid lymph nodes which drain to the deep cervical chain. ⁽⁴⁾

The innervation receives both sensory and autonomic innervation. General sensory innervation is provided by the great auricular nerve and the autonomic innervation that controls the rate of saliva production and is supplied by the glossopharyngeal nerve. ⁽⁵⁾

Though being the largest salivary gland, it only provides 25% of the total salivary volume. The serous cell predominates in the parotid and contains salivary alpha-amylase (sAA), the first step in the decomposition of starches during mastication and suggested to prevent bacterial attachment to oral surfaces. ⁽²⁻⁴⁾

The parotid appears early in the sixth week of prenatal development, and the epithelial buds of these glands are located on the inner part of the cheek, near the labial commissures of the primitive mouth, migrating posteriorly towards the otic placodes. At around 10 weeks the ducts start canalizing and the gland starts working at week eighteen. ⁽⁶⁾

Diagnosis

Almost all of the salivary neoplasms are originated in the parotid, being 80 percent benign. Pleomorphic adenoma is the most common of the benign tumors (80%), and mucoepidermoid carcinoma is the most frequent malignant tumor (34%).⁽⁷⁾

The common presentation is a painless swelling of the affected gland, that can be brief or indolent for low grade cancer. Intermittent swelling or pain is most linked to inflammatory disease.⁽⁷⁾

Highly indicative of malignancy include paralysis of all or part of the facial nerve, the presence of associated lymphadenopathy, and a fix tumor (**Figure 13-1**) to overlying skin or adjacent structures is also suggestive of a malignancy.^(8,9)

Radiological imaging of parotid is not routinely indicated but may be useful in cases involving tumors fixed in bony structures, when a plain radiograph could help determine such extension.⁽¹⁰⁾ For parapharyngeal space involvement, MRI is the best choice for staging the tumor.⁽¹⁰⁾



Figure 13-1. Advanced (Stage IV) parotid gland tumor.

The gland is easily accessible for to fine needle aspiration biopsy (FNAB) and a vast cytopathology documentation makes it reliably to distinguish salivary from non-salivary pathology and benign from malignant.⁽¹¹⁾

The histological classification (**Table 13-1**) only could be precise following an excisional or an incisional biopsy, giving the pathologist an adequate tissue sample to categorize the lesion in one of the more than 30 subtypes of tumor.⁽¹¹⁾

Mucoepidermoide carcinoma low grade and acinic cell carcinoma are cosidered low grade.The rest of tumors are considered high grade.⁽¹²⁾

Table 13-1. Malignant Histological Types of Malignance Tumor Salivary Gland⁽¹²⁾

Malignant Tumors

- Mucoepidermoid carcinoma
- Adeniod cystic carcinoma
- Acinic cell carcinoma
- Polymorphous adenocarcinoma
- Clear cell carcinoma
- Basal cell adenocarcinoma
- Intraductal carcinoma
- Adenocarcinoma, NOS
- Salivary duct carcinoma
- Myoepithelial carcinoma
- Epithelial – myoepithelial carcinoma
- Carcinoma ex pleomorphic adenoma
- Secretory carcinoma
- Sebaceous adenocarcinoma
- Carcinosarcoma
- Poorly differentiated carcinoma
 - Undifferentiated carcinoma
 - Large cell neuroendocrine carcinoma
 - Small cell neuroendocrine carcinoma
- Lymphoepithelial carcinoma
- Squamous cell carcinoma
- Oncocytic carcinoma
- Uncertain malignant potential
- Sialoblastoma

Staging

Clinical staging for Parotid malignant tumors follows the staging system most often used for salivary gland cancers, the American Joint Committee on Cancer (AJCC) TNM system 8th edition.⁽¹³⁾

Treatment

Goals of the Parotid tumors treatment are to cure the disease causing the minimal morbidity to the patient, remembering that the excision of one entire gland impacts a little in the salivary system functionality. ⁽²⁾

Surgical resection is the gold standard for all salivary glands treatment, but in the case of parotid, the facial nerve and its branches passing throughout the gland makes it more sensible because of the risk of the nerve damage. ⁽²⁾

The staging and the histological type will determine a more conservative treatment for smaller lesion and combined therapies for large tumors or metastatic ones. ⁽²⁾ Disseminated or local aggressive disease usually will determine conservative or palliative treatments, because there will be no benefits in long term submitting the patient to extensive surgery. ⁽²⁾

An exception must be reminded, that patients with adenoid cystic carcinomas can live for many years despite the presence of metastatic disease. ⁽¹⁾

The location of the tumor is very important, and borderline resectable lesions in inaccessible locations, such as the base of the skull, is better treated with nonsurgical therapy such as neutron beam irradiation. ^(1,2)

Surgical Treatment

Parotidectomy and its variations are the standard surgical procedure to treat parotid cancer and is consists in excising the superficial lobe or the deep lobe of the gland, (**Figure 13-2**) depending of the site and extension of the lesion. ⁽²⁾

As said before, because of the intimate relation between the gland and the facial nerve, every effort should be made to preserve it, but remembering that piecemeal excision of a malignant tumors violates basic oncologic principles and is condemned. ⁽²⁾ Sacrifice of all or part of the facial nerve has been required in 29 to 40 percent of reported patients with carcinoma of the parotid gland. ^(2,14)

There are advanced technics of facial nerve monitoring (FNM) helps the surgeons to identify *in vivo* the branches or its damage. (**Figure 13-3**) Posterior nerve grafting could be used to diminish the effects of the damage until six months after the surgery, because after that the neural plate losses its integrity. ⁽¹⁵⁾

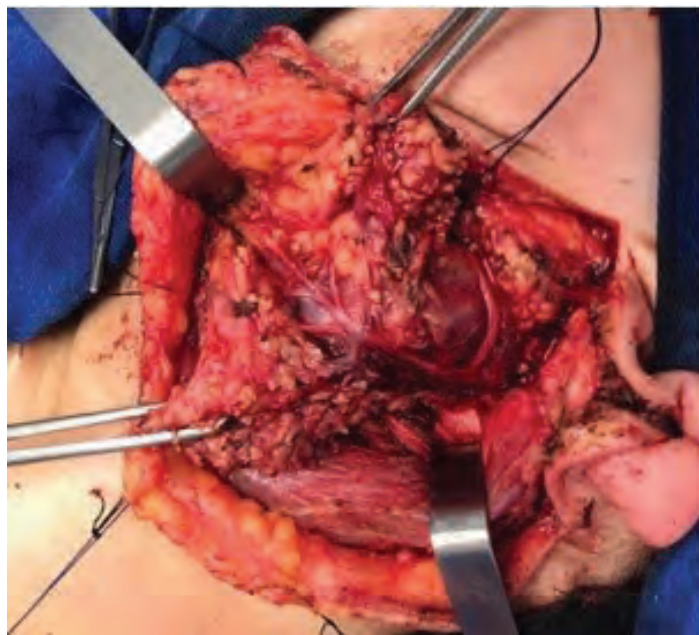


Figure 13-2. Deep lobe tumor and the facial nerve.



Figure 13-3. Facial nerve monitoring.

Some recent studies that intraoperative FNM decreases the risk of immediate postoperative facial nerve weakness but does not appear to influence the final outcome of permanent facial nerve weakness. ⁽¹⁶⁾

Tumors deep to the facial nerve (**Figure 13-2**) could be accessed by transfacial approach transoral surgery and even transoral robotic surgery, as shown by Dias *et al.* ^(2, 17-19)

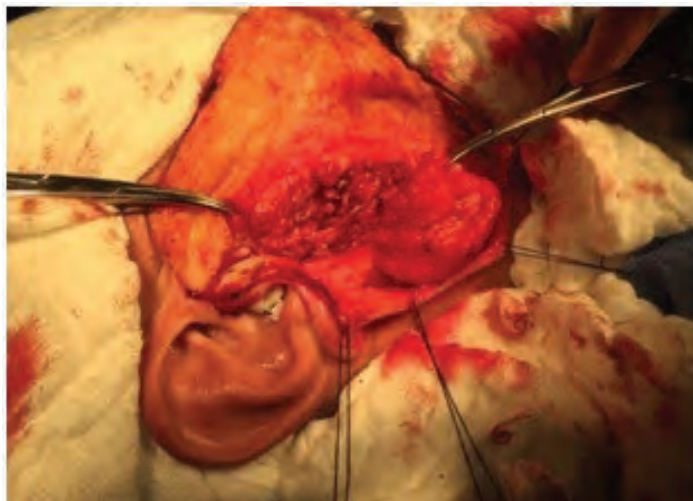


Figure 13-4. Abdomen fat graft over the parotidectomy site.

Those small lesions located near the parapharyngeal space, a paramedian mandibulotomy will occasionally be required for adequate access to the the neoplasm site. ⁽²⁾

Farias *et al.* have demonstrated that autologous fat graft in the perioperative (**Figure 13-4**) reduces effectively the incidence of Frey's Syndrome in patients submitted to parotidectomy. ^(20,21)

Neck Treatment

The patients who initially present with clinical nodal involvement require therapeutic neck dissection as a gold standard. ⁽²⁾ (**Figure 13-5**)



Figure 13-5. Radical parotidectomy with facial nerve sacrifice and radical neck resection.

In cases with limited disease in the first echelon of nodal drainage, selective neck dissection will be mandatory. ⁽²²⁾

Studies have been transforming as a standard protocol a prophylactic neck dissection for high risk patients - those with high grade squamous cell or mucoepidermoid carcinoma (any Stage), extensive disease (Stage T3 - T4), and facial paralysis at the diagnose as reported by Lima and Dias. ⁽²²⁾

Non-Surgical Treatment

In the past decades, salivary cancer in the majority was considered radiation resistant tumors, but the role of radiotherapy, mainly adjuvant with the surgical treatment have been the best choice for high risk patients. ⁽²³⁾ For tumors relatively inaccessible, primary radiotherapy becomes an attractive and sometimes the only option for an acceptable result. ^(23,24)

The neutron beam irradiation has been advocated lately as a primary therapy for salivary cancer in this setting, particularly in patients with adenoid cystic carcinoma, with acceptable loco-regional control rates, but with significant associated morbidity. This type of irradiation might be best reserved for palliative treatment or recurrent lesions. ^(24,25)

Chemotherapy or immunotherapy are not available as treatment for the main histological types and still demands studies and advances to be applied in the clinical practice. ^(2,24,25)

Prognosis

Salivary neoplasm of parotid gland has their prognosis related to the stage of lesion and the biggest involving the surgical treatment is the injury to the facial nerve. ^(1,2) Spiro *et al.* reported cumulative survival rate in 5, 10 and 15 years for parotid gland neoplasms are 82%, 67% and 55%, respectively. ⁽²⁾

Conclusions

The parotid gland malignant neoplasms have an uncommon incidence and embraces a vast number of histological types.

Treatment itself depends on the type of neoplasm, its invasive potential, always remembering to make all possible efforts to spare the facial nerve or to diminish the damage aiming a nerve graft.

The neck dissection in N0 patients is protocol in patients with high risk tumors or advanced tumors (T3 and T4), considering adjuvant radiotherapy to improve local disease control.

Nowadays with all the resources available, the 5-year survival rate reaches 82%.

The treatment of those neoplasms probably will change in the next years, considering the target therapies developing.

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SECTION III
Thyroid Cancer

Chapter 14

Thyroid Cancer

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Introduction

There has been a marked increase in the incidence of thyroid cancer in the last decades. This is associated with improved management and “overdiagnosis” of these smaller carcinomas due to increased use of diagnostic imaging and diagnostic techniques making the thyroid carcinoma the most common endocrine malignancy and the papillary thyroid carcinoma (PTC) (**Figure 14-1**) now represents the fifth most common cancer in females. ⁽¹⁾

The most thyroid cancer is indolent nature which explains relatively low death rate compared to incidence. The anaplastic variety do not have such behavior because they are more aggressive. The vast majority of thyroid cancer are differentiated (**Figure 14-2**) and usually have an excellent long-term prognosis, with 5-year survival rates approaching 100% for localized disease. The advances in the fields of molecular and genetic testing, evaluation, screening, and management of malignant thyroid disease are continually evolving and new guidelines have been

recently published regarding extent of surgical resection, role of lymphadenectomy, and adjuvant medical therapies for thyroid carcinoma. ⁽²⁾

Thyroid follicular epithelial-derived cancers are divided into three categories: papillary cancer, follicular cancer and anaplastic cancer. Papillary and follicular cancers are considered differentiated cancers (**Figure 14-1**) and patients with these tumors are often treated similarly despite numerous biologic differences. Most anaplastic thyroid cancers (ATC) (**Figure 14-2**) appear to arise from differentiated cancers, despite being undifferentiated. ⁽³⁾ Other malignant diseases of the thyroid include medullary thyroid cancer (which can be familial, either as part of the multiple endocrine neoplasia type 2 syndrome or isolated familial medullary thyroid cancer), primary thyroid lymphoma, or metastases from breast, colon, or renal cancer or melanoma. Thyroid cancers that synthesize thyroxine and triiodothyronine, leading to hyperthyroidism, are extremely rare. ⁽⁴⁾

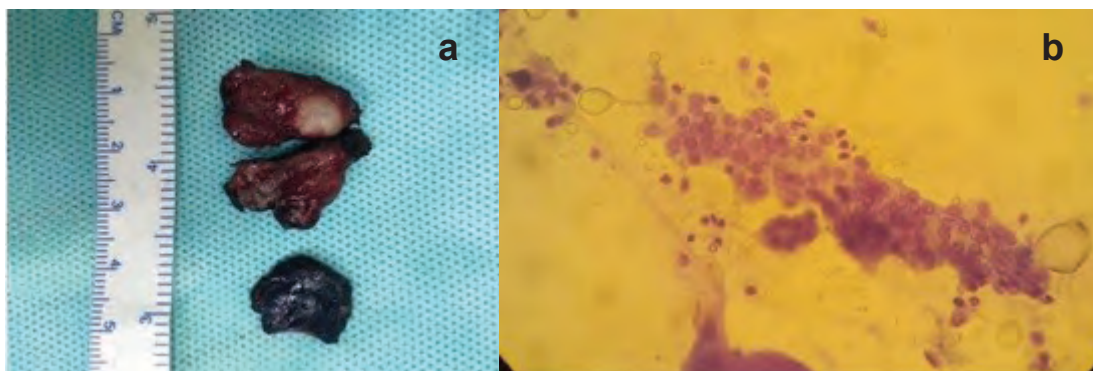


Figure 14-1. A) Differentiated thyroid tumor. B) Microscopic images of transoperative staining.

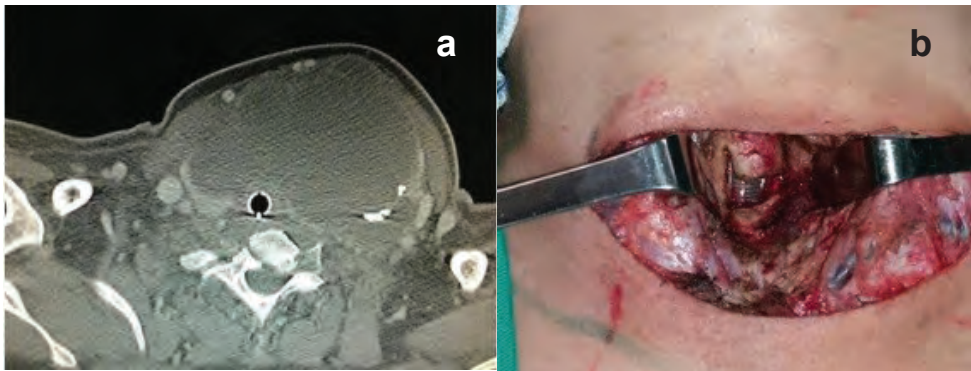


Figure 14-2. A) Tomography of thyroid anaplastic carcinoma. B) Transtumoral tracheostomy.

Bethesda System and Fine-Needle Aspiration (FNA)

The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) established a standardized, category-based reporting system for thyroid fine-needle aspiration (FNA) specimens. The 2017 revision reaffirms that every thyroid FNA report should begin with one of six diagnostic categories, the names of which remain unchanged since they were first introduced: (I) nondiagnostic or unsatisfactory; (II) benign; (III) atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS); (IV) follicular neoplasm or suspicious for a follicular neoplasm; (V) suspicious for malignancy; and (VI) malignant. ⁽⁵⁾

The 2017 revision described herein was inspired by new data and new developments in the field of thyroid pathology: revised guidelines for the management of patients with thyroid nodules, ⁽⁶⁾ the introduction of molecular testing as an adjunct to cytopathologic examination, and the reclassification of the noninvasive follicular variant of papillary thyroid carcinoma as noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). ⁽⁷⁾

Based on the panel’s recommendation, the six original general categories:

- 1) Nondiagnostic/unsatisfactory [ND/UNS]; 2) Benign;
- 3) Atypia of undetermined significance/follicular lesion of undetermined significance [AUS/FLUS]; 4) Follicular neoplasm/ suspicious for a follicular neoplasm [FN/SFN];
- 5) Suspicious for malignancy [SUS]; and 6) Malignant, have been retained in the 2017 revision, and a revised atlas is in press, with updated and expanded chapters devoted to these categories and refined definitions, morphologic criteria, and explanatory notes. ⁽⁷⁾

The six general diagnostic categories are unchanged and are shown in upper case in **Table 14-1.** ⁽⁷⁾

Table 14-1. The 2017 Bethesda System for Reporting Thyroid Cytopathology Recommended Diagnostic Categories	
I.	Nondiagnostic or Unsatisfactory Cyst fluid only Virtual acellular specimen Other (obscuring blood, clotting artifact, etc.)
II.	Benign Consistent with a benign follicular nodule (includes adenomatoid nodule, colloid nodule, etc.) Consistent with lymphocytic (Hashimoto) thyroiditis in the proper clinical context Consistent with granulomatous (subacute) thyroiditis Other
III.	Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance
IV.	Follicular Neoplasm or Suspicious for a Follicular Neoplasm Specify if Hurthle cell (oncocytic) type
V.	Suspicious for Malignancy Suspicious for papillary carcinoma Suspicious for medullary carcinoma Suspicious for metastatic carcinoma Suspicious for lymphoma
VI.	Malignant Papillary thyroid carcinoma Poorly differentiated carcinoma Medullary thyroid carcinoma Undifferentiated (anaplastic) carcinoma Squamous-cell carcinoma Carcinoma with mixed features (Specify) Metastatic carcinoma Non-Hodgkin lymphoma Other

Ali S, Cibas E 2018 *The Bethesda System for Reporting Thyroid Cytopathology: Definitions, Criteria, and Explanatory Notes. Second edition. Springer, New York, NY.* ⁽⁷⁾

For some of the general categories, some degree of subcategorization can be informative and is often appropriate. (**Table 14-1**) Additional descriptive comments (beyond such subcategorization) are optional and are left to the discretion of the cytopathologist. Notes and recommendations are not required but can be useful in certain circumstances, particularly if the cytomorphic features raise the possibility of NIFTP. NIFTP has added a wrinkle in this regard by excluding the noninvasive follicular variant of papillary thyroid carcinoma from the list of thyroid carcinomas. ⁽⁷⁾

Nondiagnostic or Unsatisfactory

Every thyroid FNA should be evaluated for specimen adequacy. Inadequate samples are reported as nondiagnostic (ND) or unsatisfactory (UNS). Given that the great majority of ND/UNS nodules prove to be benign, one may question whether the criteria for adequacy are too stringent. Lowering the required number of follicular cells would save many patients a repeat FNA. Preliminary data suggest that doing so would substantially reduce ND/UNS interpretations without significantly impacting the false-negative rate. ^(8,9) There is no consensus on a lower number, however, and therefore the criteria have been retained, with the understanding that this is an evolving area that would benefit from more evidence.

Specimens that consist only of cyst contents (macrophages) are ND/UNS. The significance (and clinical value) of a ND/UNS, cyst contents only result depends in large part on sonographic correlation. Among surgically excised nodules initially reported as ND/UNS, the malignancy rate is 9–32%. Surgically resected nodules, however, are a selected subset that were either repeatedly ND/UNS or had worrisome clinical/sonographic features or both. ⁽⁵⁾ A repeat aspiration with ultrasound guidance is recommended for cytologically ND/UNS nodules and is diagnostic in most cases, but some nodules remain persistently ND/UNS. Excision is considered for persistently ND/UNS nodules. ATA guidelines now state that there is no need to wait several months before repeating the FNA. ⁽⁵⁾

Benign

The 2017 BSRTC has essentially made no changes to the usage, definition, criteria, or usual management association for this category. Data continue to support a very low false negative rate (<3%). (**Figure 14-3**)

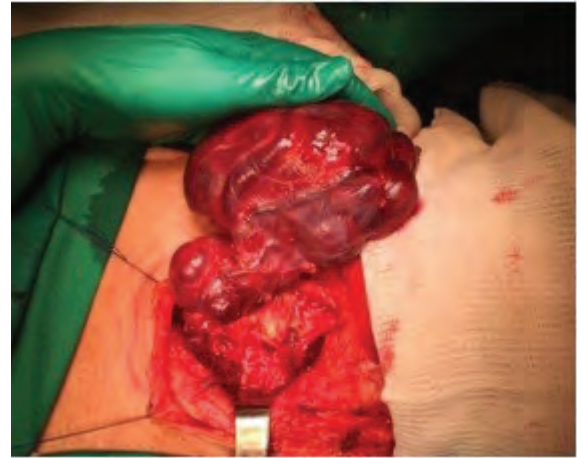


Figure 14-3. Benign multinodular thyroid goiter.

Atypia of Undetermined Significance (AUS) or Follicular Lesion of Undetermined Significance (FLUS)

This category has two alternative names. A laboratory should choose the one it prefers and use it exclusively when criteria are fulfilled for this category. It is worth pointing out that, of the two, AUS is more versatile; FLUS apply only to follicular lesions of undetermined significance and cannot be used if the cells are not clearly follicular in origin (e.g., lymphoid, parafoallicular, parathyroid, etc.).

Because only a minority of AUS/FLUS cases undergo excision, estimating the ROM based on histologic follow-up alone overestimates the ROM due to selection bias: AUS/FLUS nodules (much like Benign and ND/UNS nodules) are usually resected only if there are worrisome clinical or sonographic features, an abnormal repeat aspiration result, and/or an abnormal molecular testing result. Although the overall low-risk nature of AUS/FLUS aspirates has been borne out, new (pre-NIFTP) data suggest that the ROM is higher than originally estimated and closer to 10–30%. On the other hand, if the risk is recalculated by removing NIFTPs from the tally of malignancies, the risk diminishes to 6–18% because early data suggest that NIFTP constitutes a substantial proportion of the malignancies hidden in this category. ^(10,11)

BSRTC recommends subclassification of the atypia, even though this will not generally affect patient management. Descriptive language such as cytologic atypia and architectural atypia is preferred (rather than rule out papillary carcinoma, etc.) due to its less provoking nature, as follows: (I) Cytologic atypia. This may take one of several different forms: focal nuclear changes, extensive

but mild nuclear changes, atypical cyst lining cells, or histiocytoid cells. ⁽¹²⁻¹⁴⁾ (II) Architectural atypia. This is often a sparsely cellular sample but one that is comprised mostly of microfollicles. (III) Cytologic and architectural atypia. Cytologic atypia and architectural atypia are not mutually exclusive. (IV) Hürthle cell AUS/FLUS. This is often a sparsely cellular sample comprised exclusively of Hürthle cells. Alternatively, AUS/FLUS may be used for a moderately or markedly cellular sample composed exclusively (or almost exclusively) of Hürthle cells if the clinical setting suggests a benign Hürthle cell nodule, such as in chronic lymphocytic (Hashimoto) thyroiditis or a multinodular goiter. (V) Atypia, not otherwise specified.

Follicular Neoplasm (FN) or Suspicious for a Follicular Neoplasm (SFN)

FN and SFN are synonymous terms and should not be used to denote two distinct interpretations. SFN is preferred by some laboratories because a significant proportion of cases (up to 35%) prove not to be neoplasms but rather hyperplastic proliferations of follicular cells, most commonly those of multinodular goiter. ⁽¹⁵⁻¹⁷⁾ (Figure 14-4)

The 2017 BSRTC includes a modification to the definition and diagnostic criteria for this category in light of NIFTP.

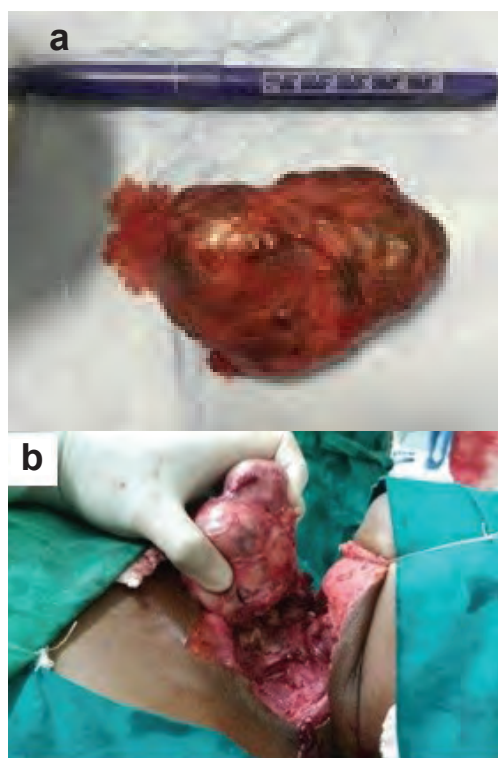


Figure 14-4. A) Benign multinodular thyroid goiter. B) Benign goiter thyroidectomy.

In the original BSRTC, cases that demonstrated the nuclear features of papillary thyroid carcinoma were excluded from this category. The new definition reads as follows: Follicular-patterned cases with mild nuclear changes (increased nuclear size, nuclear contour irregularity, and/or chromatin clearing) can be classified as FN/SFN so long as true papillae and intranuclear pseudoinclusions are absent; a note that some nuclear features raise the possibility of a follicular variant of papillary thyroid carcinoma (FVPTC) or NIFTP can be included. ⁽⁵⁾

As with AUS/FLUS, if the ROM for FN/SFN is recalculated by removing NIFTPs from the tally of malignancies, the risk diminishes. Early data suggest that NIFTP constitutes a substantial proportion of the malignancies hidden in this category as well. ⁽¹²⁻¹⁴⁾ The recommended management of a patient with a diagnosis of FN/SFN is surgical excision of the lesion, most often a hemithyroidectomy or lobectomy, but molecular testing may be used to supplement risk assessment rather than proceeding directly to surgery.

Suspicious for Malignancy

As with AUS/FLUS and FN/SFN, if the ROM for this category (SUS) is recalculated by removing NIFTPs from

Table 14-2. Thyroid Imaging Reporting and Data System – TI-RADS		
Category	US Features	Malignancy Risk %
TIRADS 1: Normal	No nodules	None
TIRADS 2: Benign	Pure cyst / Entirely spongiform	0
TIRADS 3: Low Risk	Ovoid, smooth isoechoic / hyperechoic No features of high suspicion	2-4
TIRADS 4: Intermediate Risk	Ovoid, smooth, mildly hypoechoic No features of high suspicion	6-17
TIRADS 5: High Risk	At least 1 of following features of high suspicion: • Irregular shape • Irregular margins • Microcalcifications • Marked hypoechogenicity (and solid)	26-87

Frates MC, Benson CB, Charboneau JW, et al. Management of thyroid nodules detected at US: Society of Radiologists in Ultrasound consensus conference statement. *Radiology* 2005;237:794-800. ⁽²⁴⁾

the tally of malignancies, the risk diminishes. (**Table 14-2**) Early data suggest that NIFTP constitutes a substantial proportion of the malignancies hidden in this category as well. ^(12,13) This can be useful in guiding the clinical team in the direction of lobectomy rather than thyroidectomy for this subset of SUS cases. ⁽¹³⁾

Malignant

The general category malignant is used whenever the cytomorphic features are conclusive for malignancy. Based on early studies, NIFTP constitutes only a very small fraction of cases that are interpreted as malignant. Nevertheless, the 2017 BSRTC has modified the definition and criteria for cases of papillary thyroid carcinoma that belong in the malignant category. To avoid false-positives due to NIFTP, it suggests limiting use of the malignant category to cases with classical features of papillary thyroid carcinoma (true papillae, psammoma bodies, and nuclear pseudoinclusions). ⁽¹⁸⁾

Thyroid Imaging Reporting and Data System (TI-RADS)

Thyroid nodules are exceedingly common, with a reported prevalence of up to 68% in adults on high-resolution ultrasound. ⁽¹⁹⁾ Currently, fine-needle aspiration (FNA) is the most effective, practical test to determine whether a nodule is malignant or may require surgery to reach a definitive diagnosis. ⁽²⁰⁾ However, most nodules are benign, and even malignant nodules, particularly ones smaller than 1 cm, frequently exhibit indolent or nonaggressive behavior. ⁽²¹⁾ Therefore, not all detected nodules require FNA and/or surgery.

Therefore, a reliable, noninvasive method to identify which nodules warrant FNA on the basis of a reasonable likelihood of biologically significant malignancy would be highly desirable. In 2015, committees convened by the ACR published white papers that presented an approach to incidental thyroid nodules and proposed standard terminology (lexicon) for ultrasound reporting. The purpose of the present white paper is to present our system for risk stratification, which is designed to identify most clinically significant malignancies while reducing the number of biopsies performed on benign nodules. ^(22,23)

Several professional societies and groups of investigators have proposed methods to guide ultrasound practitioners in recommending FNA on the basis of ultrasound features. Some of these systems were termed TI-RADS (Thyroid Imaging, Reporting and Data System) because they were modeled on the ACR's BI-RADS, which has been widely accepted in breast imaging. ⁽²³⁾

The ACR TI-RADS Committee agreed on the following attributes for our risk classification algorithm. It would be: founded on the ultrasound features defined in our previously published lexicon; easy to apply across a wide gamut of ultrasound practices; able to classify all thyroid nodules; and evidence based to the greatest extent possible. ⁽²⁴⁾

The ultrasound features in the ACR TI-RADS are categorized as benign, minimally suspicious, moderately suspicious, or highly suspicious for malignancy. ⁽²⁴⁾

Points are given for all the ultrasound features in a nodule, with more suspicious features being awarded additional points. ⁽²²⁾ When assessing a nodule, the reader selects one feature from each of the first four categories and all the features that apply from the final category and sums the points. The point total determines the nodule's ACR TI-RADS level, which ranges from TR1 (benign) to TR5 (high suspicion of malignancy). Note that although it is possible for a nodule to be awarded zero points and hence be characterized as TR1, all other nodules merit at least two points because a nodule that has a mixed cystic and solid composition (one point) will also gain at least one more point for the echogenicity of its solid component. ⁽²³⁾

In the ACR TI-RADS, recommendations for FNA or ultrasound follow-up are based on a nodule's ACR TI-RADS level and its maximum diameter. For risk levels TR3 through TR5, the chart presents a size threshold at or above which FNA should be recommended. We also defined lower size limits for recommending follow-up ultrasound for TR3, TR4, and TR5 nodules to limit the number of repeat sonograms for those that are likely to be benign or not clinically significant. ⁽²⁴⁾ Following **Table 14-2**.

This suggested to us that diagnosing every thyroid malignancy should not be our goal. Like other professional societies, ⁽²⁵⁾ we recommend biopsy of high-suspicion nodules only if they are 1 cm or larger. As well, we advocate biopsy of nodules that have a low risk for malignancy only when they measure 2.5 cm or more. ⁽²⁶⁾

The ACR TI-RADS is designed to balance the benefit of identifying clinically important cancers against the risk and cost of subjecting patients with benign nodules or indolent cancers to biopsy and treatment. ⁽²⁷⁾ Partial analysis showed cancer risk levels of no more than 2% for TR1 and TR2 nodules, 5% for TR3 nodules, 5% to 20% for TR4 nodules, and at least 20% for TR5 nodules. ⁽²⁷⁾

Nodules that are cystic or almost completely cystic merit no points because they are almost universally benign. ⁽²⁸⁾ Similarly, a spongiform architecture is highly correlated with benign cytology, regardless of its relative echogenicity or other features. ⁽²⁹⁾ Nodules should not be characterized as spongiform solely on the basis of the presence of a few, scattered cystic components in an otherwise solid nodule. The appearance of the solid component is more important than the overall size of the nodule or the proportion of solid versus cystic components in determining whether biopsy is warranted. Macrocalcifications are coarse echogenic foci accompanied by acoustic shadowing.

Evidence in the literature regarding their association with increased malignancy risk is mixed, especially in nodules lacking other malignant features. Given published data that show a weakly positive relationship with malignancy, ⁽³⁰⁾ macrocalcifications are assigned one point, recognizing that the risk is increased if the nodule also contains moderately or highly suspicious features that warrant additional points. Punctate echogenic foci are smaller than macrocalcifications and are nonshadowing. In the solid components of thyroid nodules, they may correspond to the psammomatous calcifications associated with papillary cancers and are therefore considered highly suspicious, particularly in combination with other suspicious features. ⁽³⁰⁾

The ACR TI-RADS is concordant with other guidelines in recommending against routine biopsy of nodules smaller than 1 cm, even if they are highly suspicious. However, because some thyroid specialists advocate active surveillance, ablation, or lobectomy for papillary microcarcinomas, biopsy of 5- to 9-mm TR5 nodules may be appropriate under certain circumstances. ⁽³⁰⁾

The committee believes that scanning intervals of less than 1 year are not warranted, except for proven cancers under active surveillance, which may require more frequent follow-up at the discretion of the referring physician. ⁽³¹⁾ We advocate timing on the basis of a nodule's ACR TI-RADS level, with additional sonograms for lesions that are more suspicious. For a TR5 lesion, we recommend scans every year for up to 5 years. For a TR4 lesion, scans should be

done at 1, 2, 3, and 5 years. For a TR3 lesion, follow-up imaging may be performed at 1, 3, and 5 years. ⁽³¹⁾

Molecular Genetics of Thyroid Carcinoma

In thyroid tumors there is no correlation between aneuploidy and malignancy and thus it cannot be used as a distinctive criterion. Aneuploidy can indeed be present in benign and malignant thyroid lesions; PTC, in particular, usually displays a diploid or near diploid DNA content. ⁽³²⁾ Despite this, an aneuploid DNA content is more frequently found in metastasizing/more aggressive PTC than in conventional PTCs. ⁽³³⁾

In general, PTC is cytogenetically characterized by normal karyotypes or, whenever abnormal, by simple cytogenetic alterations. Structural chromosomal alterations involve more frequently chromosomes 1, 3, 7, and 10. Remarkably, some cases of the follicular variant of PTC (FVPTC) are characterized by chromosomal aberrations commonly found in follicular thyroid adenomas (FTA) or follicular thyroid carcinomas (FTC), such as t(2;3) and gains of chromosomes 3, 5, 7, 9, 12, 14, 17, and 20. ⁽³⁴⁾ These findings suggest that there are cytogenetic changes preferentially associated with FVPTC and that FVPTC is closer to the FTC and FTA group of lesions than to classical PTC. ⁽³⁵⁾ Another signal of the genetic stability of PTC lies in the rare microsatellite instability in these carcinomas. ⁽³⁶⁾

Taking the apparent genetic stability of PTC together with the frequent occurrence, in young patients, of cases of multicentric PTC, it is tempting to consider that PTC tumorigenesis reflects the end product of few carcinogenic events. ⁽³⁷⁾

The indolent growth of PTC is reflected in the very low rates of proliferative activity, evaluated both by immunohistochemical markers (i.e. MIB-1) and by cytometric assessment of the S-phase. ⁽³⁸⁾

Several mutations or genetic changes can trigger a thyroid tumor. The major genetic changes in thyroid cancer are *RET*/PTC and *NTRK1* rearrangements, *BRAF* mutations, *RAS* mutations, *PAX8/PPARG* rearrangements and alterations in mitochondrial genes in PTC. There is therefore some phenotype-genotype relationship in thyroid neoplasia. ⁽³⁹⁾

FNA is the best tool for the early diagnosis of thyroid lesions. As the PTC diagnosis relies on the typical nuclear features, cases with less than typical PTC nuclei in FNA samples, as it frequently occurs in FVPTC, may be misdiagnosed as FTA or as follicular tumour. All the limitations led to the

assumption that good ancillary tools would be very useful for the FNA diagnosis of difficult thyroid tumors. PAX8-PPAR γ rearrangements and RAS genes mutations are quite prevalent in cases of FVPTC.⁽³²⁾ Yet, such genetic events are similarly frequent in the lesions we would like to distinguish from PTC – e.g. FTC and, more importantly, FTA.⁽³⁹⁾ Thus, the identification of PAX8-PPAR γ rearrangements and/or RAS mutations in FNA samples does not provide useful diagnostic improvements in difficult, concrete, follicular patterned thyroid tumors. Most studies published so far have focused on the clinical significance of RET/PTC rearrangements and, particularly, of mutant BRAF forms.⁽⁴⁰⁾

There are 2 cytological molecular tests are very promising: Mirthype and the Affirma. The Affirma gene expression classifier (GEC) is the only molecular test supported by multicenter, prospective, and blinded validation data, and the only test supported by published clinical data demonstrating a dramatic reduction in diagnostic surgery for patients with benign GEC results.⁽⁴¹⁾ Nearly 1 out of every 2 Affirms GEC tests performed yields a molecularly benign result, and >80% of patients with benign GEC result remain unoperated 3 years after the biopsy in real-world experience. Reducing unnecessary diagnostic surgery improves patient safety, reduces healthcare costs, and improves patient quality of life.⁽⁴¹⁾

Mirthype and other tests that certify the FNA's impression of Bethesda classifications III, IV and V corroborate with the improvement of screening and help in decision making.⁽⁴²⁾

Staging

Thyroid carcinoma staging is most commonly performed using the American Joint Committee on Cancer (AJCC) staging system. A number of other validated staging systems have been used to predict cause-specific survival from thyroid cancer including AGES (Age, Grade, Extent, Size), AMES (Age, Metastasis, Extent, Size), MACIS (Metastasis, Age, Completeness of Resection, Invasion, and Size), and EORTC (European Organization for Research and Treatment of Cancer).⁽⁴³⁾ Research has demonstrated the superiority of the AJCC TNM staging system in predicting cancer-related mortality.⁽⁴¹⁾ Unfortunately, no staging system, including the AJCC system, has a high predictive value in forecasting recurrent disease, especially in individuals who develop thyroid cancer at a young age.

The 8th edition (2016) of the AJCC staging system modified definitions of primary tumor and regional lymph node metastases. (**Table 14-3**) Age at diagnosis is perhaps one of

Table 14-3. AJCC Staging System for Thyroid Cancer

Definition of Primary Tumor (T) Papillary, Follicular, Poorly Differentiated, Hurthle Cell and Anaplastic Thyroid Carcinoma	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor > 2 cm in greatest dimension limited to the thyroid
T1a	Tumor < 1 cm in greatest dimension limited to the thyroid
T1b	Tumor > 1 cm but < 2 cm in greatest dimension limited to the thyroid
T2	Tumor > 2 cm but < 4 cm in greatest dimension limited to the thyroid
T3	Tumor > 4 cm limited to the thyroid, or gross extra-thyroidal extension invading only strap muscles
T3a	Tumor > 4 cm limited to the thyroid
T3b	Gross extrathyroidal extension invading only strap muscle (sternohyoid, sternothyroid, thyrohyoid or omohyoid muscle) from a tumor of any size
T4	Includes gross extrathyroidal extension
T4a	Gross extrathyroidal extension invading subcutaneous soft tissue, larynx, trachea, esophagus, or recurrent laryngeal nerve from a tumor of any size
T4b	Gross extrathyroidal extension invading prevertebral fascia or encasing the carotid artery or mediastinal vessels from a tumor of any size
Definition of Regional Lymph Node (N)	
Nx	Regional lymph nodes
N0	No evidence of locoregional lymph nodes metastasis
N0a	One or more cytologically or histologically confirmed benign lymph nodes
N0b	No radiologic or clinical evidence of locoregional lymph node metastasis
N1	Metastasis to regional nodes
N1a	Metastasis to level VI or VII (pretracheal, paratracheal, or prelaryngeal/Delphian, or upper mediastinal) lymph nodes. This can be unilateral or bilateral disease
N1b	Metastasis to unilateral, bilateral, or contralateral lateral neck lymph nodes (level I, II, III, IV or V) or retropharyngeal lymph nodes
Definition of Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
AJCC – American Joint Committee on Cancer. Cancer Staging Manual. Eighth Edition; 2017. ⁽⁴³⁾	

the most important predictive factors for patients with DTC as evident from its inclusion in the AJCC as well as each of the other staging systems noted above.

Male gender has also been shown to be an independent predictor of survival, as thyroid cancer is more aggressive in men, although this variable is not specifically included in any staging system. In general, the prognosis of patients with differentiated thyroid carcinoma is based on their age, gender, extent of disease, and the size of their primary tumor. The issue of lymph node metastases and prognosis is still debated since lymph node involvement predicts local recurrence but does not contribute significantly to patient survival. Lymph node involvement affects staging classification only in those patients older than 55 years of age. ⁽⁴³⁾

The AJCC staging for thyroid cancer stratifies patients into four stages based on the TNM classification, except for ATCs, which are always considered stage IV. Staging is based on tumor histology and patient age (for differentiated cancer), demonstrating the importance of these parameters in survival and prognosis. The 8th edition of the AJCC staging system for thyroid cancer has been updated from prior editions by increasing the age at diagnosis cut-off point for DTC from 45 to 55 years. ⁽⁴³⁾

Minor extrathyroidal extension was removed from the definition of T3 disease. T3a is now a new category and refers to tumors greater than 4 cm in greatest dimension but still limited to the thyroid gland. T3b is also a new category defined as a tumor of any size with gross extrathyroidal extension invading only the strap muscles. Importantly, the definition of central neck was expanded to include both level VI and level VII lymph nodes. Although similar for stage I disease, survival for FTC is slightly worse than PTC and is likely due to the propensity for hematogenous spread and later age and stage at presentation. ATC has one of the worst survival rates of all malignancies with a 1-year survival of 17% and a 5- year survival of approximately 6%, demonstrating the aggressiveness of this disease. In general, the prognosis for

patients diagnosed with thyroid cancer is good with survival rates >85% to 90% for most stages, likely as a result of the indolent nature of the disease. ⁽⁴³⁾

Surgical Management

Total thyroidectomy is the preferred initial surgical procedure for most patients with PTC. Arguments for total thyroidectomy rather than lobectomy include the fact that papillary foci are seen bilaterally in up to 60% to 85% of patients and 5% to 10% of recurrences after a unilateral lobectomy arise from the contralateral lobe. ⁽⁴⁴⁾ Other retrospective studies have supported these findings of lower recurrence and show only minimal improvement in survival. A third argument for total thyroidectomy is that treatment with radioiodine and the specificity of serum TG concentrations as a tumor marker become more efficacious when minimal thyroid tissue remains. Furthermore, the routine use of TSH suppression therapy by levothyroxine diminishes the argument toward preserving normal thyroid tissue. ⁽⁴⁴⁾

Some institutions still advocate unilateral surgery because of the lack of survival benefit with more extensive surgery and the lower risk of hypoparathyroidism and recurrent laryngeal nerve injury although these complications occur in less than 1% of total thyroidectomies when done by an experienced surgeon. ⁽⁴⁵⁾ Most current management guidelines favor a total thyroidectomy in the setting of a primary tumor larger than 1 to 1.5 cm if there are contralateral thyroid nodules, extrathyroidal invasion, the tumor is multicentric, histologic variants with known aggressive behavior, or regional or distant metastases are present. ⁽⁴⁶⁾ Patients with a history of head and neck irradiation undergoing thyroid surgery should have a total thyroidectomy because they are at higher risk for multicentric disease. ⁽⁴⁷⁾ **(Figure 14-5)**

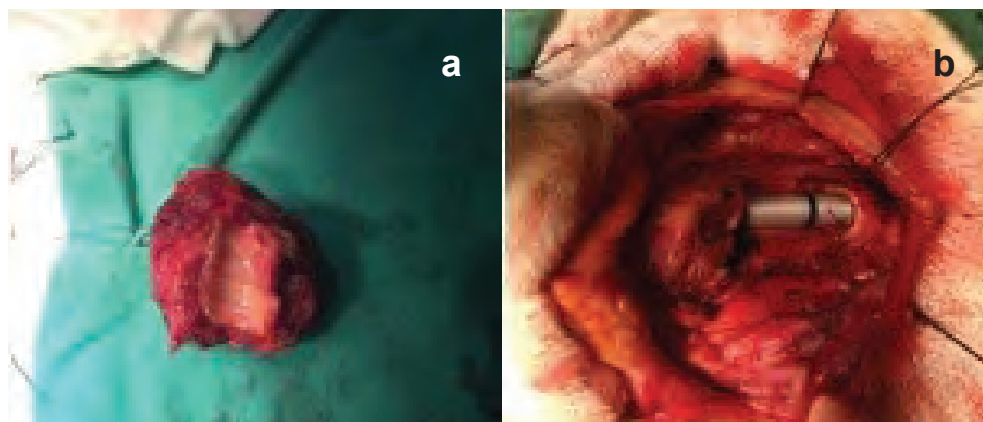


Figure 14-5. *A) Papillary thyroid carcinoma (PTC) aggressive with tracheal invasion. B) Tracheostoma after resection of tumor. Preparation for terminal tracheal anastomosis.*

Increased extent of primary surgery may improve survival for high-risk patients. Conversely, for patients whose primary tumor is smaller than 1 cm and who do not meet the previously mentioned criteria, a unilateral lobectomy may be sufficient. ⁽⁴⁷⁾ Vaisman F. emphasizes that lobectomy as primary therapy with followed with serial neck ultrasound and thyroglobulin evaluations is associated with excellent clinical outcome in well-differentiated tumors with primary tumors larger than 1 cm. ⁽⁴⁸⁾

Regional nodal metastases are present in 20% to 90% of patients with PTC, whereas 35% of patients will have grossly detectable nodal (cervical or mediastinal) metastases. **(Figure 14-6)** The presence of lymph node metastases increases the risk for disease recurrence. ⁽⁴⁹⁾ However, unlike other malignancies, it is only a minor risk factor for mortality, which is increased when metastases are present in the bilateral neck or mediastinum. ⁽⁴⁹⁾

Therapeutic central-compartment (level VI) neck dissection for patients with clinically involved central nodes should accompany total thyroidectomy to provide clearance of disease from the central neck. ⁽⁵⁰⁾ **(Figure 14-5)** Prophylactic central-compartment neck dissection (ipsilateral or bilateral) should be considered in patients with papillary thyroid carcinoma with clinically uninvolved central neck lymph nodes (cN0) who have advanced primary tumors (T3 or T4) or clinically involved lateral neck nodes (cN1b), **(Figure 14-6)** or if the information will be used to plan further steps in therapy. ⁽⁵⁰⁾ According to Vaisman F. *et al.* metastases nodal persistence was independent factor to presence of distant metastases. ⁽⁵¹⁾



Figure 14-6. Central-compartment (level VI) neck dissection.

Thyroidectomy without prophylactic central neck dissection is appropriate for small (T1 or T2), noninvasive, ATA thyroid nodule/dtc guidelines 33 clinically node-negative PTC (cN0) and for most follicular cancers. Therapeutic lateral neck compartmental lymph node dissection should be performed for patients with biopsy-proven metastatic lateral cervical lymphadenopathy. ⁽⁵²⁾ **(Figure 14-7)** Most current management guidelines favor a total thyroidectomy in the setting of a primary tumor larger than 1 to 1.5 cm if there are contralateral thyroid nodules, extrathyroidal invasion, the tumor is multicentric, histologic variants with known aggressive behavior, or regional or distant metastases are

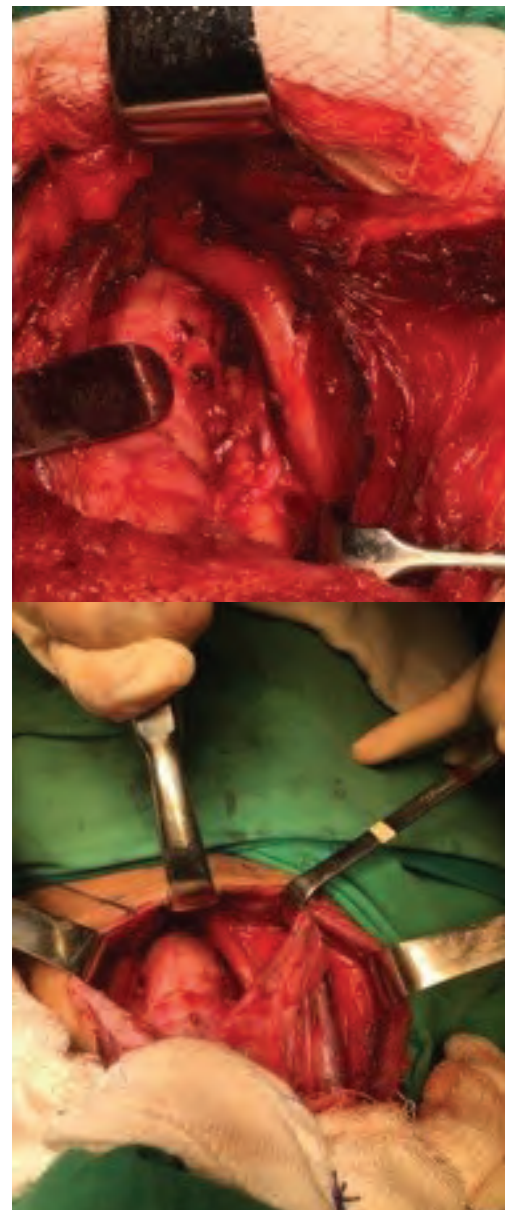


Figure 14-7. Neck dissection of level VI and VII.



Figure 14-8. Neck dissection from bilateral level II, III, IV, V and VI.

present.⁽⁵³⁾ **(Figure 14-8)** Patients with a history of head and neck irradiation undergoing thyroid surgery should have a total thyroidectomy because they are at higher risk for multicentric disease. Increased extent of primary surgery may improve survival for high-risk patients.⁽⁵³⁾ Conversely, for patients whose primary tumor is smaller than 1 cm and who do not meet the previously mentioned criteria, a unilateral lobectomy may be sufficient.⁽⁵³⁾

Regional lymph node metastases are present at the time of diagnosis in a majority of patients with papillary carcinomas and a lesser proportion of patients with follicular carcinomas.⁽⁵⁴⁾ All cause survival at 14 years was 82% for PTC without lymph node metastases and 79% with nodal metastases ($p < 0.05$). Another SEER registry study concluded that cervical lymph node metastases conferred an independent risk of decreased survival, but only in patients with follicular cancer and patients with papillary cancer over age 45 years.⁽⁵⁵⁾ A recent comprehensive analysis of the National Cancer Data Base and SEER, however, showed a small but significantly increased risk of death for patients younger than 45 years with lymph node metastases compared with younger patients without involved lymph nodes, and that having incrementally more metastatic lymph nodes up to six involved nodes confers additional mortality risk in this age group.⁽⁵⁶⁾

The importance of rigorous preoperative screening for nodal metastases and potentially raises questions about current thyroid cancer staging systems. Common to all of

these studies is the conclusion that the effect of the presence or absence of lymph node metastases on overall survival, if present, is small.⁽⁵⁷⁾

For patients with small, noninvasive, cN0 tumors, the balance of risk and benefit may favor thyroid lobectomy and close intraoperative inspection of the central compartment, with the plan adjusted to total thyroidectomy with compartmental dissection only in the presence of involved lymph nodes.⁽⁵⁸⁾ Lymph nodes in the lateral neck (compartments II–V), level VII (anterior mediastinum), and rarely in level I may also be involved by thyroid cancer. For patients in whom nodal disease is evident clinically on preoperative US and nodal FNA cytology or Tg washout measurement or at the time of surgery, surgical resection by compartmental node dissection may reduce the risk of recurrence and possibly mortality.⁽⁵⁹⁾

In child patients with preoperative evidence of central and/or lateral neck metastasis, a therapeutic central neck dissection (CND) should be performed. For this subgroup of patients, who are also at increased risk of pulmonary metastases⁽⁶⁰⁾ CND is associated with a decreased risk of persistent/ recurrent locoregional disease as well as the potential to increase the efficacy of ¹³¹I treatment for distant metastasis. The increased incidence of cervical metastasis in children suggests that prophylactic CND, as defined in the 2009 ATA consensus statement on the terminology and classification of CND for thyroid cancer, should be considered at the time of initial surgery for pediatric patients with PTC. This is particularly relevant given that decreased disease-free survival (DFS) is most strongly correlated with the presence of persistent or recurrent locoregional disease. Other research from Vaisman in Brazilian National Cancer Institute further concludes that that young patients have a more aggressive clinical presentation with more frequent lymph node and distant metastasis comparing to what is usually seen in adults.⁽⁶¹⁾

Harmonic Scalpel

New, modern devices for tissue resection have been introduced in the surgical treatment of thyroid diseases recent years.⁽⁶²⁾ The length of surgical incision, use of haemostatic instruments and ligatures, extent of resection, need of draining, operative time, intra- and postoperative complications, length of postoperative hospital stay have been examined.⁽⁶³⁾

In recent years, new methods have been introduced in the field of thyroid surgery, such as minimally invasive, video-assisted and open approach techniques, with different access

points. They all aim to minimize thyroid tissue trauma while preserving comparable efficiency and safety and providing better cosmetic results. ⁽⁶⁴⁾

The meticulous haemostasis is of crucial importance for the success of thyroid surgery and prevents the intra- and postoperative complications and helps to improve the quality and shorten the postoperative hospital stay. Hemostasis is the main operative time of a thyroidectomy; however, studies show that the harmonic scalpel is not superior to Kocher's surgery where the hemostasis is done with simple ligatures using conventional knot. ⁽⁶⁵⁾ The main advantage of harmonic scalpel is the reduction of the time it takes to perform a conventional thyroidectomy, what can compensate the financial expense with the harmonic scalpel material. ⁽⁶⁵⁾

Neuroestimulation

Intraoperative monitoring of the recurrent laryngeal nerve (RLN) (**Figure 14-9**) is to assist in the prevention of partial and total lesions of this structure, which temporary or permanent immobility of the vocal folds. ⁽⁶⁶⁾ The objectives of monitoring are: to help distinguish RLN from normal tissues and diseases; identify and map the course of the nerve using stimulation power; facilitate the excision of the lesion by electric mapping; detect early surgical trauma on the RLN, with immediate information to the surgeon, especially in

case of of a bilateral approach where, at its discretion, the continuity of the procedure may be aborted; confirm the prognosis of nerve function by means of stimulation nervous when the operation is completed; and to identify the sites and degree of neural dysfunction. ⁽⁶⁶⁾

The use of intraoperative monitoring is widely accepted for surgeries of greater risk. Thus, it is indicated when there is access to this technology, at the discretion of the surgeons, especially in situations such as reoperations, invasive tumors extracapsular, bulky goiters and in previously irradiated area. ⁽⁶⁷⁾ Thus, it is accepted that all technology that assists in the prevention of neural damage can be added to the surgical procedures that involve risk, and it is up to the surgeon to evaluate the cost-benefit analysis for each individual case. ⁽⁶⁷⁾

TOETVA

The Transoral Neck Surgery (TONS) Study Group was established at the 1st International Thyroid NOTES Conference in February 2016 with the intention of standardizing and refining thyroid NOTES techniques, including both transoral endoscopic and robotic thyroidectomy approaches. Herein, the authors report the modification of indications, preparation, and step-by-step explanations for operative techniques, as well as results and postoperative care for transoral endoscopic thyroidectomy vestibular approach (TOETVA). ⁽⁶⁸⁾

Open thyroidectomy is currently the standard surgery option for thyroid diseases. However, this approach leaves an unavoidably visible neck scar. Many modified techniques have been developed to reduce the size of the neck scar, including minimally invasive open thyroid surgery and video-assisted thyroidectomy (MIVAT). ⁽⁶⁹⁾ Many of the alternative approaches for pure endoscopic thyroidectomy move the wounds to other parts of the body such as the axilla, breast, or post-auricular area. ^(70,71) However, cutaneous scars are still apparent. Further, these approaches require a large amount of flap dissection, which contradicts the notion that they are truly minimally invasive.

Recently, Natural Orifice Transluminal Endoscopic Surgery (NOTES) for thyroidectomy was developed. ^(72,73) This surgical technique completely avoids visible cutaneous scarring with an approach through the oral cavity. Two techniques have been described, including 1) a sublingual approach, which causes severe tissue damage with a high complication rate ⁽⁷⁴⁾ an oral vestibular approach. The refined transoral endoscopic thyroidectomy vestibular approach (TOETVA) showed encouraging results with minimal complications. ⁽⁷⁵⁾



Figure 14-9. A) Orotracheal tube with electrodes for recurrent nerve monitoring. B) Monitor.

Early experience demonstrated that TOETVA can be done safely in patients who had previously undergone surgery or radiation at the chin and neck area. Inclusion main criteria includes a thyroid gland of a diameter not exceeding 10 cm comprising a benign thyroid nodule(s), ⁽⁷⁴⁾ papillary microcarcinoma with no evidence of metastasis, follicular neoplasm, or well-controlled Graves' disease, as previously described. ⁽⁷⁵⁾ Anuwong *et al.* added as new inclusion criteria substernal goiter. The exclusion criteria are unfit for surgery, unable to tolerate anesthesia, previous neck surgery, radiation on the neck and wore dental brace. Being unable to tolerate anesthesia and unfit for surgery are absolute contraindication.

The surgical technique consists of incision of the lower lip mucosa anterior to the labial frenulum to introduce the Veres needle, **(Figure 14-10)** CO₂ insufflation, coupling of the trocars, dissection of the recurrent laryngeal nerve in anterograde way and approach of the gland in a craniocaudal sense after distancing the muscles infrahyoids with spots on the skin. ⁽⁷⁶⁾ The transoral approach to the neck must be considered clean-contaminated surgery and carries an inherently greater risk of infection than clean transcervical thyroidectomy. The results are extremely positive, without major complications and with excellent aesthetic results. It seems to be a useful technique to be offered to well-selected patients (not to all patients), with favorable conditions for the

surgery and special concern for the aesthetic result. This is a surgical innovation which will certainly undergo further modifications according to experts. ⁽⁷⁷⁾

Robotic

With the advancement and adaptation of technology, there has been a tremendous evolution in the surgical approaches for thyroidectomy over the past two decades. The first endoscopic thyroidectomy was first performed in 1997, introducing the era of minimally invasive and remote-access approaches for thyroidectomy. ^(77,78) The Da Vinci robotic system (Intuitive Surgical, Sunnyvale, California) was first utilized for transaxillary thyroidectomy by Chung in 2007.

Robotic thyroidectomy has become increasingly popular worldwide attracting both surgeons and patients searching for new and innovative techniques for thyroidectomy with a superior cosmetic result when compared to the conventional open procedures. Using a robotic system helped to overcome some of the limitations of the endoscopic procedures such as reduced range of motion, and impaired eye-hand coordination. Many studies have described the safety of the remote-access robotic thyroidectomy procedures and have demonstrated comparable oncologic outcomes between the robotic and open conventional thyroidectomy. ^(79,80)

Main possibilities surgical approaches for robotic thyroidectomy: transaxillary, retroauricular transoral and the combination of both approaches. Each approach has its own technical peculiarities that are beyond the scope of this chapter. However, it is important to highlight the advantage and disadvantage of each method. ⁽⁷⁹⁾

The advantages of the transaxillary approach (TA) are: the ease of detecting the RLN, ability to perform total thyroidectomy with central and lateral neck dissections for advanced cancer and then well-established literature demonstrating safety and outcomes. Some of the main disadvantages of this approach are the possible risks of anterior chest paresthesia and brachial plexus injury. Terris has emphasized the benefits of the retroauricular approach (RA), speculating that the significantly reduced field of dissection in the RA approach when compared to the TA approach is associated with a faster recovery and decreased postoperative discomfort. However, there are some disadvantages that are inherent to this approach: injury to greater auricular and marginal mandibular nerves. ⁽⁸⁰⁾

The newest approach is the robotic transoral approach. The selection of approach is largely dependent on the training, skill,



Figure 14-10. TOETVA performed at the Brazilian National Cancer Institute.

and preference of the surgeon and/or patient. The transoral technique offers the unique advantage of accessing the thyroid gland from a natural orifice, and its midline approach allows excellent exposure to the entire thyroid gland, making this the safest approach to perform total thyroidectomy when compared to other approaches.⁽⁸¹⁾ The main disadvantages to this technique are the need for postoperative antibiotics, possibly longer length of stay (LOS) and inability to perform lateral neck dissections. There have been no reports of postoperative infections following transoral endoscopic or robotic thyroidectomy; however, postoperative antibiotics are administered for all patients given the possible risk of infection as the transoral thyroidectomy is not considered to be a clean procedure unlike its conventional open counterpart.⁽⁸¹⁾

With advancements in robotic technology, the list of advantages of robotic surgery will continue to grow. Performing more complex surgeries of head and neck will become a possibility with greater precision and safety along with the development of more sophisticated and advanced robotic tools. However, the major factor associated with successful outcomes following robotic thyroidectomy is the experience and skill of the surgeon. Therefore, robotic thyroidectomy should only be performed by experienced robotic surgeons.⁽⁸²⁾

Prognosis

Significant progress has been made over the last several years in understanding the genetic mechanisms of thyroid cancer and creating molecular tests for cancer diagnosis in thyroid nodules. The TCGA focused only on PTC. Moreover, next-generation sequencing technologies may allow detection of most of these alterations in a limited cell sample obtained by FNA.

Progress in identifying mutational, other genetic (gene expression, miRNA), and epigenetic markers of thyroid cancer is expected to result in a significantly improved accuracy of cancer detection in thyroid nodules as compared to the currently available clinical tests.⁽⁸³⁾

Molecular markers are expected to have a significant impact on cancer prognostication.⁽²⁸⁾ While the BRAF status can be considered as a relatively sensitive prognostic marker for papillary cancer, it cannot be used in isolation for tumor prognostication. However, recent results obtained by broad tumor genotyping show that several specific molecular signatures (such as presence of several driver mutations, TP53 mutation, TERT mutation in isolation or in combination with

BRAF) are found in a small fraction of well-differentiated papillary and follicular cancers and appear to be associated with more aggressive tumor behavior.⁽⁸⁴⁾

Conclusion

A large percentage of the population has thyroid nodules. There are major advances in molecular diagnosis to avoid unnecessary surgeries. The extent of thyroidectomy was great for decades. Today, in low-risk, selected cases, partial thyroidectomy is admitted, but total thyroidectomy is still indicated in most centers. Prophylactic neck dissection in the clinically negative neck is also not indicated, except for the surgical treatment of patients with advanced disease. Thyroid cancer has presented numerous technical indications in order to minimize surgical morbidity; however, open thyroidectomy is still the standard treatment. The prognosis is very good, with the exception of medullary and anaplastic thyroid carcinoma.

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Chapter 15

Differentiated Thyroid Cancer - Surgical Considerations

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Introduction and Incidence

The incidence of thyroid cancer in the United States has more than tripled over the past three decades,⁽¹⁾ and is rising worldwide, accounting for 3.1% of new cancers globally.⁽²⁾ Women are affected three times as frequently as men, with thyroid cancer accounting for 1 in 20 new cancer diagnoses in women in 2018. Fortunately, survival for most patients is excellent, and thyroid cancer accounts for only 0.4% of cancer related deaths worldwide.⁽²⁾ Differentiated thyroid cancer, arising from thyroid follicular epithelial cells, comprises the majority of thyroid cancers (>90%), with papillary thyroid cancer the most common histology (85%) followed by follicular thyroid cancers (including Hurthle cell carcinomas, 12%) and poorly differentiated (insular) thyroid cancers (3%). This is in contrast to medullary thyroid cancer, which arises from the calcitonin-producing parafollicular C-cells of the thyroid (1-2% of all thyroid cancers) or anaplastic thyroid cancer, which, although arising from epithelial thyroid cells, represents a rare and aggressive variant with a median survival of < 6 months.⁽³⁾ This chapter will focus primarily on the surgical management of differentiated thyroid cancer.

The most common differentiated thyroid cancer, papillary thyroid cancer, accounts for the majority of the increase in thyroid cancer incidence. At least part of the rise in incidence can be attributed to the increased utilization of imaging modalities, with small (<1 cm) primary tumors increasing to 39% from 25% of all newly diagnosed thyroid cancers between 1989 to 2009.⁽⁴⁾ Review of insurance claims databases nationally suggest the pace of thyroid fine needle aspiration and the number of thyroidectomies for thyroid nodules has risen sharply (16% and 12% annual increase per year, respectively, between 2006 – 2011), which may

increase detection of incidental microcarcinomas.⁽⁵⁾ These findings are concordant with autopsy studies, which suggest a much higher incidence of papillary thyroid cancer than clinically detected.⁽¹⁾ Combined, these factors lead to a pattern of “overdiagnosis.” In 2009 the American Thyroid Association released updated guidelines for the evaluation of thyroid nodules, favoring a more restrictive use of fine needle aspiration (FNA), allowing the possibility of a thyroid lobectomy for smaller papillary thyroid cancers, and shifting emphasis from a total thyroidectomy to a diagnostic lobectomy in the setting of a cytologic-indeterminate nodule.⁽⁶⁾ Despite the subsequent taper in the trajectory of new thyroid cancer cases (most noticeable in women with smaller nodules) coinciding with the more restrictive guidelines,⁽⁷⁾ the incidence of thyroid cancer has continued to rise, suggesting a true increase in thyroid cancer. Similarly, a recent large Surveillance, Epidemiology, and End Results (SEER) analysis demonstrated increase in incidence as well as associated mortality for each stage of papillary thyroid cancer, suggesting overdiagnosis alone is insufficient to explain the rise in thyroid cancer incidence.⁽⁸⁾ Environmental factors (exposure to medical radiation and/or other carcinogens), lifestyle factors (i.e., obesity), genetics, changes in the prevalence of autoimmune thyroiditis, awareness of the disease and access to healthcare all likely play a role in development of thyroid cancer.⁽⁹⁾

As the incidence of thyroid cancer continues to rise, whether it is a microcarcinoma that will likely not have long term ramifications, or a locally aggressive tumor, so does the responsibility to manage the disease. This chapter will focus on the initial evaluation of the patient with differentiated thyroid cancer and its surgical management, focusing on controversies such as extent of resection, prophylactic nodal dissection, intraoperative nerve monitoring, and active surveillance.

Preoperative Evaluation

The initial evaluation of the patient with thyroid cancer should include a full history and physical exam with focus on the presenting symptom(s) and thyroid associated complaints. Although often found incidentally on routine examination or imaging performed for other reasons, thyroid cancer may present as an enlarging mass (within the thyroid or in a lateral neck node) or be associated with dysphagia, hoarseness, dyspnea, or compressive symptoms. The timeline of symptoms may also yield a clue to the etiology, with unusually rapid presentations concerning for anaplastic thyroid cancer. A personal history of prior thyroiditis, thyroid (or neck) surgery, or thyroid cancer should be elicited. Hoarseness and/or previous neck surgery should prompt evaluation of the vocal cords with either laryngoscopy or videostroboscopy. Radiation exposure history (either therapeutic or environmental) is an important risk factor for later development of papillary thyroid cancer.^(10, 11) Family history of syndromes associated with thyroid malignancy should be evaluated (multiple endocrine neoplasia type II, Cowden syndrome, Carney complex, familial adenomatous polyposis and/or Gardner syndrome, Werner syndrome, *DICER1* syndrome), with referral to genetic counseling as indicated.⁽¹²⁾ Palpation of the thyroid with attention to mobility of the gland and surrounding cervical or supraclavicular lymphadenopathy should be performed. In the case of lymphadenopathy, systemic symptoms such as chills, night sweats, fever, or weight loss should alert the clinician to the possibility of an alternate diagnosis such as lymphoma.

Initial laboratory workup should include evaluation of thyroid function (serum thyrotropin, TSH; and free thyroxine, fT4). Preoperative measurement of thyroglobulin levels and thyroglobulin antibodies is not routinely recommended, although some data suggest high preoperative thyroglobulin levels may correlate with the sensitivity for postoperative surveillance using the same test.⁽¹³⁾ Calcitonin levels are appropriate when medullary thyroid cancer is suspected but should not be used routinely as a screening test.⁽¹³⁾

A preoperative neck ultrasound that evaluates the thyroid as well as the central and lateral compartments should be obtained.⁽¹³⁾ Solid or hypoechoic nodules with suspicious sonographic features (micro-calcifications, extra-thyroidal extension, irregular borders, and greater height than width) that are greater than 10 mm in diameter should be biopsied under most national and international guidelines.^(13, 14) On site cytopathologic assessment for specimen adequacy is encouraged to decrease inadequate sampling.⁽¹⁵⁾ Repeat biopsy may be necessary in the case of nondiagnostic or

indeterminate specimens; core needle biopsy is rarely necessary and is more likely than FNA to cause bleeding and patient discomfort.⁽¹⁴⁾ The false-negative rate for FNA biopsy ranges between 1 and 6%.⁽¹⁶⁾ In addition to facilitating FNA and subsequent cytologic diagnosis, ultrasonography identifies lymph node metastases not detected by physical exam in up to 39% of patients, thereby altering the surgical plan.⁽¹⁷⁾ Additional cross sectional imaging (computed tomography) is indicated in patients suspected of having locoregionally advanced disease (bulky primary or extensive nodal metastases), and has the benefits of delineating the tumor's relationship to the deep structures of the neck, discerning central lymph nodes obscured by the overlying thyroid on ultrasound, and evaluating substernal disease not accessible by ultrasound.⁽¹³⁾

Surgical Management

Once a diagnosis of malignancy is confirmed, most patients should undergo thyroid resection. In contrast to many cancers, even patients with distant metastases may benefit from thyroidectomy, as the removal of native thyroid tissue may facilitate systemic therapy with radioactive iodine (RAI). Additionally, total thyroidectomy facilitates serial measurement of thyroglobulin, which, in the absence of thyroglobulin antibodies, can be useful as an indicator of recurrence or response to therapy.

Extent of Operation

Until recently, total thyroidectomy was recommended for most patients with thyroid cancer, except for unifocal tumors less than 1 cm, confined to the thyroid gland in patients without a personal history of neck irradiation or a family history of thyroid cancer, in whom a thyroid lobectomy was accepted. Data now indicate that thyroid lobectomy may achieve equivalent survival as total thyroidectomy in well-selected patients with tumors between 1 and 4 cm. Large scale datasets such as the National Cancer Database and the Surveillance, Epidemiology, and End Results Program have been analyzed to assess the role of total thyroidectomy vs lobectomy for patients with tumors > 1 cm, with conflicting results.⁽¹⁸⁻²²⁾ While one study suggested a small survival advantage for patients undergoing total thyroidectomy as compared to lobectomy (98.4% vs 97.1% 10 year survival, $p < 0.05$)²⁰, others suggested that the two approaches were equivalent after controlling for disease complexity.^(18, 19, 21, 22) In each, the inclusion of patients with tumors > 4 cm, extrathyroidal extension, distant metastases, and/or use

of RAI therapy or external beam radiation therapy in the lobectomy group has called into question the appropriateness of patient selection, and highlights the limitations of using large scale datasets particularly in the retrospective setting. The American Thyroid Association currently recommends consideration of thyroid lobectomy in younger patients (≤ 45 years of age) with unifocal tumors < 4 cm in the absence of extrathyroidal extension, lymphadenopathy, or other concerning features, in whom RAI is unlikely to be utilized, with the notation that in the event of recurrence, salvage completion thyroidectomy is quite effective.⁽¹³⁾ It remains the authors' preference to favor total thyroidectomy for most patients with tumors larger than 2-2.5 cm. After considering stringent patient selection, attention to the relative value that a patient places on factors such as postoperative thyroid hormone supplementation, ease of laboratory (i.e. thyroglobulin monitoring after total thyroidectomy) or radiographic surveillance, and comfort level with the possibility of requiring a completion thyroidectomy may help guide the decision for lobectomy vs thyroidectomy, and should be an individualized decision. Continued healthcare accessibility and compliance of follow up should be discussed preoperatively. Future study of factors that impact quality of life after lobectomy versus total thyroidectomy, as opposed to the more traditional endpoints of recurrence free and overall survival, is necessary and may provide additional guidance for the clinician and patient debating lobectomy versus total thyroidectomy.

Surgical Procedure: Thyroidectomy

The patient is positioned in semi-Fowler position with the neck hyperextended and a shoulder roll placed horizontal to aid in opening the surgical field. An incision is made in a natural skin crease two fingerbreadths above the clavicles (approximately 1 cm below the cricoid cartilage). The platysma is divided. The midline raphe is separated longitudinally and the sternohyoid and sternothyroid muscles are retracted laterally; gentle lateral dissection of the natural plane between the strap muscles will further enhance exposure. The thyroid is freed from its surrounding tissues and the middle thyroid veins are divided close to the gland. The thyroid is rotated medially into the field with careful dissection along the gland. The parathyroid glands should be identified and gently dissected laterally. A conscious effort should be made to avoid dissection lateral to the parathyroid gland(s) in order to avoid isolation and subsequent devascularization. Following this, the recurrent laryngeal nerve should be identified in the tracheoesophageal groove. This is usually easiest with gentle traction of the surrounding tissues and identification at approximately 1.5 cm from its insertion. (**Figures 15-1.A and 15-1.B**) The nerve is then meticulously exposed on its anterior surface as it courses to the cricopharyngeal muscle.

The surgeon should be aware of the possibility of a nonrecurrent laryngeal nerve, which occurs in $<1\%$ of the population and is associated with an aberrant subclavian

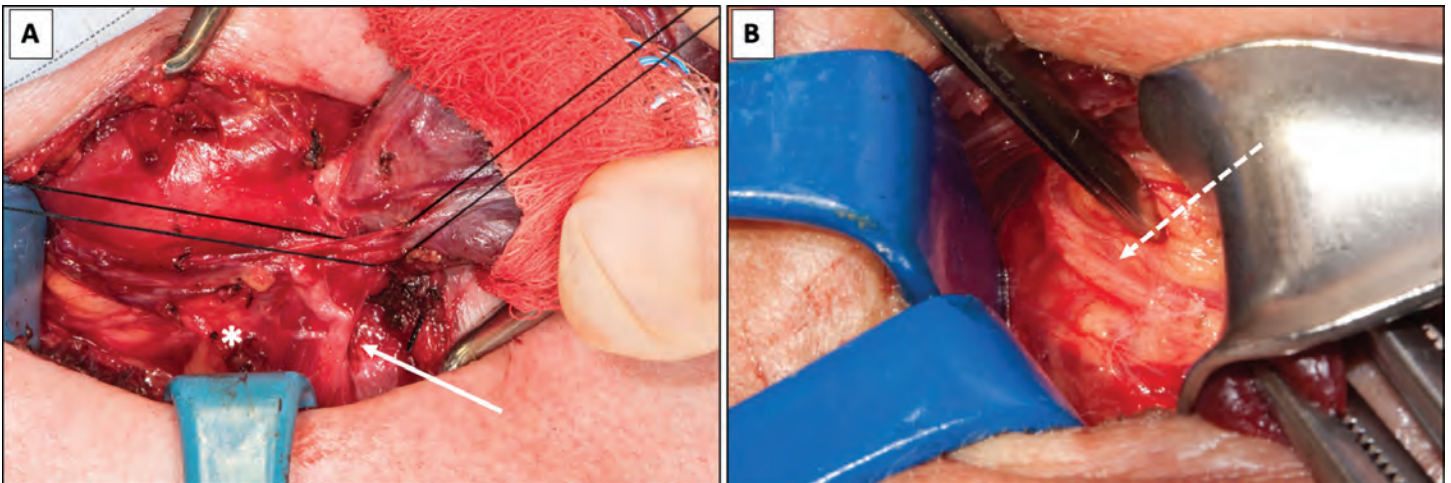


Figure 15-1. A) The right recurrent laryngeal nerve (solid arrow) dissected intraoperatively with the ligament of Berry between sutures and the right superior parathyroid preserved (star) as compared to B) a non-recurrent recurrent laryngeal nerve (dashed arrow) with the thyroid retracted medially in each.

artery (commonly retro-esophageal).⁽²³⁾ The inferior thyroid pole vessels can then be divided near the thyroid capsule as they insert into the thyroid parenchyma. The superior pole vessels are then exposed by retracting the thyroid lobe inferior and laterally. The superior pole vessels can be isolated and individually divided. The external branch of the recurrent laryngeal nerve should be identified as it courses just lateral to the cricothyroid muscle; in situations where it is not immediately visible close dissection along the thyroid capsule and skeletonization of the superior pole vessels will minimize risk of injury. As the thyroid is separated from the anterior surface of the trachea Berry's ligament is encountered. Small vessels in this area may bleed and obscure visualization of the recurrent laryngeal nerve at its insertion.

Cervical Lymph Node Dissection

The risk of cervical lymph node metastases in patients with differentiated thyroid cancer is as high as 50% at presentation and does not correlate with the size of the primary tumor.⁽¹³⁾ Therapeutic nodal dissection is indicated for clinically involved nodal basins within the neck and should be compartment oriented. For central lymph node dissection, the right and left central lymph node compartments extend superiorly from the hyoid bone inferiorly to the

innominate vein and are bounded by the medial border of the corresponding carotid artery to the midline of the trachea. Care should be taken to sweep the fibrofatty tissue off the recurrent laryngeal nerve as it courses inferiorly, and identification and preservation of the inferior parathyroid glands and their vascular pedicles is essential to prevent hypoparathyroidism. For lateral dissection, the lymphatic drainage pattern of differentiated thyroid cancer does not typically extend to the submental region, making level II the superior most aspect of dissection. **(Figures 15-2.A and 15-2.B)** Resection of the nodal tissue for levels II, III, and IV begins just superior to the level of the hyoid bone, extends inferiorly to the clavicle, and is bounded medially by the sternohyoid muscle, laterally by the posterior surface of the sternocleidomastoid muscle, and posteriorly by the precervical fascia on the scalene muscle. **(Figures 15-2.A and 15-2.B)** The carotid bundle is carefully dissected and the spinal accessory, vagus, and phrenic nerves are preserved.

Therapeutic compartment based resection of clinically positive lymph nodes is well accepted, but controversy exists regarding the role of prophylactic central compartment neck dissection (PCLND). Although ultrasound is more sensitive than physical exam in identifying nodal disease,⁽¹⁷⁾ a substantial number of patients selected for central neck dissection will demonstrate clinically and radiographically

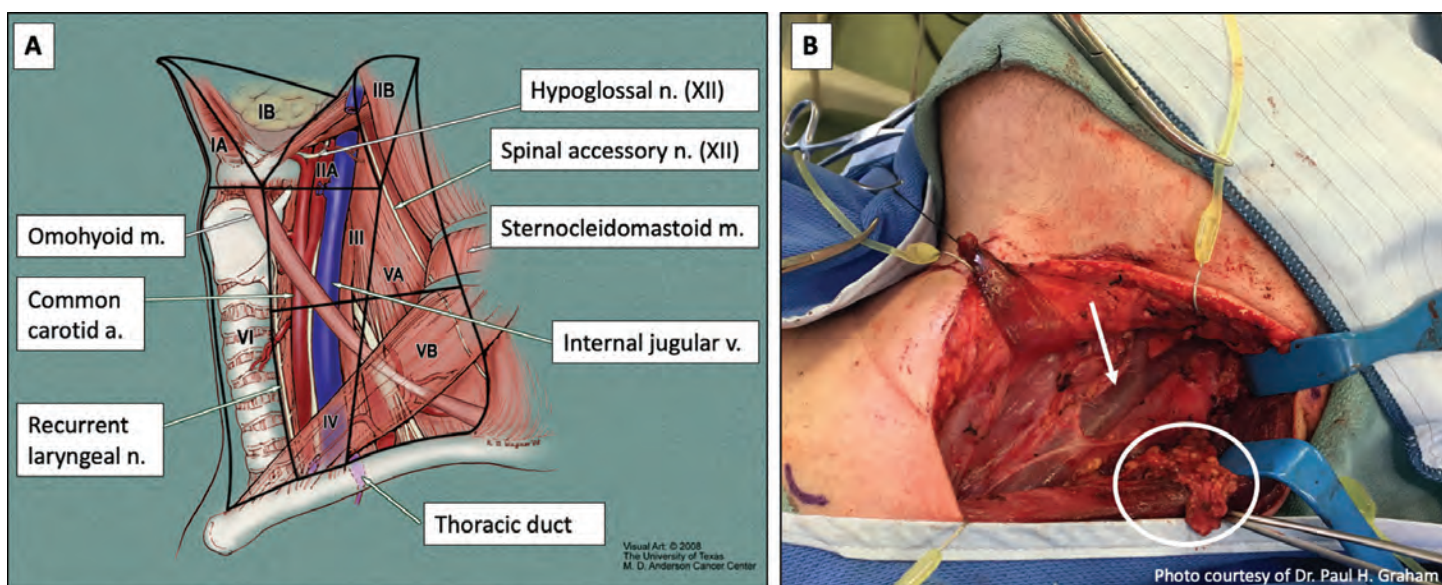


Figure 15-2. A) Schematic of the left central (compartment VI, VII not shown) and lateral neck compartments (IA – VB) and B) intraoperative photo during a left lateral neck dissection as the nodal tissue (circled) is swept inferiorly and laterally off of the internal jugular vein (arrow).

occult metastases on final pathology (24-82%).⁽²⁴⁾ Proponents of PCLND suggest that routine dissection for well-selected patients will prevent microscopic persistence (versus recurrence) of central neck disease, and cite the additional advantage of potentially avoiding a reoperative setting. Although some retrospective data support an improvement in locoregional control for patients undergoing PCLND,^(25, 26) others have shown minimal impact.^(24, 27) These findings are undoubtedly influenced by patient selection. One prospective trial of clinically node negative patients with papillary thyroid cancer randomized to either thyroidectomy (n=88) vs thyroidectomy with PCLND (n=93) demonstrated no difference in locoregional recurrence over five years, although they noted that 46% of the patients in the PCLND arm had nodal disease and this group was more likely to undergo RAI.⁽²⁸⁾ Others have also noted this advantage of information regarding stage and its influence on selection for RAI, and patients who undergo PCLND and subsequent RAI may be less likely to require additional RAI.^(24, 29) In an era of decreased use of RAI and increased use of thyroid lobectomy as treatment, there is no role for PCLND when the contralateral lobe is being kept intact. In addition, the new AJCC guidelines reflect that microscopic disease identified in lymph nodes does not upstage the patient. More extensive dissection likely carries an additive risk of complication, with most studies reporting an increased risk of postoperative hypocalcemia with PCLND⁽²⁹⁻³¹⁾ (3.45% vs 1.55% in one meta-analysis).⁽²⁴⁾ It is the authors preference to practice therapeutic central lymph node dissection when indicated and reserve PCLND for highly selected patients in whom substantial suspicion exists for clinically relevant occult metastases (T3/T4 tumors, extrathyroidal extension) in concordance with the American Thyroid Association guidelines.⁽¹³⁾ Ipsilateral central neck dissection should be performed if there is confirmation of lateral neck disease.

Perioperative Morbidity and Technical Considerations

Thyroidectomy is well tolerated, with low overall rates of morbidity (between 6 and 12%).^(32, 33) Transient or permanent hypocalcemia, recurrent or superior laryngeal nerve injury (also either transient or permanent), and postoperative hematoma are the most common thyroidectomy specific complications, although overall still rare. Case volume, as a surrogate measure of surgeon experience, is associated with risk of morbidity, with patients who undergo operation by low-volume surgeons (<25 cases/year) having an increased

risk for any complication (odds ratio 1.51, p=0.002).^(32, 34) Amongst high volume thyroid surgeons the rates of reoperation for hematoma after thyroidectomy are 0.3 – 0.7%, with permanent recurrent laryngeal nerve injury occurring in <1%, permanent hypocalcemia in <2%, and mortality in <1 in 10,000 patients.⁽³⁵⁾ Transient hypocalcemia is more common, with variable rates depending on study definition; the median incidence in one large meta-analysis was 27% (interquartile range 19-38%).⁽³⁶⁾ The extent of malignancy and corresponding extent of surgical dissection likely play a role in postoperative morbidity rates, with increased complications corresponding with increased surgical manipulation. One SEER analysis of patients undergoing surgery specifically for thyroid cancer found the conglomerate rate of transient or permanent hypoparathyroidism or recurrent laryngeal nerve injury was lowest amongst patients with localized disease, and increased with either regional (OR 1.31, 95% CI 1.19 - 1.45) or distant disease (OR 1.85, 95% CI 1.84 – 2.21); age and presence of medical comorbidities also conferred higher risk on multivariate analysis.⁽³³⁾

Intraoperative Nerve Monitoring

In addition to surgeon experience and familiarity with relevant anatomy, (**Figures 15-1 and 15-2**) attention to routine positioning and procedure, and meticulous dissection with direct visualization of the recurrent laryngeal nerve,⁽¹³⁾ intraoperative nerve monitoring (IONM) has been proposed as an ancillary measure in select operations where dynamic decision making might be needed such as when the planned operation would be altered by additional functional information. An example would include an altered approach to the extubation if preoperative knowledge of a nerve injury was present and the contralateral sole functioning nerve did not stimulate at completion of operation. Amongst high volume surgeons data exist to suggest IONM may be beneficial particularly in high risk patients including those with aggressive thyroid cancer, retrosternal or toxic goiter, and reoperative thyroidectomy.⁽³⁷⁾ In intermittent IONM a hand held probe allows for stimulation of the recurrent laryngeal nerve (or the vagus nerve) with electromyographic signal detected by feedback via an electrode incorporated into the endotracheal tube in contact with the vocal cords. Continuous IONM, which involves a temporary implantable electrode attached to the vagus, is less commonly used due to concern for vagal neuropraxia and hemodynamic instability, although data largely support its safety.⁽³⁸⁾ Importantly, IONM has not been consistently associated

with reduced risk of nerve injury, ⁽³⁹⁻⁴²⁾ although such studies are likely underpowered given the relatively low frequency of nerve injury and impacted by confounding factors such as surgeon experience, hospital volume, and variability in the definition of reported nerve injury. Surgeon familiarity with the monitoring system, the ability to troubleshoot, and correct interpretation of the signal pattern is required for successful incorporation of IONM. Currently the American Academy of Otolaryngology Head and Neck Surgery ⁽²³⁾ and the American Thyroid Association ⁽¹³⁾ support the consideration of IONM during thyroidectomy, and it is the authors practice to selectively utilize the technology.

Nonoperative Management of Differentiated Thyroid Cancer

The treatment of any patient with cancer should match the aggressiveness of the therapy with the oncologic risks of recurrence and/or cancer related death. When the latter risks are relatively small the tolerance for treatment related morbidity is less, as may occur in the patient with a small papillary thyroid microcarcinoma (<1 cm in diameter) who is unwilling to tolerate the risk of compromised quality of life from a recurrent laryngeal nerve injury, hypoparathyroidism, or even iatrogenic hypothyroidism. Ten year disease specific survival for patients with surgically treated papillary thyroid microcarcinoma is >99%, ⁽⁴³⁾ prompting some to question the natural history of the disease left *in situ*.

Active surveillance, in which patients are examined with semiannual clinical exam, ultrasound, and laboratory assessment including thyroglobulin, was initially reported prospectively in Japan. ⁽⁴⁴⁾ Later, with 10 years follow-up, the same investigators reported on 1,235 patients with papillary thyroid microcarcinoma (≤ 10 mm on US) located away from the recurrent laryngeal nerve or trachea without signs or symptoms of direct invasion or nodal or distant metastases. Tumor growth and nodal metastases were observed in 4.6% and 1.5%, respectively, with only 3.5% progressing to clinical disease (tumor size >12 mm and/or development of nodal metastases, and no patient developed distant metastases or died of thyroid cancer. Importantly, patients above the age of 60 (n=496) were least likely to experience progression: 2.2% demonstrated an increase in tumor size (vs. 5.9%, $p=0.0014$), 0.4% developed lymph node metastases (vs 5.3%, $p<0.0001$), and 1.6% experienced progression to clinical disease (vs. 8.9%, $p<0.0001$) as compared to patients younger than 40 years. Younger age (<40 in years, OR 4.348, 95% CI [2.293 – 8.196], $p<0.0001$) and larger tumor size at the time of

presentation (>9 mm, OR 4.717, 95% CI [1.961 – 11.364]) were risk factors for progression on multivariate analysis. ⁽⁴⁵⁾ A second group has shown similar results, with only 7% of well-selected patients demonstrating tumor growth and 1% demonstrating nodal metastases over 5 years. ⁽⁴⁶⁾ As with the first researchers' experiences, none of the patients who ultimately underwent an operation demonstrated recurrence or died of thyroid cancer. ⁽⁴⁷⁾

Guided by the Japanese experience, Brito and colleagues ⁽⁴⁸⁾ developed strict selection criteria for active surveillance, which include tumor, patient, and medical team specific characteristics. With a median period of 25 months, tumor growth was observed in 3.8% of 291 patients, with no patient developing regional or distant metastases. ⁽⁴⁹⁾ The authors also noted that serial assessment of tumor volume (in addition to largest dimension) may be an earlier identifier of those who will experience clinically meaningful tumor growth – an increase in volume by >50% preceded ultrasound detected change in tumor size at a median of 8.2 months.

Although current results associated with active surveillance are promising, long term follow up is necessary to ensure oncologic safety and the efficacy of salvage surgery. Surveillance fatigue is another consideration with regard to patient quality of life. Other future avenues of investigation include the identification of characteristics that may signal early failure (such as tumor kinetics), evaluation of the approach's applicability to subpopulations (such as pregnancy or pediatrics), cost-benefit analyses, and assessment of factors essential in developing and incorporating such a program.

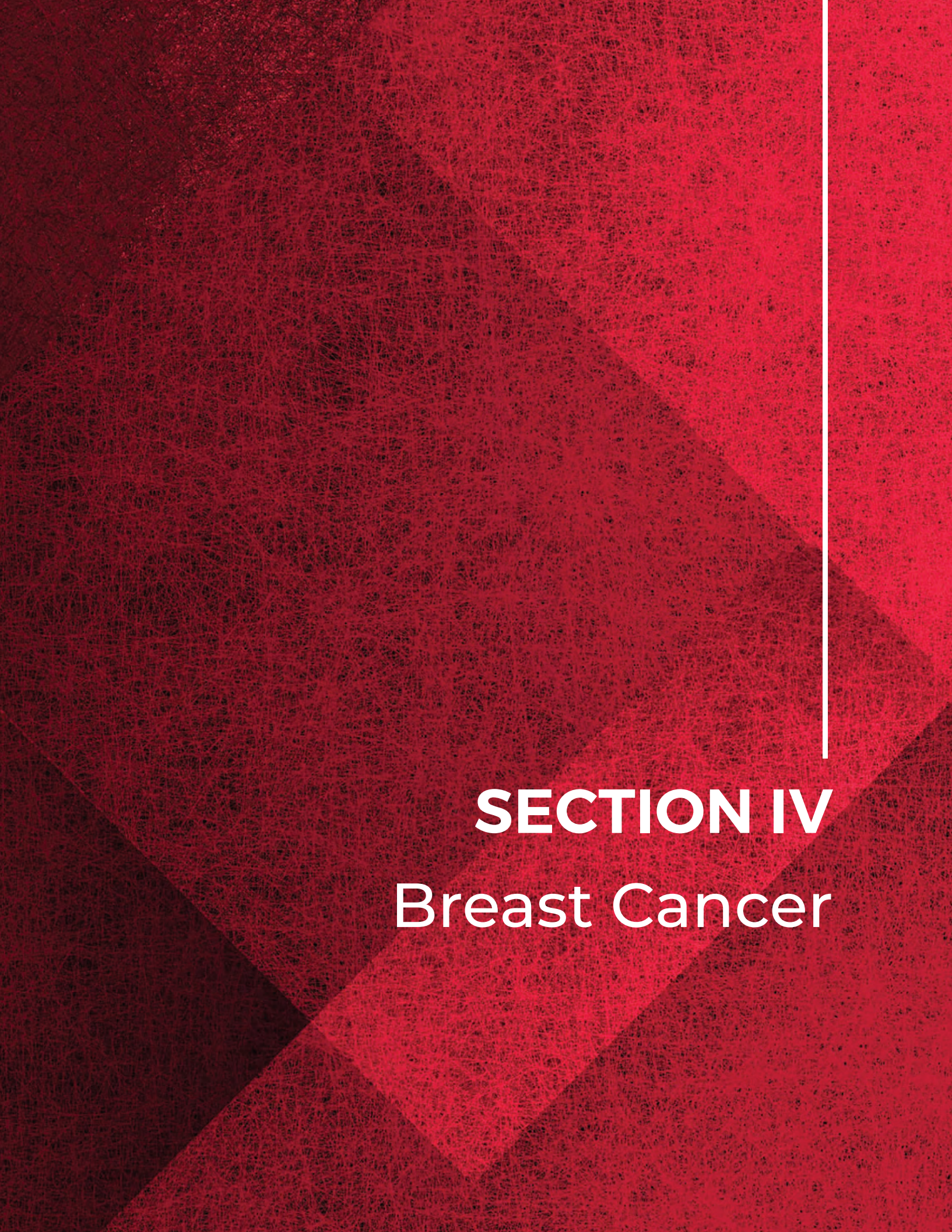
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SECTION IV

Breast Cancer

Chapter 16

Breast Cancer

Surgical Treatment

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Introduction and History

From the ancient records in the history of breast diseases (Papyrus of Edwin Smith-Luxor, Egypt, 1,700 BC) to the end of the nineteenth century, up to about 3,600 years, breast surgeries were only attempted to control the symptoms. **(Figure 16-1)** Large tumors with a serious compromise of quality of life were “amputated” with all the limitations of the time (anesthesia, hemorrhage, infection, etc.).

With Halsted (William Stewart Halsted 1852-1922) the surgical procedures on the breast took a more scientific and systematized aspect. The radical mastectomy recommended by him became standard and remains, with its variants, for almost 100 years. A team led by Veronesi, ^(1,2) during the years 1970/1980 at the National Cancer Institute of Milan, showed and convinced the medical world, that for the

results of up to 2 cm, a quadrantectomy/segmentectomy with complete axillary dissection was as effective as the radical mastectomy.

Then, the experience and the safety of the procedure allowed an increase in the size of the tumor, a smaller margin and the three axillary dissection levels being well represented by only the first two. In the 1990s, within this surgical evolution, the idea of the sentinel lymph node (SLN) emerged in mastology, which is then signed as a standard. The positive SLN was equal to axillary emptying. ^(3,4,5) At this moment, 2019, what is being consolidated is the conservative treatment, then neoadjuvant chemotherapy (QT) to reduce the size of the tumor, minimum free margin and, it is already being questioned, the need for lymphadenectomy in all cases in which the SLN is positive. ⁽⁶⁾

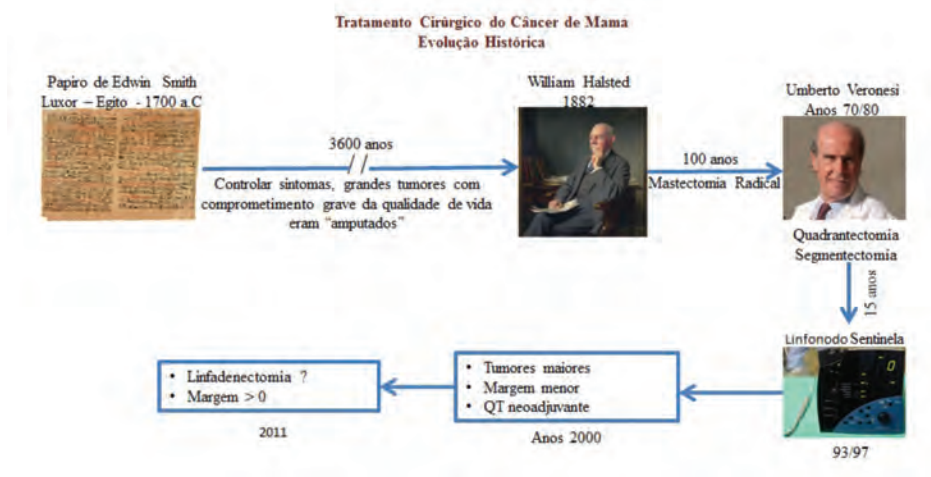


Figure 16-1. Historical evolution of conservative surgical treatment of breast cancer.

Security Evidence

In recent years, the surgical treatment of breast cancer has undergone profound changes. The halstedian concept of proliferation of the disease was replaced by Fisher's theory,⁽⁸⁾ and less mutilating procedures, with important preservation of breast tissue, were disseminated. Despite some recent adjustments to Fisher's theory, based on the importance of breast cancer screening, conservative treatment persists as a model that balances the recent principles of breast surgery: free surgical margins, absence of residual neoplasia and good aesthetic result.

The key points for the determination of a good oncological result of conservative treatment are: the integration between local control and global survival and similar results when compared to treatment once considered gold standard (radical mastectomy independent of stagin). In this sense, Veronesi's works were pioneering.⁽¹⁾

When comparing the results of global survival of patients treated with mastectomy with the group compared to conservative therapy (QUART) and obtaining statistically similar results, Veronesi showed that conservative surgery is a safe option to treat breast cancer with better aesthetic results. These studies also demonstrated the need for adjuvant complementary therapy with the goal of decreasing local recurrence.⁽⁹⁾

Several studies show that radiotherapy is the main tool in this regard. Recent meta-analyses of the Early Breast Cancer Trialists Collaborative Group (EBCTCG)⁽¹⁰⁾ presented the results of randomized clinical trials, evaluating the extent of surgery and the use of radiotherapy and its impact on mortality from breast cancer. It was shown that an increase in local control in the first 5 years of treatment results in a significant increase in both disease-free survival and overall survival 15 years after treatment. This result corroborated the unacceptable rates of local recurrence in patients undergoing only conservative treatment without adjuvant therapy and the impact of that relapse on overall survival. The oncological safety of the conservative therapy was confirmed by long-term studies published by Veronesi and Fisher, in 2002,^(11,12) and by the European Organization for Research and Treatment of Cancer 10,801 trial, in 2000.⁽¹³⁾

In 20 years of follow-up, with a local control rate of 80 to 92%, the overall survival was not statistically different, when compared to the mastectomy. Surgical resection of the tumor with free margins is the most important factor

in reducing the risk of local recurrence and the presence of compromised margins has been shown to affect disease-free survival. Therefore, inadequate surgery or an inaccurate anatomopathological study can directly influence the outcome of conservative surgical treatment. The great point of criticism of conservative treatment is the increased risk of local recurrence and the impact it may have on the survival of patients. Rescue mastectomy is the standard treatment for the group of patients with local recurrence. Studies have shown promising results with rescue procedures, however, late recurrence has shown better survival results when compared to early recurrences. Early recurrence (less than 5 years) is associated with an increased risk of distant metastatic evolution and death due to the disease, indicating the need for systemic therapy associated with rescue surgical treatment.

Preoperative

Once the histopathological diagnosis of carcinoma is made, the therapeutic planning must be fulfilled. It is necessary a complete and detailed anatomopathological analysis that includes an immunohistochemical analysis of the specimen, usual tests of staging and careful study of the breast with imaging tests. Mammography and ultrasonography (US) are fundamental, for precise information about the size of the tumor, location of the tumor in the breast, distance of the skin, nipple and chest wall and, also, possible associated injuries in the same breast and in the contralateral breast. When microcalcifications are present they should be better evaluated in terms of morphology, spatial distribution and extension. The use of magnetic resonance imaging (MRI) in mastology shows that this important technology is capable of finding additional foci of tumor in the same breast and in the contralateral breast. Based on these findings, routine use was proposed in the planning of conservative treatment of breast cancer. Many works, opinions and debates made this indication of the RM controversial.⁽¹⁴⁻¹⁸⁾

Today we know, after well designed and carried out studies, such as COMICE (Comparative Effectiveness of RM in Breast Cancer Trial),⁽¹⁹⁾ that the inclusion of routine MRI, in the preoperative evaluation of the breast seeking conservative treatment, does not improve the safety of the long-term surgical procedure and the clinical results can, eventually, be associated with damage. (**Table 16-1**) MRI, however, has important indications in mastology. With well-defined tumor characteristics and correctly performed staging, treatment should be indicated.

Indications of Conservative Surgery

When indicating a conservative surgery to treat breast cancer, several factors must be taken into consideration:

Table 16-1. COMICE. Important study showing that MRI is not necessary in the preoperative, routine, conservative surgery

Study / Author/ Year Published	Design and Study Cohort (N, Number of Subjects)	Follow up Time (Years)	Adjusted for differences between the groups under comparison	Clinical Outcome (s) Reported	Had MRI (N) proportion with outcome	Did not have MRI (N) proportion with outcome	P
Turnbull, 2010 ⁽¹⁰⁾ (COMICE) ^a	Randomized Trial: women with biopsy – proven BC scheduled for BCS after standard (triple) assessment (N=1623)	Mean 2.1	Not applicable, (two arms of randomized trial had same characteristics)	Local Recur- rence-free interval rates 3-year post-random- ization	(N = 816) 93.9%	(N = 807) 96,5%	NS
Hwang, 2009 ⁽¹¹⁾	Retrospective: women who had invasive BC excised to negative margins and had BCT (N=463)	Mean 4,5	Yes; adjusted for adjuvant therapies, patient, and tumor variables	Actuarial 8-year ipsi- lateral breast recurrence rates	N = 127) 1.8%	N = 345) 2.5%	0.67
Solin, 2008 ⁽⁷⁾	Retrospective: women with early stage invasive BC for ductal carcinoma in situ (DCIS) who had BCT (N=756)	Mean 5	Yes; adjusted for variable that differed between two groups on baseline characteristics.	Actuarial 8-year rates: any local recurrence local-only first recur- rence	(N = 215) 3% 3%	(N = 541) 4% 4%	0.51 0.32
Fisher, 2004 ⁽¹⁶⁾	Retrospective: women who had invasive BC excised to negative margins and had BCT (N=219)	Mean 3.4	No adjust- ments made for differences be- tween groups	Simple Proportion with local recurrence	(N = 86) 1.2%	(N = 133) 6.8%	<0.001

BC: breast cancer. **BCT:** breast conserving therapy. **NS:** not significant

^aBased on publication (10) and supplemented by report [Turnbull LW, Brown SR, Olivier C, Harvey I, Brown J, Drew P et al. Multicentre randomized controlled trial examining the cost-effectiveness of contrast-enhanced high field magnetic resonance imaging in women with primary breast cancer scheduled for wide local excision (COMICE). *Health Technol Assess* 2010; 14 (1)]. Available from the HTA website on <http://www.hta.ac.uk> (accessed June 2011).

Tumor Size

The tumor diameter is the primary factor and is considered at the time of conservative surgical indication. Classical works, such as Mote *et al.* ⁽²⁰⁾ found higher local recurrence rates with 2 and 5 cm than for tumors smaller than 2 cm in

diameter. The first Veronesi study ⁽²¹⁾ between 1970 and 1986 at the National Cancer Institute of Milan with 1,232 women with breast cancer, tumors smaller than 2 cm, operation with quadrantectomy, axillary dissection and radiotherapy (CUART) versus patients with the Halsted ⁽⁷⁾ mastectomy verified similar results.

Today, what we see in the literature is, the effect of the relationship between the size of the breast and the size of the tumor, lesions of up to 5 cm are undergoing conservative treatments. Increasingly, we see the use of neoadjuvant QT in the sense of reducing the dimensions of the lesions and then applying the conservative treatment (DOWN STAGING). The failure of another paradigm should be taken into account, these are presented in the chemotherapy. This clinical approach allows conservative surgery in 50% of patients with a primary mastectomy indication.

Breast Size

The breasts can be classified according to their volume in: Small - up to 250 cc, Stockings - 250 to 500 cc, Large - more than 500 cc. In small breasts, small tumors (T1 - up to 2 cm) and large breasts, larger tumors (T2 - up to 5 cm) can be indicated conservative surgery. For other situations consider neoadjuvant QT. The feasibility of conserving the breast in the presence of a nodule depends more on the relationship between the diameter of the tumor and the size of the breast than on the size of the isolated tumor.

Site of the Tumor in the Breast

According to Aurélio Zecchi, ⁽²²⁾ there is a predominance of carcinomas in the left breast, when the reference was made to 4,200 patients with breast cancer, with 52.5% on the left side, 47.4% on the right side and 0.4% bilateral and simultaneous. In relation to mammary topography, the same author found 47.7% in the upper external quadrant, 11.3% in the lower external quadrant, 8.9% in the upper internal quadrant, 5.2% in the lower internal quadrant and 18.5 % in the central region of the breast.

Haagensen ⁽²³⁾ also refers to a discrete majority of breast cancer on the left and in terms of location in the breast are percentages similar to that of Aurélio Zecchi, as we also verify in our daily practice. The localization of the tumor in the breast, by itself, does not contraindicate the conservative procedure, however retroareolar lesions are critical and care must be redoubled. In these situations, centralectomies, intraoperative pathological examinations are very useful.

Associated Breast Lesions

One of the limiting factors for conservative surgery is the presence of two or more tumors in the same breast. When

there are two small tumors in the same quadrant and it is not necessary to remove more than 20% of the breast volume, conservative surgery can be performed. Benign alterations, such as gigantomastia, ptosis, nodules, asymmetry, when associated with breast tumor, can be treated simultaneously, by oncoplastic procedures.

HISTOLOGICAL TYPES

Carcinoma *in situ*

The concept of lobular carcinoma *in situ* was presented by Foote and Stewart in 1941. ⁽²⁴⁾ In this regard, there were many discussions and today it is not considered a true breast carcinoma and a risk marker for invasive carcinoma (ductal or lobular). Generally, it involves multiple lobes, being located in the ductolobular terminal units in general, without palpable lesions, appearing in the tomography with a greater fibroglandular density pattern and microcalcifications. The therapeutic orientation is controversial. Changing lifestyle, the use of some medications, such as tamoxifen, raloxifene or exemestane and, more rarely, bilateral risk reducing mastectomy should be considered. Six-monthly physical exam and annual mammography is the standard follow-up. The concepts of conservative treatment in lobular carcinoma *in situ* are not applied. Ductal carcinoma *in situ* corresponds to a proliferation of malignant epithelial cells within the mammary ducts, having a predilection for the terminal duct-lobular unit and having, as a fundamental characteristic, the integrity of the basement membrane. The detection is usually performed by grouped and polymorphic microcalcifications found on mammography. The histological classification can be of the following types: solid, papillary, micropapillary, cribriform and mixed. The solid type may present comedone type necrosis, being associated with a more aggressive biological behavior. The initial treatment is surgical, in most cases, conservative surgery. Mastectomy with immediate reconstruction is indicated in some situations. There are some scores to facilitate surgical indication. The van Nuys Prognostic Index, one of the most widely used, considers predictors of recurrence to define the extent of surgery. (Table 16-2)

Infiltrating Carcinoma

Ductal

It is called infiltrating ductal carcinoma due to the cytoarchitectural disposition of the malignant cells and

Table 16-2. DC *in situ* – Van Nuys Index

PUNTIATION	1	2	3
SIZE (mm)	≤15	16 - 40	>40
Margin (mm)	≥10	1 - 9	<1
Pathological Clasification	No High grade. Without necrosis	No High grade With necrosis	High grade with or without necrosis
AGE	>60	40 a 60	<40
Low risk	4 – 5 – 6		
Intermedied risk	7 – 8 – 9		
High risk	10 – 11 – 12		

not of its origin site, because it occurs at the level of the ductolobular terminal unit, as well as the other histological types. In the macroscopy it presents a spiculated contour (75%), but it can be circumscribed or diffuse without defined limits with the adjacent mammary tissue. Spiculated forms, in general, are associated with lower survival rates in 10 years, when compared to the circumscribed and, more frequently, with axillary involvement.

Lobular

Infiltrating lobular carcinoma is the second most frequent histological type, accounting for 8 to 15% of mammary carcinomas. According to Rosen, ⁽²⁵⁾ the frequency is 10% and Ellis *et al.* ⁽²⁶⁾ report the frequency of this type of neoplasia as 16%. Ductal carcinomas, in general, present unifocal behavior, expansive growth and tendency to spread through the ducts, while lobular carcinoma is unpredictable, growing insidiously among local structures without a radial pattern. The lobars do not have an intraductal dissemination characteristic, but they do have multiple foci associated with different units. Radiologically, it manifests as an area of architectural distortion or localized hyperdensity. In most cases it presents as a spiculated and firm nodule, similar to ductal carcinoma. One of the characteristics of infiltrating lobular carcinoma is the higher incidence of bilaterality and multicentricity. The bilaterality appears in 10 to 20% of the cases and only in the synchronous neoplasm happens reduction in the survival. Infiltrating carcinomas can and should, in most cases, be treated by conservative surgery.

Contraindication to Conservative Treatment

Absolut

- Rejection of the patient after detailed explanations.
- Impossibility or uncertainty of obtaining free margins.

- Carriers of collagen diseases that contraindicate radiotherapy.
- Impossibility of radiotherapy.
- Forecast of poor aesthetic result.
- Pregnancy in the 1st and 2nd trimesters due to the impossibility of radiotherapy.
- Lesions associated with suspicious diffuse microcalcifications.

Relative

- High genetic predisposition.
- Prior radiation therapy in the breast.
- Multicentric lesions.
- Incorrect tracking.
- Breast carcinoma in men.

Surgical Technique

Breast

One of the main justifications for the conservative surgical treatment of breast cancer is to maintain a satisfactory aesthetic, without oncological damage. At the beginning of the conservative treatment, the resections always included a wide area of skin in the radial direction of the nipple/tumor. ⁽²⁷⁾ Currently, the incisions have a greater aesthetic concern and the choice of the incision site is, therefore, very important. ⁽²⁸⁻³⁰⁾ Today we live a moment in which we can opt for a classic incision in the vicinity of the tumor, whether arciform, circular, periareolar or using oncoplastic techniques. These techniques allow us to use established procedures of plastic surgery, respecting the vascular pedicles and thinking about the reconstruction of the breast, with a tumoral approach, many times, even more widely. The synthesis of these wounds supposes the use of local flaps that allow to correct big defects and even to offer a better mammary aesthetics.

The classic procedure ⁽³¹⁾ has the following characteristics: the incision is in the vicinity of the tumor, it is faster, the surgery is smaller, the mobilization of the tissues is smaller, it does not allow correction of possible associated deformities (gigantomastia, ptosis, etc.), it does not harm the eventual rebounds and does not harm the boost (reinforcement). ^(32,33) The oncoplastic is usually the major procedure, it can correct other associated injuries, it allows ample mammary resections, it has a good aesthetic result, however, it limits the rebounds and boost by the wide mobilization of tissues. We found that there is no right or wrong technique, what exists is better indication for specific cases. Anyway, whenever we operate a breast, we have to find a balance point, we can not forget the aesthetic and not compromise oncological safety. Periareolar incisions are possible in small lesions near the nipple-areola complex. In lesions not close to the skin (≥ 2 cm) it can be preserved. It is always interesting to see mammography in this situation: when the subcutaneous tissue is thin and the parenchyma rises next to the dermis, we tend to resect the overlying skin. In retroareolar lesions, concerns are greater. It is necessary an intraoperative histopathological study of the rest of the parenchyma that is stuck to the areola-nipple complex certifying the absence of tumor.

In 1992, in the book breast conservation, by Veronesi *et al.*, ⁽²⁷⁾ the appropriate margin proposed for conservative treatment was 1 to 2 cm. Over the years, a margin of up to 2 cm was accepted and the idea that “absence of ink in the tumor” is enough, which means to say margin different from zero. All these changes in the size of the margin were based on the work of Holland *et al.* 1985, ⁽³⁴⁾ which showed that even in a margin of 4 cm there were still, in 10% of the cases, tumor foci and that, therefore, in a significant percentage of conservative treatments, tumor foci remained and that time showed that they were effectively treated by radiotherapy. (Figures 16-2 and 16-3)

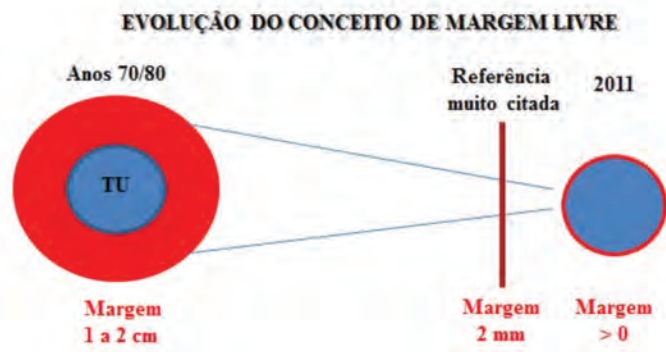


Figure 16-2. Evolution of the concept of satisfactory free margin.

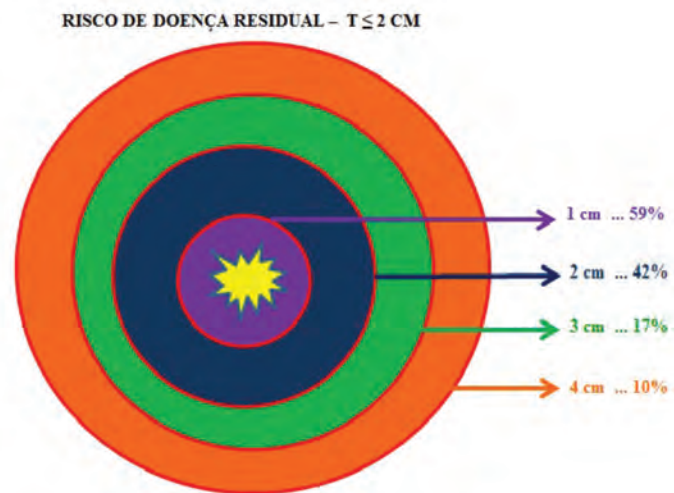


Figure 16-3. Risk of residual disease in relation to the surgical resection margin.

Holland *et al.* *Cancer - Cancer* 1985.

Axillar - Sentinel Lymph Node

The approach of axillary lymph nodes in breast cancer patients has followed the same conservation objectives observed in the treatment of the primary site. This advance was only possible thanks to the concept and the concretization of the sentinel lymph node (NLC) principles. The axillary state is one of the most important prognostic factors, currently, in the study of breast cancer, serving as a predictive parameter of adjuvant therapy and local recurrence rate. ⁽³⁵⁾ The dissection of lymph nodes in patients without metastasis does not cause no benefit and brings with it the complications and morbidities of the procedure (lymphedema, neurovascular injuries). With the intention of minimizing these effects, the concept of the NLC quickly spread in the study of breast cancer. Its principle is based on the concept that its study will reflect the status of other axillary lymph nodes in a significant majority of cases, therefore, when it is negative, the dissection of the other lymph nodes will not be performed.

History

The sentinel lymph node (SLN) concept originated in 1977 when Cabanas ⁽³⁶⁾ described the first draining lymph node in penile carcinoma. Morton *et al.* ⁽³⁷⁾ reported the identification of the sentinel lymph node using patent blue in patients with cutaneous melanoma. Krag *et al.*, In 1993, ⁽³⁸⁾ and Veronesi and Paganelli, in 1997, ⁽³⁹⁾ described the use of the radioisotope gamma probe for the identification of the sentinel lymph node in patients with breast cancer.

Since then, several works in the literature have shown the accuracy and benefits of the technique.

Technique

The main techniques used for the mapping and identification of the Sentinel Lymph Node (SLN): are mammary scintigraphy, with the use of colloidal solution marked with ^{99m}Tc followed by lymphocytinography, after the injection of radioisotope solution into the breast, for identification of the SLN in the axilla or in other regional drainages. The method can be performed guided by mammography, US or guided by digital palpation. Subsequently, a manual gamma ray detection probe is used for identification in the operative field and confirmation outside of the SLN. The other very useful technique is the patent blue dye V 2.5% with perilesional or periareolar injection of 2 to 4 ml, followed by massage for 5 minutes. The best technique seems to be the combination of the methods, although in isolation both techniques proved similar in the identification. The experience of each service with the methodologies is of fundamental importance for good detection rates.

Evidence for Validation

The technical aspect of the sentinel lymph node biopsy (SLNB) was validated by numerous studies,^(4,5,38) although the clinical validation by randomized studies is scarce. In 2003, Veronesi⁽⁵⁾ published a randomized study comparing SLNB research and axillary dissection versus SLNB without dissection when the SLN is negative. The results were shown with small statistical power to detect some difference in survival, disease-free time and lymph node recurrence between the two groups. In 2010, the results of the randomized study NSABP-B32⁽⁴⁰⁾ were published in order to establish whether sentinel lymph node resection in breast cancer patients achieved the same survival and local control as lymphadenectomy, but with less adverse effects. In a total of 3,986 patients undergoing SLNB, the results showed that overall survival, disease-free survival, and regional control were equivalents between the groups. When SLNB is negative, SLNB alone not accompanied by lymphadenectomy is an appropriate, safe method and is shown as an effective therapy for breast cancer patients with clinically negative lymph nodes.

Future Perspectives

Data from the literature, over the decades, showed that about 50% of patients with positive SLN had no other lymph node

involvement after lymphadenectomy. Different models of nomograms were used, trying to determine and establish predictive factors to select groups of patients who would not benefit from lymphadenectomy even with positive SLN, but all without impact on daily clinical behavior. At the beginning of 2011, Giuliano, Morrow *et al.*⁽⁶⁾ published an important work with the objective of establishing a group of patients who could be freed from lymphadenectomy even with positive SLN, without impact on global survival rates and local control. In the study with 891 breast cancer patients with dimensions less than or equal to 5 cm and with 1 or 2 sentinel lymph nodes positive for freezing examination, there was no benefit of axillary emptying, if the patients were treated with segmental resection, radiotherapy and chemotherapy. The overall survival was 91.8% for the group that underwent lymphadenectomy versus 92.5% for the other group. Disease free survival was 82.2 versus 83.9%. The perspective is that new studies are published with the aim of establishing strong evidence to abandon axillary emptying in the presence of limited disease in SLNB and to avoid complications associated with radical surgery.

Radiotherapy

After correctly performed conservative surgery, resection of the tumor with free margins and axillary management (sentinel lymph node with or without axillary dissection), the use of radiotherapy (XRT) is a *sine qua* condition for a correct treatment. The XRT is indicated, associated with conservative surgery, seeking to avoid surgical mutilation of the mastectomy, providing the same recurrence rates.^(2,33) The Milan TRIAL, NSABP-B06, NCI and IGR,⁽⁴¹⁾ showed that there is no difference statistics between radical mastectomy and conservative surgery followed by radiotherapy in the following aspects: locoregional control, distant metastasis, survival, second primary incidence, contralateral breast cancer and in the local control of positive axilla cases. Dosage, technique, devices, and processes may vary, but at the present time, it is not possible to identify with certainty the groups in which the XRT could be avoided. Elderly people with small tumors, *in situ*, well differentiated, wide margins, with specific genetic mutations (BRCA), even in these groups, manage to identify some benefit of the XRT. Some studies show that the association of XRT is related to the increase of disease-free survival.⁽¹¹⁾ Great advances were made in imaging techniques, tumor localization, and surgical techniques. The same happened with the XRT over the last few years: the three-dimensional XRT and the XRT with radiation intensity

modulation (IMRT), in which it is possible to protect the heart and lungs, in addition to distributing the dose of more homogeneous form, reducing the risk of acute and chronic reactions of the skin and subcutaneous tissue, made the procedure much safer and without significant compromise of aesthetics. Studies related to boost, dose fractionation, duration, association to QT, partial irradiation of the breast, intraoperative XRT are evolving and, certainly, gains will come, but, at the moment, radiotherapy is a fundamental pillar of conservative treatment of breast cancer. ⁽⁴²⁾

Chemotherapy and Hormone Therapy

Chemotherapy aims to perform the systemic treatment of micrometastases, increasing overall survival (OS) and disease-free (DFS). The conservative surgical treatment of breast cancer does not modify, therefore, any of the indications of chemotherapy or hormone therapy. ⁽⁶⁾ Women carriers of major tumors, with a mastectomy indication, may have their chemotherapy performed neo adjuvantly,

followed by re-evaluation, for possible conservative surgical treatment. ^(43,44) (Figure 16-4)

Prognosis and Recurrence

It is emphasized that local recurrences may occur after conservative surgery. In 10 years of follow-up, 5 to 10% of the cases recur, with emotional damage and negative repercussion on the oncological prognosis. ⁽⁴¹⁾ The local recurrence depends on the degree of aggressiveness of the tumor, the tumor diameter and the microscopic compromise of the surgical margins. The evaluation of margins in the intraoperative can modify the extension of the surgery and help reduce the incidence of local recurrence after conservative surgeries. When the margin was evaluated in a deferred manner and its commitment was identified, surgical reoperation is recommended. Although there is a quantum of local recurrence in the conservative treatment and, also, some commitment in the specific prognosis of this case that relapses, it is diluted in the whole and when we analyze all the conservatively treated cases the final damage in the total survival is nonexistent.

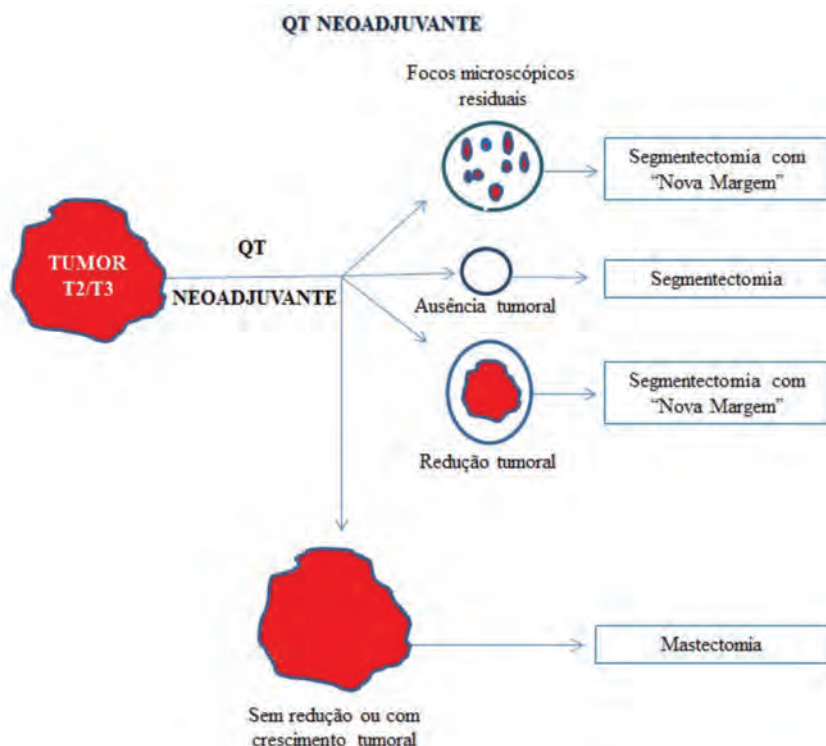


Figure 16-4. Indication of Surgery after neoadjuvant QT.

Physiotherapy

When conservative treatment includes axillary lymphadenectomy, the evaluation of the physiotherapist, in the pre- and postoperative period, is recommended. Preventing complications, such as seroma, edema of the upper limb, infections, paresthesias and motor problems at the level of the scapulohumeral joint, is always better than treating. Clear guidelines on the prevention of complications should be provided and collected in the control medical consultations. It can not be forgotten that, the possible appearances cited at the time of lymphadenectomy, all may occur, also, at the time of the sentinel lymph node technique, however, in this case, at a much lower incidence, but that they also deserve attention. ⁽⁴⁵⁾

Summary

- Much of breast tumors can and should undergo conservative surgical treatment.
- The final survival of large series treated in this way, when compared to the classic mastectomy, was not modified.
- At the present time, it is not possible to identify a subgroup of conservative treatment that can dispense RXT.
- Chemotherapy and hormone therapy do not change when conservative treatment is the option.
- In the indicated cases, the sentinel lymph node technique is the standard at the axilla level.
- The main justification for conservative treatment is oncological safety with satisfactory aesthetics and function.

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Chapter 17

Radical Surgical Treatment of Breast Cancer

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Introduction

The treatment of breast cancer was perfected in recent decades in parallel with the greater development of the pathophysiology of the disease, undergoing major changes over time. Until a few decades ago, patients were treated uniformly with radical mastectomy and total axillary dissection. Currently, conservative and selective surgical approaches in the breast and axilla, previously observed with skepticism, constitute the treatment standard for most patients.

The management of breast cancer has become increasingly complex and requires integrated knowledge of multiple issues that go beyond simple resection of the primary tumor. Advances in mammary radiology, in pathology, in nuclear medicine, in rehabilitation and in pre- and postoperative support, and in the growing variety of adjuvant therapies, local or systemic, have returned the treatment of multidisciplinary breast cancer.

More than 100 years have passed since the publication of William Halsted (1882) on the technique and results of radical mastectomy.⁽¹⁾ Until then, the surgical treatment of breast cancer consisted of an expanded dissection of the tumor, resulting in extremely high rates of morbidity and mortality. Halsted proposed that further resection could increase the possibility of local control of the disease. Although today this surgical procedure seems to be excessively mutilating for most of the cases, it is necessary to remember that Halsted treated breast tumors, in general, locally advanced and that did not have means of diagnosis to individualize distant metastasis and that, therefore, the failure of the surgery was manifested only in terms of locoregional recurrence. On the other hand, there were no other therapeutic methods outside

of surgery. Thus, radical mastectomy resulted in a significant drop in local recurrence rates and quickly became the standard procedure for breast cancer. The technique described by Halsted was the procedure of choice in breast carcinoma in the first half of the cycle.⁽²⁾

However, despite the increase in local control, the curative potential of this technique remained limited. In 1948, Patey and Dyson described a surgical technique that differs from that described by Halsted for the preservation of the pectoralis major muscle. This modification was highly successful because of the advantage of better aesthetic results and lower morbidity and mortality, maintaining the same local control rates of the disease.

In 1963, Auchincloss and, in 1965, Madden proposed the removal of the complete breast without resection of the pectoralis major and minor and dissection only of the first and second level lymph nodes. These last two techniques were recognized as a modified radical mastectomy.⁽³⁻⁶⁾

Patient Position

The patient is placed in supine position with the upper joints extended at a right angle in a well-fixed armrest, avoiding hyperabduction and extra-rotation, so that there is no lesion by stretching the brachial plexus.

Radical Mastectomy

The surgery proposed by Halsted consists in the removal of the single block mammary gland with the pectoralis major and

minor muscles and in the axillary radical lymphadenectomy (levels I, II and III). Because it is a surgery performed on large tumors, the incision does not always follow the classic tracings or previously described in the literature, being more important to delimit an incision that allows the extirpation of the tumor with cutaneous margin. In the period of description of this technique, tumor dissemination was associated with the anatomical knowledge of the progression of the breast to the axillary and interpectoral lymphatic chains. Thus, a wide locoregional surgery would be the best option for healing. Reserved, in the previous decades, basically to the cases of advanced tumors, fixed to the pectoral muscles, today it is in disuse, due to the arrival of chemotherapy and primary or neoadjuvant hormone therapy, which allow the reduction of large tumor masses and the use of other surgical options.

The result of this surgery is quite unfavorable, with major thoracic deformity depending on the removal of the pectoralis major muscle, as well as the functional impotence of the arm.

Modified Radical (MR)

The possibility of a less aggressive surgical therapy and with lower morbidity, whose final result is more acceptable than the Halsted type mastectomy, makes this technique the ideal option for patients ineligible for conservative treatment.

MR Patey

It consists of the removal, in a single block, of the mammary gland in conjunction with the aponeurosis of the pectoralis major muscle and exeresis of the pectoralis minor muscle in association with axillary lymphadenectomy (levels I, II and III) and interpectoral.

MR Madden

It consists in the removal of the mammary gland in conjunction with the aponeurosis of the pectoralis major muscle and in axillary lymphadenectomies (levels I, II and III) and interpectoral lymph node dissection, conserving the pectoralis major and pectoralis minor muscle.

The incision must be adapted to the oncological and aesthetic objectives. It must include the entire areola-nipple complex,

as well as the adjacent skin in case of superficial tumors. Excessive skin residues should be avoided, especially at the ends of the incision, as well as taut flaps, which may impair future breast reconstruction.

Indications for Radical Mastectomy

Relationship between tumor volume and unfavorable breast volume.

- Multicentric tumors.
- Invasive tumors with extensive intraductal component.
- Impossibility or uncertainty of obtaining free margins in conservative surgery.
- Lack of availability of complementary radiotherapy.
- Activity collagen disease (contraindication to radiotherapy).
- Breast carcinoma in men.
- Patients with the possibility of uncertain follow-up.
- Desire of the patient.

Simple Mastectomy

It consists in the removal of the mammary gland, aponeurosis of the pectoralis major muscle and the cutaneous segment including the surgical scar of the previous biopsy, without axillary emptying.

Indications:

- Hygienic removal of locally advanced tumors.
- Treatment of sarcomas.
- Recurrence of conservative treatment.
- Ductal carcinoma *in situ* of poor prognosis, in this situation generally associated with the evaluation of the sentinel lymph node.
- In the prevention of breast cancer in high-risk patients (prophylactic mastectomy).

Subcutaneous Mastectomy

It constitutes the removal of the entire mammary gland, preserving the skin and the areola-nipple complex. The indications are limited to benign pathologies, in particular multiple or giant fibroadenomas, phyllodes tumors, multiple papillomatosis and, more recently, risk-reducing mastectomy. The cutaneous incisions frequently practiced are: the inframammary, the transverse equatorial or the

periareolar way. The preparation of the flaps should be very careful to avoid leaving glandular tissue and, at the same time, not creating ischemic areas.

Skin Sparing Mastectomy

Initially described, in 1991, by Toth and Lappert, it consists in the removal of the mammary gland, including the areola-nipple complex, scars from previous biopsies and the overlying skin of superficial tumors.⁽⁷⁾ For the interventions in the armpit, the incision could be separated for better aesthetic result. It is a technique frequently used when the breast is reconstructed during the same operative time of the mastectomy. Its main indications are risk-reducing mastectomy and patients with carcinoma *in situ* and initial invasive disease. It presents as advantages in relation to the modified radical mastectomy: preservation of the entire cutaneous envelope and the inframammary sulcus, which translates into a better aesthetic result. The maintenance of a large part of the intact skin favors the use of expanders and prostheses, as well as a better use of autologous tissues. It also reduces the need for secondary aesthetic surgeries and symmetrizations of the opposite breast. The lower cost associated with the psychosocial benefit results in better acceptance of the procedure. The disadvantages of the technique consist of possible complications arising from the existence of longer skin flaps, within them, ischemia, necrosis and infection; such factors can generate delay in the start of adjuvant treatment, a fact that must be taken into consideration.

Nipple Sparing Mastectomy

It consists in the exclusive removal of the mammary gland, preserving all the skin and the areola-nipple complex. Recent studies admit that it constitutes an oncologically safe behavior in cases of initial breast cancer, where the primary tumor is distant from the nipple and the intraoperative examination shows that the margin of the areola-nipple bed is free.⁽⁸⁾

Recent studies show a rate of recurrence, in the areola-nipple complex, between 0 and 2%, when patients are carefully selected and well-evaluated margins. A variety of surgical techniques has been used and the making of more separate incisions of the areola associated with the use of tissue expanders has been decreasing the risk of nipple necrosis.^(9,10)

Post Operative Care

Placement of drainage system with closed suction catheter in the plastron, in position that ensures complete gravitational aspiration. Routinely, drainage is removed only when less than 30 ml serous or serosanguineous drainage was evident during a 24-hour interval.

Complications

The most feared intraoperative complication is injury to the wall of large blood vessels, especially the axillary vein. To avoid injury to this vein, only its anterior and ventral portions should be dissected. In the event of the occurrence of vascular injury, the repair of it should be carried out as quickly as possible. Given the low risk of thrombosis, there is no need for heparinization.

The patient usually experiences moderate pain at the operative site, shoulder and arm, in the immediate postoperative period. The patient may observe hypesthesia and paresthesia, as well as occasional “ghost” hyperesthesia throughout the operative site.

Hypoesthesia is a common postmastectomy symptom and results from the denervation of one or more intercostobrachial nerves, which traverse the axillary space and are sectioned in the axillary dissection. These sensations tend to disappear gradually with the healing of the wound. However, normal sensitivity does not return, most often to the denervated axilla, medial region of the arm and hemithorax.

The lesion of the long thoracic nerve, also called Bell’s nerve, causes paralysis of the serratus anterior muscle, with destabilization of the scapula, which is irreversible.

The accumulation of lymph, which results in the development of seroma, is an extremely frequent complication in the immediate postoperative period and depending on the volume of fluid collected, expectant management or drainage may be adopted.⁽¹¹⁾

In the late postoperative period, the complication that causes the worst impact in terms of quality of life of the patient is lymphedema of the upper limb on the same side. The rates of this complication are extremely variable from 6.7 to 70%, depending on the extent of the dissection, the number of lymph nodes removed and the performance of adjuvant radiotherapy.⁽¹²⁾

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Chapter 18

Surgical Treatment of Locally Advanced Breast Cancer - LABC

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Introduction

Locally advanced breast cancer (LABC) is a clinical presentation of breast cancer that does not allow surgical approach at the time of diagnosis, regardless of the histological type and with different prognoses. Historically, the definition of LABC was based on the work of Haagensen and Stout, ⁽¹⁾ published in 1943 and was associated with the high rate of local and distant recurrence, which at the time contraindicated surgical treatment: edema or cutaneous ulceration, fixation of the tumor to the skin or chest wall, satellite skin nodules, fixed axillary lymph nodes, lymph supraclavicular nodes and arm edema. These inoperability criteria are still used to select candidates for neoadjuvant chemotherapy and radiotherapy. With the introduction of conservative surgery in the 1970s and 1980s, the definition of locally advanced breast cancer went on to include operable tumors, but they need mastectomy for adequate local control, i.e., T3 - tumors larger than 5 cm.

In this group, then, patients with primary tumors larger than 5 cm in diameter and/or affecting the chest wall and/or the skin and/or having fixed axillary lymph nodes are considered. According to the 8th edition of 2018, of the American Joint Committee on Cancer (AJCC) all breast cancer classified as T3 and T4 with any N or as N2 or N3 with any T is considered locally advanced. In this way, patients with stage III and some with stage IIB ⁽²⁾ are included.

These cancers remain a clinical challenge, since such patients present a high rate of recurrence and death due to metastatic disease. ⁽³⁾

The development of combined treatment, including chemotherapy, hormone therapy, surgery and radiotherapy, have changed the prognosis of these patients.

Epidemiology

The LABC is a common presentation of breast cancer in underdeveloped countries. In India it represents 50-70% of cases. However, since the advent of mammographic screening, the presentation of patients with locally advanced disease has decreased. ⁽²⁾ In developed countries, such as the United States, the incidence of locally advanced disease is 5-6%. ⁽⁴⁾

Prognostic Factors

The prognostic factors for LABC are the same as for breast cancer in other stages. The size of the tumor and the site of the lymph node metastasis (axilla, infraclavicular, supraclavicular or internal mammary) have the greatest impact on the recurrence of the disease and on survival. ⁽³⁾ Among the prognostic factors are: age, menopause, recipients hormones, clinical staging, lymph node involvement, histological grade and neoadjuvant systemic response. ^(9,10)

There is an important association between the survival rate and the number of axillary lymph nodes involved. According to Carter, the 5-year survival was 73% for patients with metastases in 1-3 lymph nodes, compared to 46% for patients with metastasis to 4 or more lymph nodes. ⁽¹¹⁾

Tumor size is also an independent prognostic factor, even in tumors larger than 5 cm. ⁽¹²⁻¹⁴⁾ Although the expression of estrogen and/or progesterone receptors is considered a weak prognostic factor, it is strongly predictive of response to hormonal treatment. ^(15,16)

Overexpression of HER-2 is associated with reserved prognosis in patients with axillary disease in most of the studies. ^(15,16) HER-2, when present, is a predictive factor for response to trastuzumab and chemotherapy with anthracyclines. ^(17,18)

Advances in microarray technology provide better classification of breast tumors based on the expression of genes related to survival and response to chemotherapy. ⁽¹⁹⁾ The use of molecular classification of breast tumors with or without lymph nodes positive, using genetic mapping, was more sensitive than standard criteria, such as the consensus of the National Institutes of Health (NIH) and the Saint Gallen criteria in the prediction of high risk for relapse. ⁽²⁰⁾

Diagnostic

The majority of cases of locally advanced disease can be detected during the physical examination of a palpable tumor (**Figures 18-1 and 18-2**) and the diagnosis obtained by obtaining tumor tissue for histological evaluation through fine needle aspiration (FNA), needle puncture (core biopsy) or incisional biopsy.

FNA can detect the presence of malignant cells, but does not report on the architecture of the lesion (intraductal or invasive). It is important in the evaluation of secondary lesions, such as axillary or supraclavicular lymph nodes, cutaneous or subcutaneous nodules.



Figure 18-1. Vegetative lesion in right breast with associated skin edema.

The core biopsy performed with local anesthesia usually provides enough tissue to detect the invasive nature of the tumor, nuclear grade, hormone receptors, Ki-67 and HER-2. It also allows the introduction of the radiopaque clip at the site where the biopsy is performed, it is important in patients with indication of neoadjuvant treatment for adequate future surgical planning. ⁽⁵⁻⁸⁾

At present, incisional biopsy is reserved in those cases in which the core biopsy was inconclusive.

Mammography, ultrasonography, and magnetic resonance imaging of the breast help assess the extent of the disease. Bilateral mammography is essential to determine the presence of clinically occult lesions in the affected or contralateral breast. Mammary ultrasonography may be useful in evaluating tumor size in dense breasts and lymph node involvement. Magnetic resonance imaging demonstrates greater accuracy in assessing the extent of disease, tumor size, multicentricity, and invasion of adjacent soft tissues. ⁽⁵⁻⁸⁾

Other tests to identify the disease at a distance include: lab tests, chest and abdominal computed tomography, and bone scintigraphy.

Magnetic resonance of the skull is indicated only in the presence of symptoms related to the central nervous system.



Figure 18-2. Important cutaneous edema and hyperemia occupying the entire right breast and focally in the contralateral breast.

Treatment

The multimodal treatment includes radiotherapy, surgery and systemic therapy that includes chemotherapy and therapeutic monoclonal antibodies, such as trastuzumab, in addition to hormone therapy, which, when indicated, should be widely used in these patients. The treatment of locally advanced breast cancer involves the oncological surgeon, clinician, and radiotherapist, with the objective of locally controlling the disease and eradicating any distant microscopic metastases. ⁽²¹⁾

Although isolated chemotherapy results in high response rates, it rarely eradicates the tumor in the breast and armpit. Radiation therapy and surgery, on the other hand, control the disease locally, but do not treat microscopic and distant disease. Combination therapy using surgery and radiotherapy results in an increase in local control from 70% to 86%. ⁽²²⁾

Treatment should be initiated with neoadjuvant chemotherapy, which treats early microscopic and distant disease and facilitates surgical treatment, which is usually followed by radiotherapy.

Neoadjuvant Treatment

Neoadjuvant chemotherapy allows initially inoperable tumors to undergo mastectomy and, also, allows the performance of conservative surgery on tumors that would be treated with a mastectomy according to the tumor response. This response has a prognostic value in the survival of these patients. The works have shown a correlation between the amount of residual disease in the surgical piece and the survival.

Overall survival resembles that of patients undergoing adjuvant chemotherapy. ^(10,23-25)

The benefit of the use of chemotherapy associated with surgery and radiotherapy was demonstrated in a study with 120 operable phase III breast cancer patients who were randomized after the modified radical mastectomy to receive exclusive radiotherapy or chemotherapy with vincristine, doxorubicin (adriamycin) and exclusive cyclophosphamide (VAC) or both. Disease-free survival was better in combination with radiotherapy and chemotherapy than in the exclusive surgery ($P < 0.001$). The overall survival in 3 years was 57% in the exclusive radiotherapy, 72% in the

exclusive chemotherapy and 90% in the combined therapy ($P < 0.001$). ⁽²¹⁾

Survival was also better with anthracycline-based regimens than with the regimen based on cyclophosphamide, methotrexate, and 5-fluorouracil. ⁽²⁶⁾

The National Surgical Breast and Bowel Project (NSABP) B-18 study included 1,523 women with operable breast cancers - T1-T3, N0-N1, and M0, randomized to receive four cycles of neoadjuvant doxorubicin and cyclophosphamide or the same schedule adjuvant form. After 16 years of follow-up, the comparison of both groups revealed no differences in 5, 8, 16 years in disease-free survival (67, 55 and 39% X 67, 58 and 42%) and overall survival (80, 72 and 55% X 81, 72 and 55%). According to Rastogi, there is a favorable trend to neoadjuvant therapy in women under 50 years. ⁽²³⁾

These findings are comparable to those found by Henderson and Mamounas, in which patients with operable breast cancers were randomized to neoadjuvant and adjuvant chemotherapy, from the European Organization for Research and Treatment of Cancer (EORTC) Breast Cancer Cooperative Group. This study selected 698 patients with stage T1c-T4b, N0-N1, and M0 operable to receive four cycles of fluorouracil, epirubicin and cyclophosphamide (FEC) neoadjuvant to surgery or four cycles of the same chemotherapy regimen adjuvant to surgery. With a mean follow-up of 56 months, there was no difference between the groups in relation to global survival, disease-free survival and locoregional recurrence time. The ideal chemotherapeutic scheme, duration and sequence have not yet been defined. However, the National Comprehensive Cancer Network (NCCN) prefers neoadjuvant schemes containing anthracyclines and taxanes because of the superior response of this scheme in adjuvant regimens in patients with compromised axilla. ^(27,28)

In patients with overexpression of HER-2 / neu, the use of trastuzumab-associated with anthracyclines and taxanes in a neoadjuvant manner increases the number of patients with a complete clinical response (cCR) and complete pathological response (pCR), ^(29,30) however, the evaluation time must be longer so that global survival and disease-free survival are evaluated.

The use of adjuvant hormone therapy with tamoxifen in premenopause ⁽³¹⁾ and aromatase inhibitors in postmenopause ⁽³²⁾ increase disease-free survival and its use is indicated in patients with positive estrogen and progesterone receptor.

The NCCN recommends postmastectomy radiotherapy in all patients with four or more involved lymph nodes, T3 tumors or clinical stage III. ⁽³³⁾ However, there is no consensus on its use in patients treated with neoadjuvant chemotherapy.

The ASCO also evaluates that there are insufficient data on the role of the use of radiotherapy in patients undergoing neoadjuvant treatment. ⁽³⁴⁾ There are no studies evaluating the use of adjuvant radiotherapy in patients who underwent neoadjuvant chemotherapy.

Surgical Treatment

Modified radical mastectomy remains the standard therapy for LABC, (**Figure 18-3**) however, breast-conserving surgery, after neoadjuvant chemotherapy, has been performed. A recent study by the MD Anderson Cancer Center retrospectively analyzed stage IIIA and IIIB patients after three cycles of neoadjuvant cyclophosphamide, doxorubicin, vincristine and prednisone, with a complete and partial pathological response of 16 and 84%, respectively. Based on the criteria for breast-conserving surgery in early stages, 23% of cases could undergo conservative surgery after neoadjuvant. ⁽³⁵⁾

A report of the M.D. Anderson, in 2004, analyzed locoregional recurrence in 130 patients with stage IIIA-IIIC who performed neoadjuvant and breast-conserving surgery,

with recurrence-free survival and loco-regional relapse-free survival of 95% and 91%, respectively. Chen *et al.* ⁽³⁶⁾ demonstrated that conservative surgery after neoadjuvant results in low recurrence in patients with ALS, citing the presence of disease in N2 and N3, residual tumor greater than 2 cm, multifocal disease and lymphovascular invasion as predictors in the increase of recurrence. Sentinel lymph node biopsy in patients diagnosed with LABC who routinely receive neoadjuvant chemotherapy presents questionable accuracy. Some institutions have adopted sentinel lymph node biopsy as a strategy prior to neoadjuvant. ⁽³⁷⁾ Despite the concept that tumor embolization and sclerosis of lymphatic vessels induced by chemotherapy could lead to a high rate of failures or errors in identification. of the sentinel lymph node after chemotherapy, identification has been reported in approximately 100% of the approaches, with a false negative rate as low as 3%. ^(38,39) The NSABP study B-27 demonstrated a rate of 85% of identification of the sentinel lymph node and 11% of false negative in 428 patients in eight centers, reinforcing that sentinel lymph node biopsy can be applied in patients with LABC who are candidates for neoadjuvancy. ⁽³⁵⁾ However, it is still recommended axillary dissection of levels I and II for staging and control of the axillary disease of this patient outside of the research context.

At INCA, we performed modified radical mastectomy as a standard treatment for patients with LABC who were or not undergoing neoadjuvant treatment. (**Table 18-1**)



Figure 18-3. A-B. Thoracic wall defect after extensive resection of lesion in right breast with closure with local flap rotation.

Table 18-1. Summary of Diagnosis and Treatment of LABC

CLINICAL DIAGNOSIS
- Clinical examination, mammography and ultrasonography - In young patients, dense breasts, MRI
PATH DIAGNOSIS
Core biopsy to confirm the invasive nature of the tumor and obtain estrogen receptor, progesterone receptor and HER-2
STAGING
Laboratory tests, chest and abdomen CT and osseous scintigraphy
QT NEOADYUVANTE
With anthracyclines, taxanes and hormone therapy in patients ER / PR +
LOCAL TREATMENT
- Surgery - mastectomy or segmentectomy followed by XRT. - In patients who are not candidates for surgical treatment after neoadjuvant CT, XRT is indicated
ADJUVANT TREATMENT
All ER / PR + patients must receive hormone therapy for 5 or more years.

Survival

Patients with locally advanced breast cancer have a high risk of recurrence and death due to metastatic disease, although the long-term evolution of these patients is rarely reported.

Statistical data from the National Cancer Database show that stage III patients undergoing modified radical mastectomy, radiotherapy and systemic treatment have a relative survival in 3 years of 68%, in 5 years of 50% and in 10 years of 36%.⁽⁴⁰⁾

According to Newman, analyzing data from the United States Surveillance Epidemiology and End Results (SEER), for patients diagnosed between 1999 and 2005, the 5-year relative survival rate of 98% for patients with locally advanced disease, 84% for patients with regional disease and 27% with distant disease, at the time of diagnosis.⁽²⁾

According to the TNM staging, the 5-year relative survival rates for patients in stages I, IIA, IIB, IIIA, IIIB and IV are 98, 85, 70, 52, 48 and 18%, respectively.⁽²⁾

Locally advanced breast cancer comprises a heterogeneous group of tumors with prognosis and evolution that depend on the TNM stage and the molecular characteristics of the tumor. The introduction of highly effective systemic agents, such as taxanes, trastuzumab, lapatinib and aromatase inhibitors, has determined an increase in the survival of these patients.

Conclusions and Recommendations

Locally advanced breast cancer remains a clinical challenge and despite ideal therapy, the disease reappears in some patients.

The early introduction of systemic chemotherapy, even in patients with resectable tumors, seems advantageous due to the high frequency of systemic disease in these patients.

The use of the entire chemotherapy regimen in neoadjuvant patients increases the possibility of complete pathological response and allows a safer, effective and well tolerated surgical and radiotherapy approach.

The use of schemes containing taxanes and anthracyclines confers a survival benefit when compared to other existing schemes.

In patients with overexpression of HER-2/neu, the addition of trastuzumab to the neoadjuvant chemotherapy regimen improves the response of these patients to treatment, although the duration and the ideal sequence are not yet defined.

Patients with a response to neoadjuvant treatment should undergo mastectomy or conservative surgery followed by radiotherapy.

In premenopause, the patient with a positive hormone receptor will receive 5 years of tamoxifen or, if she becomes postmenopausal during treatment, she will be able to receive 2 or 3 years of tamoxifen followed by aromatase inhibitor.

In postmenopausal patients with a positive hormone receptor, we must use aromatase inhibitors for 5 years.

Patients who do not respond to neoadjuvant treatment should undergo a modified radical mastectomy if they have operable tumors. In the case of unresectable masses, primary radiotherapy with third line of treatment, with posterior surgery in those that would respond.

Reconstruction techniques may be used to close the defects of the chest wall.

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Chapter 19

Surgical Treatment of Breast Cancer After Neoadjuvant Systemic Therapy

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Definitions and Epidemiology

Breast cancer corresponds to the most frequent malignancy among women worldwide. In Brazil, the number of new cases of this disease, scheduled for 2018, according to the National Cancer Institute - INCA (as per its initials in Spanish), was 59,700, with an estimated risk of 56.3 cases per 100,000 women. ⁽¹⁾

It is important to highlight that in Brazil, on the occasion of the initial diagnosis of breast cancer and taking into consideration the women treated in the public and private networks, 26.3% of them are in stage III of the disease. ⁽²⁾ The percentage described in women diagnosed with locally advanced breast cancer (LABC) in the United States and in Europe corresponds to 8.5 and 4%, respectively. ⁽³⁾

The LABC comprise tumors with more than 5 cm in diameter, which involve the skin or the pectoral muscles, which involve the axillary, supraclavicular, infraclavicular and / or internal mammary chain lymph nodes, as well as inflammatory carcinomas of the breast. ⁽⁴⁾ In this context, stages IIB (T3N0) and III fall within the definition of LABC.

Historically, only 20% of patients with LABC remained alive after five years of follow-up and some of them, due to the large local extension of the disease, were not eligible for surgical treatment with curative intent. ⁽⁴⁾ For patients who were operable, radiotherapy in the surgical bed and in the lymph node drainage areas in the postoperative period conferred a benefit in terms of local control, without, however, impacting on overall survival in five years. ^(5,6)

In the mid-1980s they suggest the first accounts of the reduction of LABCs through systemic chemotherapeutic treatment. In this way, initially unresectable tumors became

operable. ⁽⁷⁾ Neoadjuvant or preoperative systemic treatment is defined as the administration of chemotherapy, biological therapy or hormonal therapy prior to definitive surgical treatment.

The objectives of the neoadjuvant systemic treatment are: to reduce the dimensions of the initially unresectable tumors and, in this way, to make them resectable; allow the performance of less extensive surgeries in the breast and the axilla; favoring conservative surgeries in women with unfavorable tumor / breast relation; allow the evaluation of the *in vivo* response to conventional or experimental treatment and provide prognostic indicators of the risk of recurrence and the need for complementary treatments after surgical treatment. ^(8,9)

With regard to the gain in overall survival, the recent meta-analysis showed that preoperative systemic treatment in patients with locally advanced tumors and at high risk of distant recurrence has no impact on mortality reduction higher than that obtained with the administration of that in the adjuvant setting, that is, in the postoperative period. ⁽¹⁰⁾

Although initially applied to patients with LABC, neoadjuvant systemic treatment has been increasingly used for patients with operable breast tumors, in order to avoid mastectomy and limit, when possible, the extension of the axilla approach.

It is important to emphasize that the decision of the best neoadjuvant therapeutic strategy for breast cancer is based on cooperation between mastologists, radiologists, clinical oncologists, radio-oncologists and pathologists.

In this chapter, diagnostic methods and clinical staging of patients eligible for neoadjuvant systemic treatment will

be discussed; the predictive and predictive factors in this scenario; the rational for the selection of the treatment from the molecular subtypes of breast cancer and the principles and techniques of the surgical treatment of that disease.

Diagnosis and Initial Clinical Evaluation

In view of the clinical or radiological suspicion of a breast cancer, it is necessary to obtain tissue fragment, so that it is carried out, ideally in reference laboratories, the confirmation of the histological subtype and the quantification of the immuno-histochemical expression of the estrogen receptors. and of progesterone, of the cell proliferation index (Ki-67), in addition to the receptor-2 of the human epidermal growth factor (HER-2). In doubtful cases regarding the expression of HER-2 in immunohistochemistry (++) / (+++), fluorescence *in situ* hybridization (FISH) should be requested for confirmation of the amplification of the HER-2 gene.

The identification of these biomarkers should be carried out as a priority before treatment, since the expression of the estrogen, progesterone, Ki-67 and HER-2 receptors can be modified or even disappear after the exposure of the tumor to the drugs used, neoadjuvant therapy. ^(11,12)

The clinical staging of patients eligible for neoadjuvant systemic treatment consists of anamnesis and physical examination, as well as the request for some complementary tests. A simple laboratory evaluation should be performed with a complete blood count, liver and kidney metabolic panel, as well as calcium and alkaline phosphatase, which, in asymptomatic patients, may indicate a possible metastatic bone attack.

The documentation of the locoregional extension of the disease should be given through the request of bilateral mammography, ultrasonography of the breasts and axilla and, in selected cases, magnetic resonance imaging (MRI) of the breasts. ⁽¹³⁾

The use of breast MRI in the context of neoadjuvancia is especially useful in the evaluation of the local extent of the disease in cases of axillary involvement without identification of the primary tumor in the breast by mammography, in the identification of multicentric tumors, in the evaluation of response to treatment and eligibility for post-treatment conservative treatment. ⁽¹⁴⁾ The assessment and management of the axilla of patients eligible for neoadjuvant treatment will be addressed in another session of this chapter.

In patients with an anatomical stage (AJCC / 8th Ed) IIB or higher, it is recommended to perform computed tomography of the thorax and abdomen with contrast, in addition to bone scintigraphy. In selected cases, the MRI of the abdomen with contrast can be launched in substitution to the tomography of that region. ⁽¹³⁾

The use of positron emission computed tomography (PET-CT) is especially useful for the detection of metastases in regional lymph nodes suspicious and for the clarification of equivocal or suspicious findings in the aforementioned examinations, especially among patients with LABC. ⁽¹⁵⁾ In the rest of the patients, since asymptomatic, it is possible to proceed to systemic treatment without the need for complementary tests for the investigation of distant disease.

Prognostic and Predictive Factors

Prognostic factors are those that are related to better or worse clinical outcomes of a disease. Predictive factors are related to the probability of response to a certain therapeutic modality.

The pathological response to treatment, age less than 35 years at diagnosis, post-treatment residual tumor size, extension of lymph node attack, residual multifocal disease, lymphovascular invasion, cell proliferation rate and presence of circulating tumor cells in the peripheral blood correspond to the main prognostic factors related to the evolution of breast cancer in the long term. ⁽¹⁶⁾

Among these, the complete pathological response (CPR) to the neoadjuvant systemic treatment (ypT0ypN0, AJCC / 8th edition) deserves to be highlighted. The CPR is defined as the absence of invasive neoplastic disease or the exclusive presence of an *in situ* component in the surgical specimen; that is, in the breast and in the axillary content. ⁽¹⁷⁾

The CPR is described in several clinical trials as a surrogate outcome for overall survival among patients with breast cancer, especially for the triple negative and HER-2 enriched molecular subtypes. ⁽¹⁸⁾ Thus, when planning a systemic treatment, if opted, whenever possible, by the one most likely to result in CPR and, consequently, in better overall survival.

Regarding the predictors of response to treatment, the expression of estrogen and progesterone receptors (luminal molecular subtypes A and B), hyperexpression of HER-2 (enriched HER-2 molecular subtype) and the absence of hormone receptors are highlighted. and of the HER-2 molecule, triple negative molecular subtype. ⁽¹⁹⁾ **(Table 19-1)**

Table 19-1. Definition of Molecular Subtypes of Breast Cancer by the Classification of Saint Gallen 19

Molecular Subtypes	ER e PR	HER-2	Ki-67
Luminal A	ER e/ou PR (+)	HER-2 (-)	Ki-67 < 14%
Luminal B	ER e/ou PR (+)	HER-2 (-)	Ki-67 ≥ 14%
Luminal B HER-2 (+)	ER e/ou PR (+)	HER-2 (+)	Any Ki-67
HER-2 enriched	ER e PR (-)	HER-2 (+)	Any Ki-67
Triple negative	ER e PR (+)	HER-2 (-)	CK5/6 (+) ou EGFR (+)

The first group tends to obtain better therapeutic responses from endocrine treatments. The second one benefits from therapeutic interventions capable of blocking the HER-2 receptor such as trastuzumab and pertuzumab, for example. The latter tends to obtain higher rates of CPR with the addition of platinum agents.

Recent studies pointed out that the presence of residual neoadjuvant post-treatment disease among patients with the triple negative molecular and enriched HER-2 subtypes, initially taken as a mere factor of poor prognosis, was shown to improve survival results after treatment administration specific systemic adjuvant such as capecitabine and trastuzumab-entansine, respectively. ^(20,21)

Selection of Neoadjuvant Systemic Treatment

The selection of neoadjuvant systemic treatment should take into account the histopathological type of breast cancer, its different molecular subtypes, **(Table 19-2)** the need to obtain a higher response rate, the presence of comorbidities and the clinical conditioning of the patients. In that sense, we will describe the rational for the selection of treatments based on the molecular subtypes of this disease and draw some comments on the therapeutic strategies adopted for inflammatory carcinomas of the breast.

Table 19-2. Neoadjuvant Systemic Treatment from Molecular Subtypes

	Pre-Menopause Luminals B	Neoadjuvant Chemotherapy		
Luminals			Surgery	Radiotherapy Adjuvant Hormone Herapy
	Post Menopause Luminals A Co-morbidities	Neoadjuvant Hormone Therapy		
			Complete Pathological Response (CPR)	Radiotherapy Trastuzumab +/- Pertuzumab
HER-2 +	Chemotherapy Trastuzumab Pertuzumab	Surgery		
			Residual Disease (RD)	Radiotherapy TDM-1 Emtansine
	Neoadjuvant Chemotherapy:		Complete Pathological Response (CPR)	Radiotherapy
Triple Negative	Anthracycline Taxane	Surgery		
	Dose-Dense Platinas (?)		Residual Disease (RD)	Radiotherapy + Capecitabina

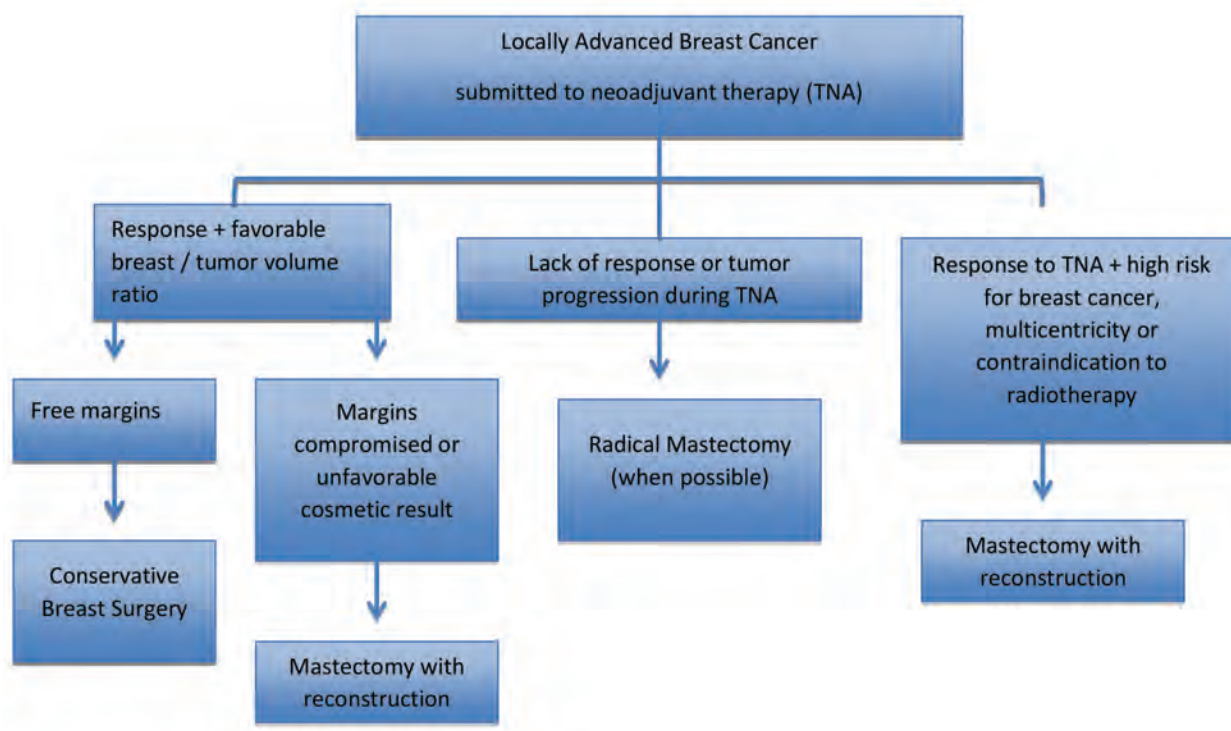


Figure 19-1. Algorithm for Neoadjuvant Systemic Treatment from two Molecular Subtypes

Luminous Tumors

Luminal tumors are characterized by the immuno-histochemical expression of estrogen and / or progesterone receptors greater than 10%. Although it is still controversial between studies, tumors whose expression of these receptors between 1 and 10% tend to behave, biologically, as a triple negative tumor. It is also highlighted that light tumors may present superexpression of the HER-2 receptors, being called hybrid luminal or Luminal B HER-2 positive, which, for treatment purposes, will be addressed as patients of the enriched or superexpressed HER-2 molecular subgroup.^(22, 23)

HER-2 negative luminal tumors tend to have lower rates of response to systemic chemotherapeutic treatment than the other molecular subtypes of breast cancer. The rate of CPR for luminous tumors ranges from 2 to 10% of patients and tend to be higher among those with tumor histological grade 3 and luminal subtype B. However, there is no consensus on the value of the occurrence of CPR among luminous tumor countries as a substitute for global survival, as occurs in the other molecular subtypes.⁽²⁴⁾

Neoadjuvant hormone therapy (NAHT) is indicated more frequently for postmenopausal patients and with limitations to receive systemic chemotherapy.

Among premenopausal patients with luminous tumors, the indication of systemic chemotherapy is still the rule and must follow the first principles of selection of adequate treatment to tumors with negative hormone receptors. Of the small phase II studies that compared the response rates obtained by comparing chemotherapy versus hormone therapy, they scored lower results with the use of NAHT.^(25,26)

In most cases, most people who suffer from Human T-cell Lymphotropic Virus (HTLV), who do not feel like people suffering from HTLV, especially those with tumors that strongly express hormone receptors (coloration > 50% of estrogen receptors or Allred score 8 or 9) cell proliferation indices (Ki-67 less than 14%); that is, preferably patients with luminous tumors A.⁽²⁷⁾

Among postmenopausal women for whom NAHT is indicated, the use of any aromatase, anastrozole, letrozole or exemestane inhibitor was superior to that of tamoxifen in

terms of response rate (clinical and radiological) and success in obtaining of breast-conserving surgery. ⁽²⁸⁾ It is emphasized that the documentation of response to NAHT occurs later than that obtained with chemotherapy and can be perceived about three to four months after the start of treatment. If the disease progresses, immediate surgical rescue should be considered.

A meta-analysis compiled the data obtained from 20 prospective and randomized studies, with a total of 3,490 postmenopausal women undergoing monotherapy with neoadjuvant aromatase inhibitor or neoadjuvant polychemotherapy. As a result, it was demonstrated that the use of aromatase inhibitor such as NAHT led to results similar to the chemotherapy group in terms of clinical response, radiological response and conservative breast surgery. ⁽²⁸⁾

Although there is ample evidence of the benefit of NAHT for patients with luminal tumors with negative HER-2 and in postmenopause, it is observed that this strategy is still not widely used in clinical practice, being reserved for women who refuse chemotherapy or that present some limitation to the use of it, as limiting comorbidities or frailty syndrome, for example.

The search for predictive tools to benefit NAHT as the PEPI score (pathological score obtained from tumor size, nodal status, histological grade, estrogen receptor and Ki-67 after two weeks of NAHT and whose result “0” points to the greatest benefit of NAHT) and the use of genetic panels with OncotypeDx have been studied in order to better select patients eligible for NAHT. ^(29,30) However, they are still considered experimental. In addition, NAHT associations have been investigated with treatments targeting specific targets such as inhibitors of cyclin-dependent kinases (CDK-4/6) and PI3K. ⁽³¹⁻³³⁾

Tumors with Enriched HER-2

The blockade of the HER-2 oncoprotein with trastuzumab in patients whose tumors present amplification of the gene or overexpression of that molecule on the surface of the cells revolutionized the treatment of this subgroup of patients in all possible breast cancer scenarios: adjuvant, neoadjuvant and palliation.

The NeoSphere and TRYPHAENA phase II studies evaluated the benefit of double blockade of the HER-2 receptor on the surface of the tumor cell with trastuzumab and pertuzumab. Pertuzumab acts by preventing the dimerization of HER-2 with other receptors of the HER family, especially HER-3. Patients with tumors larger than 2 cm, with compromised

axilla or with inflammatory breast carcinoma were included in these studies. ^(34,35)

As a result, it was observed that the increase in the double blockade of HER-2 significantly increased the CPR rate which, as discussed above, is considered a substitute outcome for overall survival. At NeoSphere the CPR rate for the groups with and without the double blockade of HER-2 with docetaxel was 45.8 and 29%, respectively. In this study, patients underwent four cycles of preoperative treatment and, after surgery, systemic adjuvant treatment with adjuvant chemotherapy based on anthracycline (FEC) and trastuzumab until completing one year of treatment with this drug. ⁽³⁴⁾

The TRYPHAENA study evaluated the benefit of double blocking of HER-2 with treatment protocols that contained or not anthracyclines. The CPR rates were very similar among the groups analyzed and varied between 54.7 and 63.6%. Although it did not reach statistical significance, the protocol group without anthracyclines (carboplatin, docetaxel, trastuzumab and pertuzumab) obtained the highest rate of CPR. ⁽³⁵⁾ Thus, the use of anthracyclines can be dispensed for the composition of neoadjuvant treatment protocols in this specific subgroup.

After performing the surgical treatment, the occurrence or non-occurrence of CPR in the breast and in the axillary content should be verified. In the case of CPR, we chose to complete one year of adjuvant treatment with the double blockade of HER-2. This recommendation is supported by extrapolation of the results of the AHINITY study, which showed small benefit with this combination in the adjuvant scenario. ⁽³⁶⁾

If a residual disease occurs, it is recommended, based on the results of the KATHERINE study - which has shown benefit in terms of reduction in the risk of distant disease recurrence of the order of 40% - carrying out 14 cycles of trastuzumab-entasin (conjugated molecule of trastuzumab with a cytotoxic agent of intracellular release) at intervals of 21 days. ⁽²¹⁾

For elderly patients with frailty syndrome or with poor clinical conditioning, the use of trastuzumab entasin or weekly paclitaxel with trastuzumab may be chosen for 12 weeks, followed by surgery and complementation of anti-HER2 therapy until one year. Another option for this profile of patients with triple-positive tumors is the combination of aromatase inhibitor with trastuzumab. ⁽³⁷⁻³⁹⁾

Patients undergoing treatment with protocols that block the HER-2 receptor should be monitored for cardiac toxicity due to the risk of symptomatic or asymptomatic reduction of the systolic ejection fraction.

Triple Negative Tumors

Triple-negative breast tumors are defined as those with immuno-histochemical expression of estrogen and progesterone receptors less than 1% and negativity for the HER-2 receptor. In most cases of triple negative tumors, 20% of breast cancer cases have mutations of the BRCA-1 BRCA-2 genes. ⁽⁴⁰⁾

The backbone of triple-negative breast cancer treatment in the neoadjuvant scenario remains cytotoxic chemotherapy. The sequential use of anthracyclines and taxanes represents the treatment pattern for this disease at the present time and the CPR rates achieved with these protocols range from 28 to 36%. ⁽⁴¹⁾

The use of sequential schemes containing anthracyclines and taxanes was compared with combinations without anthracycline (docetaxel and cyclophosphamide) in a study involving 4,242 women with initial breast cancer and in the adjuvant setting. Especially for patients with triple negative tumors, the addition of anthracycline to chemotherapy resulted in significantly less invasive disease-free survival than in the group without that drug. ⁽⁴²⁾

Several other strategies have been developed in order to increase the CPR which, as described above, corresponds to a substitute outcome for overall survival. Among them, the adoption of chemotherapy protocols in dense doses and the addition of platinum to neoadjuvant treatment stand out.

The target dose treatment protocols point to greater tumor destruction at the expense of the administration of chemotherapy in a shorter time interval. A recent meta-analysis conducted from seven phase III studies, in adjuvant and with 9,851 women, evaluated the benefit of treatment protocols in dense doses in terms of disease-free and global survival. In the majority of patients without the expression of hormone receptors and positive lymph nodes, there was an expressive gain in terms of overall survival when this type of strategy was used (HR 0.77, $p = 0.001$). ⁽⁴³⁾

There are not very consistent data the analysis of the same type of strategy used in the neo-adjuvant scenario. In this way, in clinical practice, many protocols of previous chemotherapy

in dense doses are adopted from the extrapolation of the favorable results obtained in the adjuvant.

Two phase II studies, the GeparSixto Trial ⁽⁴⁴⁾ and the CALGB 40603, ⁽⁴⁵⁾ and another Phase III study, the BrighTness, evaluated the benefit of incorporating carboplatin into neoadjuvant chemotherapy schemes containing, in general, anthracyclines and / or taxanes. In them, the addition of the platinating agent was effective in the increase of the CPR, but at the expense of greater toxicity. It is important to emphasize that this benefit occurred independently of the presence or absence of mutation in the BRCA-1 or BRCA-2 genes. Despite not having shown convincing results in terms of survival gain, the addition of carboplatin to younger and liver disease patients in which it is desired to obtain higher response rates can be considered.

Thus, it is understood that for patients with triple negative breast cancer, should be opted, whenever possible, by treatment protocols containing anthracyclines and taxanes, ideally in dense doses. More robust data are expected as to the benefit of the addition of platinum agents. However, this strategy can be considered in special cases, as discussed above.

The phase III CREATE-X study was performed with 900 women who did not obtain CPR after neoadjuvant chemotherapy and who were randomized to administration of placebo or capecitabine at a dose of 2,500 mg / m² divided into two doses per 14 days, every 21 days, for eight cycles. For patients in the experimental group, there was a statistically significant benefit in terms of disease-free interval and overall survival. ⁽²¹⁾ As a result, adjuvant capecitabine should be offered to patients with triple-negative breast cancer undergoing neoadjuvant chemotherapy and with residual disease in the surgical specimen.

Inflammatory Carcinoma of the Breast

Inflammatory breast carcinomas are characterized by embolic neoplastic invasion of the lymphatic vessels of the mammary derma and are clinically translated by the presence of erythema, edema and heating of the breast region in at least one third of its extension. They are tumors that present a poor prognosis and a high risk of metastatic dissemination. ⁽⁴⁶⁾

For this type of breast cancer, breast-conserving strategies are not recommended and, thus, mastectomy still represents

the best choice of local treatment, complemented by adjuvant radiotherapy.

With regard to the selection of neoadjuvant systemic treatment, the aspects discussed for each molecular subtype of breast cancer should be taken into consideration.

Evaluation of Response to Treatment

During the course of neoadjuvant systemic treatment, it is very important to monitor the tumor response at regular intervals. In the case of progression of the disease or of a non-expressive response in the period of neoadjuvant systemic treatment, the systemic treatment must be altered or discontinued in favor of locoregional surgical treatment, if feasible, or with neoadjuvant radiotherapy plus or not chemotherapy. ^(47,48)

The clinical response is evaluated by the bidimensional measurement of the tumor and the regional lymphatic chains at each medical visit and, preferably, carried out by the same examiner. In addition to the clinical examination, mammography and ultrasonography of the breasts and underarms can contribute to the evaluation of the response to treatment, although they may present limitations in the definition of residual tumor dimensions. ⁽⁴⁷⁾

The breast MRI has shown results that better correlate with the CPR, although it is associated with high rates of false positive results and, consequently, the overestimation of residual invasive disease. ⁽⁴⁹⁾

In general, I launch complementary imaging tests at the end of the neoadjuvant treatment, aiming at the programming of the surgical treatment.

Principles for Surgical Treatment

Breast-Conserving Surgery

The breast-conserving surgery was responsible for a significant change in the form of treatment, when Veronesi, in 1981, published the prospective, randomized study, favoring the removal of the tumor with partial preservation of the breast, followed by Fisher *et al.*, in 1985. With this, the idea of the conservative treatment of the breast followed by radiotherapy treatment in breast cancer in the initial stages favored a survival equal to that of the mastectomy,

had its definitive recognition and became standard in the treatment of cancer in all the world.

Significant advances in chemotherapy drugs and in pre-surgical or neoadjuvant chemotherapy have occurred for almost 30 years, allowing surgical treatment in initially inoperable tumors, with a response rate of 65% to 90%, associated with an increase of survival. Thus, it became the primary treatment for stage III tumors. ^(50,51) The significant decrease of the tumor volume with Neoadjuvant Therapy (NAT) and the consecration of the conservative treatment in patients with early stage breast cancer, made possible the breast-conservative surgery after neoadjuvant chemotherapy for tumors over 3 cm (Stages II and III). ^(50,52,53)

The eligibility criteria for conservative treatment after NAT respects the precepts usually used such as the desire of the woman to preserve the breast, the volume / size ratio of the tumor that allows surgical resection with free margins and satisfactory aesthetic results and clinical response and radiological (for example, in the case of women, in the group of women: absence of diffuse microcalcifications, ductal or segmental distribution, absence of multifocality and multicentricity, absence of skin involvement (permeation lymphatic skin) and / or chest wall, (N2) or N3), available radiotherapy and absence of contraindication to this section. In these circumstances, performing a mastectomy with or without reconstruction should be discussed with the patient.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) Protocols B18 and B27 consisted of randomized, double-blind prospective studies to evaluate the efficacy of neoadjuvant systemic therapy compared to adjuvant therapy in operable tumors (T1-T3, N0-N1, M0) and showed no difference in survival between the two groups. The NSABP-B18, when comparing the surgical treatment pre and post-chemotherapy in 1,523 patients, observed, in 683 patients undergoing neoadjuvant an objective clinical response rate 79%, being 36% with complete clinical response and 13% with CPR. In addition, the rate of conservative surgery increased and there was no difference between the two groups in 5-year survival rates. However, local recurrence rates were higher (15% in 5 years) in the group of patients who evolved for conservative treatment after neoadjuvant chemotherapy, even with free surgical margins, in relation to those with initial indication of conservative surgery (7.9%). It is important to highlight that in this study negative margins were considered only absence of tumor compromise, independently of the distance between the tumor and the edge of the resection and

some authors consider that it may be beneficial to obtain greater margins for the reduction of local recurrence in this situation, although this data is not consensual. Only the CPR was able to predict an increase in the overall survival rate from 77 to 87% in 5 years, regardless of tumor size, axillary involvement or age. ⁽⁵⁰⁾

The NSABP-B27 showed that the association of taxane (docetaxel) in neoadjuvant significantly increased the clinical ($64.8 \times 40.4\%$) and pathological ($25.6 \times 13.7\%$) response rates in relation to AC (adriamycin + cyclophosphamide) isolated. It also showed that when there is CPR to CA in neoadjuvant treatment, the adjuvant is no longer necessary. However, the conservative surgery rate did not increase. ^(50,55,56)

Risk factors for local recurrence after conservative surgical treatment were considered: axillary lymph nodes N2 or N3, residual tumor to pathology greater than 2 cm, vascular and lymphatic invasions, multifocal disease and lobular histology and, in these cases, reconsideration mastectomy. ⁽⁵⁰⁾ Neoadjuvant chemotherapy was considered protective for local recurrence in young patients. ⁽⁵⁰⁾

Surgical Techniques for the Conservation of Breast

The basic concept of conservative treatment is that there should be removal of a volume of healthy breast tissue near the tumor that is sufficient to obtain surgical margin free of neoplasia. In most cases, 85% of all tumors recur near the bed of the primary tumor. ⁽⁵⁹⁾ The greater the volume of healthy tissue removed, the lower the probability of incomplete removal of the neoplasm and the lower the probability of local recurrence. However, the greater the volume of breast tissue removed, the lower the chances of a satisfactory aesthetic result. ⁽⁵⁸⁾

In patients undergoing previous incisional or excisional biopsy without safety margins, the incision of the definitive surgery must cover the anterior incision and the surgical specimen must not be segmented. ⁽⁵⁸⁾ Surgical margins are identified, generally using surgical threads at their extremities: cranial, medial, lateral and anterior, so that the pathologist performs, in the best possible way, intraoperative verification of free surgical margins. ⁽⁵⁰⁾

In the past, surgery in women with locally advanced breast cancer (LABC) was performed when there were tumor resectability conditions, regardless of the number of

scheduled chemotherapy cycles, returning after surgery to complete the chemotherapy. Currently, surgery should only be performed, using the same principles of conservative surgery for initial tumors, after performing the whole neoadjuvant chemotherapy treatment, as it may increase the possibility of CPR and thus increase survival disease free and overall survival. In addition, as in any conservative surgery, adjuvant radiotherapy must be performed, which reduces the local recurrence rate by 30% to 50%. ⁽⁵⁰⁾

The breast-conserving surgery in women with LABC is associated with the principles of oncological treatment and the foundations of cosmetic surgery with periareolar oncoplasty techniques, upper and lower pedicles, classic quadrants followed by glandular remodeling, dermoglandular fragments or even with lipofilling (fat grafting) ⁽⁵⁴⁾ and can be performed as long as the free margins are respected and the tumor limits are respected.

Should the Entire Anterior Tumor Bed be Resected After the NAT?

Before the start of neoadjuvant therapy, there is a need for bed marking previously, but there is not yet a standard method to mark the tumor. There are, basically, five types of tumor bed identification, which must be performed in the preoperative period, aiming at the resection of the tumor area, namely: the photograph, the marking with cutaneous tattoo, the placement of a metal clip in the center of the wall placing four metal clips around the lesion and placing a non-absorbable material on the margins. However, there is no consensus and controlled prospective studies that evaluate which of the methods is more effective. ^(50,60) After the NAT, a re-evaluation of the image of the tumor response to chemotherapy should be performed by mammography, if there is no MRI available, which is considered the Gold Standard. According to the pathological response with palpation in 19%, with a mammography in 26%, with an ultrasound in 35% and with MRI in which an increase in the size of the tumor was observed (volumetric calculation). ^(50,61,62,63)

In some cases, the limitation of the magnetic resonance of the breast occurs, with the non-detection of the residual tumor as a consequence of the dispersed pattern of the lobular carcinoma or the reduction of the multifocal tumors. the clinical response, there are residual microscopic foci of tumor cells in 40 to 97% of the cases. ^(50,64)

One Crucial Question is: Does Tumor Shrinkage Lead to the Appearance of a New Sea?

However, it is necessary to consider that the definition of the types of response is controversial and there is a risk of presence of microscopes foci of residual cells in the tumor bed. ^(65,66) The NSABP adopts some criteria, including the absence of invasive tumor cells and the presence of small cells in the desmoplastic or hyaline stroma, as partial response findings.

The complete response is only characterized in the absence of invasive breast and lymph node disease, even with the presence of carcinoma *in situ*. ⁽⁶⁷⁾

Despite these considerations, after the tumor clip and the neoadjuvant treatment, retention should be made only of the clip or residual tumor, without the need to remove any previous tumor mass.

Can the Sentinel Lymph Node Biopsy (SLNB) Technique be Performed in Patients with LABC?

The surgical treatment of breast cancer classically included the removal of all axillary lymph nodes, with a therapeutic goal, when they were grossly compromised, or a prognostic goal when they were clinically negative. However more recent studies showed that the evaluation of the entire axilla could safely be omitted in many patients with clinically negative lymph nodes, providing lower morbidity. Patients with negative lymph nodes who undergo sentinel lymph node biopsy, without lymphadenectomy (axillary emptying), have the same survival with lower morbidity and better functionality than those subjected to axillary emptying. In addition, it presents lower cost and less surgical time. ⁽⁵⁷⁾

The axillary evaluation before neoadjuvant QT should consider a thorough physical examination and guided ultrasonography with the possibility of performing a fine needle aspiration puncture (FNA) for cytological evaluation or core biopsy for lymph node histological sampling. These examinations allow an adequate initial evaluation of the axillary state and the planning of the adjuvant radiotherapy, in cases in which there is ganglion conversion with neoadjuvant therapy. ^(68,69)

The neoadjuvant QT can compromise the accuracy of the SLNB due to fibrosis that affects the lymphatic drainage, in addition to producing an unequal tumor response in the

axilla, but it is precisely the fibrosis that characterizes the disappearance of nodal involvement. ^(55,70)

Negative axilla before chemotherapy (cN0 → QT → cN0) = patients with clinically negative axils before chemotherapy can be subjected to SLNB, in the same way as those with initial cancer. Several studies evaluated the false negative rates (FNR) and also the impact on the prognosis and demonstrated that the technique is safe. Class J *et al.* presented the results of the GANEA 2 study, one of the first prospective studies on the subject, in 2016 (SABCS Oral Presentation). In that study we evaluated 432 women with negative axilla before chemotherapy who performed only SLNB. After the 3-year follow-up, overall survival was 98.7% and disease-free survival was 94.8%, comparable to patients treated with axillary clearance.

In most cases, the positive axilla becomes negative after the Neoadjuvant QT (axillary residual disease is present in around 50 to 60% of cases). ^(71,68) Studies sought to evaluate the possibility of performing the technique of SLNB in that group of patients. There are 3 studies that evaluated FNR in patients with clinically positive axilla: SENTINA trial, SN FNAC and ACOSOG Z1071. In these investigations, the patients received neoadjuvant chemotherapy and, subsequently, they underwent SLNB followed by axillary emptying.

SENTINA trial, ^(72,68) a prospective, multicenter and randomized study, evaluated 1,737 patients divided into four arms: arm A - biopsy of Sentinel Lymph (SL) pre-chemotherapy in patients with clinically negative axilla (cN0); In the case of patients with heart failure, an increase in the incidence of Chagas disease was observed at the time of vaccination. (CN1) subjected to neoadjuvant chemotherapy, resulting in clinically negative axilla after (ycN0), performed SL biopsy, followed by EA; In the C-arm patients, the SL detection rate was 80.1, while in the C-arm patients, the SL detection rate was 80.1, (95% CI: 9.9% to 19.4 %), in patients in arm B (resentinel), SL detection rates were 69.8% and false negative 51.6% (IC95%: 55.6% to 65%). The authors conclude that a second evaluation of SL (resentinela) presents unacceptable rates of low detection and false negative, regarding the rejection of axillary status after neoadjuvant chemotherapy in the state, the authors do not recommend the use of SL for axillary evaluation.

The SN FNAC evaluated 153 patients, whose criteria for axillary eligibility were cN1-2 patients, mandatory biopsy to confirm axillary metastasis, with an SL identification rate of 87.6% and a false-negative rate of 13.4%.

The ACOSOG Z1071 study evaluated false-negative rates when SL biopsy was performed after neoadjuvant chemotherapy in initially positive patients. ^(73,68) We evaluated 701 patients, T0 to T4, 663 with cN1 and 38 with cN2, all confirmed with FNAC or core biopsy. After neoadjuvant chemotherapy, 582 patients did not have palpable lymph nodes (83%). In the surgery, the combined technique (technique + blue patent) was used, and the patients underwent SL biopsy and then EA. In 525 patients, at least two lymph nodes were resected; of these, 41% (215) had a CPR and 310 had residual disease, 39 of which had the negative sentinel lymph node and the false negative rate of 12.6% (IC90%: 9.95% to 16.05%),

When the SL was identified by adding the two techniques, the false-negative rate was 10.8%, and when the resection of at least three SL was made, the false negative rate fell to 9.1%. The study demonstrates that the adequate technique of identification and exeresis of the SL diminishes the false negative rate, being fundamental the attention of the attending physician for that aspect in that context.

Most studies report greater identification of SL when there is double labeling, that is, two associated methods (radiocolloid and patent blue) and when there is the removal of 3 or more nodes, providing false-negative rates of less than 10%. ^(74, 69)

In the case of biopsy with the use of radioactive seeds, the results of the biopsy with the use of radioactive seeds allowed even lower results of FN (1.4%).

Thus, in patients who have clinically positive axilla and undergo QT-neo, and who respond with clinically negative axilla, SLNB can be performed with double labeling and removal of at least 3 lymph nodes. If the histopathological result is negative for metastasis, there was CPR and it is not necessary to empty the axilla. However, if the histopathological result brings mestastasis, micrometastasis or even isolated tumor cells, axillary emptying is mandatory. We have to wait for the results of studies still underway, such as Alliance 11202 and B51, to define what to do with these post-QT ganglia without CPR.

Mastectomy

Mastectomy is still a fairly used treatment after NAT. Its indication occurs in cases of initially inoperable tumor

or that during the course of NAT, the disease persists in progression: mastectomy is also indicated after NAT, for multicentric tumors, high family or personal risk for breast cancer, cases in which there are contraindications of postoperative radiotherapy, as in pregnant women. Finally, small breasts in which the final aesthetic effect after conservative surgery will be unfavorable or compromise the margins of surgical resection, during the performance of conservative surgery. ^(50,75,76)

The main benefits of NAT are: the conversion of locally advanced mammary carcinomas into operable tumors or tumors of size in which conservative surgery can be performed, with effective local control and favorable aesthetic results. ^(54,50) However, some studies show the indication but in most cases, it was observed that most people suffer from this cases.

Surgical Mastectomy Techniques

The systematic standardization of the surgical treatment of breast cancer began in the late 19th century with Halsted. His radical mastectomy technique was widely used, practically until the middle of the 20th century. ⁽⁵⁴⁾ With the passage of time, other mastectomy techniques emerged, each with indication, according to the stage, location and size of the tumor:

- Modified Radical (Patey).
- Modified Radical (Madden-Auchincloss).
- Simple mastectomy.
- Sub-Radical Mastectomy.
 - Skin Preservation Mastectomy (Skin Sparing Mastectomy - SSM).
 - Preservative Mastectomy of the Areola-papillary Complex (Nipple Sparing Mastectomy).

The multidisciplinary and the constant evolution of adjuvant treatments - chemotherapy, hormone therapy and radiotherapy - contributed to the greater control of the disease. The additional benefit promoted by NAT, in locally advanced tumors, is the realization of mastectomy with the possibility of immediate reconstruction, maintaining the principles of oncological safety, associated with psychological benefit and good aesthetic results. ^(77,78,79) For this, a multidisciplinary team is necessary, involving mastologist, clinical oncologist, radiotherapist and, occasionally, plastic surgeon. ⁽⁸⁰⁾

Probably, due to the increase of breast procedures in oncoplasty surgery, a greater number of publications of the skin sparing mastectomy (SSM) technique have been observed. This technique was initially described by Freeman in 1962 for benign lesions of the breast, ⁽⁸¹⁾ being modified for breast cancer by Toth and Lappert, in 1991. ⁽⁸²⁾ The SSM is characterized by retaining the maximum of skin forming fine pieces (the ideal is approximately 0.5 cm), using the various types of incisions. (**Figure 19-2**)

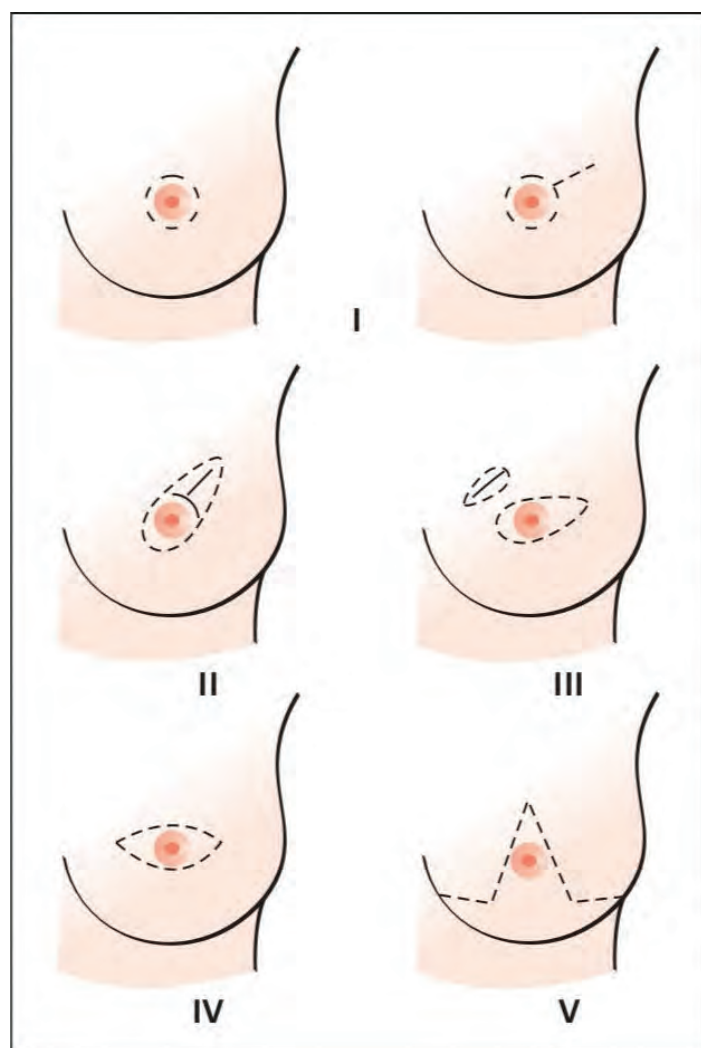


Figure 19-2. Types of incisions: I. Periareolar and periareolar in racket; II. Periareolar elliptical that incorporates scars from previous biopsies; III. Periareolar elliptical with independent incision of previous biopsy; IV. Periareolar elliptical for small papillae; V. Standard for reduction mammoplasty.

They are principles in addition to the SSM to resect the scar of the previous biopsy, preserve the inframammary sulcus, remove the entire mammary gland according to the limits established by the radical techniques and remove up to the areola-nipple complex. ^(75,77, 83) In the case, the diagnosis is made by fine needle puncture or central biopsy, these scars do not need to be removed. The confection of the flap in the sternal border should be carried out with caution to avoid lesions in the dermal branches of the perforators of the internal mammary artery, responsible for the irrigation of the medial part of the flap. ⁽⁷⁵⁾ In the case of this mastectomy technique, it can be performed after NAT in tumors of up to 5 cm, or smaller and multicentric tumors, ^(54,50,75,84) being contraindicated in inflammatory carcinoma or tumors that compromise the skin. ^(75,85) The SSM must also be evaluated on a case-by-case basis. When there are situations of risk of dermal necrosis, such as previous radiotherapy, obesity, diabetes and heavy smokers.

SSM, when compared to non-skin-saving techniques, does not present an increased risk of flap necrosis, as well as does not promote an increase in local recurrence, when compared to the other radical mastectomy techniques. ^(75,77, 83, 86)

The evidence suggests that SSM in terms of safety is probably similar to radical mastectomy techniques, and should be performed by experienced mastologists and that it provides satisfactory results in the reconstruction, offering appropriate surgical margins. (**Figure 19-3**)

Prophylactic mammary adenectomy, also known as mastectomy with preservation of nipple-areola complex (NAC), was initially published by Petit *et al.*, in 2006, ⁽⁸⁷⁾ and these authors recommended this technique associated with intraoperative electron radiation therapy with a single dose of 16 Gy (ELIOT) in the NAC region and immediate reconstruction. The nipple sparing mastectomy (NSM) is indicated in selected cases, in which the mastectomy would be the standard procedure, the technique of the SSM is combined with the preservation of the NAC, associated with immediate breast reconstruction by various techniques, obtaining aesthetic results very satisfactory. In the last century, the removal of NAC was mandatory in mastectomies, although its involvement was rare. The neoplastic involvement of the nipple is more evident in Paget's disease and *in situ* carcinomas near the retroareolar region. He wonders if the preservation of the NAC could represent a "reservoir of tumor cells".

At MD Anderson, they evaluated the participation of NAC in 326 mastectomized women with skin preservation and

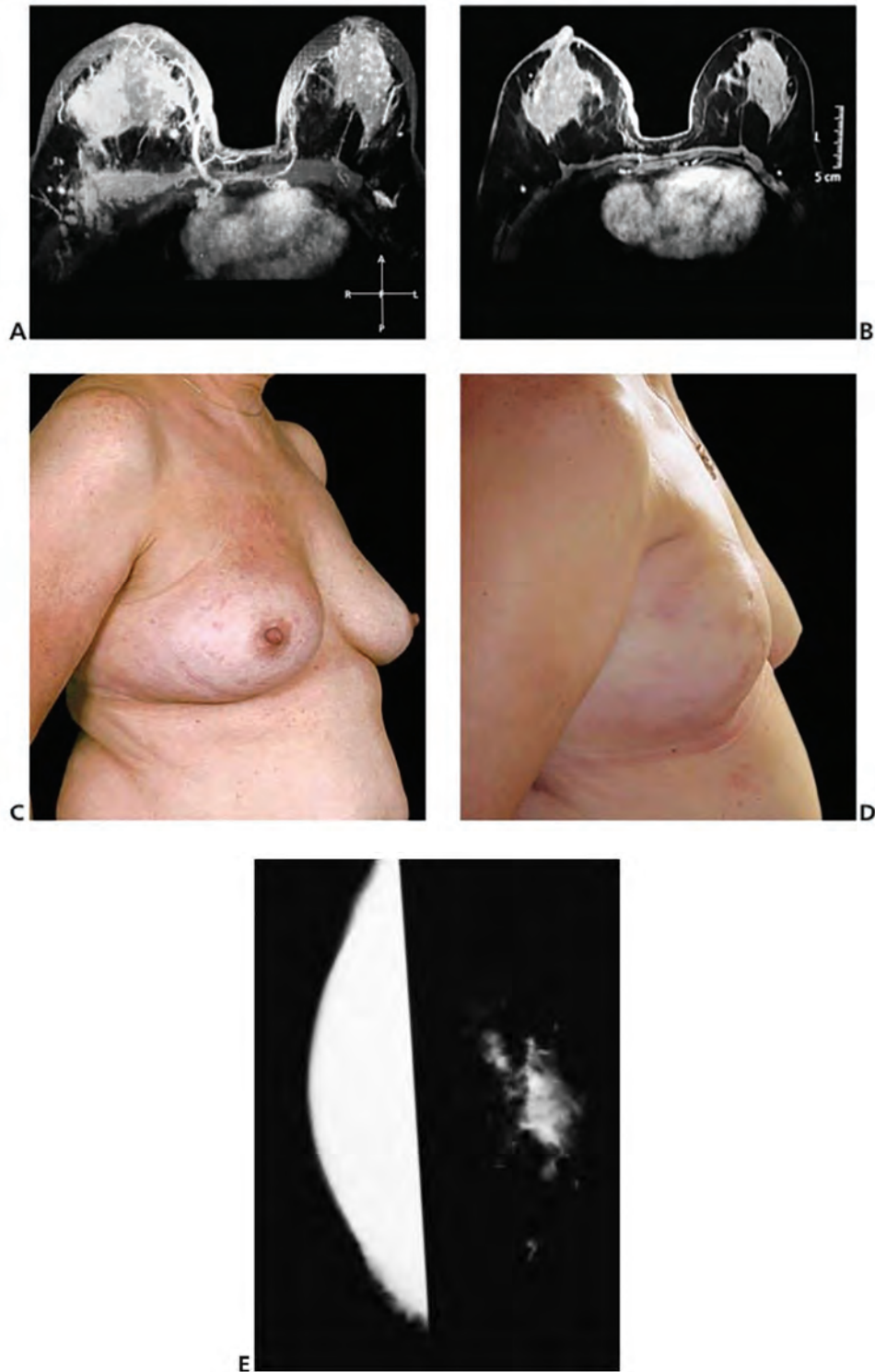


Figure 19-3. Patient submitted to MPP with removal of the pectoral musculature and lymphadenectomy, rotation of the dorsal MG and prosthesis, posterior radiotherapy. (A) MR before chemotherapy (QNA n1) in CDI tumor, HER-2 positive and hormonal receptor negative, right breast, with 5.7 cm, located in the thickness of the pectoralis major and axillary lymph node positive. (B) MRI after chemotherapy (QNA n2). (C) Preoperative (55 year old patient). (D) Post-operative period of 5 months. (E) CC mammography in the postoperative period of 10 months.

found an incidence of 5.6% hidden wrapping, ^(88,68) believing that 25% of cases of hidden tumors could be detected by means of the freezing of a retroareolar sector. They conclude that, in patients with negative axilla and non-central tumors, NSM can be offered as an adequate alternative to traditional mastectomy. It is estimated that in this selected group the risk of a hidden tumor in the NAC would be less than 2%.

In cases where the mastectomy is planned with immediate reconstruction, the NAT is a safe option and does not seem to increase the rate of postoperative complications, avoiding even the delay of chemotherapy in patients who develop post-operative complications. One of the most frequent complications in patients undergoing mastectomy with immediate reconstruction after NAT is the infection derived from neutropenia. According to Peled *et al.*, When the group that performed NAT was compared with another group in which chemotherapy was performed after surgery, there was a slight increase in infection in the second group, although it did not reach significance.

Breast reconstruction can be performed with autologous tissue, which is usually the lower abdominal wall or the large dorsal muscle. Autologous tissue techniques may be associated with the placement of prostheses. When implants are used, these can be expansive prostheses of the Becker type or subepithelial expanders. The use of one or another reconstruction technique will depend on each institution or the preference of the surgeon, since there is no absolute contraindication for any of them. ^(75,86)

Frequent postoperative complications derived from breast reconstruction are: seroma, hematoma, infection, dehiscence of the operative wound, skin necrosis, loss of the flap, extrusion of the prosthesis and thromboembolism. ^(78,89) Risk factors for reconstruction are: older women, obese, diabetics and smokers. ⁽⁸⁹⁾

At present, only the skin adjacent to the tumor is removed in cases where this tumor is so close to the skin that it does not allow a margin of oncological safety.

Clinical Follow-Up

The objectives of the clinical follow-up of patients treated for breast cancer seek the early recognition of relapses and the second primary tumors of the breast, potentially curable; the identification of complications related to treatment, such as lymphedema after axillary emptying, for example;

in addition to detecting symptoms that may indicate the presence of distant metastases. ⁽⁹⁰⁾

Patients should be directed to seek medical attention when there is identification of signs and symptoms that may correspond to the presence of metastatic disease. In addition, patients with an increased risk of hereditary breast cancer should be advised to seek genetic counseling. It is important to note that the request for multiple imaging tests and / or tumor markers periodically does not bring any benefit in terms of survival for breast cancer survivors. ^(91,92) It is recommended that only these patients undergo an anamnesis and physical examination of every 3 to 6 months, in the first two years, every 6 to 12 months in the following 3 years and, subsequently, annually. You should also request mammography at least once a year. In patients who received radiotherapy, it is recommended to start the mammographic screening at least 6 months after the completion of this treatment.

The addition of breast ultrasound as a complementary screening to mammography, in women with dense breasts, has been able to detect small invasive carcinomas, not visualized on mammography, with a detection rate of 3 to 4 cancers / 1,000 exams. In the case of patients using tamoxifen, the Pap test should be recommended, in addition to the annual visit to the gynecologist. For users of the aromatase inhibitor, annual densitometry is recommended to monitor bone loss.

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Chapter 20

Sentinel Lymph Node Biopsy

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Introduction

The incidence of female breast cancer increased 0.5% since 2000, according to the report by the International Agency for Research on Cancer. This number is higher in developing countries due to the increase in life expectancy in these countries and the change in behavior, resulting in greater exposure to risk factors.

Staging of lymph nodes was defined as an early event performed during the initial evaluation of the patient. In developed countries, about 20 to 30% of all cases are diagnosed very early (*in situ* lesions, DCIS) and 79% of patients diagnosed in stage I and II have negative axillary lymph nodes. It is believed that these values are different in developing countries, where more than 50% of cases are diagnosed in advanced stages of the disease.

According to Parkin, in Europe, the overall survival rate is 91% after the first year and 65% after 5 years. These values increase to 96.8% after the first year in the United States. Early detection and treatment in the initial phase of the disease are, therefore, the most important measures for its control. The diagnostic methods available include: clinical examination of the breasts, mammography, breast ultrasonography and puncture by aspiration biopsy, incisional biopsy, among others.

Until 1990, the evaluation of the axillary state of a patient with breast cancer depended on the histopathological examination of the lymph nodes of the complete axillary dissection (AD). With the definition of the sentinel lymph node as the first structure that receives the drainage of the tumor area, it was possible to guarantee the means for the adequate staging of the axilla and to establish the therapeutic approach by less invasive surgery techniques.

Currently, it is admitted that the presence of axillary lymph nodes with metastatic disease is the main predictor of prognosis and of subsequent therapy in the course of malignant neoplasia of the breast. In the recent past, the dissection of axillary lymph nodes was the rule for all breast cancer patients, resulting in complications.

Sentinel Lymph Node Biopsy in the Surgery of Breast Cancer

The involvement of the axillary lymph nodes is one of the most important prognostic factors in women with early-stage breast cancer and histological examination of them is the most accurate method to evaluate the spread of the disease to the axilla.

Until 1990, AD was routine in the treatment of early breast cancer. The benefits of AD include its impact on local control of the disease (i.e. axillary recurrence and survival), its prognostic value and its role in the selection of adjuvant treatment. However, the anatomical alteration caused by AD can result in lymphedema, local infections, nerve damage and shoulder dysfunction, compromising functionality and quality of life.

AD continues to be the standard approach for women who have clinically positive axillary lymph nodes for neoplasia by diagnostic methods, such as ultrasound-guided fine needle aspiration or sentinel lymph node biopsy (SLNB). For patients with clinically negative axillary lymph nodes, SLNB is a method with lower morbidity than AD, and is also useful for axillary staging.

The technique for sentinel lymph node (SLN) research is based on the observation that the migration of tumor cells from a primary breast tumor can metastasize specifically to one or some of the axillary lymph nodes, before involving all the rest of the lymph node chain. Thus, the injection of vital blue dye and/or radioactive colloid around the tumor area would allow the identification of an SLN in most patients and its status would be able to predict the status of the remaining axillary lymph nodes.

In patients with breast cancer with a clinically negative axilla, SLNB identifies patients without axillary involvement, thus avoiding the need for more extensive surgery. Several studies have shown that the risk of morbidity particularly, arm lymphedema, sensory loss, and shoulder abduction deficits is significantly less for the group that only performs SLNB than for those who perform the standard axillary dissection. As an example, the risk of lymphedema after 12 months was reported as 2% after SLNB alone, compared with 13% after SLNB followed by axillary dissection in the American College of Surgeons Oncology Group study (ACOSOG) Z-0011.

Most surgeons in the main oncology treatment centers adopt the SLNB as a standard means of axillary evaluation. In a study with more than 490,000 women with early breast cancer from the National Cancer Database, the use of SLNB increased from 27 to 66% between 1998 and 2005 in the USA. Similar trends were reported in Canada and the United Kingdom. The SLNB is endorsed as an alternative for AD in the diagnosis of axillary metastases in patients with early breast cancer and clinically negative axilla in the guidelines of the American Society of Clinical Oncology (ASCO), of the International Consensus Panel on the Primary Therapy of Early Breast Cancer and others.

Despite the variability in the selection and technical criteria, the SLN is consistently identified in about 96% of the cases and predicts the status of remaining axillary lymph nodes in more than 95% of cases in most series. The false negative rate of SLNB was originally reported as 5-10% (sensitivity of 90 to 95), but lower rates are achievable by experienced surgeons.

The main concern with the SLNB is the potential false negative result, which could increase the rate of axillary recurrence and impair the programming of the adjuvant treatment. However, despite finding a false-negative rate around 5-10% in studies in which an AD was performed after SLNB, several series suggested that axillary recurrence rates are low after a negative SLNB in early breast cancer (recurrence between 0 and 4.5%). The details of the trials that validated the SLNB will be described below.

A multicenter study with 443 patients with initial breast cancer demonstrated that the SLNB technique can be learned and successfully applied by a diversified group of surgeons, whether they are in specialized or general settings. In this study, all patients underwent SLNB, using a radioactive colloid followed by AD. At least one SLN was identified in 98% of the cases and the negative predictive value was 96%, with a false negative rate of 11% (sensitivity of 88%).

A more complete pathological evaluation of the false negative cases with deeper histological sections of the sentinel lymph node and with immunohistochemical staining increased the rate of metastases not previously identified in 18%.

A systematic review conducted by the ASCO included 69 trials on SLNB in early stage breast cancer, which resulted in information from 8,059 patients. The SLN was used radioactive colloid, blue dye or both. The identification of the SLN was successful in 95% of the patients. The false negative rate was 7.3% (confidence interval: 0 to 29%). The combination of radioactive colloid and blue dye resulted in a significantly higher success rate in NLC mapping with a lower false-negative rate, compared to blue dye or radioactive colloid alone.

The study Adjuvant Surgical Breast and Bowel Project (NSABP) B-32, published after the systematic review, involved 5,611 patients with clinically negative axillae and the comparison of SLNB was made immediately against SLN of AD only in the patients who entered the SLN positive. The NLC was identified in 97% and the false negative rate was 9.8%. No significant differences were observed in regional control, global survival or progression-free survival of the disease between the groups in an average follow-up of almost 8 years.

The SLNB is not usually performed if the information regarding the axillary status does not affect the decision for the adjuvant treatment planning. For example, women over 70 years of age have a small positive estrogen tumor receptor (<2 cm) and clinically uninvolved axilla can be treated by SLNB. Although elderly patients have not been at greater risk of complications after axillary emptying, retrospective analyzes and randomized trials have questioned their value in older women with breast cancer (IBCSG, 1996). Interestingly, in the axillary lymphatic mapping versus axillary nodal clearance (ALMANAC) study (comparing sentinel lymph node biopsy and standard axillary treatment) that used validated scales to assess quality of life and morbidities, older women (above of 65 years), regardless of the type of axillary approach that were submitted, presenting better quality of life than younger women with 18 months of follow-up.

It is also known that SLN should be performed in women with high-grade ductal carcinoma *in situ* (DCIS), who undergo a mastectomy. The SLN will not be possible after the mastectomy, in case the disease is invasive in the pathology report, requiring a complete axillary dissection in these cases.

When a SLNB is not successful or when clinically suspect lymph nodes are present in the axilla after all the sentinel lymph nodes have been removed, the surgeon must perform an axillary dissection for staging and to ensure locoregional control.

For women with clinically suspicious lymph nodes, preoperative axillary (US) ultrasonography with fine needle aspiration (FNA) or core biopsy of suspicious areas provides a means to identify patients who have positive nodules and, therefore, need for AD instead of an SLNB. For example, in a series of 653 patients, the rate of preoperative diagnosis of axillary disease was 23% using US and FNA, thus avoiding the need for a second operation in 150 women. The effectiveness of this approach is quite variable among the centers, because the accuracy of the ultrasonographic examination depends on the operator.

SLNB and Histopathological Analysis

Approximately 40% of patients with SLN positive for mammary neoplasia harbor another focus of disease in the other lymph nodes of the axilla. In this way, the disease was classified in the SLN as a deposit of tumor cells, which may be micrometastasis or macrometastasis, depending on the size of the main tumor deposit in the SLN. Thus, the treatment options will depend on the clinical situation and the histopathological report, which may include the conclusion of the axillary dissection.

Isolated Tumor Cells

The 8th edition of the breast cancer staging system of the American Joint Committee on Cancer (AJCC) includes a rigorous classification for the histopathological results of the sentinel lymph node. Small groups of cells no greater than 0.2 mm, or non-confluent or almost confluent clusters of cells not exceeding 200 cells in a histological section of the lymph node are classified as isolated tumor cells and are considered negative nodules for neoplasia. Therefore, malignant cells in a regional nodule no greater than 0.2 mm (detected by H & E or IHQ are referred to as pN0 (i +).

The guidelines of ASCO and the National Comprehensive Cancer Network (NCCN) recommend that AD should be performed for micrometastases detected in NLC by standard hematoxylin and eosin (H & E) test. However, these indications for AD due to micrometastasis are still controversial.

Isolated tumor cells are not considered an indication for axillary surgery, radiotherapy or adjuvant systemic therapy.

The SLNB allows the pathologist to perform a more detailed study of one or some of the lymph nodes most likely to contain metastases, compared to 15-25 lymph nodes obtained with AD. This fact has the potential to improve the accuracy of finding lymph node involvement due to neoplasia, but it led to an increase in the identification of micrometastatic nodal involvement. For this reason, there is a separate denomination of pN1 mi (> 0.2 mm and not greater than 2.0 mm) to indicate micrometastasis.

The Role of Immunohistochemistry (IHC) and Polymerase Chain Reaction (RT-PCR) in the SLN Evaluation

The term “hidden micrometastases” refers to nodal metastases that are not observed in the H & E test but are only detected by IHC or by RT-PCR. The meaning of occult micrometastases in terms of surgical treatment and patient evolution seems to be insignificant.

The preliminary results of the ACOSOG Z0010 study, a prospective multicenter study of 5,210 patients with almost 8 years of follow-up, confirmed that the metastases detected by IHC or RT-PCR have no significant impact on overall survival. Thus, IHQ or PCR should not be recommended for routine SLN evaluation, according to guidelines published by ASCO, NCCN, and other institutions. Currently, if a patient only had lymph nodes considered positive for IHC neoplasia or RT-PCR and H & E evaluation was negative, it should be classified as pN0 disease in the TNM staging system for breast cancer.

Predictive Nomograms

The SLNB followed by an AD, results in significantly greater morbidities than the SLNB alone. As it is known that

most patients with metastases in the SLN will not have more lymph nodes. Although routine coloration for cytokeratin is not indicated for most breast cancers, it may be useful for the examination of sentinel lymph nodes in patients with invasive lobular carcinoma, since the morphology of lobular cancer can be difficult to detect in H & E. In general, the IHC should be used to definitively diagnose an area that is suspected of containing neoplasia by the H & E test, but not for the direct diagnosis of lymph node metastasis, that is, the IHC should not be used as a routine method. In the evaluation of lymph nodes in cases of invasive lobular cancer but should complement the evaluation.

SLNB in Certain Clinical Contexts

There are some clear indications and some in which the surgical approach is considered controversial. There is a general acceptance for the following situations:

For patients with positive SLNB, who show micrometastases in three or more lymph nodes or macrometastases, with the pattern detected by H & E, AD is recommended for diagnostic purposes and to ensure local control. The timing of the procedure (i.e., [an operation] immediate versus delayed [two separate operations]) does not seem to affect the total lymph nodes removed or the rate of long-term complications (especially lymphedema).

In contrast, the need for AD is controversial in patients with positive SLNB, showing metastasis in less than three lymph nodes, with the pattern detected by H & E examination. SLN is the lymphatic node that carries a single tumor in up to 60% of cases in general and in almost 90% of patients who harbor only micro-metastasis. These observations led to speculation that AD may not be necessary for selected patients with a positive SLN for micrometastases in less than three nodules because the need for systemic therapy is the rule and the risk of axillary recurrence appears to be low.

The ACOSOG study Z-0011 was designed to also judge the need for AD for patients with T1 or T2 tumors who had clinically negative axilla and less than three sentinel lymph nodes positive, all patients were treated with adjuvant radiotherapy in the breast. The study would analyze data from 1,900 patients, but it was closed prematurely with the enrollment of only 425 patients in the SLNB group alone and 388 in the SLNB plus AD group. The majority of patients had estrogen receptor-positive tumors. At a mean follow-up of 6.3 years, there were no significant differences between the

groups (SLNB plus AD vs. SLNB alone) in the locoregional recurrence rate (in breast recurrence 3.7 vs. 2.1%, nodal recurrence 0.6 vs. 1.3%), overall survival (91.9 vs. 92.5%) or disease-free survival (82.2 vs. 83.8%). Estrogen receptor status and adjuvant systemic therapy were independent predictors of survival.

Based on the apparent lack of benefit and low risk of that study's events, some have suggested that AD is not necessary for women with T1 or T2 tumors who have a clinically negative axilla with less than three positive SLNs who will be treated with radiation therapy. Whole breast, particularly in women with estrogen receptor positive tumors. Others prefer to wait for results from two ongoing randomized clinical trials that studied the benefit of AD for clinically negative armpit women with positive SLN: the AMAROS EORTC study 10981-22023 and study 23-01 of the International Breast Cancer Study Group (IBCSG).

The SLNB Continues to be Controversial in Certain Clinical Contexts

1. In Male Breast Cancer

The vast majority of the published studies of SLNB for breast cancer was performed in women. The data is limited to male breast cancer (MBC) because it is rare, representing approximately 1% of all cases. A retrospective study of 30 men with breast cancer reported a 100% identification rate of the SLN and a false negative rate of 0%. Prospective studies to establish the sensitivity and specificity of the SLNB in the MBC have not been carried out. However, the guiding principles of the SLNB in women seem to apply to men. In a recent publication, in a retrospective analysis of 21 men with breast cancer, the SLNB in males is a reproducible, useful, safe and reliable technique which avoids unnecessary axillary lymphadenectomy and prevents the appearance of undesirable effects. Faced with the limited amount of data, the ASCO, in the 2016 guidelines, did not make any specific recommendation on the use of the SLNB in the MBC, although it has been considered an "acceptable" method.

2. In Large Breast Tumors

The majority of studies with SLNB were performed in patients with T1 or T2 tumors less than 5 cm in size, given that it is known that larger tumors have a higher probability of positive axillary lymph nodes. However, some studies

have shown that it is possible to use SLNB in patients with T3 tumors and a clinically negative axilla. Therefore, many doctors do not recognize that large breast tumors represent a contraindication to SLN research, provided that the axilla is clinically negative.

However, patients with T4 tumors (locally advanced) or inflammatory breast cancer are not considered candidates for SLNB. The false negative rate is high in patients with inflammatory breast cancer, presumably due to the presence of partially obstructed lymphatic ducts.

The recommendations of the International Expert Panel consensus published in 2010, considered inflammatory breast cancer as one of the few absolute contraindications for SLNB. In addition, SLNB was not recommended for T4 tumors.

The 2016 ASCO guidelines do not recommend the routine use of SLNB in patients with large or locally advanced (tumor size T3/T4) or inflammatory breast cancer, to whom AD was recommended to ensure locoregional control.

3. In Neoadjuvant Chemotherapy

Many women with large breast tumors are referred for neoadjuvant chemotherapy before definitive locoregional therapy. The ideal time for SLNB in patients receiving neoadjuvant therapy has been the subject of debate because some studies reported a higher rate of false negatives for SLNB performed after induction therapy. Other uncontrolled studies support SLNB in such patients.

The ASCO through the guidelines of 2016 recommended that the Clinicians may offer SLNB for women who have operable breast cancer who have the preoperative/neoadjuvant systemic therapy.

The GANEA2 study was designed to assess accuracy and safety of SLN after neo-adjuvant chemotherapy (NAC) in breast cancer patients and concluded that patients with no initial node involvement, negative SLN after NAC allows to safely avoid an ALND.

There were 3 studies evaluating the false negative rate in patients with clinically positive armpit prior to chemotherapy: ACOSOG Z1071, Sentina and SN FNAC. In these studies, the patients received neoadjuvant chemotherapy and were subsequently submitted to SLNB, followed by axillary emptying. As a result, double labeling of SLN (patent blue and radiololol) and removal of 3 or

more lymph nodes resulted in the false negative rate less than 10%.

Galimbert *et al.* in 2016 assessed 396 patients, cT1-4, cN0/1/2, who became or remained cN0 after neoadjuvant treatment and underwent SNB with at least one sentinel node (SN) found, and AD not performed if the SN was negative. After a median follow-up of 61 months (interquartile range 38-82), five-year overall survival was 90.7% (95% CI, 87.7-93.7) in the whole cohort, 93.3% (95% CI, 90.0-96.6) in those initially cN0, and 86.3% (95% CI, 80.6-92.1) in those initially cN1/2 ($P = 0.12$). These findings suggest that SNB is acceptable in cN1/2 patients who become cN0 after neoadjuvant therapy.

4. In Patients with Multicentric Disease

Studies that evaluated the functional anatomy of lymphatic drainage supported the theory that all quadrants of the breast drained to the same sentinel lymph node. Thus, subareolar injection and intradermal injection (instead of peritumoral) of the colloid drug or the blue dye makes viable SLNB for patients with the multicentric disease.

The success of SLNB for the multicentric disease was demonstrated in several studies. In a study of 142 women with multicentric breast cancer, SLNB was successful in 91%, with a false negative rate of 4%. However, the number of patients who needed an AD due to a positive SLN was greater compared to those with a unicentric disease. The probability of finding lymph node involvement due to neoplasia in non-sentinel lymph nodes was also higher in the group with multicentric disease. The ASCO guidelines of 2016 conclude that SLNB is appropriate for women who have operable breast cancer with the multicentric disease.

5. In Ductal Carcinoma *in situ* (DCIS)

The majority of women with ductal carcinoma *in situ* (DCIS) do not require an evaluation of the axillary lymph nodes by SLNB, particularly if they underwent breast-conserving surgery. However, women with DCIS may be candidates for SLN mapping if they underwent a mastectomy since the performance of SLNB will be impracticable at a later time, if an invasive disease is found. An intact lymphatic system is necessary for injection of the blue dye and the radioisotope. Some recommend that SLNB should be considered in patients who undergo breast-conserving surgery or mastectomy for ductal carcinoma *in situ*, only if the risk of metastasis is considerably greater, as in the case of extensive high-grade DCIS, a strong suspicion of invasive

disease based on axillary imaging tests or documentation of a micro-invasive component in the core biopsy. In addition, SLNB, associated with mastectomy, should be performed, in cases where it is an extensive or multifocal DCIS, where the risk of a hidden invasive component is greater.

The finding of isolated tumor cells (ie, pN0 [i +]) in the SLN of patients with ductal carcinoma *in situ* changes the clinical stage of the disease to stage IB, according to the 8th edition of the TNM staging system of the AJCC.

The 2016 ASCO guidelines recommends that doctors be able to offer SNB to women who have *in situ* breast cancer that is operable when mastectomy is performed. Does not recommend the SNB for women who have ductal carcinoma *in situ* when conservative breast surgery is planned

6. In Pregnant Women

The safety and performance of SLNB during pregnancy have not been fully evaluated. Some dyes, such as isosulfan blue, should not be administered to pregnant women. The available data suggest that the radiation dose to the fetus is minimal using radiocolloid during, therefore the SLNB with Technetium 99 can be performed. However, the 2016 ASCO guidelines do not recommend the use of SLNB in pregnant women with early-stage breast cancer.

7. In Breast or Previous Axillary Surgery

The feasibility of SLNB in women who underwent other types of non-oncological breast surgery, such as reduction or augmentation mammoplasty with breast implants, is unclear. The panel of specialists convened by ASCO does not make a recommendation for or against the SLNB in these women due to insufficient data. They suggest that, if the SLNB were considered in this scenario, performing a preoperative lymphatic mapping would be the most prudent.

SLNB after axillary surgery has not been widely studied. In a retrospective series, the SLN could not be identified in 25% of the 32 cases, in which SLNB was performed in women who underwent previous axillary surgery. The ASCO 2016 guidelines do not contraindicate SLNB in women who underwent Prior breast and/or axillary surgery. There are several favorable reports of a second SLNB in patients with local recurrence of breast cancer after a previous SLNB. SNB should be performed, in case the sentinel lymph node biopsy is repeated, since these patients usually have alternative drainage patterns.

8. In the Internal Mammary Lymph Nodes (IMLN)

SLN techniques can identify non-axillary metastases in up to 43% of cases, depending on the volume and type of colloid injected, the injection technique, and the location and size of the primary tumor. Whether this was useful or not remains controversial, given that most data on treatment decisions and outcomes come from the evaluation of only axillary lymph nodes.

IMLNs are more common with medial tumors larger than 2 cm in size. The clinical relevance of finding and treating nodal disease in the internal mammary (IM) in breast cancer is highly controversial.

Patients with multiple positive lymph nodes normally have the IMLN chain included in the radiotherapy treatment field, if it can be easily performed without a significantly high dose to the heart. However, it is not yet clear whether the inclusion of IMLN in the treatment field is responsible for the observed survival benefit when the chest wall is irradiated. A definitive demonstration of the possible benefit of the inclusion of IMLN in the field of radiation requires a clinical trial in which women are randomly distributed among those who performed radiotherapy sessions located in the IM or not. Two randomized trials are nearing completion: one sponsored by the EORTC (protocol 22922) and the other by the National Cancer Institute of Canada (MA 20 protocol).

Patients with clinically negative axilla may harbor regional metastases to IMLN in 8 to 10% of cases. The diagnosis of positive IMN can mainly benefit patients who are not candidates for adjuvant systemic therapy. Some have suggested that patients with IMLN possibly identified as SLN by lymphadenectomy should receive radiotherapy treatment oriented to the bed of the lymph node. However, many surgeons do not use the injection of the radiopharmaceutical and use only an intraoperative injection of blue dye to identify the sentinel lymph node, a fact that limits visualization mainly in centers that do not have structured services to address this chain surgically. Additional non-invasive methods for the evaluation of IMLN may be useful, such as magnetic resonance or PET, although these imaging methods are not able to identify definitively positive lymph nodes.

There are also limitations to the SLN identification techniques for IMLN. The SLNB is not reliable in the identification of these lymph nodes due to the interference of the

radioactivity of the injection site of the radiopharmaceutical as a consequence of the proximity between them. There is a high rate of technical failure (20 to 39%) in patients with warm para sternum points in the lymphoscintigraphy. In addition to that, not all hot spots in the region represent IMLN involved by disease.

In addition, IMLNs are difficult to approach surgically in case a hot spot is identified in this area by lymphocytelography. Although we perform the IMLN biopsy at the time of the mastectomy, dividing the fibers of the pectoralis major muscle, a biopsy of this type during a breast-conserving surgery procedure requires a second incision, which is aesthetically visible in many types of clothing. In addition, the procedure can be complicated by pleural effusion, pneumothorax, or bleeding.

As expected, there is disagreement among specialists on the issue of surgical treatment of positive IMLN. There is no consensus on the need to dissect them in women with the detection of an SLN in the lymphatic chain of the internal mammary. IMLNs are not routinely dissected in patients undergoing breast-conserving surgery or mastectomy with axillary clearance. Thus, in the absence of definitive data, the emptying of lymph nodes of the internal mammary with biopsy of the sentinel lymph node should still be considered experimental.

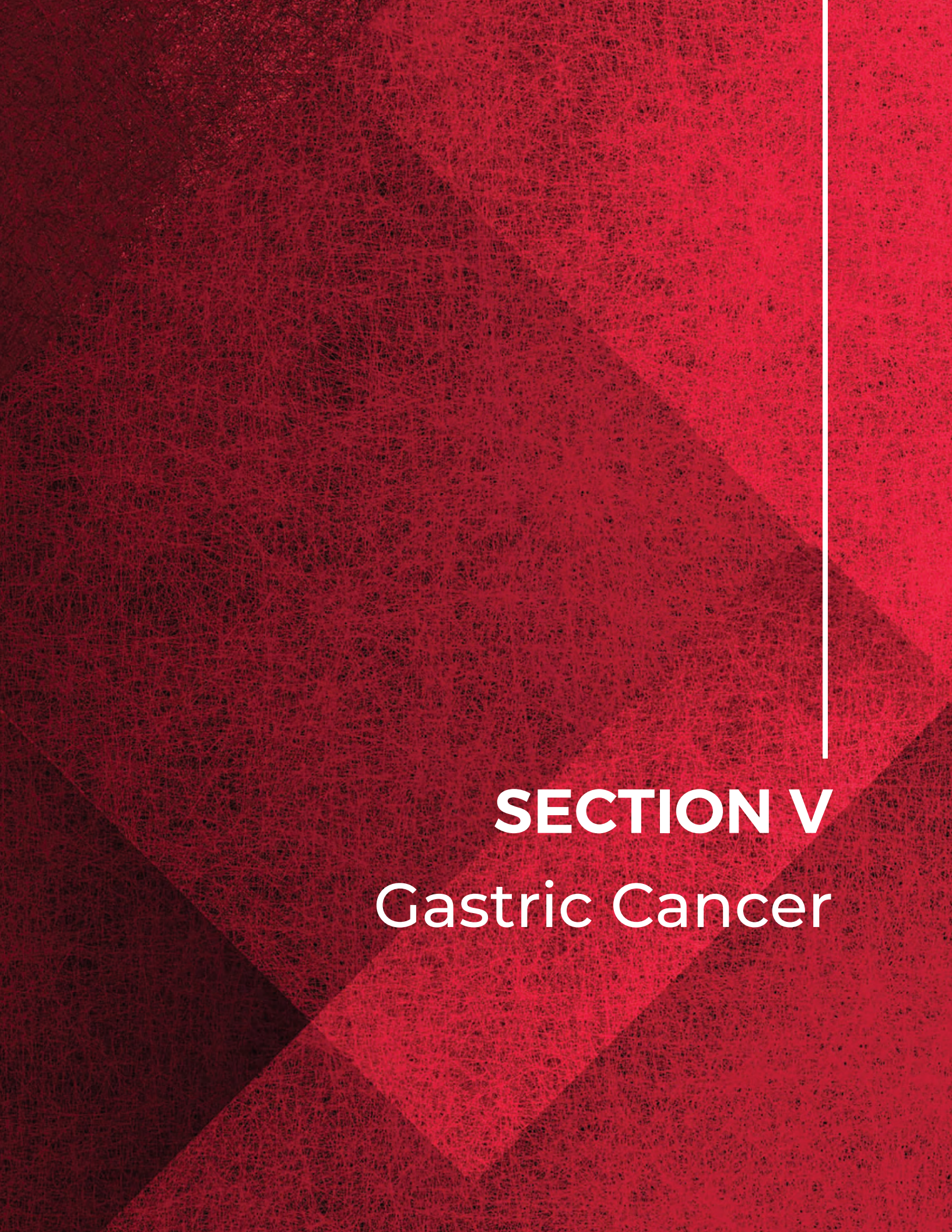
Several reports documented the identification of IMLN in SLNB, although few have explored the clinical significance of this finding. IMLNs are present in 1 to 28% of women with breast cancer. Several series showed that, when there is lymph node involvement of the internal mammary chain, there is an increased risk of axillary lymph node involvement due to the neoplasm. If the IMLN contained neoplastic tissue, they have the same prognostic significance of a positive axillary SLN. The AD should be considered for women with positive IMLN in SLNB, although the armpit is clinically negative, due to the high rate of axillary lymph node involvement in these women.

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SECTION V

Gastric Cancer

Chapter 21

Gastric Cancer

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Introduction

Stomach cancer, also referred as gastric cancer (GC), is the growth of cancer cells in the lining and wall of the stomach. The first case of GC was probably reported on the Eber Papyrus dated from 1550 BC, and by Hippocrates studies referred by Galeno in the 2nd century BC.

However, the official history of GC surgery began in 1879, when Jules Emile Pean, a French surgeon performed the first gastric resection for cancer. Unfortunately, the patient died on the 5th day post-operative. The first well succeeded GC surgery, a subtotal resection with gastroduodenal anastomosis, was performed on January 22nd, 1881 by Christian Albert Theodore Billroth in Vienna, the patient lived 4 months after the surgery. Sixteen years later, in Zurich, Karl Schlatter successfully performed the first total gastrectomy with fourteen months survival. ⁽¹⁾

Nowadays, GC has been subject of debate, due to increasing number of cases most often proximal tumors related to obesity and gastroesophageal reflux disease. This fact could also be linked to increased life expectancy rates all over the world.

Adenocarcinoma of the stomach was the first cause of cancer-related deaths around the world in most of the 20th century. Today, it is the fifth cause of death after lung, breast, colorectal and prostate cancers ⁽²⁾ with an estimated 989.000 new cases diagnosed every year and 738.000 deaths (10% of all cancer-related deaths) worldwide. ⁽³⁾ In Western countries, the incidence of gastric cancer has decreased, probably due to changes in dietary habits, food storage and preparation advances, and other environmental factors, such as *Helicobacter pylori* eradication and anti-smoking campaigns.

The declining incidence has been notorious in the United States, where the disease ranked sixth as cancer-related death from 2000 to 2005. ⁽⁴⁾ It was estimated that in 2009, 21,130 new gastric cancer cases were diagnosed in the United States, with approximately 10,600 deaths. ⁽⁴⁾ Data regarding this matter was updated for 2014 where an estimated 22,220 new cases were diagnosed in the United States, with approximately 10,990 deaths. ⁽⁵⁾

Prognosis is dismal excluding some countries, such as Japan, South Korea and China where aggressive surveillance programs contribute to high early diagnosis rates. The reasons behind this finding depend on several factors. Poor defined risk factors and disease-specific symptoms, along with low incidence of GC seen in many Western countries (including Panama) is crucial for the advanced stage at diagnosis in the majority of cases. According to Panamanian National Cancer Registry, in 2011, GC ranked the sixth highest incidence and cancer mortality rate in this country. ⁽⁶⁾

Gastric Cancer is an endemic disease in Japan, where more patients receive diagnosis at an early stage, reflecting in higher overall survival (OS) rates. Incidence decline has been limited to non-cardia gastric cancers. ⁽⁷⁾ There has been, however, a six-fold increase in the number of newly diagnosed cases of proximal gastric and esophagogastric junction (EGJ) adenocarcinomas since the mid-1980s. ⁽⁸⁾

The mainstay of curative treatment is complete surgical resection. Recent efforts are being made in the fields of neoadjuvant, adjuvant and perioperative chemoradiation and even immunotherapy seeking better results. Gastric adenocarcinoma is the most frequent histologic type, responding for nearly 90-95% of cases. Some other

less common gastric malignancies are lymphoma (4%), neuroendocrine tumor (NETs) with 3% and Gastrointestinal Stromal tumors (GISTs) being 2% of all cases; ⁽⁹⁻¹²⁾ these less-common tumors would not be addressed in this chapter.

Epidemiology and Risk Factors

Worldwide, there is considerable geographic variation in the incidence of gastric cancer, with the highest reported in the Far East, specifically Japan and Korea; Central America; and Eastern Europe. The disease is more common in older populations, usually appearing in the seventh and eighth decades of life. The mean age at diagnosis was 67 years in one large series. ⁽¹³⁾ Although previously suspected, it is not clear as to whether gastric cancer in young patients is associated with a worse clinical outcome. ⁽¹⁴⁾ Many studies relate gastric cancer to elevated ingestion of salted, defumated foods, smoking habits and *Helicobacter pylori* infection. A list of risk factors associated with GC is presented in **Table 21-1**.

Adenocarcinoma is the most common malignancy of the stomach, accounting for nearly 95% of gastric tumors. ⁽¹⁵⁾ Pathologically, there are two types of gastric adenocarcinoma based upon location: cardia, or proximal, and distal, non-cardia adenocarcinomas. These should be considered as separate entities because of differing epidemiologic relationships, associated risks and prognosis. ⁽¹⁶⁾ Historically, distal gastric carcinoma was the most common type. However, because the rate of cardia tumors continues to increase while that of distal gastric cancers decreases, ^(17, 18) the incidence of proximal adenocarcinoma has surpassed that of distal cancers in recent years. This is an unfortunate change in the epidemiology of the disease since cancers of the gastric cardia generally have worse prognosis than distal gastric cancers. ^(15, 18)

Histologically, gastric cancer is divided into two main types: well-differentiated, intestinal type, and undifferentiated, diffuse type. ⁽¹⁵⁾ The latter occurs in the setting of diffuse gastritis without atrophy. This histologic type is seen throughout the world, whereas the intestinal type occurs in areas with a high incidence of gastric cancer and follows a predictable stepwise progression of cancer development from metaplasia.

In 1994, the International Agency for Research on Cancer and The World Health Organization classified *Helicobacter pylori* as a type I carcinogen, but the exact mechanism leading to gastric carcinoma is not clearly understood. The effects of *H. pylori* infection on gastric cancer appear

Table 21-1. Gastric Cancer Risk related factors

Precursor Conditions

- *Helicobacter pylori* infection
- Gastric adenomatous polyps
- Chronic atrophic gastritis and intestinal metaplasia
- Pernicious anemia
- Partial gastrectomy for benign disease

Dietary

- Highly salted foods
- Smoked foods, high fat or contaminated oil intake
- Low consumption of sake or contaminated alcoholic beverages

Cultural

- Low socioeconomic status

Environmental

- Acidic or peaty soil
- High nitrate content in water
- Elevated lead or zinc in water
- Volcanic rock background
- Exposure to environmental talc
- Extensive use of nitrate fertilizers
- Urban residency
- Genetic
- Family history of gastric cancer
- Blood type A
- Hereditary non-polyposis colon cancer syndrome
- Familial adenomatous polyposis syndrome
- Peutz-Jeghers syndrome
- Li-Fraumeni syndrome
- Hiperplastic gastric polyposis
- Familial diffuse gastric carcinoma

Occupational

- Workers in mines and quarries
- Painters
- Fishermen
- Ceramic, clay, and stone workers
- Metal industry workers
- Agricultural workers
- Textile workers
- Printers and bookbinders

Lockhart. M; Canon. C, *Gastric Cancer*, 2010, 1- 7.

multifactorial, involving host and environmental factors as well as differing bacterial strains. *H. pylori* is most closely associated with intestinal gastric cancers, which follow a stepwise pathway toward malignancy, similar to that in the colon. In the Correa model of gastric carcinogenesis, gastric inflammation leads to mucosal atrophy, metaplasia, dysplasia, and, ultimately, carcinoma. ⁽¹⁹⁾ Studies have

shown that *H. pylori* infection is an independent risk factor for distal gastric cancer, with a 3- to 6-fold increased risk relative to those without the infection. ^(20, 21, 22) However, the great majority of infected individuals will never develop gastric neoplasia: approximately 40% of patients infected with *H. pylori* will develop gastric metaplasia but less than 1% will develop cancer. Gastric atrophy also increases susceptibility of the cells to carcinogens. In patients with *H. pylori*, the presence of specific gene polymorphisms increases the risk of developing gastric carcinoma. Genes that encode tumor necrosis factor alpha (TNF- α), and interleukins IL-1, IL-8, and IL-10 have each been associated with higher cancer rates in the setting of *H. pylori*. ⁽²³⁾ While intestinal gastric cancer is strongly associated with chronic *H. pylori*, this strong link is not seen in diffuse gastric cancer. Diffuse or cardia gastric cancer, however, has been associated with other risk factors such as higher socioeconomic class, obesity, ⁽²⁴⁾ and type A blood. ⁽²⁵⁾

Classification

There are many classifications used in the diagnosis of gastric cancer, most of them are closely related with prognosis of the disease. ⁽²⁶⁾ Macroscopically, it could be classified, according to Borrmann (1926), a German pathologist, in four types, being the type IV associated with poorer survival rates:

- **Type I** – Protruding, Polypoid.
- **Type II** – Fungating, ulcerated with sharp raised margins.
- **Type III** – Ulcerated with poorly defined infiltrative margins.
- **Type IV** – Infiltrative, predominantly intramural lesion, poorly demarcated. Also referred to as linitis plastica, due to its abundant fibrous component carrying gastric wall rigidity.

The Japanese Classification (Japanese Gastric Cancer Association which was founded in 1962), divides in early (EGC) and advanced gastric cancer (AGC). Early gastric cancer is a tumor limited to the mucosa and/or submucosa, independent of lymph node status.

Advanced gastric cancer occurs when the tumor invades further the submucosal lining of the gastric wall. This classification is also related to prognosis of the disease.

Survival rate in patients treated from early gastric cancer is higher than 90%, however in cases of advanced gastric cancer these rates do not exceed 30% in 5 years. ^(27, 28) The Japanese Classification also subdivides EGC according to the macroscopic appearance in the endoscopy:

- **Type I** – Protuberated.
- **Type II** – Flat divided in 3 types:
 - **Type IIa** – Flat, superficially elevated.
 - **Type IIb** – Flat, not elevated.
 - **Type IIc** – Flat, slightly depressed.
- **Type III** – Excavated (Full thickness of submucosa).

Gastric cancer is also classified, from the pathological point of view, in two fundamental types (Lauren Classification, 1963):

- Intestinal or well-defined, which arises from the intestinal metaplasia of the mucosa in the stomach and, from the pathologic view, is formed by tubular and papillary tubular adenocarcinomas – both, when installed, follow the usual intestinal type differentiation.
- Diffuse type, or undifferentiated or infiltrative, constituted pathologically by the mucinous cell form, arising from normal gastric mucosa following its normal differentiation pathway. (**Figure 21-1**)

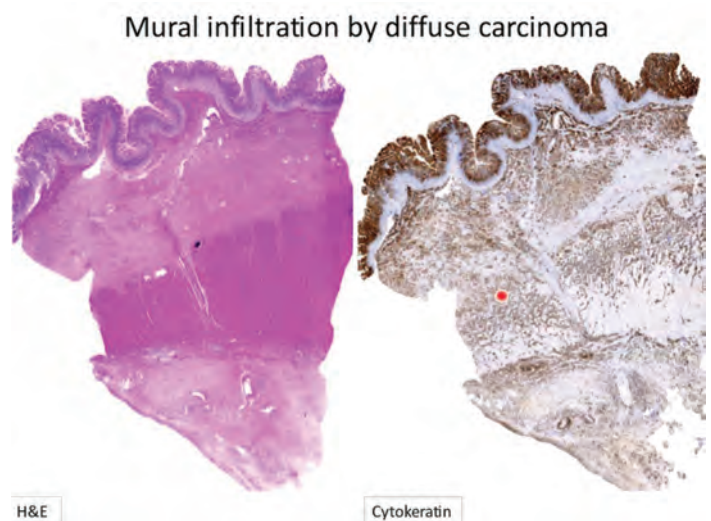


Figure 21-1. Advanced Gastric Cancer (AGC).
Infiltrative growth of poorly differentiated
discohesive malignant cells.

Clinical Presentation

The diagnosis in gastric cancer is usually difficult and in early stages of the disease most of the symptoms are unspecific, vague and imprecise; becoming a real challenge for most health care providers. The diagnosis could be achieved from findings in a double contrast esophago-duodenum series or a gastroscopy, showing different magnitude lesions in the mucosa of the stomach. One third of patients presenting a gastric neoplasm show symptoms of the upper GI tract, varying in intensity, thus a meticulous history could allow us to suspect the presence of it. This symptoms are commonly vague such as nausea, vomits,

abdominal distention, epigastric pain/heartburn and pyrosis; but they could also be suggestive of this type of disease, like lack of periodicity and rhythm of pain, early satiety, selective repugnance to foods, palpable mass, weakness, presence of umbilical, supraclavicular or cul-de-sac nodules, ascites, anemia that could be symptomatic, upper or lower gastrointestinal bleeding. Physical examination adds little, or no information at all, in early stages of the disease. The variety of presentations, from almost asymptomatic to metastatic, makes the diagnosis often simple and evident but it sometimes is achieved through an endoscopy ordered for any other reason and even as an incidental finding in a routine examination.

Table 21-2. Classification of Gastric Staging of Cancer by UICC / AJCC.

Primary tumor (pT)

- **TX:** Primary tumor cannot be assessed
- **T0:** No evidence of primary tumor
- **Tis:** Carcinoma in situ: intrapapillary tumor without invasion of the lamina propria; high grade dysplasia
- **T1:** Tumor invades the lamina propria, muscularis mucosae or submucosa
 - **T1a:** Tumor invades the lamina propria or muscularis mucosae
 - **T1b:** Tumor invades the submucosa
- **T2:** Tumor invades the muscularis propria
- **T3:** Tumor penetrates the subserosal connective tissue without invasion of the visceral peritoneum or adjacent structures
- **T4:** Tumor invades the serosa (visceral peritoneum) or adjacent structures
 - **T4a:** Tumor invades the serosa (visceral peritoneum)
 - **T4b:** Tumor invades adjacent structures/organs

Regional lymph nodes (pN)

- **NX:** Regional lymph nodes cannot be assessed
- **N0:** No regional lymph node metastasis
- **N1:** Metastasis in one or two regional lymph nodes
- **N2:** Metastasis in three to six regional lymph nodes
- **N3:** Metastasis in seven or more regional lymph nodes
 - **N3a:** Metastasis in seven to 15 regional lymph nodes
 - **N3b:** Metastasis in 16 or more regional lymph nodes

Note:

- Regional lymph nodes include the greater curvature, greater omental, lesser curvature, lesser omental, right and left pericardial (cardioesophageal), suprapyloric, gastroduodenal, infrapyloric, gastroepiploic, left gastric artery, celiac artery, common hepatic artery, hepatoduodenal, portal, splenic artery, and splenic hilum nodes.

Distant metastasis (pM)

- **M0:** No distant metastasis
- **M1:** Distant metastasis

Diagnosis and Staging

Upper Digestive Endoscopy is the most important exam in the diagnosis of gastric cancer. The endoscopy allows the visualization of the lesion and its macroscopic classification, for the earliest phases and for the advanced as well. It also helps in the surgical planning, defining tumor location, (upper, medial or inferior third, lesser or greater curvature, anterior or posterior wall of the stomach), therefore demarking the resection that should be achieved. Histologic confirmation is obtained through tissue biopsy.⁽²⁷⁾

The visual interpretation of a trained endoscopist added to biopsy achieves diagnostic success in approximately 98,5% of cases.⁽²⁹⁾ The contrasted radiological exam (barium) of the esophagus, stomach and duodenum allows to evaluate macroscopic characteristics of the lesion, although these findings are very important in the differential diagnosis between cancer and some benign diseases of the stomach, however, it has been poorly used nowadays due to most precise information obtained through the endoscopy with biopsy.

The Classification of Gastric Staging of Cancer by UICC / AJCC, (**Table 21-2**) aims to establish the extent of the disease (**Figures 21-2 and 21-3**) and, consequently, allows to define the most appropriate therapy.⁽³⁰⁾

A Computed Tomography (CT scan) of the thorax, abdomen and pelvis (**Figure 21-4**) and Magnetic Resonance Imaging (MRI) have similar sensitivity for GC staging. Positron Emission Tomography (PET) scan makes possible the diagnosis of distant metastasis, since cancer cells have a higher metabolic rate than noncancerous cells. Because of this high level of chemical activity, cancer cells show up as bright spots on PET scans, thus this is not possible with MRI or CT scans. (**Figure 21-5**)

Endoscopic ultrasound (EUS), evaluates depth of the lesion in the gastric wall, and also with less precision, it could identify peritumoral lymph nodes, playing an important role in early gastric cancer cases. Video assisted laparoscopy allows surgeons to clarify doubts regarding the nature of hepatic images, collection of material for pathology or even peritoneal lavage for histologic and

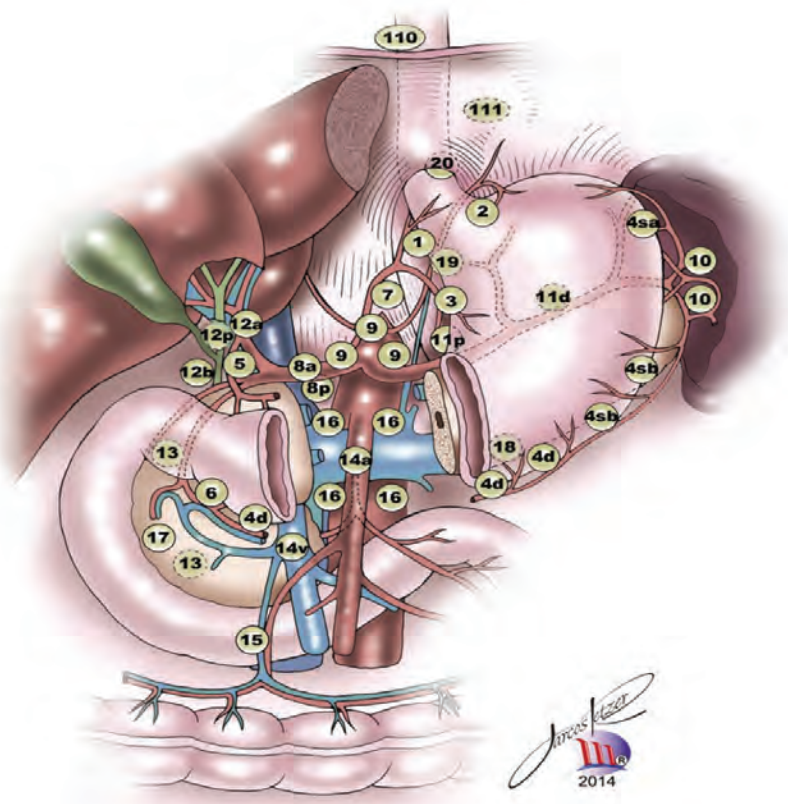


Figure 21-2. Numbering and locations of lymph node (LN) stations according to the 1st edition of “the General Rules of the Japanese Research Society for Gastric Cancer” (JRS GC). Adapted from “Gastric Cancer: current status of lymph node dissection” by Degiuli M et al., *World J Gastroenterol* 2016 March 14; 22(10): 2875-2893.

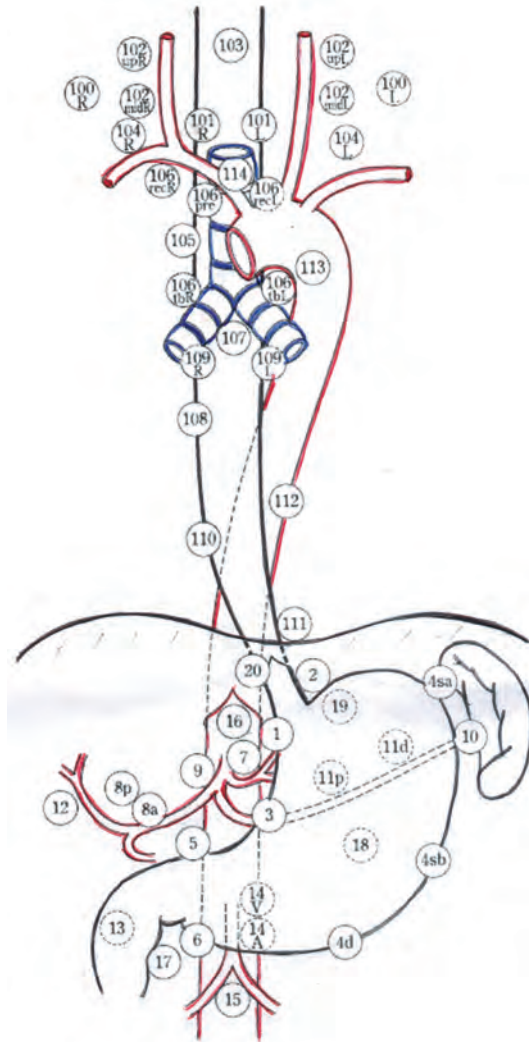


Figure 21-3. Location of lymph nodes (LNs) in the esophageal hiatus and in the infradiaphragmatic and para-aortic regions.

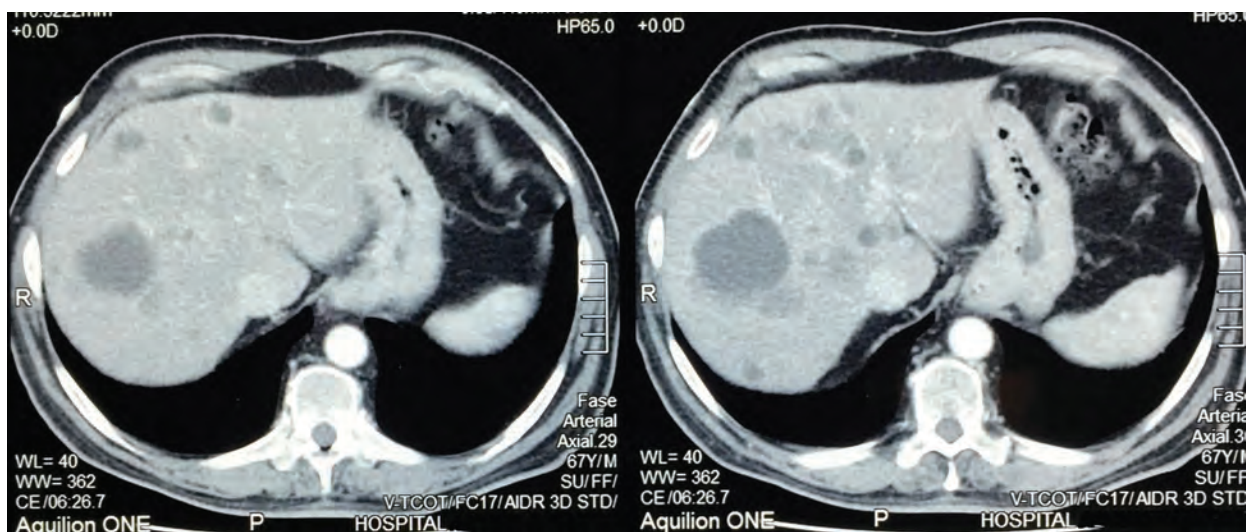


Figure 21-4. CT Scan demonstrating advanced gastric cancer with multiple liver metastasis at initial diagnosis.

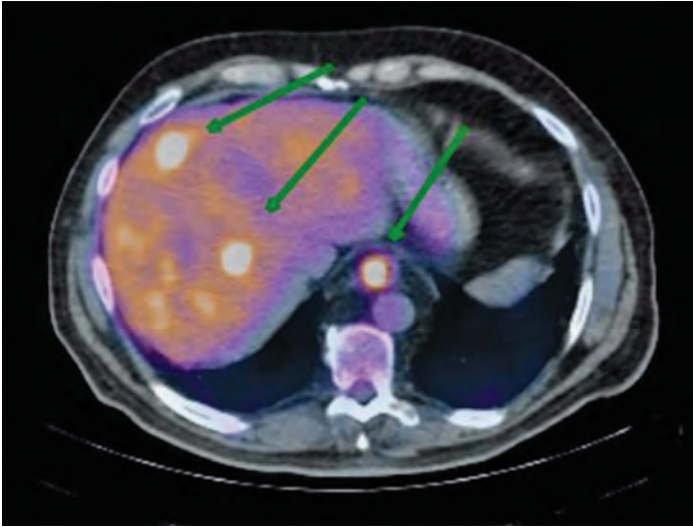


Figure 21-5. 18 Fludeoxyglucose PET/CT scan shows advanced gastric cancer located at the Esophago-Gastric (EG) Junction and the bright spots indicate liver metastases with high 18 FDG-uptake.

cytology confirmation and it also offers the possibility of visualize eventual peritoneum implants that were not detected through conventional imaging methods. Therefore, laparoscopy contributes to tumor staging and it also helps in the contraindication of surgery for curative intent.^(31, 32)

Surgical Treatment

Definitive gastric cancer cure can only be obtained by radical surgical treatment. The surgical curative treatment of GC has two main purposes:⁽³³⁾

- Resection of the primary tumor with adequate margins, free of neoplasia.
- Stage directed resection of regional lymph nodes eventually infiltrated by the tumor.

In cases of Early Gastric Cancer, safety margins of 2 cm are enough, this is, macroscopically free of neoplasia tissues, however in advanced tumors this margin should be at least 5 cm.⁽³⁴⁾ Detailed recent studies suggest that these margins should be expanded to 6 to 8 cm in undifferentiated tumors, assuring the radical intent of the resection. In the treatment of AGC located in the proximal third of the stomach, the resection would include, beyond total gastrectomy, the

distal portion of the esophagus.⁽³⁵⁾ For tumors located in the gastric middle third, total gastrectomy is also advised. In this case, in order to maintain the 6 to 8 cm free of neoplasia margins, the inclusion of the cardia and a portion of the duodenum is often mandatory. When the tumor is located in the distal third of the stomach, it is possible to respect the macroscopic safety margin of 6 to 8 cm and perform a subtotal gastrectomy. An adequate resection of regional lymph nodes is directly linked to elevated overall survival rates.

In AGC of the proximal or middle third arising from the greater curvature, or in those cases with invasion of the serosal layer of the posterior gastric wall, an splenectomy should be associated to the resection, and, in selected cases, depending upon lymph node invasion macroscopically evident in the splenic artery nodal station, a body-tail pancreatectomy might be needed.^(36, 37) Although lymphadenectomy is considered an important part of the oncologic treatment of advanced gastric cancer, 5-year survival rates are persistently disappointing,^(38, 39) however, superior to cases were is not performed, being that, results in Brazil and many other Western series have remained around 10 to 30%.⁽³⁷⁾ Risk factor habits modification, predisposing factors avoidance, early detection and surgical resection according to oncologic principles are the main weapons to avoid relapse of the disease or, when present offer the best perspective of cure to the patient.

Early Gastric Cancer Treatment

As technological methods for early detection progress, approximately 65% of overall gastric cancer diagnosed in Japan are early type. In Brazil, according to data from the Brazilian Gastric Cancer Association (ABCG), those rates do not exceed 14%. Evidently, surgical treatment performed at the time of early diagnosis allows a 5-year survival rate superior to 95%.

Lymph node metastasis incidence is rare (0-3%), when the tumor is limited to the mucosa and up to 19% when the submucosa is compromised.⁽⁴⁰⁾ The classic treatment for EGC is surgery, however, since 1980 the Japanese School introduced endoscopic treatment, initially indicated for those cases were surgical risk was elevated or the patients refused surgery. Today, with the aid from endoscopic ultrasound, which allows a precise evaluation of the tumoral infiltration depth in the gastric wall (T), the endoscopic treatment or EGC is the gold standard and considered radical, therefore of curative intent, in the following situations:

- Tumor that is limited to the mucosa.
- Non ulcerated lesions.
- Well Differentiated histologic type.
- Less than 2 cm diameter.

Nowadays, these indications have been revised and extended to bigger lesions and those with moderate or even poorly differentiated tumors of less than 1 cm in diameter. ⁽⁴¹⁾ The endoscopic resection is considered complete and curative whenever the vertical and horizontal margins of the specimen are free of carcinoma. A distance of 1 mm free of neoplasia is considered enough and safe. In cases of incomplete resection or disease recurrence, the treatment becomes surgical, being gastrectomy with D2 lymphadenectomy the method of choice; in exceptional cases, the D1 lymphadenectomy might be useful and even laparoscopic wedge resections.

Main complications related to endoscopic treatment are hemorrhage and gastric perforation. Hemorrhage related to the endoscopic procedure in up to 4,1% of cases has been reported and a 1,4% of gastric perforation. Hemorrhage could be managed endoscopically, in selected cases, however, prompt surgical management is advised in perforations. ^(42, 43)

Neoadjuvant, Adjuvant Treatment and Palliative Care

Gastric cancer recurrence after surgical treatment is frequent, urging necessity of association with other therapeutic procedures. In patients with positive lymph nodes, a 5-year survival rate varies between 70% (T1N1) and 10% and 5% and 15% (T3N2). For this group of patients, it became obvious the indication for a completing treatment. Chemotherapy with 5-fluorouracil (5FU) and folinic acid, added to radiation therapy (Rtx), increases survival and reduces recurrence rates. ⁽⁴⁴⁾

Care must be taken when planning the radiation fields in order to avoid organs near the stomach such as liver, kidneys and small intestine. Patients who are treated with a D2 gastrectomy could be candidates to chemotherapy consisting of XELOX or 5FU and Oxaliplatin. ^(45, 46) For locally advanced resectable tumors, perioperative chemotherapy with ECF (Epirubicin, Cisplatin, and 5FU) is indicated, since results showed higher resectability and

overall survival rates. ⁽⁴⁷⁾ Aiming to diminish toxicity, and in order to facilitate treatment adherence, Oxaliplatin can be substitute to Cisplatin, and Capecitabine, to 5FU.

Chemotherapy scheme consists of 3 cycles preoperative and 3 cycles postoperative every 21 days. For patients with unresectable or metastatic disease there is no consensus on which is the better approach for this clinical entity. Some of the more used schemes consist of ECF, (or EOX), XELOX (capecitabine and oxaliplatin), FOLFOX (5FU, folinic acid and oxaliplatin), FOLFIRI (5FU, folinic acid and irinotecan), 5FU and cisplatin, capecitabine and cisplatin, irinotecan and cisplatin, docetaxel and cisplatin or DCF (docetaxel, cisplatin and 5FU).

Upon failure of any of these regimens, some other can be prescribed as a second-line therapy with promising rates of success. ^(48, 49) They could induce objective response in 50% of patients with a median survival of 10 months and 2-year survival rates from 6 to 10% against no response at all for patients receiving no treatment, justifying, therefore, the indication of chemotherapy. Almost 20% of all cases are HER2 positive. In those patients, trastuzumab added to other chemotherapies such as cisplatin and fluoropyridimine have showed higher median survival rates when compared to chemotherapy alone. ^(50, 51)

Summary

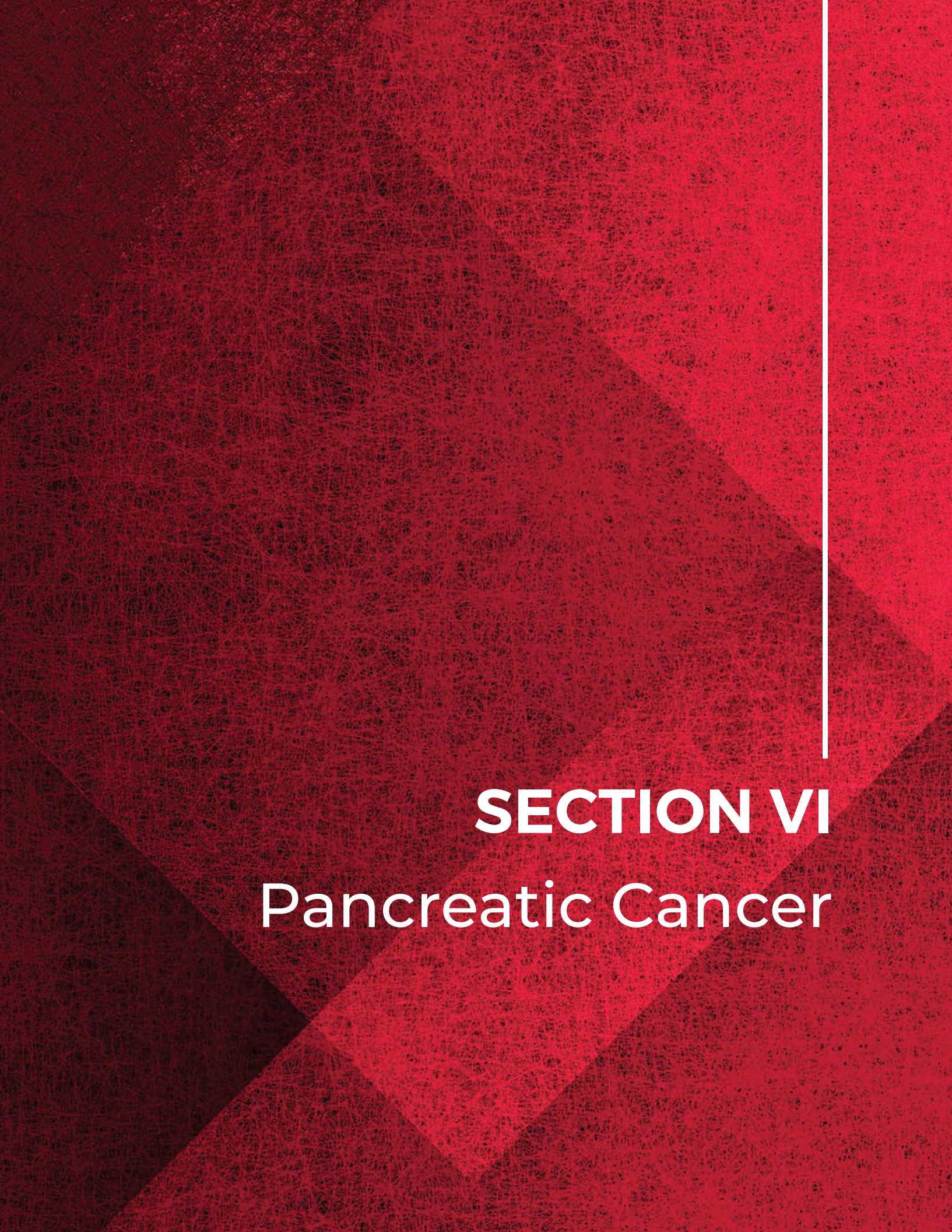
- Gastric cancer is one of the most prevalent neoplasms.
- Ingestion of salty, smoked foods, *H. pilory* infection increase the risk of gastric cancer.
- Total or subtotal gastrectomy added to D2 lymph node dissection decreases the risk of recurrence and allows a better staging of the disease.
- Adjuvant chemotherapy and radiation or perioperative chemotherapy decrease the risk of recurrence.

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SECTION VI

Pancreatic Cancer

Dedicated to Dominique and her Brightness

Chapter 22

Adenocarcinoma of the Pancreas

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Introduction

The pancreatic gland is located deep in the retroperitoneum, in close contact with other vital structures: these factors are responsible for difficult access for diagnostic and therapeutic procedures. **(Figure 22-1)** In this chapter we will explore the most common and debated topics on pancreatic adenocarcinoma trying to focus on future perspectives.

Epidemiology

Pancreatic cancers arise from both the exocrine and endocrine parenchyma of the gland; however, nearly 95%

of cases occur within the exocrine portion and only 2% of them are benign. The most common pancreatic cancer is ductal adenocarcinoma (PDAC), accounting for 80% of all pancreatic cancers. PDAC represents nowadays the 4th cause of cancer death in Europe in both sexes, after lung, colorectal, and prostate cancers in men, and after breast, colorectal and lung cancers in women ⁽¹⁾ but it is expected, by 2020, to raise up to 2nd cause of cancer death after lung. The mortality rate of PDAC has increased by around 20% in the last 10 years; ⁽¹⁾ incidence and mortality rates are very similar, due to the dismal prognosis of this tumor, with a life expectancy of 5% at 5 years, which has not significantly improved over the last 20 years. ⁽¹⁾ The main age at diagnosis is 71 and 75 years in men and women, respectively.

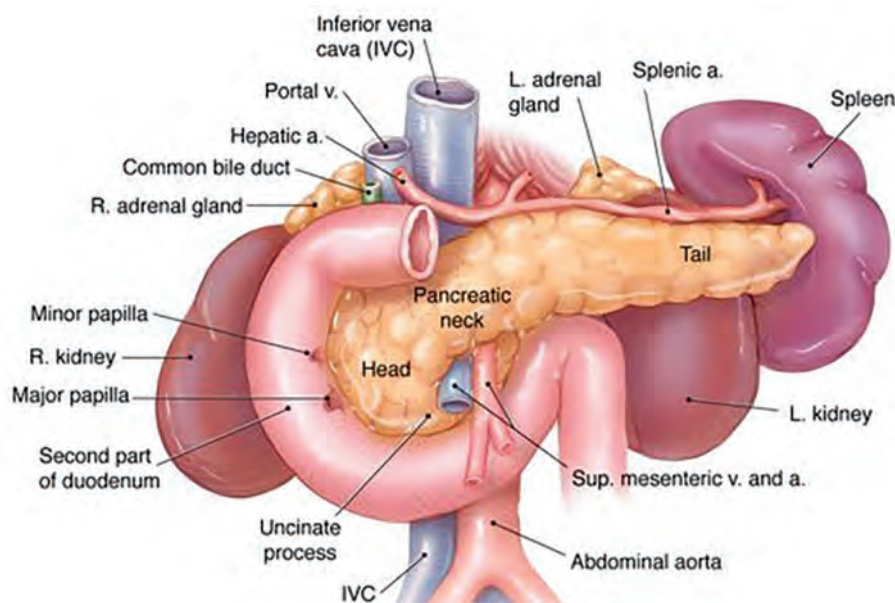


Figure 22-1. Anatomy of pancreatic gland and surrounding vessels.

Cancer Trends for Hispanics and Latinos in US

Hispanics are the second largest racial group in the US after non-Hispanic whites (NHWs) and cancer epidemiology in this population is a public health issue for different reasons: higher incidence of poverty and therefore the presence of barriers for optimal health, higher incidence of specific risk factors like obesity and type 2 diabetes, the rapidly growing rate of the population which will double by 2060.^(2,3)

Estimate new cases of PDAC in 2018 are 2300 for men (3% of all new diagnosis) with an expected cancer death of 1900 cases/year (8% of all cancer deaths) while in women PDAC is not cited in the 10 most frequent new diagnosed cancer but it accounts for 1600 deaths/year. Although cancer risk in US Hispanic overall is generally low compared with other groups, rates among Hispanic descendants' approach or surpass those in NHWs, which will result in a growing cancer burden. The need for effective strategies to decrease cancer rates among Hispanics is urgent and these strategies can include the use of culturally appropriate health advisors, other than community-based intervention programs to increase screening rate and encourage healthy lifestyles.⁽⁴⁾

Risk Factors and Genetic Mutations

Most (>80%) PDACs are caused by sporadic genetic alterations. The most relevant acquired risk factors for PDAC are cigarette smoking (overall relative risk -ORR- 1.74) and obesity (body mass index > 30 kg/m²), which is associated with an increase by 20-40% of death from pancreatic cancer. Other risk factors include diabetes (ORR for type 1 and type 2 diabetes, 2.0 and 1.8, respectively), alcohol consumption and chronic pancreatitis.⁽⁵⁾ Additionally, *Helicobacter pylori*, hepatitis B and human immunodeficiency virus infection have been associated with an increase in relative risk of pancreatic cancer;⁽⁵⁾ between dietary factors, regardless of their role in causing obesity, butter, saturated fat, red meat, and processed foods are considered risk factors for pancreatic cancer, whereas a high fruit and folate intake may have a protective role.⁽⁶⁾

Many chemical substances and heavy metals (such as beta-naphthylamine, benzidine, benzene, chlorinated hydrocarbons, nickel and nickel compounds, chromium compounds, pesticides, asbestos and silica dust) have been reported to increase the relative risk of developing pancreatic cancer.⁽⁷⁾ The association between PDAC and diabetes deserves particular attention: according to a large population-based, approximately 1% of patients

diagnosed with diabetes at an age of 50 years or younger will be diagnosed with pancreatic cancer within 3 years.⁽⁸⁾ However, also long-term diabetes is associated with PDAC development, and it is not clear whether the diabetes is caused by the cancer or constitutes itself a risk factor for pancreatic cancer.^(9,10) Moreover, the use of anti-diabetic drugs seems to modify pancreatic cancer risk, with some drugs (i.e. insulin or sulfonylureas) being associated with an increased risk for pancreatic cancer and others, such as metformin, being associated with a reduced risk for PDAC.⁽¹¹⁻¹⁶⁾

Finally, about 5-10% of PDACs are caused by inherited germline mutations⁽⁵⁾ and are defined familial PDACs; this condition should be suspected and investigated when at least two first-degree relatives have been diagnosed with pancreatic cancer. The genetic basis of this inherited predisposition is not known in most cases;⁽¹⁷⁾ however, some familial cancer syndromes are associated with an increased risk for pancreatic cancer. Mutation in BRCA2 is the most common known inherited disorder in familial PDAC; germline mutation in other genes, such as p16 (responsible of the melanoma-pancreatic cancer syndrome), ATM, STK11 (Peutz-Jeghers syndrome), PRSS1/PRSS2, SPINK1, PALB2, and DNA mismatch repair genes (Lynch syndrome), are associated with pancreatic cancer risk increase.⁽⁵⁾

Clinical Presentation

About two thirds of PDACs (60-70%) arise in the head of the pancreas, 20-25% in the body and in the tail, and 10-20% involve diffusely the pancreas. Symptoms are strictly connected with the tumor location within the gland: pancreatic head tumors often present with "compressive" effect to surrounding structures like the common bile duct with subsequent jaundice, or upper gastroduodenal obstruction due to infiltration of the duodenum; body-tail tumors are generally associated with non-specific symptoms:⁽¹⁸⁾ upper abdominal pain radiated to the back, significant weight loss, steatorrhea, newly-onset diabetes or worsening of a pre-existing.

Every case of acute pancreatitis in absence of a known cause (gallstones or alcohol abuse) should be investigated, after the resolution of the acute episode, for occult malignancy with obstructive effect on the main pancreatic duct (MPD). The incidental finding of a dilated MPD imposes further investigations to rule out (or confirm) the presence of a solid tumor: chronic progressive MPD obstruction impairs

pancreatic function and justifies the above cited symptoms. Delay in diagnosis has been previously shown as a significant independent prognostic factor for survival and it is usually because many of these symptoms overlap with those of numerous benign abdominal conditions.⁽¹⁹⁾ Young patients, early stage, the absence of jaundice and initial presentation with pancreatitis or non-specific abdominal pain, increases this risk. When metastasis is evident at first presentation, the location of primary tumor has been recently associated with different outcome: pancreatic tail tumors spread to multiple sites and more often to the peritoneum with worse prognosis.⁽²⁰⁾

Imaging in Pancreatic Cancer

Currently available pancreatic imaging has a key role in the characterization of pancreatic focal lesions, initial staging, surgical and therapeutic planning, and assessment of treatment response. When clinical suspicion arises, the diagnostic works out must drive to the suspected diagnosis or to alternative hypothesis.^(21,22)

Imaging must detect a PDAC and define its local and distant staging, therefore its resectability, given the fact that surgical resection gives, up to now, the only chance for cure. Pancreatic adenocarcinoma staging is based on tumor size, location within the pancreas, involvement of surrounding vessels and presence of metastatic disease.⁽²³⁾ Therefore, a correct diagnostic path will help to give correct indication for surgery and, at the same time, spare surgery for those patients who would not get advantage from it.

Ultrasound

Ultrasound (US) is usually the first step to investigate a persistent upper quadrant abdominal pain or a rapidly deteriorating/new onset of diabetes. It is a noninvasive and cost-effective modality. Different factors have an impact of US sensibility and specificity that vary depending on series from 70% to 98%: operator experience, posterior location of the gland, BMI of the patient and interposition of intestinal gas. This latter represents an impenetrable physical obstacle to US beam, becoming often the principal limit to a correct view. PDAC appears as a solid hypoechoic, hypovascular mass if compared to the adjacent healthy parenchyma and this is due to the very low acoustic impedance of neoplastic tissue and to the high desmoplasia and the low vascular density, respectively. It happens that, due to a rapidly increasing mass with a slower neo-angiogenesis, the central

portion of the tumor appears necrotic, mimicking a cystic area. Blood flow in PDAC is very low and margins are usually hard to define with a precise clear-cut: infiltrative behavior to surrounding structures suggests its malignant nature.

The so called double duct sign is a typical finding in PDAC of the pancreatic head infiltrating both the common bile duct and the main pancreatic duct while, any other location in the pancreatic gland, usually infiltrates and therefore obstructs the pancreatic duct: as said before, a dilated duct with no apparent reason, should always be investigated with a second line imaging method. However, in cases of pancreatic body and tail cancers, tumor detection is difficult due to the presence of gas bubbles in the stomach and transverse colon, which cause posterior shadowing.⁽²⁴⁾ Incidental finding of a small solid pancreatic lesion (less than 15mm) is something different from PDAC in almost 80% of cases.⁽²⁵⁾ US detection of chronic pancreatitis in absence of the most common risk factors (i.e. smoking, alcohol, previous pancreatitis) raise the attention to other possible causes of duct obstruction. The introduction of contrast agents has strengthened diagnostic capability of US (CE-US) and its accuracy in detecting and characterizing PDAC in this real time method. The PAMUS study reported the high accuracy of CEUS in characterizing pancreatic masses, confirming an accuracy of 91.7% for correctly characterization in respect to pathology of solid pancreatic lesions, and an accuracy of 87.8% when suggestion the diagnosis of PDAC. (**Figure 22-2**)

The high performance of CE-US to help faster diagnosis and to suggest correcting further second line investigation

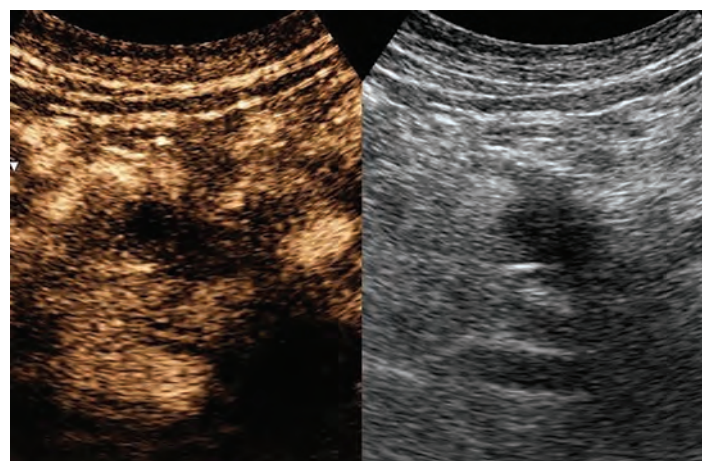


Figure 22-2. Hypoechoic PDAC baseline image (right) and contrast administration (left) showing different vascular supply compared to surrounding gland.

should be promoted and associated to basic US exam. The evaluation of the whole liver follows positive pancreas examination: each solid hypoechoic focal liver lesion detected during the late phase should be considered a metastasis until otherwise proven.

Computed Tomography

Multislice computed tomography is worldwide considered the gold standard in characterization of PDAC. It merges, with a good spatial resolution, a wide anatomic coverage with an optimal definition of vascular involvement: local resectability can be therefore assessed with a positive predictive value, sensitivity, and specificity of 89%, 100%, and 72%, respectively. ⁽²⁶⁾

A pancreatic specific protocol is a four-phase technique: pre-contrast images, early arterial phase, pancreatic phase and portal venous phase. Pancreatic phase images show peak pancreatic parenchymal enhancement, portal phase images are helpful to assess the extent of venous involvement and to identify possible liver metastases. PDAC appears at CT scan as hypoattenuating mass. (**Figure 22-3**)

However, approximately 10% of pancreatic adenocarcinomas are iso-attenuating relative to the background pancreatic parenchyma, especially in small tumors 2 cm or less, thus making diagnosis more difficult. In these situations, indirect signs, such as pancreatic duct dilation or the double-duct sign caused by pancreatic and common bile duct obstruction, are helpful for diagnosis. In addition, the pancreas distal to the tumor usually also appears atrophic. ⁽²⁴⁾



Figure 22-3. PDAC of the head with secondary pancreatic duct obstruction.

Magnetic Resonance

Although multi-detector row computed tomography currently has a major role in the evaluation of PDAC, Magnetic Resonance (MRI) facilitates better detection of tumors at an early stage by allowing a comprehensive analysis of the morphological changes of the pancreas parenchyma and pancreatic duct. Although MRI is never the first line examination it may become the problem-solving tool and it is reserved to all cases with contraindications to iodate contrast or when a CT is not exhaustive. The superior tissue contrast of MR is particularly helpful in cases of iso-attenuating pancreatic cancers that may be difficult to detect on CT scan. ⁽²⁷⁾

MRI has a specific role of in the screening of high-risk population due to its low complications rate and low radiation risk, and it has been proposed as baseline imaging by the Italian Association for the Study of the Pancreas. The incidence of PDAC in the surveilled group was higher (2.6%) than previously reported and the authors identified age >50, smoking habits and >2 relative affected by PDAC as risk factors for detection of malignant or pre-malignant lesions. ⁽²⁸⁾ On MRI, pancreatic adenocarcinoma presents as a hypointense mass on non-contrast-enhanced and contrast enhanced T1-weighted images and mildly hyperintense mass on T2-weighted images. Indirect signs of PDAC as MPD or biliary duct dilatation, double duct sign, (**Figure 22-5**) pancreatic parenchymal atrophy represents again suspect stigmata.

The ability of MRI to identify tissue with high cellularity and fibrotic changes (that impedes the free movement of

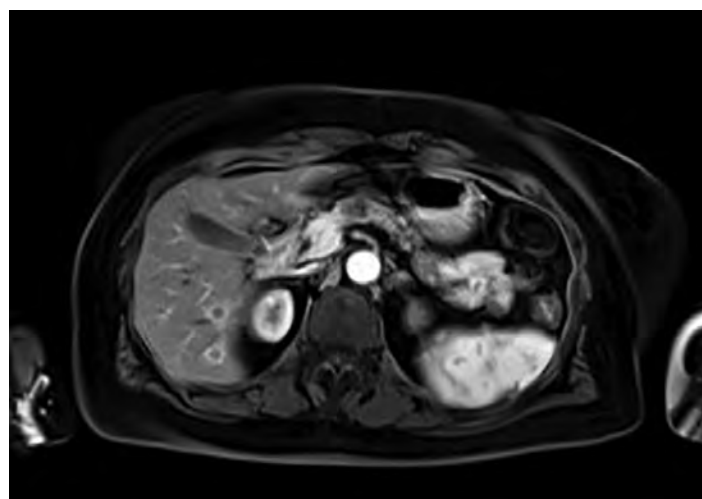


Figure 22-4. Double duct sign.

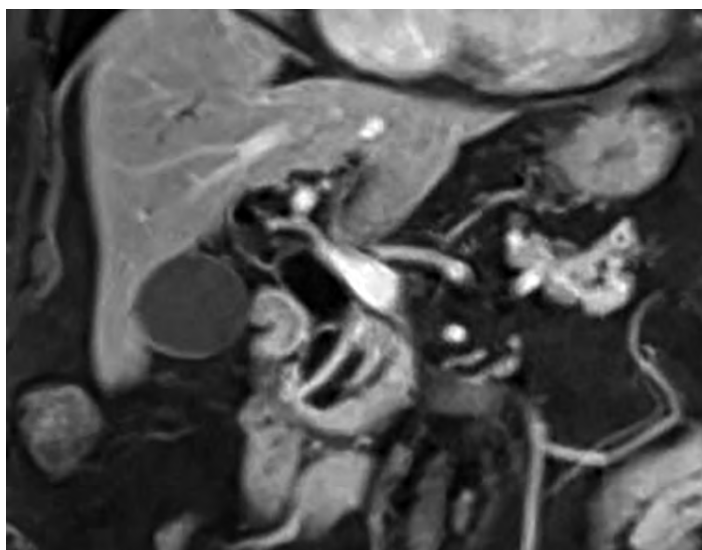


Figure 22-5. Small PDAC of the pancreatic body.

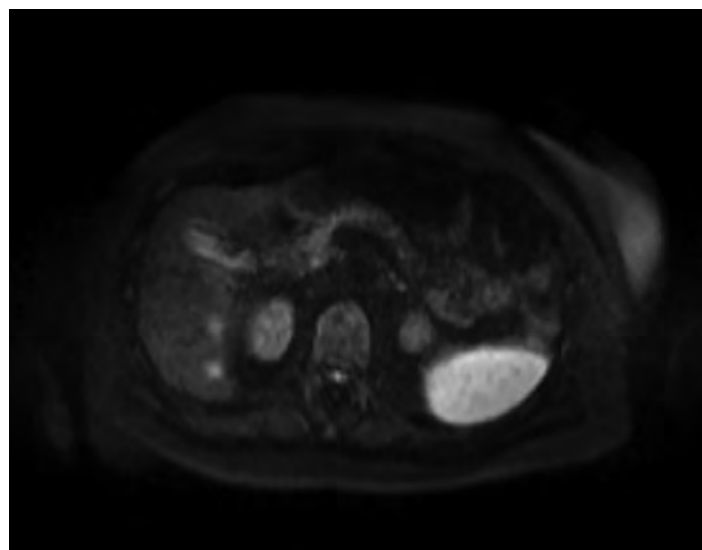


Figure 22-6. DWI sequences showing 2 metastases of the liver.

water molecules within the nodule) is due to diffusion-weighted imaging (DWI) and restriction diffusion results in low apparent diffusion coefficient (ADC). The reported values for ADC of pancreatic adenocarcinomas are lower compared to background pancreas thus helping to identify even smaller lesions (**Figure 22-4**) with a higher sensitivity (98%) if compared to traditional MRI (76%). Moreover, MRI is superior to CT in the characterization of indeterminate liver lesions and in the detection of subtle liver metastases, ^(29,30) therefore upstaging patients from potentially resectable disease, to metastatic disease. (**Figure 22-6**) Limitations to the use of MRI imaging include the higher cost, as well as patient cooperation.

Endoscopic Ultrasound

Endoscopic ultrasound (EUS) uses a high-resolution EUS probe that is advanced through the mouth into the stomach and duodenum. While this is user dependent, and therefore subject to variability, in expert hands, it is highly sensitive for the detection of pancreatic lesions. ⁽³¹⁾ Pancreatic adenocarcinoma typically appears as a heterogenous hypoechoic mass on EUS.

EUS is not considered first line imaging, but is very useful for preoperative tissue sampling, to obtain a tissue diagnosis prior to institution of therapy. While biopsy proof of malignancy is not a requisite prior to surgical resection, this is important prior to the institution of neoadjuvant chemotherapy or

chemoradiation. It is also useful as a second line investigation when a primary lesion is suspected, and no definitive mass can be identified on cross-sectional imaging. The great advantage of EUS other than its diagnostic power, is the opportunity to perform, for example, repeatable ablative therapies for unresectable cancers.

Staging

Staging of pancreatic carcinoma is based on the TNM classification, which considers the following parameters: dimension and extension of the primary tumor (T), presence or absence of metastatic lymph nodes (N), presence or absence of distant metastases (M). ⁽²²⁾ The most adopted staging systems are provided by the American Joint Committee on Cancer (AJCC) ⁽³²⁾ and the National Comprehensive Cancer Network (NCCN). ⁽³³⁾ The added value of these staging systems goes further a simple morphological description of local or distant extension of PDAC: it is represented by the attempt to offer prognostic value of different stages and therefore management guidelines. The Eight and latest Edition of AJCC significantly changed the meaning of T and N, highlighting the relevance of major vascular infiltration (other than size itself) and the number of positive harvested nodes more than total nodes or node ratio. The concept of staging has evolved from a simple descriptive image of tumor extension/diffusion to the more complex evaluation of resectability. This is particularly true when facing the new entity of borderline resectable (BR) PDAC.

PDAC is classified as clearly resectable if:

- Does not interface with adjacent arteries (celiac trunk CA, hepatic artery HA, superior mesenteric artery SMA),
- Presents a possible contact with superior mesenteric vein (SMV) and/or portal vein (PV) $<180^\circ$ of circumference. **(Figure 22-7)**

PDAC is unresectable when:

- Presents solid contact $>180^\circ$ with CA, SMA and aortic face. **(Figure 22-8)**
- Is deep infiltrating with or without lumen occlusion PV and SMV with no options for reconstruction.
- Presents distant metastasis (including non-regional lymph nodes).

BR-PDAC has been the most debated definition since when first described by Metha *et al.* in 2001: ⁽³⁴⁾ this terminology has been officially adopted by NCCN in 2006 and referred to patients who were at high risk for a margin positive resection and for whom neoadjuvant therapy should be considered. Since then, all major cancer groups (MD Anderson Cancer Center – MDACC, Americas Hepato Pancreato Biliary Association - AHPBA, Society of Surgical Oncology - SSO,

Society for Surgery of the Alimentary Tract - SSAT and Intergroup Alliance) have proposed their modified version of this definition, and a huge effort was made during the 20th meeting of the International Association of Pancreatology in 2016 in Sendai, ⁽³⁵⁾ from worldwide international experts, to reach a common vision of this heterogeneous entity.

The most intriguing concept born from this working group was the triple value of BR PDAC:

- Anatomical BR: risk of R1, R2 resection is high and can be reduced by neoadjuvant chemotherapy. This is the case of PV or SMV involvement $>180^\circ$ not exceeding the inferior duodenal border, or tumor contact with CA or SMA $<180^\circ$. **(Figure 22-9)**
- Biological BR: findings like Ca19.9 $>500\text{U/mL}$ or positive regional lymph node (biopsy or PET CT) suggests (without certitude) an extra-pancreatic disease resulting in resection rate $<70\%$ and OS of 20 months.
- Conditional BR: performance status (PS >2) and comorbidity increase the risk of postoperative morbidity and mortality (even in case of R0 likely resection) and correlates with poor prognosis. In some cases, this status can be reversible by addressing patients to medical consult, nutritional support and rehabilitation before facing surgery.



Figure 22-7. Resectable PDAC with 70° contact with SMV.

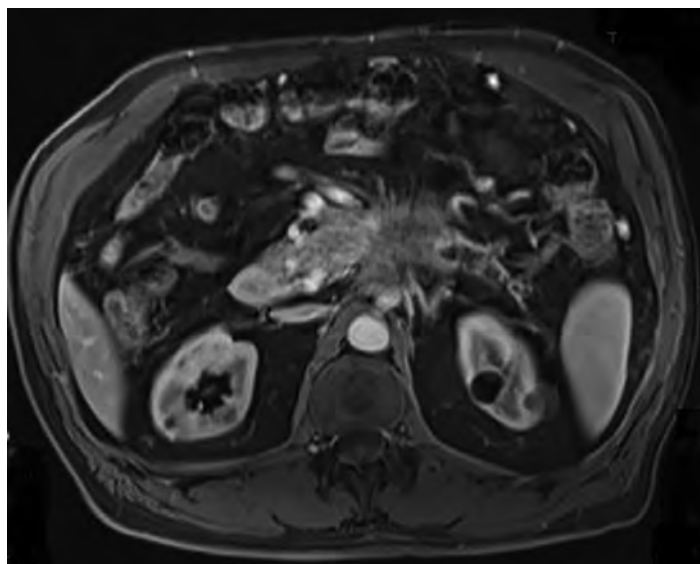


Figure 22-8. Diffuse body PDAC infiltrating CA and pre-aortic plan.



Figure 22-9. Uncinate process PDAC with 180° solid contact with SMA.

Given the original meaning of BR PDAC it is easy to understand how much BR definition is influenced by experience and skills of different surgical teams and their synergy with radiologists and medical oncologists.

Surgery

Surgical technique has not significantly changed in the past two decades and description of surgical steps can be easily available. In this paragraph we want to focus on open issues in the surgical treatment of pancreatic cancer.

Surgical and Oncological Outcome

It is widely accepted that pancreatic surgery should be performed in high volume centers (HVCs) to significantly reduce postoperative morbidity, mortality rate and length of stay, and only hospitals performing 50–100 resections per year with a mortality rate of 5% can be defined as HVCs.⁽³⁶⁾ A trend toward an increasing concentration of procedures in high-volume hospitals was most pronounced since year 2000,⁽³⁷⁾ however, depending on the geographical area, regionalization of surgical care to high-volume centers can be impractical. Therefore, a simultaneous effort has been made to identify quality indicators specific for pancreatic cancer care⁽³⁸⁾ that can be used either for guidance in medium/low volume centers aiming to grow, or to standardize care in already well established HVCs.

Adherence with guidelines and consensus recommendations for pancreatic cancer management may vary between hospitals for different reasons but experience and training of the clinical team play a major role. Surgeon's volume as well has an impact on postoperative outcome, specifically regarding pancreatic fistula (POPF) being this latter inversely proportional to surgeon's experience: however, postoperative mortality or severe complications are not increased for low experienced surgeons, probably due to the intensive care support and specific skills available in HVCs.^(39,40) When evaluating the performance of a secondary referral center, it is important to consider structural, technological and organizational facilities necessary to support any adverse event occurring during or after surgery. Adequate selection of the patient candidate for surgery is a very crucial step in surgical oncology: multidisciplinary audit with all the specialists involved in pancreatic cancer patients is essential to define the therapeutic option with highest potential benefit. Surgeons, medical oncologists, radiotherapists, gastroenterologists, radiologists and pathologists are players of the same team, everyone with his specific skills and ability.

Expertise of high-volume hospitals and cancer centers influences the oncological outcome: HVCs have been shown to provide care concordant with guidelines more frequently than low-volume centers. Awareness of what is the best available treatment and standard of care for PDAC will ensure to our patients the higher chances to prolonged survival.

The appropriate use of curative resection and the completeness of resection are the first steps for best oncological results.^(41,42) Many studies have already demonstrated that a surgical resection with positive margins leads to poor prognosis and the only potentially curative resection must be R0. In a retrospective series Kostantinidis introduced the distinction between resection R0 wide, free margin >1mm, and a R0 close, free margin of 1mm or less: this latter group of patients had better prognosis of R1 (16 Vs 14 months) but lost their survival benefit if compared to wide R0 (35 months).⁽⁴²⁾

Other than performing correct surgical technique, it is equally important to define a uniform protocol for the assessment of pancreaticoduodenectomy specimens among institutions and moreover, the intraoperative frozen section to examine surgical margin is mandatory for an adequate definition of surgical strategy. Adequacy of nodal examination and correct surgical nodal harvesting has been largely debated in the past years:⁽⁴³⁾ a consensus from the International Study Group of Pancreatic Surgery defined the

standard of care regarding lymphadenectomy in resection for PDAC. ⁽⁴⁴⁾

During pancreaticoduodenectomy an extended versus standard lymphadenectomy failed to demonstrate a benefit in long term survival, therefore adhesion to this standard could avoid side effects like chronic diarrhea and weight loss. Harvesting of right lateral SMA nodes (Ln 14) and nodes within the hepatoduodenal ligament (Ln 5,6,8a,12b,12c) is recommended as standard while, positive para-aortic nodes (Ln16) are associated with a poor prognosis and are considered from some surgical groups as distant metastasis, therefore a contraindication for resective surgery. In this decision-making process other several factors need to be considered: comorbidity, age and local staging. In left pancreatic resection for PDAC most common metastatic nodes are located along the splenic artery, the inferior border of the gland and along the common hepatic artery, which are harvested in the standard procedure. When a suspicious node is found outside the standard area of resection a frozen section is necessary to drive following surgical strategy, knowing that for every surgeon it would be difficult to abandon an *easy* resection because of a single unexpected positive node.

There is strong evidence in literature of negative correlation between node ratio (positive nodes/total harvested nodes) and survival with a 20% of node ratio associated to poor prognosis, moreover, a total number of positive nodes is found to be an independent prognostic factor for survival. A total of 15 ⁽⁴⁵⁾ and 12 nodes ⁽³³⁾ are the minimum recommended number of examined nodes for an accurate staging but, at the same time, the total examined nodes reflects the total harvested nodes and it is related to surgeon's experience and pathologist's expertise.

Medical Therapy

Adjuvant Chemotherapy

Radical surgical resection improves survival of patients with resectable disease at diagnosis. ⁽⁴⁶⁾ However, despite optimal surgery, the long-term prognosis of these patients remains poor, with a median overall survival (mOS) of 18 months and a 5 year survival rate of 20%. ⁽⁴⁶⁾ In order to improve patient survival, a multimodality treatment strategy integrating surgery and chemotherapy with or without radiotherapy has been proposed. To assess the role of adjuvant chemotherapy and chemoradiotherapy, the ESPAC-1 trial randomized 289 patients with resected pancreatic ductal adenocarcinoma to 73 treatment with chemoradiotherapy alone (fluorouracil

plus RT 20 Gy over a two-week period), chemotherapy alone (fluorouracil), both chemoradiotherapy and chemotherapy, and observation. Comparisons were made between patients who received chemotherapy versus those who didn't, and between patients treated with or without chemoradiotherapy.

After a median follow up of 47 months (IQ range, 33-62), the 2-year OS (primary endpoint) was significantly superior among patients who received chemotherapy than among those in the non-chemotherapy arm (40% vs 30%; HR 0.71, p 0.009), whereas the use of chemoradiotherapy resulted detrimental, leading to a 2y OS of 29% versus 41% (HR 1.28, p 0.05). Median OS and 5y OS were, respectively: 21.6 months and 29% in the chemotherapy alone arm; 13.9 months and 7% in the chemoradiotherapy alone arm; 19.9 months and 13% in the combined chemotherapy plus chemoradiotherapy arm; and 16.9 months and 11% in the observation arm. The benefit of chemotherapy persisted after adjustment for major prognostic factors. ⁽⁴⁸⁾ The detrimental effect of chemoradiotherapy in this trial was explained first of all with the delay of the administration of full-dose chemotherapy, which was associated with delayed local and distant recurrences; on the contrary, the local recurrence rates were not significantly different between patients who received chemoradiotherapy and those who did not. ⁽⁴⁷⁾

Besides ESPAC-1, other two randomized trials compared adjuvant chemoradiation to surveillance alone: the GITSG trial suggested, at an interim analysis, a survival benefit for the chemoradiation arm, but was stopped early after the inclusion of 40 patients due to a low enrolment rate; ⁽⁴⁸⁾ the EORTC trial showed no significant difference in survival between the chemoradiation and the surveillance arms. ^(49,50) A meta-analysis of randomized adjuvant trials conducted with the aim of more deeply understand the role of adjuvant chemotherapy and chemoradiation in PDAC confirmed these observations, reporting a significant reduction in the risk of death with the use of chemotherapy (HR 0.75, 95% CI: confidence 0.64 -0.90, p = 0.001) but not with chemoradiation (HR 1.09, 95% CI: 0.89-1.32, p = 0.43). ⁽⁵¹⁾ Subgroup analyses suggested that chemoradiation may be more effective than chemotherapy alone in patients with positive microscopic resection margins (R1), ⁽⁵¹⁾ but this result was not further investigated in prospective studies.

Further trials focused the attention on the best chemotherapy regimen in the adjuvant setting for PDAC. The CONKO 001 trial randomized 368 patients to receive adjuvant gemcitabine (1000 mg/mq d 1, 8, 15 q 28 for six months) or observation. After a median follow-up of more than 11 years (136 months, interquartile range, 104-144), the median disease-free survival (DFS, primary endpoint)

was 13.4 months (95% CI, 11.6-15.3) in the treatment group compared with 6.7 months (95% CI, 6.0-7.5) in the observation group (hazard ratio, 0.55 [95% CI, 0.44-0.69]; $P < .001$). The treatment effect on DFS was seen consistently across all the predefined subgroups (tumor stage, nodal status, resection status). The treatment led also to a significant 24% improvement in overall survival, with a median OS of 22.8 months compared with 20.2 months with observation alone (HR, 0.76 [95% CI, 0.61-0.95]; $P = .01$); survival rates at 5 and 10 years were 20.7% (95% CI, 14.7%-26.6%) and 12.2% (95% CI, 7.3%-17.2%), respectively, in the gemcitabine group and 10.4% (95% CI, 5.9%-15.0%) and 7.7% (95% CI, 3.6%-11.8%) in observation group. ⁽⁵²⁾

The ESPAC-3 trial was conducted to determine whether 5-fluorouracil or gemcitabine was superior as adjuvant treatment following surgery for PDAC. In this trial, 1088 patients were randomized to receive, after complete macroscopic resection, adjuvant chemotherapy with 5-FU (folinic acid 20 mg/m² iv bolus followed by 5FU 425 mg/m² iv bolus, d1→5 q 28) or gemcitabine (gemcitabine 1000 mg/m² iv infusion over 30 minutes, d 1, 8, 15 q 28) for 6 cycles. Median follow-up was 34.2 months (IQR, 27.1-43.4; range, 0.4-86.3). No significant difference was observed in OS, the primary endpoint, between the two treatment arms: median OS was 23 months (95% CI, 21.1-25.0) for patients treated with fluorouracil plus folinic acid, and 23.6 months (95% CI, 21.4-26.4) for patients treated with gemcitabine ($P = .39$; HR, 0.94 [95% CI, 0.81-1.08]). Similarly, there was no significant difference in PFS between the two groups: median PFS was 14.1 (95% CI, 12.5-15.3) and 14.3 (95% CI, 13.5-15.6) months for patients treated with 5FU and gemcitabine, respectively ($P = .53$; HR, 0.96 [95% CI, 0.84-1.10]). Overall, toxicity was higher with 5FU, with a severe adverse events (AEs) rates of 14% vs 7.5% with gemcitabine ($p < 0.001$); in particular, patients receiving fluorouracil plus folinic acid had significantly increased grade 3/4 stomatitis ($P < .001$) and diarrhea ($P < .001$), whereas patients receiving gemcitabine reported significantly increased grade 3/4 hematologic toxicity ($P = .003$). ⁽⁵³⁾

Based on this study, both 5FU/leucovorin and gemcitabine are listed in most international guidelines as category 1 options for PDAC adjuvant treatment, though gemcitabine is often preferred in clinical practice due to the lower G3/4 AEs rate and the more convenient treatment schedule. ⁽³³⁾ Recently, the ESPAC-4 trial tested a combination regimen (gemcitabine plus capecitabine) as adjuvant treatment for PDACs. In this open label, multicentric phase 3 trial, 732 patients were randomized to receive gemcitabine plus

capecitabine (gemcitabine 1000 mg/m² iv d 1,8,15 q 28 plus oral capecitabine 1660 mg/m² d 1→21 q 28) for six cycles or gemcitabine alone (gemcitabine 1000 mg/m² iv d 1,8,15 q 28). Over a median follow-up of 43.2 months (95% CI 39.7–45.5), median OS was 28.0 months (23.5–31.5) in the combination arm, versus 25.5 months (22.7–27.9) in the gemcitabine group (HR 0.82 [95% CI 0.68–0.98], $p = 0.032$). As expected, treatment related toxicity was higher in the combination arm, although considered acceptable. ⁽⁵⁴⁾ However, this study was criticized for a series of bias (i.e., high rate of patients with R1 and N1 disease, 60% and 80%, respectively; postoperative restaging not requested by inclusion criteria; absence of postoperative CA19.9 cut-off for patient inclusion) and has a relatively short follow-up, therefore these results should be cautiously considered. Accordingly, international guidelines added the combination of capecitabine and gemcitabine as an adjuvant treatment scheme, but gemcitabine alone remains an option. ^(33, 18)

Finally, the phase 3 PRODIGE 24/CCTG PA.6 trial randomized 493 patients after macroscopically radical surgery to receive mFOLFIRINOX or gemcitabine for 6 months. At a median follow-up of 33.6 months, the median DFS in the mFOLFIRINOX group was almost two-fold that of the gemcitabine group (21.6 vs 12.8 months), and also the median OS was significantly higher in the first treatment group (54.4 vs 35.0 months). As expected, the rate of severe AEs was significantly higher in the mFOLFIRINOX group than in the gemcitabine group (76% vs 53%), and this should be carefully considered, as patients undergoing adjuvant therapy are virtually disease free. ⁽⁵⁵⁾ In conclusion, the standard approach for resectable disease is surgery followed by adjuvant chemotherapy; at present, no chemoradiation should be proposed to patients after surgery except in clinical trials. ⁽¹⁸⁾ Adjuvant chemotherapy should be administered within 12 weeks after surgery, allowing the patient to fully recover from surgery. Completion of all six cycles of planned adjuvant chemotherapy, rather than early initiation, is an independent prognostic factor for survival. ⁽⁵⁶⁾ Radical surgery followed by adjuvant chemotherapy lead to median survivals of 20.1 to 28 months under the most optimal clinical trial conditions. ^(47,52-54)

Neoadjuvant Therapies

In order to improve patient's outcome, a neoadjuvant approach has been proposed, especially for high risk patients (i.e. high CA19.9, large primary tumor, suspicion of regional lymphadenopathy at imaging, highly symptomatic disease,

etc.). The potential benefits of neoadjuvant therapy include: the possibility to treat a larger number of patients through the anticipation of systemic treatment before surgery, thus avoiding the attrition caused by surgical complications; a better selection of patients undergoing surgery, excluding those with rapidly progressing, micrometastatic disease (about 20% of treated patients); and the downsize of the tumor, thus increasing the likelihood of radical (R0) resection. ^(57,58) If neoadjuvant therapy is chosen, histologic confirmation of disease is mandatory before treatment administration, and, in case of jaundice, biliary decompression is recommended, especially through stent placement. ⁽⁵⁹⁻⁶¹⁾

Chemotherapy alone, chemoradiation and the sequence of both (chemotherapy followed by chemoradiation) have been proposed as neoadjuvant treatment strategies; retrospective analyses of available data suggest that the inclusion of neoadjuvant chemoradiation may lead to better local control compared to chemotherapy alone, though without significant differences in survival between these approaches. ⁽⁶²⁾ Similarly, different chemotherapy regimens have been applied, including FOLFIRINOX, gemcitabine/albumin-bound paclitaxel, and gemcitabine/cisplatin. Surgery following neoadjuvant treatment appears to be safe, ^(63,64) but it should only be attempted if there is a high likelihood of achieving an R0 resection. Surgery should be proposed even if no apparent tumor shrinkage is observed after neoadjuvant treatment, as radiologic response does not always correlate with pathologic response. ^(65,66) The ideal timing for surgery is between 4 to 8 weeks after therapy. Neoadjuvant strategies are actually subject of phase II/III clinical trial; at present, they should be only considered for high risk patients with resectable disease outside clinical trials.

Borderline Resectable Disease

Preoperative treatment is the recommended option for patients with borderline resectable disease. In fact, despite the lack of high-level evidence, a preoperative treatment strategy seems to provide higher likelihood to achieve a R0 resection and better survival compared with upfront resection. ^(33,18) At present, due to heterogeneity of the small studies available, it is not possible to recommend a specific schedule of treatment: most studies conducted in this setting used full-dose radiotherapy paired with either capecitabine, 5-FU or low-dose gemcitabine, but more recent polichemotherapy regimens, such as FOLFIRINOX, may lead to even better results. ⁽⁶⁷⁾ Moreover, a multimodality

treatment strategy, starting with full dose chemotherapy followed by chemoradiation and finally, if there's no evidence of progression of disease, surgery, seems to be particularly effective, ⁽⁶⁸⁾ and is considered the best option for patients with borderline resectable lesions. ^(33,18)

Locally Advanced and Metastatic Disease

As above mentioned, most patients with PDAC are diagnosed at an advanced stage of disease, that ranges from unresectable to metastatic. The best treatment strategy in each patient needs to be discussed by a multidisciplinary team in order to define treatment goals and possible ways to achieve them.

In case of locally advanced disease, treatment goals include palliation of symptoms, lengthening of survival and, possibly, tumor downsizing and downstaging to a resectable disease. Median survival for patients with locally advanced disease ranges from 9-12 months of oldest studies to 16 months in a recent trial. ⁽⁶⁹⁾ The best treatment strategy in this setting is highly controversial. Chemoradiation showed a survival benefit compared with best supportive care, ⁽⁷⁰⁾ and radiotherapy alone. ⁽⁷¹⁾ Concerning the comparison with chemotherapy alone, different randomized trials led to conflicting results. ⁽⁷²⁻⁷⁶⁾ The sequential use of full-dose chemotherapy followed by chemoradiation in patients without evidence of progressive disease after 3 months was suggested as a treatment strategy that could combine the advantages of both chemotherapy and chemoradiation. ^(69,74-76) However, no advantages in favor of chemoradiation, compared with continuing chemotherapy alone, were demonstrated in a recent large randomized trial, in which 449 patients with locally advanced disease were treated with 4 months of gemcitabine ± erlotinib (first randomization) and then randomized to receive either two supplementary months of gemcitabine or chemoradiation: the median OS showed no significant difference between the chemoradiation and the chemotherapy-alone groups (15.2 versus 16.4 months, respectively). ⁽⁶⁹⁾ The conversion rate of unresectable tumors to surgically resectable disease is around 4%. Therefore, at present, the standard of care for these patients remains as 6 months of gemcitabine. Several trials are ongoing using polichemotherapy regimens as FOLFIRINOX or gemcitabine/nab-Paclitaxel in this setting with the aim of obtaining higher response rates and improved survival.

In the metastatic setting, the main treatment goal is palliation; for patients with good performance status (ECOG 0-1),

adequate biliary drainage and liver function, lengthening of survival is another possible purpose, that may be pursued through systemic therapy. ⁽³³⁾

For patients with poor performance status, besides symptom-directed measures, gemcitabine single agent may be considered, in view of the clinical benefit demonstrated with this drug. ⁽⁷⁷⁾ Gemcitabine alone represents a first line option also for patients with good performance status due to the modest survival advantage observed with this agent over 5-fluorouracil bolus; ^(33,77) however, since the development of more effective polychemotherapy combinations, gemcitabine monotherapy is not usually the preferred choice. In fact, after several disappointing results obtained through the combination of gemcitabine with potentially synergistic chemotherapeutic agents (such as cisplatin, oxaliplatin, 5-fluorouracil, capecitabine, irinotecan, and epirubicin + cisplatin + fluoropyrimidine) or targeted agents (i.e. erlotinib, sorafenib, bevacizumab, and different multi-target TKIs), ⁽³³⁾ two relevant phase III trials changed the clinical practice, demonstrating a clinically relevant survival benefit with FOLFIRINOX ⁽⁷⁸⁾ and Gemcitabine/Nab-paclitaxel ⁽⁷⁹⁾ over gemcitabine alone.

The randomized phase III PRODIGE trial compared the combination of 5-fluorouracil, oxaliplatin, leucovorin and irinotecan (FOLFIRINOX) with gemcitabine monotherapy in 342 patients with naïve, metastatic PDAC and good performance status (ECOG 0-1). ⁽⁷⁸⁾ The trial obtained impressive results: median overall survival (mOS), primary endpoint of the study, was 11.1 months in the FOLFIRINOX group as compared with 6.8 months in the gemcitabine group (HR 0.57; 95% CI, 0.45-0.73; $p < 0.001$); median progression-free survival (mPFS) was 6.4 and 3.3 months in the experimental and control arm, respectively (HR 0.47; 95% CI, 0.37-0.59; $p < 0.001$), and the objective response rate (ORR) was 31.6% versus 9.4% in the two groups ($p < 0.001$). However, toxicity was significantly superior in the in the FOLFIRINOX group, in which serious (G3-4) treatment related adverse event (TRAE) rates were 45.7% for neutropenia (5.4% for febrile neutropenia), 12.7% for diarrhea, 9.1% for thrombocytopenia, and 9% for sensory neuropathy; ⁽⁷⁸⁾ no toxic deaths were reported, but it should be considered that the population enrolled in the trial was highly selected: besides the good performance status required as inclusion criteria, median age was 61 years (range 25-76), only a minority of patients (16.7%) had received a biliary stent and the median number of metastatic sites was 2 (range 1-6). ⁽⁷⁸⁾ In this context, despite treatment toxicity, quality of life was maintained and even improved with FOLFIRINOX compared with gemcitabine,

⁽⁸⁰⁾ probably due to the lengthening of the progression-free interval in this highly symptomatic disease. In order to limit toxicity and extend the use of FOLFIRINOX in the real-world scenario, different modified schedules with good activity and acceptable TRAEs profile have been proposed, with 5-FU and irinotecan dose reductions and routine growth factor support. ⁽⁸¹⁾

The open label, phase III MPACT trial randomized 861 naïve patients with Karnofsky performance status 70-100 (corresponding to an ECOG PS 0-2) to receive gemcitabine alone or in combination with albumin-bound paclitaxel, a nanoparticle form of paclitaxel. ⁽⁷⁹⁾ The primary endpoint, mOS, was met: 8.7 months with the combination as compared with 6.6 months with gemcitabine monotherapy (HR 0.72, 95% CI 0.62-0.83; $p < .0001$); mPFS was 5.5 and 3.7 months (HR 0.69; 95% CI, 0.58-0.82; $P < 0.001$) and the ORR was 23% versus 7% in the two groups, respectively ($P < 0.001$). The most common G3-4 TRAEs were neutropenia (38%, with a rate of febrile neutropenia of 3%), fatigue (17%), and neuropathy (17%). ⁽⁷⁹⁾

No data are available regarding a direct comparison between the two treatment regimens, FOLFIRINOX and Gemcitabine/NabPaclitaxel; thus, either of these two options can be offered to patients with adequate biliary drainage (serum bilirubin levels $< 1.5 \times$ ULN) and good performance status (ECOG 0-1), whereas Gemcitabine/NabPaclitaxel should be preferred in very selected patients with intermediate performance status (ECOG 2) due to tumor load. ⁽¹⁸⁾ Interestingly, familial PDACs related to BRCA1 or BRCA2 mutations seems to be more sensitive to platinum compounds: in these cases, FOLFIRINOX or cisplatin-containing regimens should be considered. ⁽⁸²⁾

In the PRODIGE trial, responding patients were treated up to six months, while in the MPACT trial treatment was continued until disease progression, death or unacceptable toxicity; as a result, median duration of treatment with Gemcitabine/NabPaclitaxel was 3.9 months (range 0.1-21.9), with 32% of patients receiving treatment for at least 6 months. After 6 months of therapy or when dose-limiting toxicity appears, options for responding patients include stopping treatment or dropping the most toxic agents; switch maintenance strategies are currently on study. ⁽³³⁾

Unfortunately, virtually all patients will eventually experiment progressive disease during or after first line therapy; in this situation, considering the dismal prognosis of PDAC, second line treatment options have to be weighed in terms of risk/benefit for the patient. If the performance status remains acceptable, options of second line therapy

for gemcitabine-refractory PDAC include the combination of 5FU, folinic acid and oxaliplatin (OFF regimen), that demonstrated a survival advantage over 5-FU and folinic acid alone in a small randomized trial,⁽⁸³⁾ although not confirmed by another recent study that used the same drugs combined in the mFOLFOX6 regimen,⁽⁸⁴⁾ and the combination of 5FU folinic acid and MM-398, a nanoliposomal form of irinotecan (NALIRI). The randomized, open label, phase III NAPOLI-1 trial conducted on 417 patients previously treated with gemcitabine-based therapy demonstrated a significant OS benefit (primary endpoint; HR 0.67, 95% CI 0.49–0.92; $p=0.012$) with the use of nanoliposomal irinotecan plus 5FU and folinic acid (mOS 6.1 months, 95% CI 4.8–8.9) compared with 5FU/folinic acid alone (mOS 4.2 months, 95% CI 3.3–5.3) or nanoliposomal irinotecan monotherapy (mOS 4.9 months, 95% CI 4.2–5.6). Serious TRAEs with the combination included neutropenia (27%), diarrhea (13%), vomiting (11%), and fatigue (14%).⁽⁸⁵⁾

In conclusion, for patients previously treated with gemcitabine-based combinations that maintain an acceptable performance status, combination of 5FU, folinic acid and nanoliposomal irinotecan, when available, represents the best option due to the level of evidence supporting its ability to confer an OS advantage, whereas the addition of oxaliplatin to the fluoropyrimidine/folinic acid backbone need further studies to establish its role in this setting.⁽⁸⁶⁾

After failure of first line FOLFIRINOX therapy, the optimal treatment strategy is less clear as data are lacking in this subset of patients. Retrospective analyses suggest that gemcitabine alone⁽⁸⁷⁾ or in combination with synergistic agents, such as nab-paclitaxel⁽⁸⁸⁾ might be acceptable options, but confirmatory trials are needed.

What is Next?

New treatment strategies are under investigation in order to improve the dismal prognosis of patients with advanced PDAC.

Targeting the stroma. PDAC is characterized by an extensive desmoplastic stroma rich in pancreatic stellate cells (PSCs), fibroblasts, vascular and immune cells, and extracellular matrix (ECM) proteins. This fibrotic “scar” acts as a barrier to the delivery of cytotoxic drugs; moreover, such microenvironment, producing growth factors and proangiogenic molecules, and inducing a significant immunosuppression, is the major responsible of cancer progression, invasiveness, metastases and chemoresistance.⁽⁸⁹⁻⁹⁰⁾ In order to enhance drug delivery to the tumor, the

use of a pegylated recombinant hyaluronidase (PEGPH20) has been evaluated, with promising results in preclinical settings and improved patients survival in a phase I trial;⁽⁹¹⁾ however, the significant side effects related to this drug limited up to now its application. Similarly, as the dense fibrotic stroma creates an hypoxic environment around tumor cells, hypoxia-activated cytotoxic prodrugs, targeting tumor cells with minimal toxicity on normal tissues have been evaluated; above others, TH-302 (evofosfamide) significantly improved progression-free survival in preclinical models⁽⁹²⁾ but failed to improve overall survival in patients with advanced PDAC.⁽⁹³⁾ Matrix metalloproteinases (MMPs) are enzymes involved in stroma production, and several MMPs subtypes are overexpressed in PDAC; MMPs inhibitors have been evaluated in humans (i.e. marimastat, tanomastat), however with negative results.⁽⁹⁴⁻⁹⁶⁾ With the purpose of directly targeting and eliminating the fibrotic stroma, sonic hedgehog (SHH) inhibitors have been applied: SHH signaling plays a crucial role in the interaction between tumor and stromal cells, and in models, blocking this pathway resulted in a significant depletion of stromal components and enhanced drug delivery to the tumor.⁽⁹⁷⁾

However, SHH inhibition ultimately resulted in increased vascularity to the tumor and cancer invasiveness;⁽⁹⁸⁾ in fact, increasing evidence suggest that complete depletion of tumor stroma leads to more aggressive tumor behavior and decreased survival, as tumor stroma in part contributes to restrain tumor growth.⁽⁹⁰⁾ Modulating and reprogramming, more than completely eliminating tumor stroma seems to be the best treatment strategy. TGF- β is a growth factor that, in pathologic conditions, induces tumor growth, epithelial-to-mesenchymal transition, extracellular matrix remodeling, and evasion of immune surveillance. The TGF- β inhibitor galunisertib, in combination with gemcitabine, led to improved overall survival in a randomized phase 2 trial compared with gemcitabine alone;⁽⁹⁹⁾ further trials are ongoing with this drug. Other potential ‘stroma modulators’ currently under investigation include connective tissue growth factor antagonists, angiotensin inhibitors, vitamin A and D analogs (with the potential of restore quiescence in activated PSCs through the alteration of their gene expression profile) and miRNAs.⁽⁹⁰⁾

Immunotherapy. Despite the success observed in a variety of cancer types, immunotherapy with immune checkpoint inhibitors (i.e. ipilimumab, atezolizumab) led to disappointing results in PDAC.^(100,101) Similarly, preliminar clinical evidence with cancer vaccines (i.e. GVAX) failed to show significant activity as monotherapy in PDAC

patients.⁽¹⁰²⁾ Again, the reason should be found in the stroma. PDAC desmoplastic stroma has not only the ability to act as a barrier to immune cell infiltration, but also to induce immune suppression and promoting tumor escape of immune surveillance: in PDAC microenvironment, Treg, myeloid-derived suppressor cells, and M2-polarized tumor-associated macrophages are prevalent; moreover, activated carcinoma-associated fibroblasts produce chemokines and proteins that enhance immune suppression.⁽¹⁰³⁾

Depletion of these activated fibroblasts with concurrent immune activation by cancer vaccines or checkpoint inhibitors led to promising results in preclinical models.⁽¹⁰⁴⁾ Similarly, targeting the chemokine ligand CXCL12, overexpressed by activated stroma fibroblasts and PSCs, by its competitive inhibitor AMD3100 increased the accumulation of cytotoxic T-cells in the tumor microenvironment and reduced tumor growth in preclinical models;⁽¹⁰⁵⁾ AMD3100 is in phase I clinical trial in patients with PDAC. Another promising option is to target CD40, a cell surface molecule expressed by immune cells that modulates both cellular and humoral immunity.^(104, 106) Combination treatment with a CD40 agonist plus chemotherapy led to tumor regression and increased survival in mice;⁽¹⁰⁷⁾ tumor response was seen also in about 20% of patients treated with the CD40 agonist monoclonal antibody (moAb) and gemcitabine in a phase I clinical trial.⁽¹⁰⁸⁾

Even more promising are preclinical data about combination of a CD40 agonist moAb with chemotherapy and an immune checkpoint inhibitor. This treatment strategy is under clinical investigation: a Phase I/II trial (NCT03214250) of CD40 agonist plus gemcitabine/ nab-paclitaxel with and without nivolumab, and a phase I trial (NCT02304393) of CD40 agonist plus atezolizumab are ongoing. Similarly, with the aim of overcoming resistance, combination therapies of multiple immunotherapy (i.e. vaccines plus immune checkpoint inhibitors) and chemotherapy are under evaluation.

PARP inhibitors (BRCA-mutated tumors). The vast majority of PDACs are sporadic, but 5-10% of cases are linked to inherited syndromes. In particular, around 3-5% of PDAC patients harbor pathogenic BRCA2 or BRCA1 germline mutations. Although the prevalence of germline mutations is small, whole genome sequencing studies revealed that up to 14-35% of PDAC cases carry sporadic mutations in BRCA1/2 or other genes involved in the homologous recombination mechanism and might behave similarly to germline mutated tumors (BRCAness phenotype).^(109,110) It has been largely demonstrated in ovarian and breast cancer that BRCA-mutation, being associated with a deficient

homologous recombination mechanism, confers increased tumor sensitivity to platinum agents; several case reports and case series suggest a similar influence of BRCA-mutation in PDACs.⁽¹¹⁰⁾ More recently, PARP-inhibitors have been developed with the aim of obtaining synthetic lethality in tumors with defective homologous recombination system,⁽¹¹¹⁾ and are actually approved for BRCA-related breast and ovarian tumors. Several PARP inhibitors (i.e. olaparib, veliparib, rucaparib) are under investigation for PDAC treatment. After promising early clinical results,⁽¹¹²⁾ the phase III POLO trial was planned with olaparib as maintenance therapy for PDAC patients carrying a germline BRCA1/2 mutation who achieve disease control after platinum-based chemotherapy (NCT02184195). Veliparib, alone or in association with chemotherapy, demonstrated activity in early phase trials, and results of phase II studies with this drug and chemotherapy/chemoradiation are awaited (NCT01585805, NCT01908478, NCT0148986). Similarly, a phase II trial is ongoing with rucaparib in previously treated PDAC patients with somatic or germline BRCA1/2 mutation (NCT02042378).

Surgery After Neoadjuvant Chemotherapy for BR and LA Pancreatic Cancer

If something has changed in pancreatic surgery within the last decade this is represented by resection rate after a course of neoadjuvant therapy on initial unresectable PDAC. The availability of new drugs combination recruited a not negligible number of patients for explorative and resective surgery. In a meta-analysis Gillen *et al.*⁽¹¹³⁾ highlighted some surprising events when evaluating resection and response rate after preoperative chemotherapy in resectable versus locally advanced PDAC: first, it is reported a similar percentage of progression in both groups, thus meaning that distant spreading is not related only to initial stage of disease then, a high resection rate of 73,6% in initially resectable group was expected, while it was surprising when found to reach 33.2% in locally advanced tumors, most of them being a R0 resection. Third, better results in terms of downstaging of LA PDAC were associated to combination chemotherapy instead of single drug treatment (respectively 33% and 27.3%). This new panorama of advanced cancer responsive to neo-adjuvant treatment raised unexpected dilemma: interpretation of diagnostic imaging from a different perspective.

Ferrone *et al.*⁽¹¹⁴⁾ clearly showed that 40 patients with BR and LA PDAC treated with FOLFIRINOX and external radiotherapy, underwent successful surgical resection and

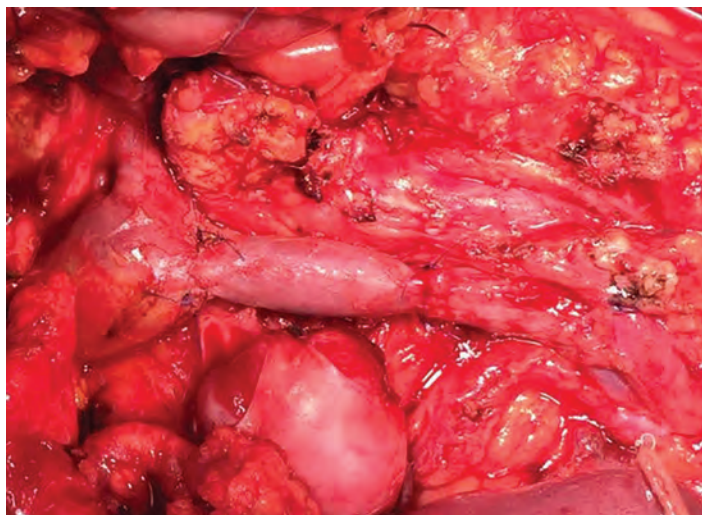


Figure 22-10. Jugular interposition after 4cm segmental resection of SMV after downstaging.

reached significantly higher R0 resection, lower positive node rate, lower lymphatic and neural invasion if compared to patients directly undergone to surgery for resectable PDAC. This happened despite pre-operative radiology reviewed by expert pancreatic surgeons, suggested persistent BR and LA PDAC at least in 70% of them. The lesson to be learned from this initial experience and then confirmed from more recent studies was that, in all BR and LA cases without progressive disease after a course of neo-adjuvant chemo-radiotherapy, a surgical exploration must be proposed. Biological factors like serum markers and performance status are essential in the global evaluation of these patients. As said before, not much has changed in the surgical technique, but a lot has done regarding the indication for surgery and attempt to resection. A most aggressive surgery with vascular resection is justified only in case of persistent infiltration of PV or SMV. (**Figure 22-10**) However, the need of vascular resection is lower than expected from pre-operative CT findings. Arterial resection is still associated with poor surgical and oncological outcome and therefore it is debated whether it can find a place in the modern pancreatic surgery. ⁽¹¹⁵⁾

Surgery After Downstaging of Metastatic Disease

As said, metastatic PDAC (mPDAC) has always been an ‘off-limits’ area for surgeons, and still is, but recently published data consider surgery as an option for synchronous oligometastatic patients, showing a possible benefit in OS. Some authors ^(116,117) demonstrated this benefit compared

with same-stage patients who received chemotherapy only: they conclude to consider surgery as an option for super-selected cases. In a different setting, patients with mPDAC may be considered eligible for surgery after complete or partial response to chemotherapy ⁽¹¹⁸⁾ following the principle that allows to aggressively treat patients who previously responded to therapies, so called responders. The largest reported series of 24 metastatic patients undergone surgery after a complete downstaging has been recently published ⁽¹¹⁹⁾ OS is encouraging as is DFS, being 56 and 27 months respectively, supporting the fact that, at the time of resection, distant liver metastasis were successfully treated. In this study it is stressed that different chemotherapy regimens had similar results, with no better response for one treatment over another. This highlights the concept of PDAC as a various entity with different biological behaviors and therefore prognosis: the four different genotypes of PDAC identified by Bailey *et al.* ⁽¹²⁰⁾ may explain the different response to both chemotherapy and surgery and are the basis for the future of PDAC therapy.

Ablative Therapies in PDAC

Ablative therapies may play a role in multidisciplinary approach to advanced PDAC and raised interest and gained relevance in the past decade. Radiofrequency ablation (RFA) and Irreversible Electroporation (IRE) represent the most popular options and seem to offer a benefit in survival and progression free survival. ^(121,122) These results come from non-randomized study and therefore need to be confirmed. Nowadays we have the opportunity to perform ablative therapies percutaneously ⁽¹²³⁾ or during EUS, ⁽¹²⁴⁾ therefore reducing the biological impact of the procedure.

Role of Minimally Invasive Surgery (MIS)

Global interest in minimally invasive approaches to pancreatic carcinoma has been progressively increasing in the past years although up to now recently data to support the presumed superiority compare to open surgery are lacking ⁽¹²⁵⁾ Indication for pancreatic resection do not differ for minimally invasive or open surgery but strictly depends on surgeon’s training.

Most studies report superior outcome of minimally invasive approach mainly regarding intraoperative blood loss and length of stay. Large series on robotic resections reported low conversion and mortality rate (6%; 1-2%) both for pancreaticoduodenectomy and distal pancreatectomy. ⁽¹²⁶⁾

Aiming to oncologic endpoints (such as radical resection rate, lymph node retrieval and postoperative survival) large studies of laparoscopic vs open distal pancreatectomy are lacking although evidences suggest comparable efficiency. ⁽¹²⁷⁾ Compare to other digestive tract surgeries laparoscopic and robotic pancreatic resections, due to intrinsic technical difficulties related to the resection itself, play a minor role in the wide set of pancreatic resections making the learning curve crucial.

Mininvasive approach to pancreatic head tumor is initially performed in small tumors excluding patients with vascular involvement, preoperative comorbidity or previous extensive abdominal surgery, leading to a selection bias which leads to unreliable statistics. Due to the long learning curve for laparoscopic pancreaticoduodenectomy, mainly for the reconstructive phase, robotic platform is advocated as the best option for pancreatic tumors despite a comparable learning curve and an increase of costs. The benefits of robot, due to 3D vision and articulated wrists, can potentially accelerate the learning curve once established as a standard approach in most pancreatic high-volume centers and increase the rate of pancreatic surgeons, with intermediate level of proficiency in mininvasive pancreatic resections, able to approach to the platform.

Conversely laparoscopic and/or robotic distal pancreatectomy, more widely performed in many centers, seems to decrease the risk of complications, including the rate of delay gastric emptying, surgical site infection, blood loss and, especially in benign disease, increase the likelihood of splenic preservation despite the postoperative pancreatic fistula rate does not differ in the two groups. ⁽¹²⁸⁾

Ultimately laparoscopic and robot-assisted pancreatic resections, although still largely affected by a long learning curve, promise good results in pancreatic oncological resections. Randomized controlled trials will definitively have to confirm the safety and efficacy on a larger scale.

Fellowship in Surgical Oncology

Surgical oncology is a competitive field, and the promotion and tenure processes are frequently vague without definitive milestones or benchmarks. ⁽¹²⁹⁾ Young surgeons develop their clinical, and eventually teaching, and research portfolios in the hopes of becoming leaders in surgical oncology. In the present section we sought to identify the role, the characteristics and the limitations of the fellowship training in surgical oncology worldwide.

The global cancer burden is expected to rise in the next few decades. At least 11% of the global burden of disease requires surgical management and 19% of the surgical burden is related to malignant neoplasms. The ability to tackle this rising cancer burden requires the presence of an adequately trained surgical oncology workforce, which is dependent on credible training pathways. ⁽¹³⁰⁾

As defined by the American Board of Surgery, a surgical oncologist has specific knowledge and skills related to the diagnosis, multidisciplinary treatment, and rehabilitation required by patients with cancer, especially those with complex presentations or requiring complex surgical procedures, or with rare or unusual cancers. ⁽¹³¹⁾ Unfortunately, a significant variability, with regard to educational curricula and training paradigms, is recorded globally. In many countries surgical oncology is not recognized as a defined specialty, in turn very few surgeons play a major role in national cancer-control policies, given the lack of an oncology expertise within their careers. ⁽¹³²⁾

Despite the diversity, in recent years, the number of general surgery residents trying to pursue fellowship training, and specifically in surgical oncology, has increased. Several factors impact on the acceptance of applicants in surgical oncology fellowship, such as a university-based surgical residency of academic prestige, the exposure to surgical oncology cases and research from an earlier time point, letters of recommendation from academic leaders in the field, academic achievements including high quality publications and presentations at national and international meetings. ⁽¹³⁰⁾ Despite the formal core curricula in surgical oncology training, ^(133,134) a meaningful educational program should be tailored on each trainee, and should focus on both acquisition of knowledge and technical skills, and development of personal learning skills to count on for continuous self-improvement. ⁽¹³²⁾

Fellowship training usually last 1–3 years and is a requirement for some countries in the training of their surgical oncologists. Countries that did not offer domestic fellowships for surgical oncologists usually collaborate with foreign surgical oncology fellowship programs and send their trainees abroad for training. Training international surgeons in surgical oncology is an undervalued intervention for improving global cancer care. A trainee who has had the opportunity to see better standards of care can lead the process of assessment, planning, implementation, training, and innovation to improve pre-existing realities in her/his country. ⁽¹³²⁾

In a recent study conducted at a single comprehensive cancer center, Memorial Sloan Kettering Cancer Center (MSKCC), describing the clinical training program of international surgeons, promising results have emerged. In particular, while participating in all perioperative care, obtaining direct surgical experience in the operating rooms, wards, and clinics, developing ownership of the patients and participating in all therapeutic decision making, the surgeons enrolled in the International General Surgical Oncology Fellowship at MSKCC have developed an intellectual and surgical expertise background that serve them in their lifetime practice as surgical oncologist. Perhaps more importantly, most of the graduates have returned to their country of origin and contributed to education and research there. To create a global surgical oncology workforce, countries without domestic fellowship should proactively partner with foreign countries that offer surgical oncology fellowships. The training should be tailored based on the need of the trainee and of the country. The activity should be monitored, tested and supported by accrediting bodies or national organizations. This is where the Society of Surgical Oncology can play a leading role.

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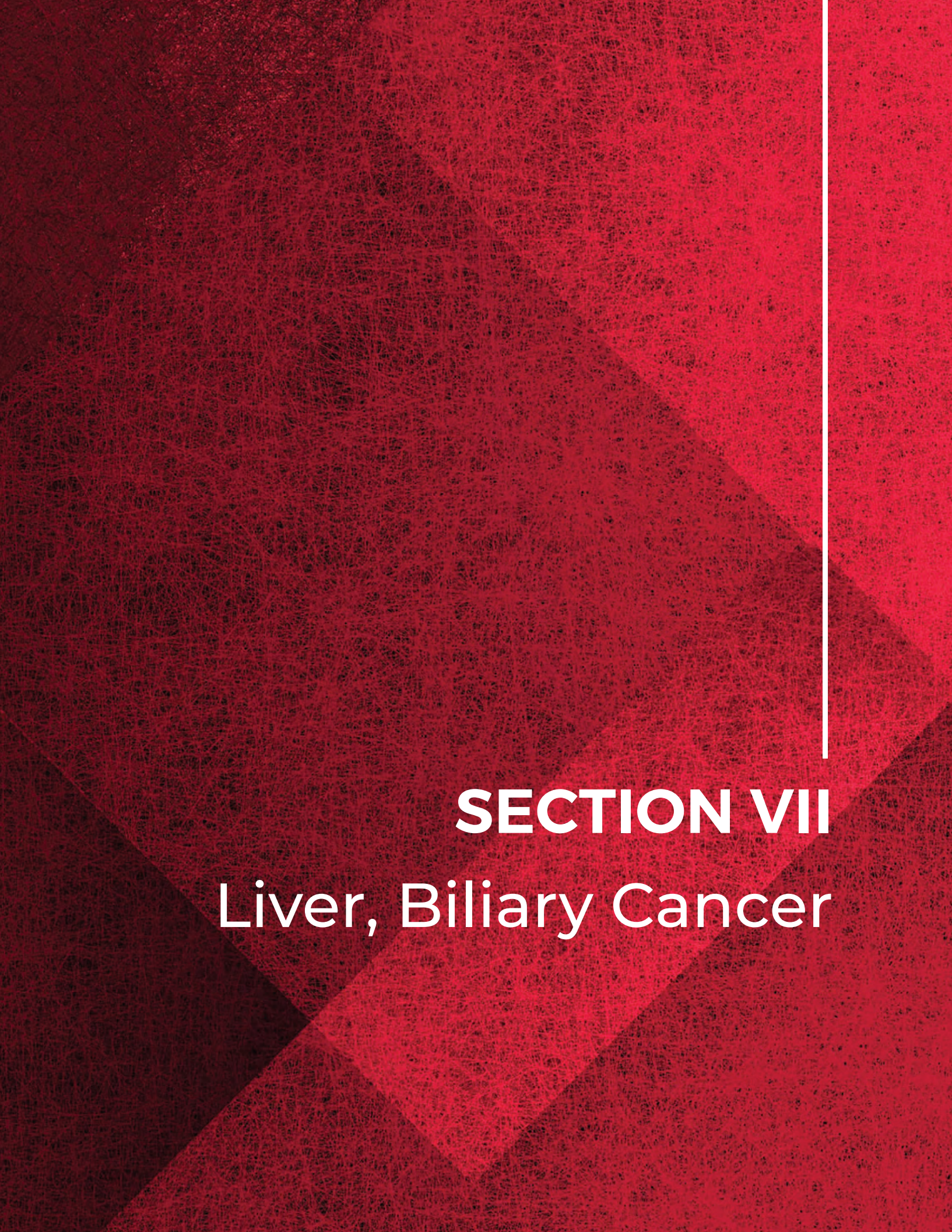
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SECTION VII

Liver, Biliary Cancer

Chapter 23

Historical Aspects of Liver Surgery

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The liver was the single organ which summarized the custom of predicting the future among the Babylonians, Etruscans, Greeks and Romans and was considered the site of the soul, the vital organ and the central place of the human body. ⁽¹⁾

Hepatobiliary surgery and specifically surgery for liver metastases had to await the advent of general anesthesia and antisepsis to evolve, mainly after WW II. But there are some anecdotal reports, such as that of Berta in 1716, when he accomplished a partial hepatectomy in a war open wound. In 1886 Lius described the first elective resection of a hepatic adenoma, followed by the unfortunate death of the patient and 1888, Langenbuch in Germany made the first planned partial lobectomy. ⁽²⁾ This patient required reoperation to control bleeding. In 1898 Cantlie described the delimitation of the anatomical division between the two hemilivers, through studies with vascular casts naming it the main lobar fissure. This work was extended by Hjostsjo and Healy and Schroy, who demonstrated the sectorial lobular divisions, and both paved the way for a few courageous hepatic surgeons. ⁽³⁾

The first surgeon to describe an elective resection of liver tumor was Tiffany in 1890. ⁽⁴⁾ An important step towards a safer liver resection occurred in 1908, when J. Hogarth Pringle, a Scottish surgeon, published an article in the *Annals of Surgery* using the cross clamping of the liver pedicle for control of hepatic hemorrhage in trauma drawn from his experiences with rabbits. In this initial report four patients died despite the maneuver. ⁽⁵⁾

One of the first reports of successful surgery for CCLM was made by Catell in 1940. ⁽⁶⁾ In 1948 Raven reported an anatomical lateral left sectorectomy for liver metastasis of colorectal cancer. ⁽⁷⁾ In 1949, Honjo in Japan performed an anatomical right hepatectomy. ⁽⁸⁾

For a long time, hepatectomies were considered as exceptions and were mostly performed for biliary disease, until Lortat-Jacob performed the first hepatectomy with vascular control in 1952. Later, the physiologic vascular segmentation of the liver would be described by Couinaud in 1957, in the magnificent book *“Le foie: études anatomiques et chirurgicales. Masson, Paris”*.

In the second half of the twentieth century, important technical advances were introduced, such as anatomic segmentectomies, total hepatic exclusion and subsegmentectomies. ^(9,10,11)

More recently, maneuvers such as Jacques Belghiti’s “Liver hanging maneuver” and the use of intra-hepatic Doppler ultrasonography to aid the resection of the venous trunks described by Torzilli, have increased the tactical arsenal of surgeons. ^(12,13)

Hepatectomies for metastasis have remained occasional, since the vast majority of metastases are large or multiple at presentation. The cases usually indicated for resection were initially those of single and indolent metastases, in highly selected patients. It was then that some initial publications started to report long-term survivals with the combination of surgery and chemotherapy in the second half of the XX century. After the association of 5FU and Leucovorin, standardized by the Mayo Clinic, new chemotherapeutic drugs and drug associations with a higher degree of response emerged. The first publication aiming conversion of unresectable metastases was that of Prof. Henri Bismuth, with the article “Resection of Irresectable Metastases”. ⁽¹⁴⁻¹⁷⁾ For the first time that group obtained an effective response with size reduction of CCLM using the combination of Oxaliplatin, 5FU and Leucovorin, in “chronomodulation”, in about 12% of the patients, which doubled the number of possible resectable patients at that time.

The observation of the liver behavior of patients with hepatocellular carcinoma involving with one side portal tumor thrombosis had a contralateral hypertrophy, especially when the surgeon decided to tie this thrombosed side of the portal vein, in order to avoid the tumor thrombus to progress to the portal trunk, as described by Honjo.⁽¹⁸⁾ It was observed that, although there was no direct tumor effect, there was sufficient contra-lateral hypertrophy to make a hepatectomy possible. Since then, previous portal embolization has been performed with this objective, establishing a functional hepatectomy prior to the now possible anatomical hepatectomy, as described by Kinoshita.⁽¹⁹⁾

The limits of hepatic hypertrophy were also amplified with the advent of two-time hepatectomy and more recently the ALLPS, by Schlitt, in Regensburg Germany 2007.⁽²⁰⁾

At the same time, methods of local thermal tumor destruction were developed, such as cryoablation (cold) and radioablation (heat), which allowed tumor destruction in those patients who, for technical or clinical reasons, could not be resected, and to the use of non-bleeding sections in hepatectomies as proposed by Nagy Habbib.⁽²¹⁾

Also, the surgical techniques themselves have been improved, with the use of hepatic parenchymal dissection technologies with less bleeding such as with the use of ultrasonic dissectors or with jet of water, reducing bleeding and allowing the dissection of areas before difficult to access as the vascular pedicles.⁽²²⁾

In hemostasis there were also advances such as the creation of argon beam coagulators and the invention of new surface hemostatic agents (patch, powder, glue) and energy equipment as Electrothermal Bipolar tissue Sealing System and Ultrasonic scalpel, with the idea was derivate from cable end fusion in sailing boats.

Imaging diagnosis also evolved to integrate the surgical field with the use of Intraoperative Ultrasound, first described by Makuuchi in 1983. Ultrasound makes the liver transparent to the eyes of the surgeon, reducing the risk of intraoperative bleeding and detailing the position of the lesions and their relationship with vessels. There is also the added benefit of potentially detect unsuspected lesions and avoiding unnecessary surgeries, besides allowing guided intraoperative biopsies and treatments.^(23,24)

The preoperative imaging tests also evolved greatly with more sensitive CT and Magnetic Resonance (MR) techniques with specific hepatocellular contrasts and Nuclear Medicine was associated with these advances and

positron emission tomography (PET CT) became part of the imaging armamentarium for diagnosis and treatment planning. PET CT impacted the selection of patients detecting extrahepatic lesions in about 25% of the cases, resulting in a better survival in those selected patients.⁽²⁵⁾

The development of minimally invasive techniques introduced by Videolaparoscopy for liver resections, as reported by Gagner in 1992, and more recently with robotic liver resections in the XXI century, has made possible the diminution of incisions, reduction of post-operative pain and enhancement of surgical recovery.^(26,27,28)

Besides Dr Thomas Aloia, of MD, proposed certain ways to enhance post-operative recovery in conventional open surgeries with the protocol known as Enhanced Surgery and Enhanced Recovery with have been adopted worldwide for liver resections.⁽²⁹⁾

Even the way of approaching synchronous liver and colorectal lesions evolved to the reverse approach proposed by the late Gilles Mentha, who reversed the paradigm of oncological resections, proposing the resection of the metastatic liver before the primary colorectal, using the rationale that would often be the hepatic metastases that would lead to the patient death, not the primary one, obviously after analyzing the severity of each tumor.⁽³⁰⁾

Since opportunity has always been the mother of inventions, Pal Dag Line, a Norwegian surgeon, in view of the surplus of organs for liver transplantation in his country, began to transplant patients with unresectable liver disease restricted to the liver, exceeding 60% of survival in 5 years. This experience has revived the curiosity around the world about this indication for liver transplantation.⁽³¹⁾

Navigated liver surgery, derived from the Neuronavigation, associated or not with the virtual or expanded reality is in its dawn. This technique has been developed in many different countries and institutes. The patient's individual anatomy is matched with the reconstructed 3D images, allowing, for example, the location of metastases that have disappeared with chemotherapy (missing metastases) and the navigation of instruments during minimally invasive surgeries.

Presently the collaboration of Hepatobiliary Surgeons, Clinical Oncologists, Hepatologists, Radiologists and Interventional Radiologists in multidisciplinary meetings have become central in the correct management of the patient with CCLM, increasing resectability and survival of many.

The union of all those techniques and approaches had led to what Prof Dong from Beijing calls as “Precision in Liver Surgery”, adopting the best way of treatment individualized for each patient. ⁽³²⁾

The comprehensive book written by Prof. Leslie H Blumgart entitled “Hepatobiliary-Pancreatic Surgery”, first released in 1988, was the first of a growing series of international literature on specific hepatobiliary-pancreatic surgery that have been guiding surgeons for generations. ⁽³³⁾

Many other surgeons were instrumental in this evolutionary process, producing scientifically and publishing publications creating specialized medical societies, such as IHPBA.

IHPBA dates back to 1978 when it was founded as the International Biliary Association (IBA) in San Francisco, California. The new IHPBA was formally inaugurated at its first General Assembly on May 31st, 1994 in Boston, Massachusetts-USA. The IHPBA was incorporated as a non-profit organization with the goals of finding effective treatment for the disorders of the liver, pancreas and biliary tree: to promote understanding, encourage change, study problems, foster friendship in the field of HPB surgery, strive towards highest ethical standards and advance education and career development in the field.

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Chapter 24

Morphologic Anatomy

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The liver is the largest organ of the body, accounting for approximately 2% to 3% of average body weight. Located in the right upper quadrant of the abdominal cavity beneath the right hemidiaphragm, it is protected by the rib cage and maintains its position through peritoneal reflections, referred to as ligamentous attachments. Although not true ligaments, these attachments are avascular and are in continuity with the Glisson capsule or the equivalent of the visceral peritoneum of the liver. The falciform ligament is an attachment arising at or near the umbilicus and continues onto the anterior aspect of the liver in continuity with the umbilical fissure. The falciform ligament courses cranially along the anterior surface of the liver, blending into the hepatic peritoneal covering coursing posterosuperiorly to become the anterior portion of the left and right coronary ligaments; the coronary ligament lies anterior and posterior to the bare area of the liver comprised of peritoneal reflections of the diaphragm. These areas converge to the left and right of the liver to form the left and right triangular ligaments, respectively.

Of surgical importance, at the base of the falciform ligament along the liver, the hepatic veins drain into the inferior vena cava (IVC). Within the lower edge of the falciform ligament is the ligamentum teres (round ligament), a remnant of the obliterated umbilical vein (ductus venosus) that travels from the umbilicus into the umbilical fissure where it is in continuity with the ligamentum venosum as it joins the left branch of the portal vein. The ligamentum venosum lies within a fissure on the inferior surface of the liver between the caudate lobe posteriorly and the left lobe anteriorly, where it is also invested by the peritoneal folds of the lesser omentum (gastrohepatic ligament).⁽¹⁾

During hepatic surgery, mobilization of the liver requires division of these avascular attachments. The IVC maintains

an intimate relationship to the caudate lobe and right hepatic lobe by IVC ligaments. These caval ligaments are bridges of broad membranous tissue that are extensions of the Glisson capsule from the caudate and right hepatic lobe. Of surgical importance, these ligaments are not simple connective tissue but rather contain components of hepatic parenchyma, including the portal triads and hepatocytes. Hence, during liver mobilization, these ligaments must be controlled in a surgical manner to avoid unnecessary bleeding or bile leakage during hepatic surgery.⁽²⁾

The liver has a dual blood supply from the portal vein and common hepatic artery. The portal vein is responsible for approximately 70% and the hepatic artery for 30% of the blood flow of the liver. In the liver, arteries, portal veins, and bile ducts are surrounded by a fibrous sheath, the Glissonian sheath. Hepatic veins in the hepatic parenchyma lack such protection.⁽³⁾

Anatomic understanding of the portal anatomy is essential to hepatic resection and associated vascular and biliary reconstructions. Within the porta hepatis is the common bile duct, hepatic artery, and portal vein that course in a lateral, medial, and posterior configuration, respectively. These structures are the anterior limit of the Winslow foramen, an important landmark for performing the Pringle maneuver.⁽⁴⁾

Functional Anatomy

Although somewhat complex, the description by Couinaud is the most complete and its exactitude and usefulness for the surgeon have been proven by a large experience. It is that description which is used in this chapter.

The study of the functional anatomy of the liver permits the description of a hepatic segmentation based upon the distribution of the portal pedicles and the location of the hepatic veins. The 3 main hepatic veins divide the liver into 4 sectors, each of which receives a portal pedicle, with an alternation between hepatic veins and portal pedicles. The 4 sectors individualized by the 3 hepatic veins are called portal sectors, for these portions of parenchyma are supplied by independent portal pedicles. For the same reason, the scissurae containing the hepatic veins are called portal scissurae, while the scissurae containing portal pedicles are called hepatic scissurae: the umbilical fissure corresponds to a hepatic scissura.

According to this functional anatomy, the liver appears to be separated into 2 livers (or hemi- livers), the right and left livers, by the main portal scissura also called Cantlie's line. It is better to call them right and left livers rather than right and left lobes, for this last nomenclature causes some confusion with the anatomical lobes. The main portal scissura goes from the middle of the gallbladder's bed anteriorly to the left side of the vena cava posteriorly.

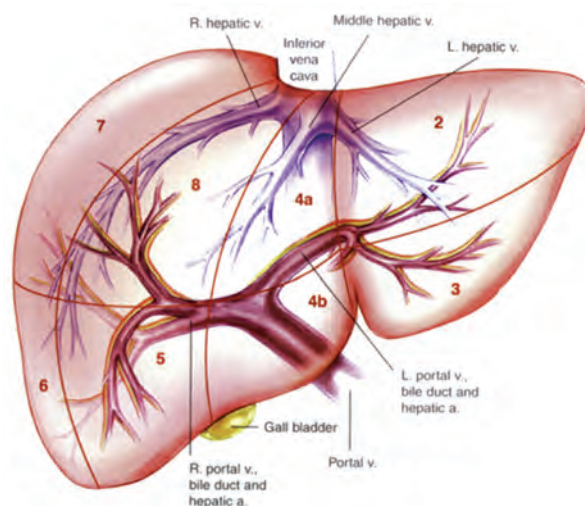
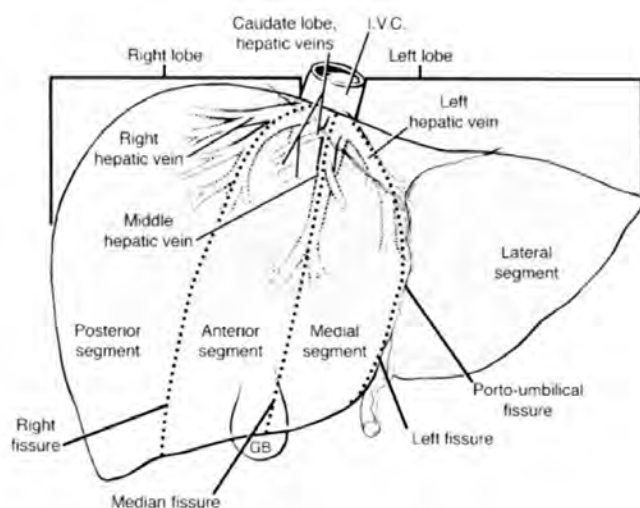
In conclusion, the liver appears to be divided into 2 livers by the main hepatic scissura where the middle hepatic vein runs.

1. The right liver is divided into 2 sectors by the right portal scissura where runs the right hepatic vein. Each of these

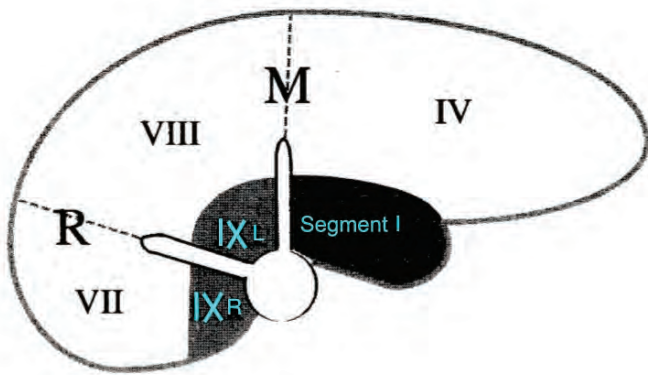
2 sectors is divided into 2 segments: anteromedial sector - segment V, anteriorly and segment VIII, posteriorly; and the posterolateral sector -segment VI, anteriorly and segment VII, posteriorly.

2. The left liver is also divided into 2 sectors by the left portal scissura where the left hepatic vein runs. First, the anterior sector is divided by the umbilical fissure into 2 segments: segment IV, the anterior part of which is the quadrate lobe, and segment III, which is the anterior part of the left lobe. Second, the posterior sector is comprised of only 1 segment, segment II, which is the posterior part of the left lobe. This is an exception to this nomenclature.
3. The Spiegel lobe (or segment I) must be considered from the functional point of view as an autonomous segment, for its vascularization is independent of the portal division and of the 3 main hepatic veins. It receives its vessels from the left but also from the right branches of the portal vein and hepatic artery; its hepatic veins are independent and end directly into the inferior vena cava. ^(5, 6)

Based on an initial embryologic and comparative anatomic analysis, Couinaud and Filliponi proposed that the portion of the posterior sector to the right of the middle hepatic vein might be a separate segment, segment IX (**Figure 24-1.C**), ⁽⁷⁾ but this nomenclature is not standardized between surgeons and anatomist and is still considered a controversial subject.



Figures 24-1.A and 24-1.B. **A)** The four fissures. GB, gallbladder; IVC inferior vena cava. (Adapted from Colburn GL, Skandalakis LJ, Gray SW, et al. *Surgical anatomy of the liver and associated extrahepatic structures. Part 3 - surgical anatomy of the liver. Contemp Surg* 1987;31:25. **B)** Intrahepatic vascular and biliary anatomy, anterior view. Adapted from Cameron JL, Sandone C. *Atlas of gastrointestinal surgery, Vol. 1. 2nd edition. Hamilton (ON): BC Decker; 2007. p. 121 [Fig. 1]; the People's Medical Publishing House—USA, Shelton, CT.*



Figures 24-1.C. Dorsal sector of the liver and segment IX. IXR – the right portion.
IXL – the left portion

Classification of Hepatectomies

Liver resections can be separated into 2 groups:

1. Typical hepatectomies, which are defined by the resection of a portion of liver parenchyma following one or several anatomical scissurae. These resections are called hepatectomies (left or right), sectoriectomy, and segmentectomies according to the Brisbane 2000 terminology. (Tables 24-1, 24-2, 24-3 and Addendum)⁽⁸⁾
2. Atypical hepatectomies which consist of the resection of a portion of parenchyma not limited by anatomical scissurae.

Hepatectomies can also be classified as major (defined as the resection of three or more contiguous segments) or minor.⁽⁹⁾ Central resections, also called mesohepatectomies comprise segments IV, V and VIII, with or without segment I.

Table 1. First-order division Schematic diagram of the segments for reference in the table (for purposes of clarity SgI is not shown)			
Anatomical term	Couinaud segments referred to	Term for surgical resection	Diagram (pertinent area is in heavy black outline)
Right hemiliver OR Right liver	Sg5–8(+/- SgI)	Right hepatectomy OR Right hemihepatectomy (stipulate +/- segment I)	
Left hemiliver OR Left liver	Sg2–4 (+/- SgI)	Left hepatectomy OR Left hemihepatectomy (stipulate +/- segment I)	
Border or watershed: The border or watershed of the first-order division which separates the two hemilivers is a plane that intersects the gallbladder fossa and the fossa for the IVC and is referred to as the <i>midplane of the liver</i>.			

Table 24-1

Tables 24-1, 24-2, 24-3 and Addendum - The Brisbane 2000 Terminology of Hepatic Anatomy and Liver Resections - Terminology Committee of the IHPBA. Terminology of liver anatomy and resections. HPB. 2000;2:333–339.

Table 2. Second-order division

Anatomical term	Couinaud segments referred to	Term for surgical resection	Diagram
Right anterior section	Sg5,8	Add '-ectomy' to any of the anatomical terms as in <i>Right anterior sectionectomy</i>	
Right posterior section	Sg6,7	<i>Right posterior sectionectomy</i>	
Left medial section	Sg4	Left medial sectionectomy OR Resection segment 4 (also see under third order) OR Segmentectomy 4 (also see under third order)	
Left lateral section	Sg2,3	Left lateral sectionectomy OR Bisegmentectomy 2,3 (also see under third order)	
Right hemiliver plus left medial section	Sg4-8 (+/-Sg1)	Right trisectionectomy or Extended right hepatectomy or Extended right hemihepatectomy	
Left hemiliver plus right anterior section	Sg2,2-5,5,8 (+/-Sg1)	Left trisectionectomy or Extended left hepatectomy or Extended left hemihepatectomy	

Borders or watersheds:
The borders or watersheds of the sections are planes referred to as the *right and left intersectional planes*. The left intersectional plane passes through the umbilical fissure and the attachment of the falciform ligament. There is no surface marking of the right intersectional plane.

Table 24-2

Table 3. Third-order division

Anatomical term	Couinaud segments referred to	Term for surgical resection	Diagram
Segments 1–9	Any one of Sg1 to Sg9	Segmentectomy	
(Segmentectomy 6)			
2 contiguous segments	Any two of Sg1 to Sg9 in continuity	Bisegmentectomy	
			(Bisegmentectomy 5,6)

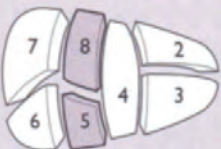
Borders or watersheds:

The borders or watersheds of the segments are planes referred to as *intersegmental planes*.

It is also acceptable to refer to ANY resection by its third-order segments, e.g. right hemihepatectomy can also be called resection Sg5–8.

Table 24-3

Addendum. Alternative second-order division (second-order division based on portal vein)

Anatomical term	Couinaud segments referred to	Term for surgical resection	Diagram
Right anterior sector OR Right paramedian sector	Sg5,8	Add '-ectomy' to any of the anatomical terms, as in Right anterior sectorectomy OR Right paramedian sectorectomy	
Right posterior sector OR Right lateral sector	Sg6,7	Right posterior sectorectomy OR Right lateral sectorectomy	
Left medial sector OR Left paramedian sector	Sg3,4	Left medial sectorectomy OR Left paramedian sectorectomy OR Bisegmentectomy 3,4	
Left lateral sector OR Left posterior sector	Sg2	Left lateral sectorectomy OR Left posterior sectorectomy OR Segmentectomy 2	

Right anterior sector and right anterior section are synonyms. Right posterior sector and right posterior section are synonyms.

Left medial sector and left medial section are NOT synonyms and are NOT exchangeable terms. They do not describe the same anatomic areas.

Left lateral sector and left lateral section are NOT synonyms and are NOT exchangeable terms.

Borders or watersheds:

The border or watersheds of second-order division based on the portal vein are referred to as *right and left intersectoral planes*. These have no surface markings.

Addendum

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Chapter 25

Liver Regenerative Properties

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Mauro Monteiro, MD, PhD

Diseases such as hepatitis, alcoholic or non-alcoholic hepatic steatosis, hepatocellular carcinomas and hereditary liver metabolic disorders are on the rise in the general population, and these diseases are known to possess high mortality and morbidity rates.⁽¹⁾

The usual course of treatment is liver transplant or cancer resection, as pharmacological courses yield poor results. Although surgery is an efficient method, it has a major downside: the limited supply of donors, immunological side effects and economic reasons.⁽²⁾

Ever since the 1930's, liver regeneration has been extensively studied in the literature. Initially, Higgins and Anderson described a compensatory hyperplasia after the excision of 2/3 of the liver in a partial hepatectomy in rats.⁽³⁾ Thereafter, a major interest of liver regenerative properties was stimulated, as hepatectomies are the primary treatment option for hepatocellular carcinoma.⁽⁴⁾

This regeneration happens because the liver is a key organ involved in metabolism, and as such, it needs to resist insults from toxic and infectious agents. Studies have shown that the liver may be able to restore its volume even after a 70% removal of the organ. This process is mediated through proliferation and differentiation of mature liver cells.⁽⁵⁾

However, this regeneration may not be successful in numerous situations, such as in cases of small-for-size syndrome where the transplanted liver fails to regenerate to full size, causing hepatocyte dysfunction and liver failure or when the liver exhibits poor regeneration after surgery due to underlying diseases like cirrhosis.⁽²⁾

These questions and the lack of concrete answers motivated a vast number of researchers throughout the world to better understand the kinetics and mechanisms of liver regeneration after hepatectomies, which we will explore next.

Firstly, it is important to know that the hepatocyte is a cell highly susceptible to stimuli and with a high proliferation potential. The partial hepatectomy leads to compensatory hypertrophy followed by hyperplasia roughly 10 to 12 hours after surgery, but, studies have shown that there are signaling changes 15-20 minutes after the partial hepatectomy on the urokinase plasminogen activator of the hepatocyte, as well as migration of Notch1 (NICD) and beta catenin to the hepatocyte nuclei, which are known to be sprouting factors.^(2,6)

The urokinase plasminogen activator leads to extracellular matrix remodeling, and this further activates hepatocyte growth factors (HGF). These factors are present in stellate cells, Kupffer cells, resident and bone marrow derived endothelial cells and platelets, and they act directly in hepatocyte proliferation and DNA synthesis.⁽⁷⁾ This reiterates the role of the extracellular matrix of the liver during its regeneration.

Another key growth factor that induces hepatocyte proliferation and DNA synthesis is the epidermal growth factor (EGF), which is constantly produced in Brunner's glands of duodenum and is secreted into the intestinal lumen, as such, it is absorbed by the portal circulation and liver.^(8,9) These growth factors are the only two known receptor tyrosine kinases to directly act during mitotic phase and directly stimulate cell proliferation and as such are key to liver regeneration.⁽⁶⁾

Despite that, as previously stated, this process is regulated by a great number of signaling cells/factors, such as: tumor necrosis factor α (which regulates secretion of interleukin-6 thus leading to protein synthesis), produced by the hepatocytes; metalloproteinases (acts on the extracellular matrix), produced by endothelial cells; vascular endothelial growth factor (VEGF) (which induces angiogenesis), produced by Kupffer cells; serotonin (which induces hepatocyte mitosis through transforming growth factor β inhibition), produced by the platelets, for instance. ^(2, 9-11)

Furthermore, the role of immune cells in liver regeneration also remains obscure, although some studies observed that eosinophil-lacking mice showed compromised regeneration rate of the liver and that eosinophil-derived interleukin-4 (IL4) was auxiliary to hepatocyte proliferation. Other interleukins (IL6, IL7 and IL22) are known to have a role in hepatocyte proliferation as well, although considered auxiliary. ^(6, 12, 13, 14)

In short, liver regeneration can be divided in three distinct phases:

1. priming, which is characterized by growth factors activation (EGF and HGF) and cytokine release, thus, primary signaling;
2. proliferation, which is promoted by the aforementioned factors plus auxiliary signaling (e. g. interleukins and vascular endothelial growth factor) promoted by early gene/transcription factor activation;
3. termination, governed by signal transduction pathways and likely governed by signal transduction pathways, such as the TGF- β -TGF β R-mediated pathway and the Hippo/Yap pathway, with the purpose to correct liver size. ^(6, 9, 15, 16)

However, constant injury to the liver parenchyma (e. g. alcohol, drugs, viruses) can cause a disturbance in these phases. This is due to the presence of reactive oxygen species, which causes oxidative stress and genomic alterations of the hepatocytes, which can lead to cancer or fibrosis. ^(6, 17, 18)

In conclusion, regenerative properties of the liver are unique and complex, the main purpose being to maintain the regular liver size and function. It is highly mediated by growth factors and protein signaling and the molecular aspects of this regeneration are still unknown.

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Chapter 26

Hepatocellular Carcinoma - HCC

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Epidemiology

Hepatocellular carcinoma (HCC) is the most common primary hepatic malignancy in the world, with an increasing worldwide prevalence ⁽¹⁾ and is the third most common cause of cancer related death worldwide. According to the Global Burden of Disease 2015 study of 195 countries, the number of liver cancer cases increased by 75% between 1990 and 2015. ⁽²⁾

The lowest incidence rates are consistently found among whites (3.8 in men and 1.4 in women). Gradually increasing rates are found in the Japanese (5.5 in men and 4.3 in women), African American (7.1 in men and 2.1 in women), Hispanic white (9.8 in men and 3.5 in women), Filipino (10.9 in men and 2.4 in women), Chinese (16.2 in men and 5.0 in women), and Korean American (20.7 in men and 10.4 in women) populations.

In most high-risk areas, such as Southeast Asia (Qidong in China) or the West Coast of Africa (Bamako in Mali), rates of liver cancer increase after 20 years of age and peak or stabilize at the age of 50 years and above. In these countries, liver cancer is not a rare event at ages 20 to 35 years. The age-adjusted incidence rate ratios of liver cancer in men and women are extremely consistent in 157 registries worldwide: Correlation coefficient (CC) = 0.953, $P < .001$). An excess of liver cancer incidence among men compared with women has been well documented. Worldwide, the ratios in the gender-specific incidence rates range from 1.4 to 3.3. ⁽³⁾ The sex disparity in rates is not well understood, although most liver cancer risk factors are more prevalent in males than females.

Risk Factor

The single largest risk factor for development of HCC is cirrhosis of any etiology, which is present in 70–90% of those who have primary liver cancer. In developing countries, viral hepatitis (hepatitis B and C) represents the major risk factor, whereas in developed countries, the epidemic of obesity, diabetes and nonalcoholic steatohepatitis (NASH) contribute to the observed increase in HCC incidence. ⁽⁴⁾ Among the diseases that affect the liver, Genetic hemochromatosis (GH) deserves attention. It is a condition characterized by excess iron absorption due to the presence of mutations in the HFE gene. A study from the National Center for Health Statistics found that patients with a known diagnosis of hemochromatosis at death were 23 times more likely to have liver cancer than those without GH. ⁽⁵⁾ Another important risk factor is exposure to aflatoxin. Dietary exposure to aflatoxin B1, derived from the fungi *Aspergillus flavus* and *A. parasiticus*, is an important co-factor for HCC development in some parts of Africa and Asia. Epidemiologic studies have shown a strong correlation between the dietary intake of aflatoxin B1, TP53 mutations and incidence of HCC, specifically in HBV-infected individuals. ⁽⁶⁾

Pathology

Three gross morphologic types of HCC have been identified: nodular, massive, and diffuse. Nodular HCC is often associated with cirrhosis and is characterized by well-circumscribed nodules. The massive type of HCC, usually

associated with a noncirrhotic liver, occupies a large area with or without satellite nodules in the surrounding liver. The less common diffuse type is characterized by diffuse involvement of many small indistinct tumor nodules throughout the liver.

Fibrolamellar hepatocellular carcinoma (FLHC) is a variant of HCC that makes up a small number of all HCCs. Patients with FLHC tend to be younger and have a generally better prognosis than those with HCC, though recurrences following resection are common. FLHC also is rarely, if ever, associated with hepatitis, cirrhosis, or elevated alpha-fetoprotein (AFP) levels. ⁽⁵⁾

Clinical Manifestation

HCC is asymptomatic for much of its natural history. Nonspecific symptoms associated with HCC can include jaundice, anorexia, weight loss, malaise, and upper abdominal pain. Physical signs of HCC can include hepatomegaly and ascites. Paraneoplastic syndromes, although rare, also can occur and include hypercholesterolemia, erythrocytosis, hypercalcemia, and hypoglycemia. Apparently, the presence of paraneoplastic syndromes in hepatocellular carcinoma patients is an unfavorable prognostic factor (excluding the occurrence of erythrocytosis). ⁽⁷⁾

Screening for HCC

The purpose of a cancer screening test is to identify the presence of a specific cancer in an asymptomatic individual in a situation where early detection has the potential to favorably impact patient outcome. Tests that can be used in HCC surveillance include serological and imaging examinations. The target population that we should offer such tests is summarized in **Table 26-1**.

The imaging test most widely used for surveillance is ultrasonography (US). US has an acceptable diagnostic accuracy when used as a surveillance test (sensitivity ranging from 58% to 89%; specificity greater than 90%). ⁽⁸⁾ There are no data to support the use of multidetector computed tomography (CT) or dynamic magnetic resonance imaging (MRI) for surveillance. Practical experience suggests that the rate of false-positive results that will trigger further investigation is very high and non-cost-effective.

Serological tests that have been investigated or are under investigation for early diagnosis of HCC include alpha-fetoprotein (AFP), des-gamma-carboxy prothrombin (DCP) – also known as prothrombin induced by Vitamin K Absence II (PIVKA II) – the ratio of glycosylated AFP (L3 fraction) to total AFP, alpha-fucosidase, and glypican 3. AFP is the most widely tested biomarker in HCC. It is known that persistently elevated AFP levels are a risk factor for HCC development and can be used to help define at-risk populations. When used as a diagnostic test, AFP levels at a value of 20 ng/ml show good sensitivity but low specificity, whereas at higher cut-offs of 200 ng/ml the sensitivity drops to 22% with high specificity. ⁽⁶⁾

A randomized controlled trial we found that after 5-year follow-up, screening by combined AFP testing and ultrasonography examination every 6 months led to a reduction of 37% in HCC mortality in individuals aged 35 - 59 years with HBV infection or a history of chronic hepatitis. The result was obtained with 58.2% compliance to screening. ⁽⁹⁾ However, there are many studies that have failed to demonstrate the efficacy of AFP as a screening method.

Finally, cost-effectiveness studies have shown that semi-annual US-based surveillance improves quality-adjusted life expectancy at a reasonable cost. ⁽¹⁰⁾

Table 26-1. HCC Surveillance Candidates and Level of Evidence
1. Cirrhotic patients, Child-Pugh stage A and B*
2. Cirrhotic patients, Child-Pugh stage C awaiting liver transplantation**
3. Non-cirrhotic HBV carriers with active hepatitis or family history of HCC***
4. Non-cirrhotic patients with chronic hepatitis C and advanced liver fibrosis F3****

* Evidence 3A; strength B1.
** Evidence 3D; strength B1.
*** Evidence 1B; strength A1 for Asian patients; Evidence 3D; strength C1 for Western patients.
**** Evidence 3D; strength B1 for Asian patients; Evidence 3D; strength B2 for Western patients.

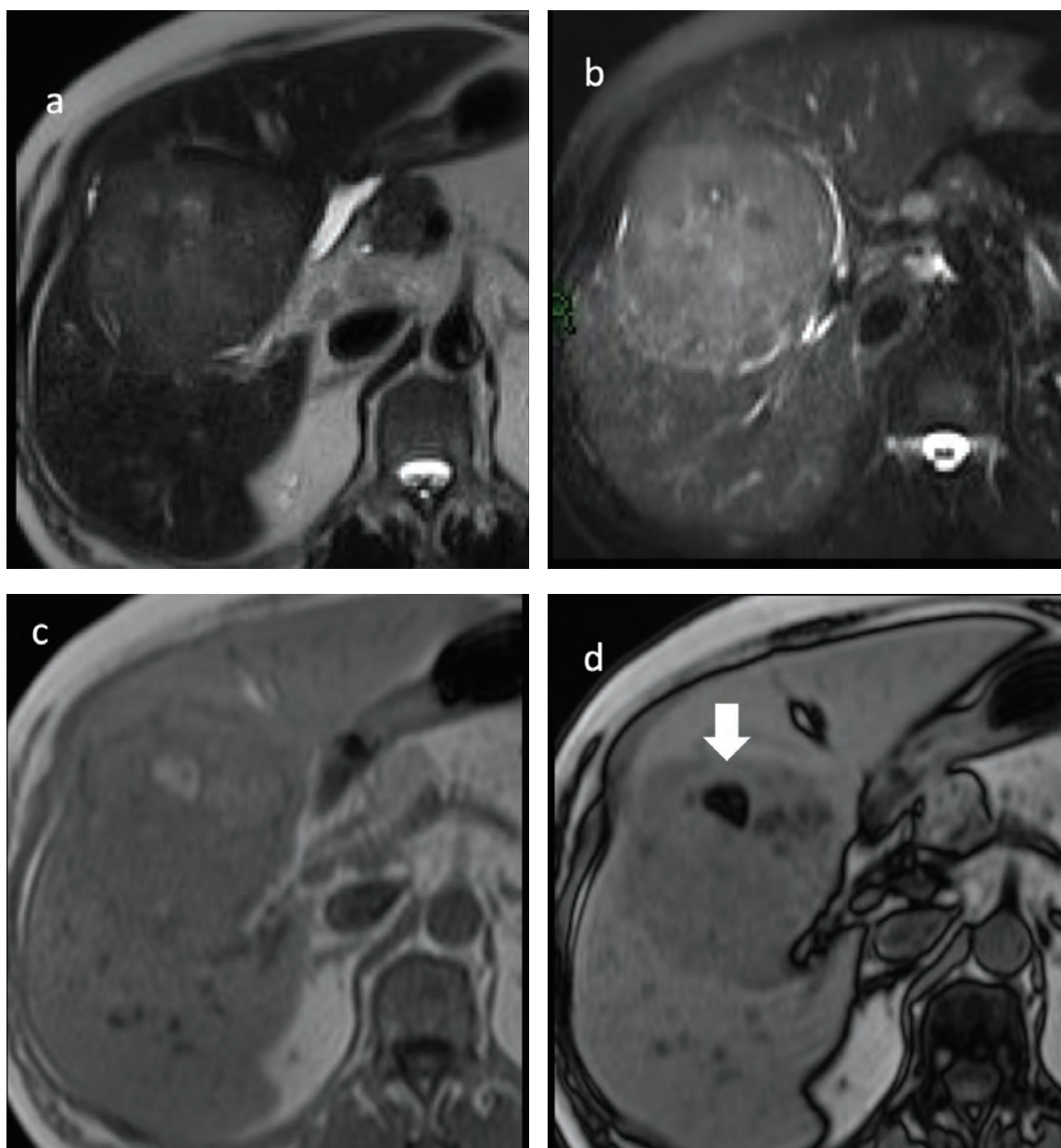


Figure 26-1. Hepatocellular carcinoma.

(a, b) The right liver lobe mass is moderately hyperintense on T2 weighted images,
 (c) Isointense on T1 weighted image and
 (d) Shows signal dropout (arrow) on opposed-phase image indicating
 presence of fat. Gadolinium-enhanced T1-weighted images shows,
 (Images courtesy of Luiza Labrunie, MD, Oncologist Radiologist, National Cancer Institute, Brazil).

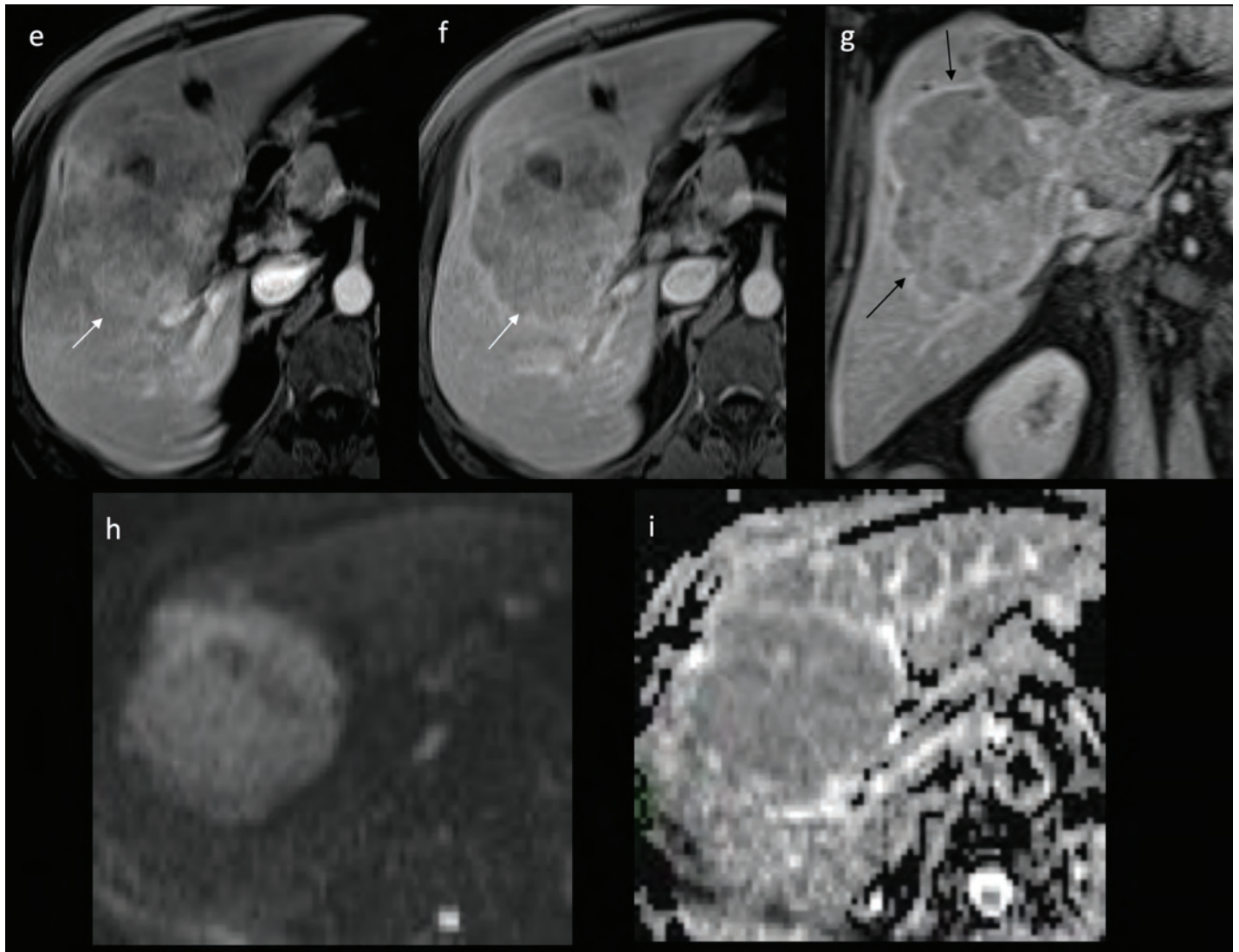


Figure 26-1 (cont.). Hepatocellular carcinoma.

- (e)** Enhancement in arterial phase,
 - (f)** Early washout, becoming hypointense to the liver, with enhancement of the pseudocapsule seen on portal venous phase image which
 - (g)** Persists into delayed phase (black arrows).
 - (h)** High signal intensity on diffusion weighted image (DWI) with
 - (i)** Corresponding low signal on ADC map reflects high tumor cellularity.
- (Images courtesy of Luiza Labrunie, MD, Oncologist Radiologist, National Cancer Institute, Brazil).

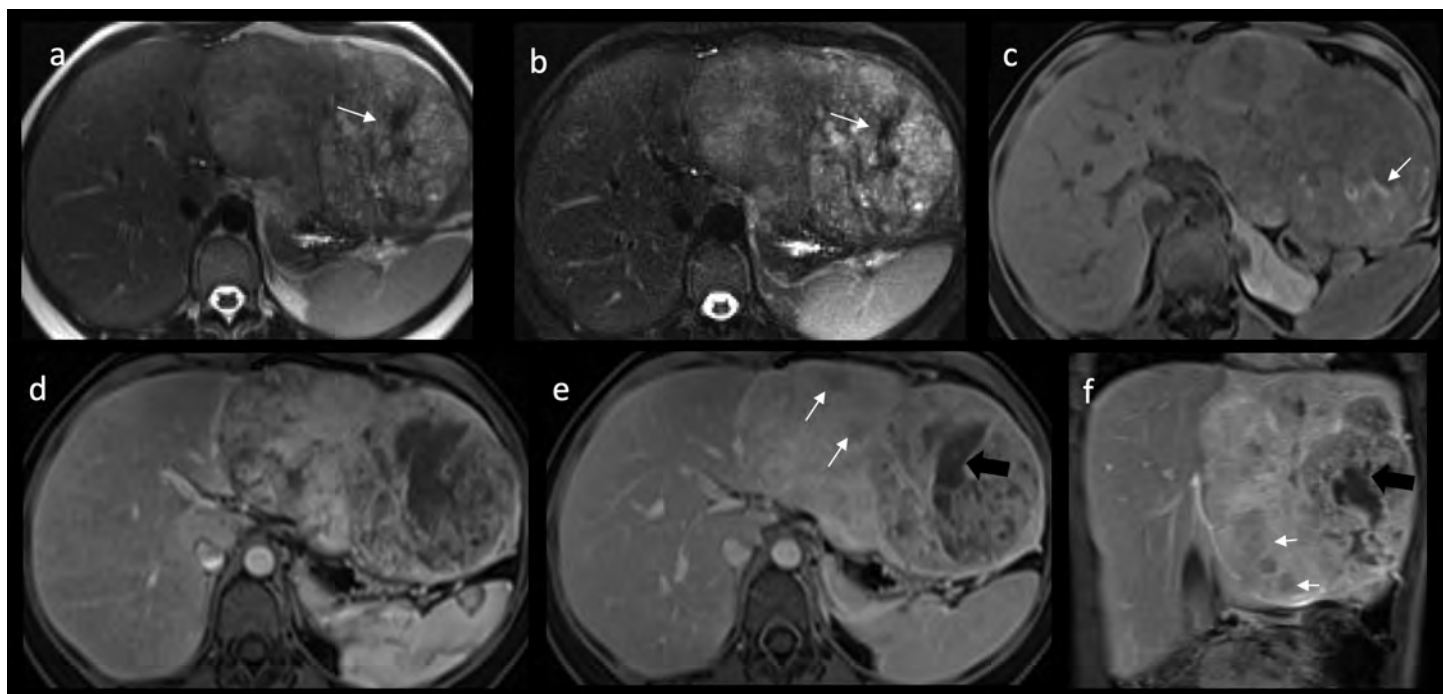


Figure 26-2. Fibrolamellar hepatocellular carcinoma.

Left liver lobe single heterogeneous mass in a non-cirrhotic liver is:

- (a, b) Mildly hyperintense on T2 weighted images, with an hypointense central scar (arrow), and
 (c) Hemorrhage on T1 fat-suppressed weighted image. Gadolinium-enhanced T1- weighted images show
 (d) Heterogeneous enhancement on the arterial phase,
 (e) Early washout areas on portal venous phase and on
 (f) The delayed phase (white arrows).
 (e, f) No enhancement is seen within central scar (black arrows).

(Images courtesy of Luiza Labrunie, MD, Oncologist Radiologist, National Cancer Institute, Brazil).

Diagnosis

Diagnostic HCC imaging involves the use of multiphasic liver protocol CT with IV contrast or multiphasic contrast-enhanced MRI. The classic imaging profile associated with an HCC lesion is characterized by intense arterial uptake or enhancement followed by contrast washout or hypointensity in the delayed venous phase.

To improve standardization and consensus regarding performance, interpreting, and reporting CT and MRI examinations of the liver in patients at risk for HCC, LI-RADS (Liver Imaging Reporting and Data System) was launched in March 2011 and adopted by many clinical practices throughout the world. LI-RADS categorizes nodules recognized at CT or MRI, in patients at high risk of HCC, as definitively benign, probably benign, intermediate probability of being HCC, probably HCC, and definitively

HCC (corresponding to LI-RADS categories 1-5). LI-RADS should not be applied to the general population, but rather is intended only for individuals at increased risk for HCC, whether or not a nodule has previously been noted by US or other imaging. ⁽¹¹⁾ (Figure 26-3)

It is important to point out that the HCC radiological hallmark only occurs in a small proportion of patients with tiny tumors (1–2 cm), and thus biopsy or tissue biomarkers will be required in most instances. Delaying diagnosis beyond 2 cm leads to increased levels of treatment failure or recurrence, since it is known that satellites and microscopic vascular invasion rise exponentially beyond this size cut-off. ⁽⁷⁾

Biopsy may be done in patients who are not considered high risk for developing HCC (i.e., patients who do not have cirrhosis, chronic HBV, or a previous history of HCC). It may be indicated in patients with conditions associated

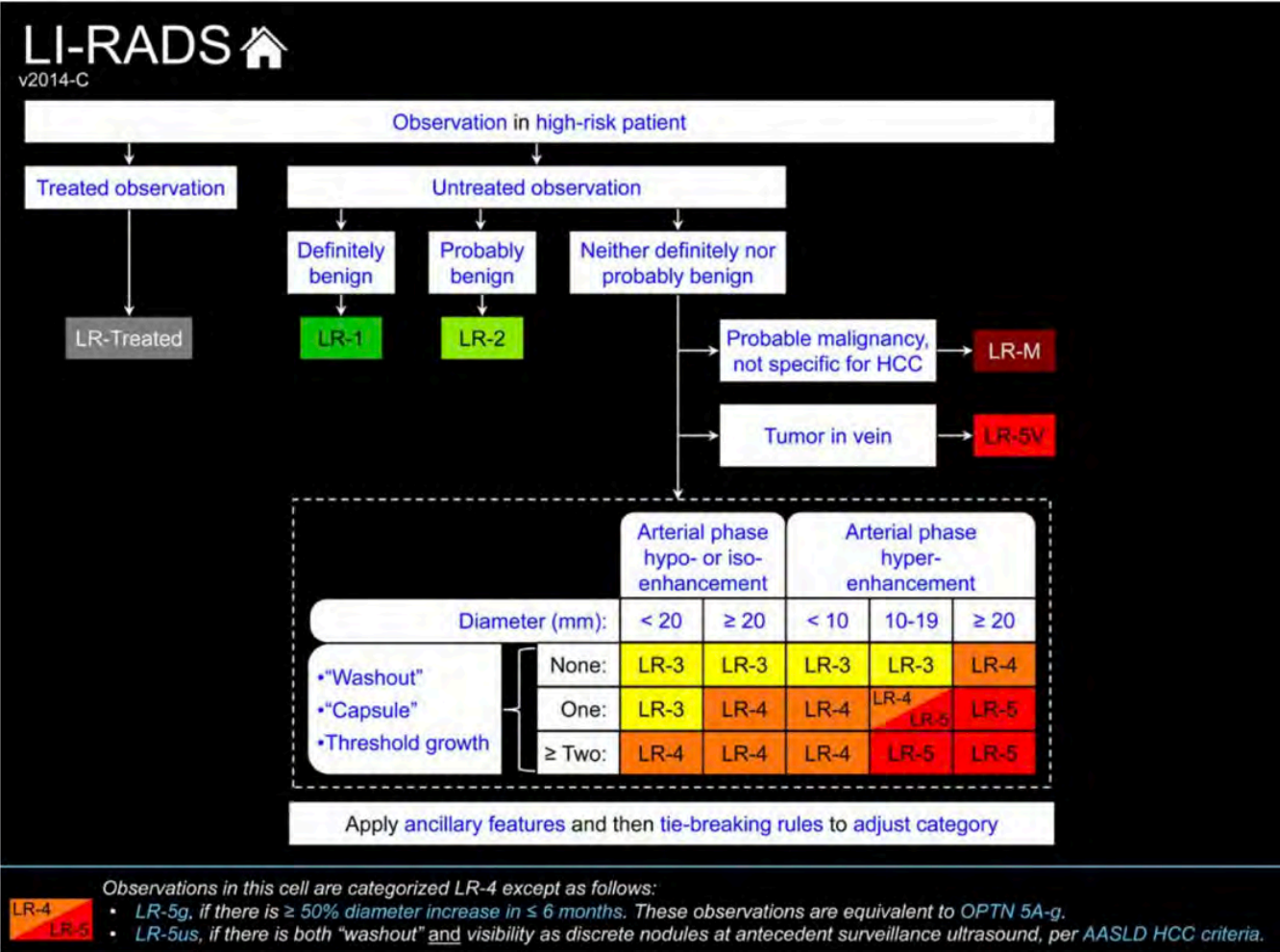


Figure 26-3. Liver Imaging Reporting and Data System (LI-RADS) Classification.

with formation of nonmalignant nodules that may be confused with HCC during imaging. These conditions include cardiac cirrhosis, congenital hepatic fibrosis, or cirrhosis due to a vascular disorder such as Budd-Chiari syndrome, hereditary hemorrhagic telangiectasia, or nodular regenerative hyperplasia. Finally, biopsy may be considered in patients with elevated CA 19-9 or CEA, in order to rule out intrahepatic cholangiocarcinoma. ⁽⁵⁾

Staging

There have been many studies comparing various staging systems in HCC and have found variable results (American Joint Committee on Cancer (AJCC), Tumor-Node-Metastasis (TNM), Okuda staging, Cancer of the Liver Italian Program (CLIP), GRETECH system, Barcelona Clinic Liver Cancer (BCLC), Chinese University Prognostic Index (CUPI), and

Japan Integrated Staging (JIS), Child-Pugh classification). Of six staging systems, BCLC had the highest area under ROC (AUROC; 0.821) for overall survival, followed by JIS (0.809), Tokyo score (0.771), CLIP (0.746), CUPI (0.701) and GRETCH (0.685) system. In both subgroups stratified according to treatment strategy (curative vs. palliative), BCLC also showed the best AUROCs (curative, 0.708/ palliative, 0.807) for overall survival.

The best staging system should not only look at the prognosis without treatment but should also provide guidelines about treatment and the prognosis after treatment. The system should take in to account the tumor status, liver function and general health status of the patient. BCLC is one such classification which takes into account most of these aspects. (Figure 26-4) Most of the American literature supports BCLC and it has also been endorsed by the European Association

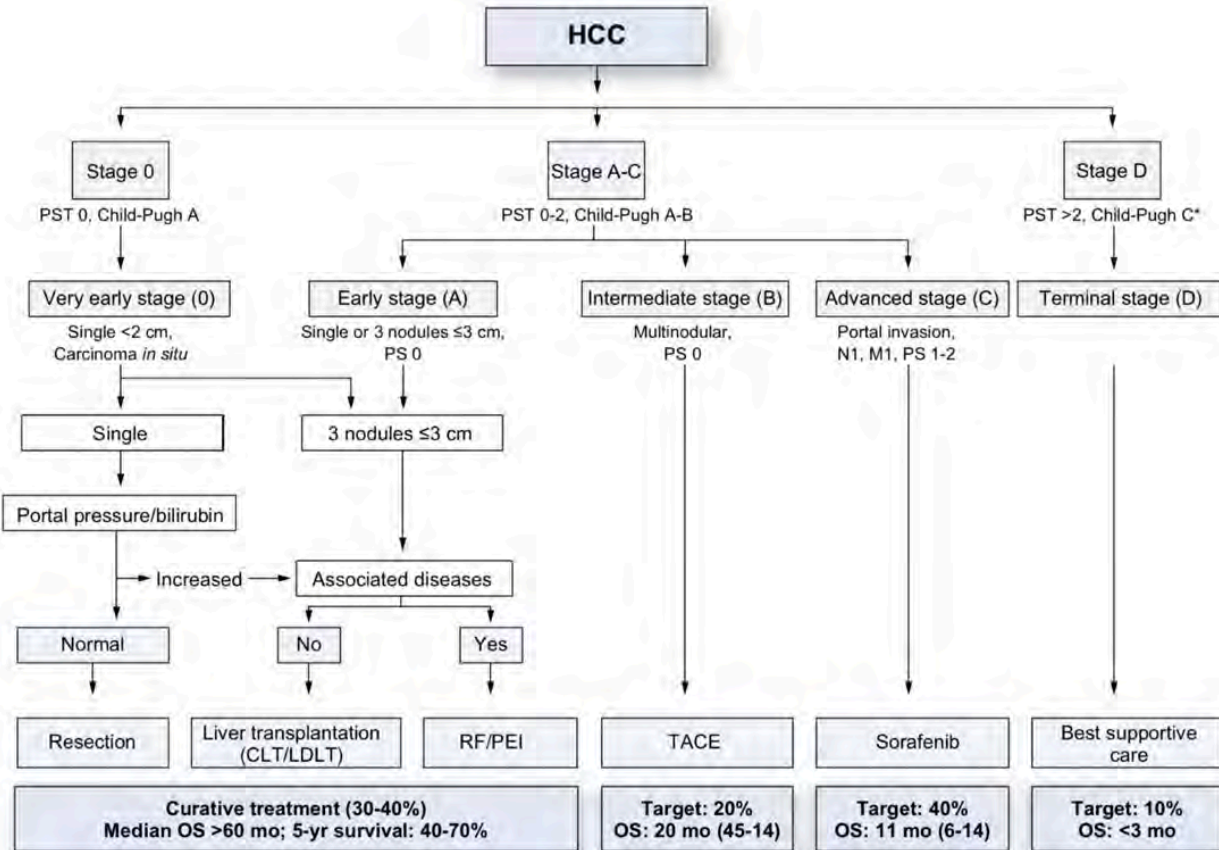


Figure 26-4. Barcelona Clinic Liver Cancer (BCLC) Staging and Treatment Algorithm.

for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD).⁽¹²⁾

Treatment Options

All patients with HCC should be carefully evaluated for the many available treatment options. It is important to reiterate that the management of patients with HCC is complicated by the presence of underlying liver disease. The treatment of patients with HCC often necessitates multidisciplinary care with the involvement of hepatologists, cross-sectional radiologists, interventional radiologists, transplant surgeons, pathologists, medical oncologists, and surgical oncologists, thereby requiring careful coordination of care.

Surgical Resection

Liver resection (LR) is the standard treatment modality for HCC and is considered to be the mainstay of curative therapy, but only 10–15% of these patients have resectable tumors.⁽¹³⁾ It is well known that patients with a normal liver tolerate large hepatectomy without significant risk of liver failure. However, in patients with chronic liver disease the tolerance to liver resection and long-term outcome is reduced in parallel to the degree of liver function impairment and appearance of portal hypertension. The presence of a hepatic vein pressure gradient greater than 10 mmHG is associated with a higher risk of postoperative liver decompensation and of poor long-term outcome. Therefore, surgical resection is reserved for patients with preserved hepatic function (Child A) and without portal hypertension.⁽¹⁴⁾

Ablation

This is another therapy that can provide complete tumor elimination and long-term cure. To achieve this aim, the patients have to fit into an optimal profile in terms of tumor burden and location. The two most widely used techniques are ethanol injection and radiofrequency (RF), while other techniques such as laser, microwave, high intensity ultrasound, cryotherapy or acetic acid injection are less common or validated in terms of efficacy and safety.

RF can be used in tumors up to 3 cm, but overall survival and disease-free survival is only equated to LR when the tumor is ≤ 2 cm.⁽¹⁵⁾ In small recurrent HCCs after LR, RF achieved similar overall survival (OS) and disease-free survival (DFS) than those with repeated LR and also had a shorter hospital stay.⁽¹⁶⁾

Liver Transplantation (LT)

LT is an attractive, potentially curative therapeutic option for patients with early HCC. It removes both detectable and undetectable tumor lesions, treats underlying liver cirrhosis, and avoids surgical complications associated with a small future liver remnant (FLR). However, organ donation is low, so LR remains a good option.

The Milan criteria have been universally adopted to screen potential candidates for deceased donor liver transplantation (DDLT) for the treatment of HCC. **(Figure 26-5)** The 4-year OS and DFS rates were 85% and 92%, respectively, when liver transplantation was restricted to a subgroup of patients with HCC meeting the Milan selection criteria.⁽¹⁷⁾

Salvage LT may be offered as an option in patients who relapsed after LR. Mainly those who underwent resection outside the Milan criteria.⁽¹⁸⁾

Milan Criteria (Mazzaferro *et al.*, 1996)

- Single tumor < 5 cm, or
- 2 – 3 tumors none exceeding 3 cm, and
- No vascular invasion and/or extrahepatic spread

Figure 26-5. Milan Criteria for HCC.

Transarterial Chemoembolization (TACE)

Patients with HCC of BCLC stage B should be considered for TACE. Conventional TACE (c-TACE) involves intra-arterial infusion of chemotherapy (usually doxorubicin or cisplatin), frequently mixed with Lipiodol (ethiodized oil) to increase exposure of the tumor to the drug, followed by embolization of the feeding vessel(s) with agents such as gelatin sponge. This causes cytotoxicity and ischemia. Not all patients with intermediate-stage HCC can be considered for TACE. Some absolute and relative contra-indications exist, including tumor burden (size > 10 cm) and impairment of liver function. The best candidates for TACE are asymptomatic patients with a solitary or limited multifocal HCC without vascular invasion or extrahepatic spread and with well-preserved liver function (Child–Pugh class A or B-7 points without ascites).⁽¹⁹⁾ Transarterial chemoembolization is also widely used in transplant centers as a means of downstaging patients with unresectable HCC, thereby “bridging” patients on wait lists to surgery and preventing drop-offs. Neoadjuvant TACE is associated with longer overall survival in patients who receive a liver transplant for HCC.⁽²⁰⁾

Systemic Therapy

The majority of patients diagnosed with HCC have advanced disease, and many are not eligible for potentially curative therapies. Clinical studies evaluating the use of cytotoxic chemotherapy in the treatment of patients with advanced HCC have typically reported low response rates. In 2006, there was no FDA-approved first line treatment for patients with advanced HCC. This scenario has changed as a result of the data reported showing survival benefits from patients receiving sorafenib.⁽²¹⁾ Sorafenib is an oral multikinase inhibitor of Raf, vascular endothelial growth factor receptor (VEGFR), platelet- derived growth factor receptor (PDGFR), c-kit, Flt-3, and RET that suppresses tumor cell proliferation and angiogenesis. It is the first line therapy for patients BCLC – C.^(5,6)

Nevertheless, the median survival of these patients is 6 months. Other drugs have also been used (regorafenib, nivolumab, cabozantinib), but none showed an expressive increase in survival.

Best Supportive Care

Patients with end-stage disease are characterized by presenting with tumors leading to a very poor Performance

Status (ECOG 3–4), which reflects a severe tumor-related disability. Their median survival is 3–4 months or 11% at 1-year. The best treatment for those is supportive care.

Adjuvant Therapy

Adjuvant therapies have not proven to improve outcome of patients treated with curative intent. ⁽⁶⁾

Recurrence

The risk of recurrence depends on the modality of treatment used, as well as patient and tumor characteristics. **Tables 26-2 and 26-3** summarize the risk factors. ⁽²²⁾

Follow up

Although data on the role of surveillance in patients with resected HCC are very limited, recommendations are based on the consensus that earlier identification of disease may facilitate patient eligibility for investigational studies or other forms of treatment. The recommendation is ongoing surveillance — specifically, multiphasic high-quality cross-sectional imaging of the chest, abdomen, and pelvis every 3 to 6 months for 2 years, then every 6 to 12 months. Multiphasic cross-sectional imaging (i.e., CT or MRI) is the preferred method for surveillance following treatment because of its reliability in assessing arterial vascularity, which is associated with increased risk of HCC recurrence following treatment.

Table 26-2. Recurrence Risk Factors for Resectional Treatment

Treatment	Recurrence	Risk factors
Liver resection	Early	Tumor size > 5cm High histological grade (G4) Microvascular invasion Resection technique Genetic profile
	Late	Stage of liver disease Multinodularity Age Gender (male) AST > x 2 normal values Genetic profile
Orthotopic liver transplant		Milan criteria Vascular invasion Bilobular nodules Tumor grade Tumor size > 5 cm Total number of lesions

Table 26-3. Recurrence Risk Factors for Ablative Treatment

Treatment	Risk Factors
Percutaneous ethanol injection	Tumor size $\geq$ 2-3cm Multinodularity Peritumoral capsule
Percutaneous radiofrequency ablation	Tumor size > 2-3 cm Position of nodule near large vessels or diaphragm
Transarterial chemoembolization	Multifocality Partial necrosis Age > 60 Pattern of lipiodol accumulation (partial or heterogeneous)

AFP levels are associated with poor prognosis following treatment and should be measured every 3 months for 2 years, then every 6 to 12 months. ⁽⁵⁾

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Chapter 27

Liver Metastases

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Epidemiology

The liver is the most common site of bloodborne metastases for all primary cancers in the splanchnic viscera. The percentage of patients with liver metastases (LM) at postmortem examination is 56% for colorectal cancer, 44% for gastric carcinoma, 70% for pancreatic carcinoma, 78% for gallbladder carcinoma, and 30% for esophageal carcinoma. Even primary cancers from outside of the portal venous drainage area find the liver rich soil for the growth of secondary tumors. Autopsy studies show LM in 13% of patients with carcinoma of the prostate, 42% of patients with carcinoma of the lung, and 53% of patients with carcinoma of the breast. ⁽¹⁾

Clinical Manifestation

Most patients with liver metastases have no symptoms related to those metastases for most of the time they have disease in the liver, symptoms come late. Liver enlargement due to tumor growth is usually gradual and therefore painless, but acute hemorrhage and/or necrosis may produce pain that fortunately often disappears after a few days. Secondary tumors in the liver may obstruct intrahepatic and extrahepatic bile ducts, causing jaundice. Liver metastases may grow so large that they cause symptoms by their bulk alone, for example, early satiety, abdominal distention, or even respiratory embarrassment.

Eventually, metastatic disease may involve enough of the liver to reduce its metabolic activities. Fortunately, this is a very late phenomenon in most patients and death usually follows within days or, at most, weeks after metabolic decline and failure. ⁽¹⁾

Colorectal Liver Metastases

Colorectal cancer (CCR) remains the second leading cause of cancer-related death in the United States, with 63,000 deaths annually. Approximately 50% to 60% of patients diagnosed with CCR develop metastases, and 80% to 90% of these patients have unresectable metastatic liver disease. Metastatic disease most frequently develops metachronously after treatment for locoregional CCR, with the liver being the most common site of involvement. However, 20% to 34% of patients with colorectal cancer present with synchronous liver metastases. ⁽²⁾

Surgical resection of colorectal liver metastases (CRLM) remains the only therapy with potential for cure and five-year survival rates of 25% to 35% have been reported in the literature. ⁽³⁾

Diagnosis and Staging

The most commonly used diagnostic modalities are CT, PET / CT and MRI. Gadoxetate disodium-enhanced MRI show the highest sensitivity (93.1%) and FDG PET/CT show the highest specificity (93.9%) for diagnosing CRLM, although its specificity did not differ significantly from that of MRI. In addition, we know that the use of neoadjuvant chemotherapy may impair the analysis of these results. ⁽⁴⁾

Intraoperative ultrasound (IOUS) was developed as the most reliable imaging tool to find tiny liver tumors in the 1990s. More recently, contrast-enhanced intraoperative ultrasound (CE-IOUS) has been developed as the ultimate imaging modality with the best accuracy for CLRM diagnosis. ⁽⁵⁻⁷⁾

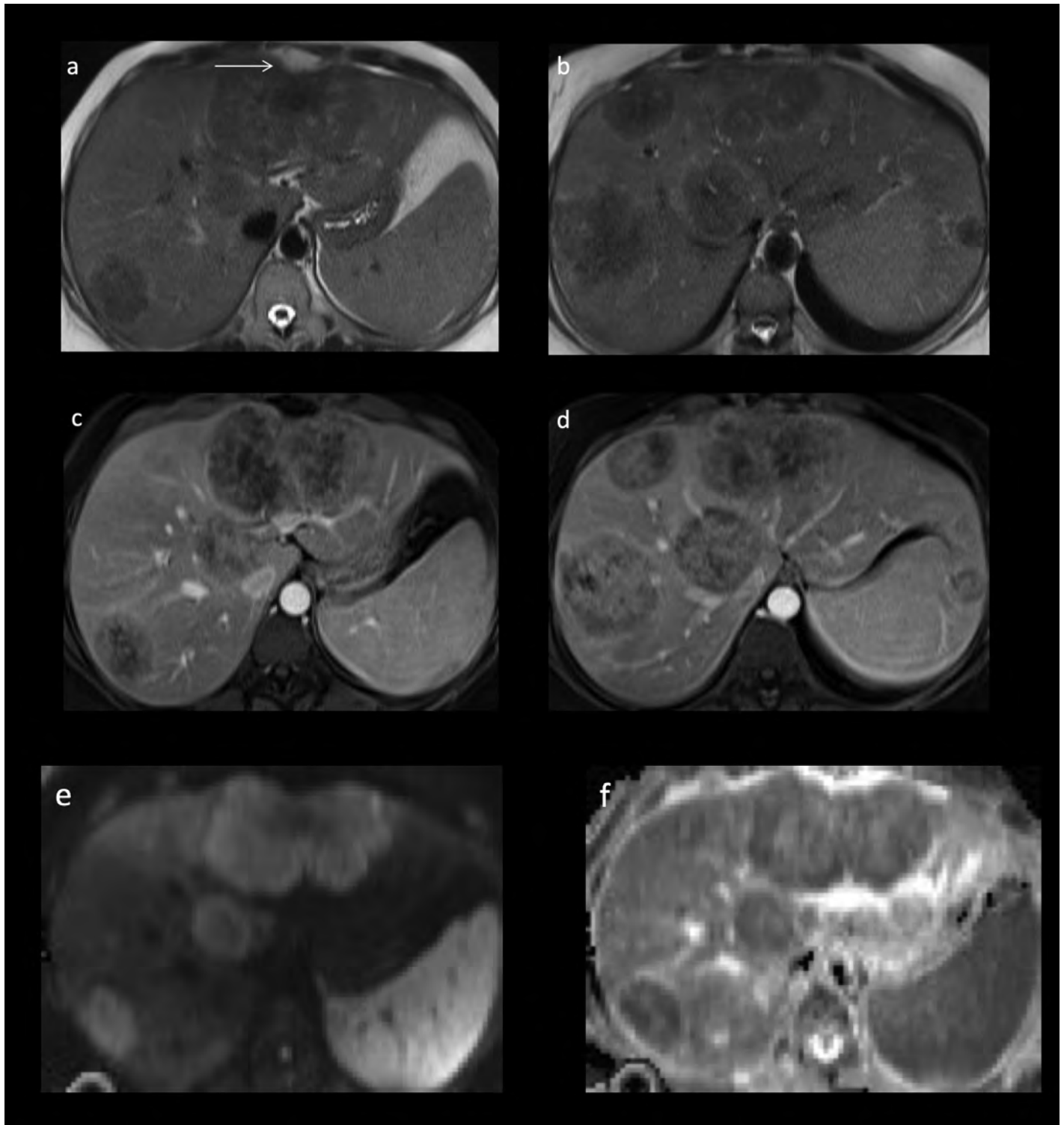


Figure 27-1. Colorectal Metastases. Multiple heterogeneous liver lesions are slightly hyperintense on T2-weighted images (**a, b**) with central hypointensity, corresponding to fibrosis. Capsular retraction is seen adjacent to the greater lesion in the left lobe (arrow). (**c, d**) Gadolinium-enhanced T1-weighted images show ring enhancement with central heterogeneity. (**e, f**) Peripheral restricted diffusion demonstrates higher cellularity. (Images courtesy of Luiza Labrunie, MD, Oncologist Radiologist, National Cancer Institute, Brazil).

Treatment

Surgical Management of Colorectal Metastases

Liver resections are considered the gold standard treatment and can cure the disease. However, only 20-30% of patients can present with potentially resectable lesions at the time of diagnosis.⁽³⁾

Although hepatectomy is considered a safe procedure nowadays, rates of morbidity and mortality are still higher when we compare major hepatectomies with minor resections.⁽⁸⁾ The concept of sparing liver surgery is very important in this scenario. In addition to reducing the possibility of liver dysfunction because it guarantees an adequate future liver remnant (FLR), it also increases the chance of future new resections in case of recurrences, which occur between 60-70%.⁽⁹⁾ To achieve this goal, it is important to preserve the vessels that “enter” in the liver (in-flow) and those that “leave” the liver (“outflow”). Even if it is necessary to sacrifice some of the supra-hepatic veins or even the three, you can perform the parenchyma sparing surgery since exist communicating vessels for the outflow of the liver. **(Figure 27-2)**^(10,11) It is also possible to perform a vascular R1 surgery as there is no impact on overall survival.⁽¹²⁾

Despite the possibility of conservative surgery, radical surgeries may be necessary to achieve a curative treatment, such as two-stage hepatectomy (TSH), Associating Liver Partition and Portal vein ligation for Staged hepatectomy (ALLPS) and ex-situ resections and autotransplantation. The idea of using TSH or ALLPS is to avoid postoperative liver failure (PLF) by ensuring adequate FLR (20% in normal and 30% in cirrhotic livers) through techniques that hypertrophy the FLR. They are quite complex surgeries and with a considerable morbidity and mortality, so they must be carefully indicated.⁽¹³⁾

It is worth remembering that the majority of the patients who undergo these surgeries have undergone previous chemotherapy and may present impairment of liver function by chemotherapy - sinusoidal obstructive syndrome (SOS), associated with the use of oxaliplatin, and chemotherapy-associated steatohepatitis (CASH), associated with the use of irinotecan.⁽¹⁴⁾

Recently the University of Oslo group has advocated liver transplantation for the treatment of unresectable CRLMs. The results appear promising especially when patients are well-selected (CEA <80, the largest tumor <5.5 cm, more than 2 years of disease and response to chemotherapy). However, it is still not considered a standard treatment. **(Figure 27-3)**⁽¹⁵⁾

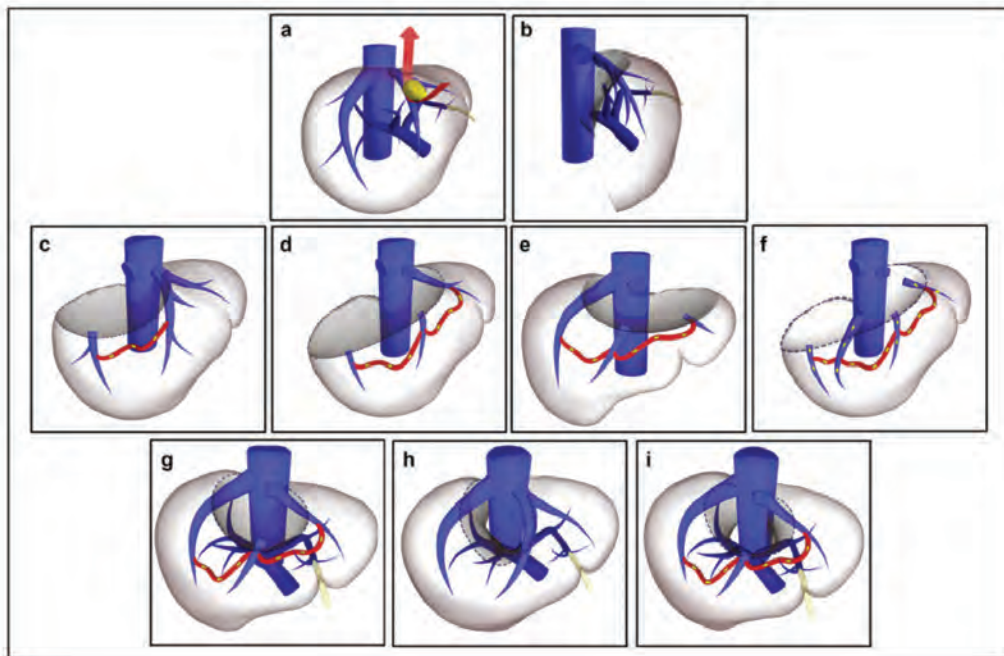


Figure 27-2. Types of “radical but conservative” liver resections. Torzilli G, et al., Twelve-year experience of “radical but conservative” liver surgery for colorectal metastases: impact on surgical practice and oncologic efficacy, *HPB* (2017). <http://dx.doi.org/10.1016/j.hpb.2017.05.006>

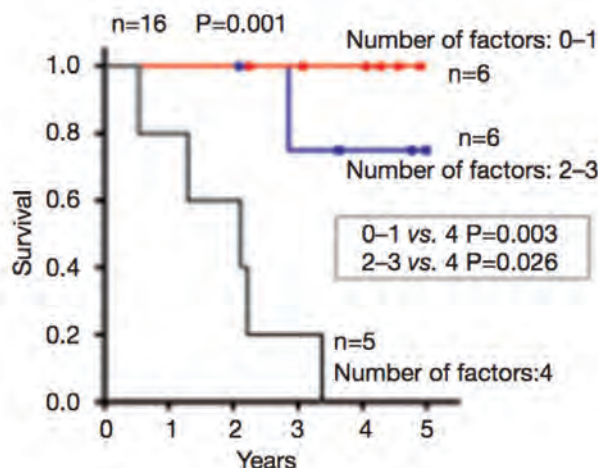


Figure 27-3. Overall survival in CRLM treated with liver transplantation according the number of prognostic factors (CEA > 80, the largest tumor > 5.5 cm, less than 2 years of disease and no response to chemotherapy or progression disease). Andres A, Oldani G, Berney T, Compagnon P, Line PD, Toso C. Transplantation for colorectal metastases: on the edge of a revolution. *Transl Gastroenterol Hepatol* 2018;3:74

When patients present with colorectal cancer and synchronous liver metastases, resection of the primary tumor and liver can be performed in a simultaneous or staged approach (liver or colon first), each case must be individualized.

Local Therapies for Metastases

The standard of care for patients with resectable metastatic disease is surgical resection. If resection is not feasible, image-guided ablation is indicated for small metastases that can be treated with margins. Stereotactic body RT (SBRT) is also a reasonable option.

Tumor Ablation

Ablative techniques include radiofrequency ablation (RFA), microwave (MW) ablation, cryoablation, percutaneous ethanol injection, and electro-coagulation. A small number of older retrospective studies have compared RFA and resection in the treatment of liver metastases. Most of these studies have shown RFA to be relatively inferior to resection

in terms of rates of local recurrence and 5-year OS. Patients with tumor size < 3 cm, the survival outcomes of RFA and LR seems to be identical. ⁽¹⁶⁾

It is important to note that the morbidity of RFA is much lower than LR, so it is an important tool in patients who are not candidates for surgery.

Stereotactic Body Radiotherapy (SBRT)

Stereotactic body Radiotherapy involves precise tumor imaging, RT planning, delivery to a focused target, and motion management for the safe treatment of liver tumors.

The Mayo Clinic demonstrated that SBRT treatment for liver metastasis is an effective and safe treatment. Survival and local control (86%) of patients treated with SBRT is comparable to reported series of surgery and minimally invasive techniques such as RFA. ⁽¹⁷⁾ However, there are no studies comparing SBRT with other local therapies.

Hepatic Arterial Infusion

Consists in a surgical placement of a hepatic arterial port or implantable pump with subsequent infusion of chemotherapy directed to the liver metastases through the hepatic artery. It has been used in the treatment of unresectable colorectal metastases with liver restricted disease. It has shown higher benefit for surgical conversion to surgery than systemic chemotherapy. ⁽¹⁸⁾ There was no superiority in the adjuvant treatment scenario. ⁽¹⁹⁾

Limitations on the use of Hepatic Arterial Infusion include the potential for biliary toxicity and the requirement of specific technical expertise. ⁽²⁰⁾

Neoadjuvant and Adjuvant Chemotherapy

The choice of chemotherapy regimen in the perioperative setting depends on several factors, including the chemotherapy history of the patient, whether disease is synchronous or metachronous, and the response rates and safety/toxicity issues associated with the regimens.

The optimal sequencing of systemic therapy and resection remains unclear. Patients with resectable disease may undergo resection first, followed by postoperative adjuvant chemotherapy. The most common neoadjuvant chemotherapy regimens are FOLFOX (infusional 5-FU, LV,

oxaliplatin, FOLFOXIRI (infusional 5-FU, LV, oxaliplatin, irinotecan) and FOLFIRI (infusional 5-FU, LV, irinotecan). The addition of cetuximab to FOLFOX or FOLFIRI in patients with wild-type KRAS exon 2 increases the resectability rate. ⁽²¹⁾ Data seem to suggest that bevacizumab modestly improves the response rate to irinotecan-based regimens. ⁽²²⁾

During treatment with preoperative systemic therapy, frequent evaluations (every 2 months) must be undertaken to avoid excessive exposure to the preoperative regimen and facilitates an appropriately timed surgical intervention.

Palliative Chemotherapy

The current management of disseminated metastatic colon cancer involves various active drugs, either in combination or as single agents: 5-FU/LV, capecitabine, irinotecan, oxaliplatin, bevacizumab, cetuximab, panitumumab, pembrolizumab, ramucirumab, regorafenib, nivolumab, vemurafenib and ipilimumab. The first line treatment is usually the same as the neoadjuvant treatment regimen with or without targeted agents.

Neuroendocrine Liver Metastases

Metastatic disease is very common in neuroendocrine tumors (ELM), about 65-95% show hepatic metastasis (excluding appendiceal, gastric, and rectal ELM). Indeed, liver metastases represent the most crucial prognostic factor, irrespective of the primary ELM site. ⁽²³⁾ Despite various complex management strategies, surgery is the only treatment that offers potential for cure.

Candidates for LR include: grade 1 or 2 tumors; when no evidence of non-resectable extrahepatic disease exists; type I or II metastatic growth assessable for R0 or R1 resection, when no evidence of advanced carcinoid heart disease exists. The overall survival after hepatic resection is 46–86% at 5 years and 35–79% at 10 years.

Neuroendocrine liver metastases are an accepted indication for LT, because most show low biological aggressiveness and grow slowly. The 5-year overall survival is 36–90% and disease-free survival is 30–77% in single centers. Contraindications for transplantation include poorly differentiated tumors, non-portal system tumor drainage, extrahepatic metastases (apart from perihilar lymph nodes), and severe carcinoid heart disease. ⁽²⁴⁾

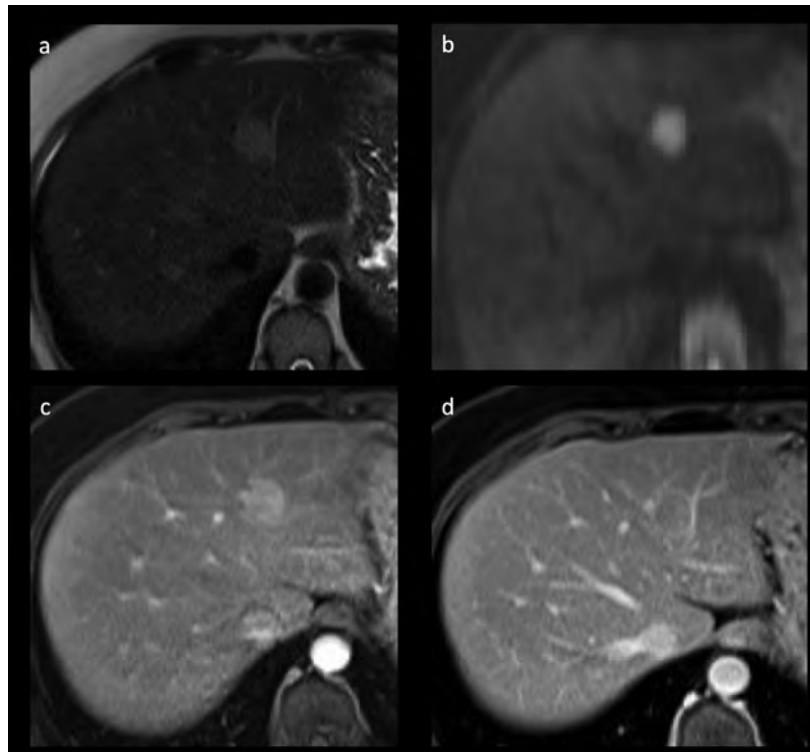


Figure 27-4. Neuroendocrine Metastases. Left liver lobe lesion is (a) moderately hyperintense on T2 weighted images; (b) presents restricted diffusion; and shows (c) arterial enhancement after Gd-based contrast agent administration (hypervascularity) (d) becoming isointense on portal venous phase. (Images courtesy of Luiza Labrunie, MD, Oncologist Radiologist, National Cancer Institute, Brazil).

Non-Colorectal Non-Endocrine Liver Metastases (NCNELM)

Hepatic resection of liver metastases originating from non-colorectal and non-neuroendocrine tumors which have spread via the systemic circulation remains controversial.

Many series report experiences comparable to CRLM (Table 27-1) when appropriate patient selection is performed.^(25,26) Better prognosis has been observed from the resection of small tumors, non-gastrointestinal metastases, an R0 resection margin and a long disease-free interval from the primary disease.⁽²⁷⁾

Table 27-1. Clinical and Survival comparative results for liver resection.						
Length of stay and survival data by pathological classification						
	CLM	HCC	PBC	ELM	NCNELM	Benign
Length of stay	7	10	9.5	8.5	7	6
ICU/HDU stay	1	1	1	1	1	1
90 day mortality	2 (1.1)	3 (4.3)	1 (2.6)	0 (0)	1 (2.1)	1 (11)
Median follow up	31	32	36	21	24	44
1 year survival	94.9	90.0	86.1	95.8	93.1	98.9
3 year survival	74.1	81.8	83.0	67.6	82.8	96.2
5 year survival	57.9	67.3	59.8	67.6	60.8	96.2

CLM, colorectal liver metastases; ELM, neuroendocrine tumours; HCC, hepatocellular carcinoma; ICU/HDU, combined intensive care unit and high dependency unit stay; NCNELM, non-colorectal non endocrine liver metastases; PBC, cholangiocarcinoma and gallbladder carcinoma.

Gandy RC, Bergamin PA, Haghighi KS. ANZ J Surg. 2017 Oct;87(10):810-814. doi: 10.1111/ans.13470. Epub 2016 Mar 31.

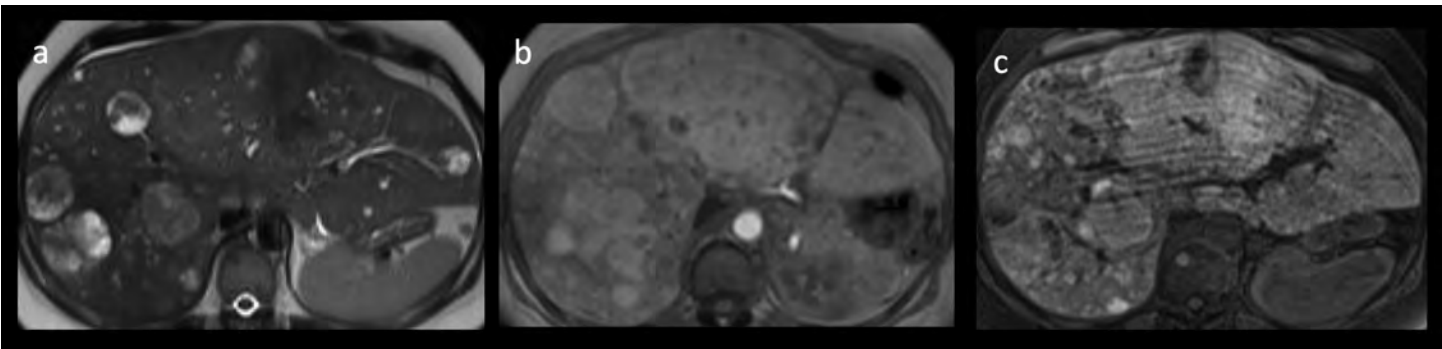


Figure 27-5. Melanoma Metastases. Multiple heterogeneous liver lesions are seen (a) on T2-weighted images with (b, c) typically T1-weighted hyperintensity secondary to melanin and hemorrhage. (Images courtesy of Luíza Labrunie, MD, Oncologist Radiologist, National Cancer Institute, Brazil).

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Chapter 28

Gallbladder Cancer

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Epidemiology

The commonest epithelial type of gallbladder cancer is the adenocarcinoma. The worldwide occurrence of gallbladder cancer (GBC) is less than 2/100000 individuals, but it shows a substantial geographic variation worldwide. Mapuche Indians from Chile show a gallbladder cancer rate as: 12.3/100000 for males and 27.3/100000 for females and American Indians in New Mexico, USA, have also very high average annual rate of GBC (8.9/100000). Other places with high incidence are: China; Northern India (21.5/100000); South Pakistan (13.8/100000); Poland (14/100000). Some regions show intermediate incidence, such as: South Americans of Indian descent (3.7 to 9.1 per 100000), Israel (5/100000) and Japan (7/100000).

Although Gallbladder cancer is more common in females still in some countries like Korea, Iceland and Costa Rica, higher mortality rate has been reported for males as compare to females. ⁽¹⁾

In Brazil GBC and extra-hepatic cholangio carcinoma (EHCC) accounted for 16,808 deaths in the period 2007–2012, and the majority corresponded to women (66.8%). In Uruguay there were 1,058 deaths due to GBC and EHCC during the period 2006–2010, and 63.1% of them were women. In Argentina, GBC and EHCC accounted for 5,262 (1.5%) of all cancer deaths in the period 2007–2011. ⁽²⁾

A North American study conducted by Liu C. *et al.* from a National Cancer Database found no difference in overall survival (OS) for GBC patients with Hispanic ethnicity, but this is not a consensus. ⁽³⁾ Another study comprising 7,507 patients with GBC, from the 2000–2013 Surveillance,

Epidemiology and End Results (SEER) from 18 registries in the US, showed that, in spite of the lack of differences in staging at presentation, blacks and Hispanics were less likely to receive curative surgery and optimal lymph node (LN) clearance than whites. ⁽⁴⁾

Nevertheless, the ominous prospect of GBC does not seem to spare developed health systems. There has been no improvement in the overall survival rate in between 2000–2014 in Sweden, despite the improvement in diagnosis and staging. ⁽⁵⁾

Ethiology

Distinct risk factors have been associated with the development of GBC, such as: age (above 50y), female gender, genetic background, chronic cholecystitis (70%), red chili pepper consumption and aflatoxin and typhoid disease. Some differences in term of RAS, TP53, FHIT and p16 genes abnormalities have been found in GBC from South America compared to tumors from other regions. ⁽²⁾ Adenomatous polyps are considered pre-neoplastic lesions. ⁽⁶⁾

The American Hepato-Pancreato-Biliary Association (AHPBA), sponsored consensus meeting of expert panelists in 2014 recommended the resection of all gallbladder polyps of >1.0 cm in diameter and those with imaging evidence of vascular stalks. ⁽⁷⁾

Other known associated risk factors are: porcelain gallbladder, abnormal implantation of the biliary ducts. ⁽⁸⁾

Diagnosis

Diagnosis of GBC is made in different clinical circumstances. Unexpected GBC may be found in between 0.4% to 1% of cholecystectomies. ⁽⁹⁾ An experienced radiologist can usually differentiate a cholesterol polyp from an adenomatous one, but in difficult cases the use of contrast-enhanced ultrasound may help in the differential diagnosis of malignant and benign lesions. ⁽¹⁰⁾

Within high incidence areas, the assessment of routine gallbladder specimens should include the microscopic evaluation of a minimum of three sections and the cystic duct margin; specimens with dysplasia or proven cancer should be extensively sampled. The minimum staging evaluation

of patients with suspected or proven gallbladder cancer includes contrasted cross-sectional imaging and diagnostic laparoscopy. Adequate lymphadenectomy includes assessment of any suspicious regional nodes, evaluation of the aortocaval nodal basin, and a goal recovery of at least six nodes. ⁽⁷⁾

In others instances the patient will present with upper abdominal pain, icterus and cholestasis and liver mass, with or without associated gallstones (ALOYA). In such cases the collaboration between surgeon and radiologist is crucial. CT scans and MRI are usually diagnostic of advanced GBC, but in a few doubtful cases a preoperative biopsy might be necessary for histological analysis before defining treatment strategy. ⁽¹¹⁾

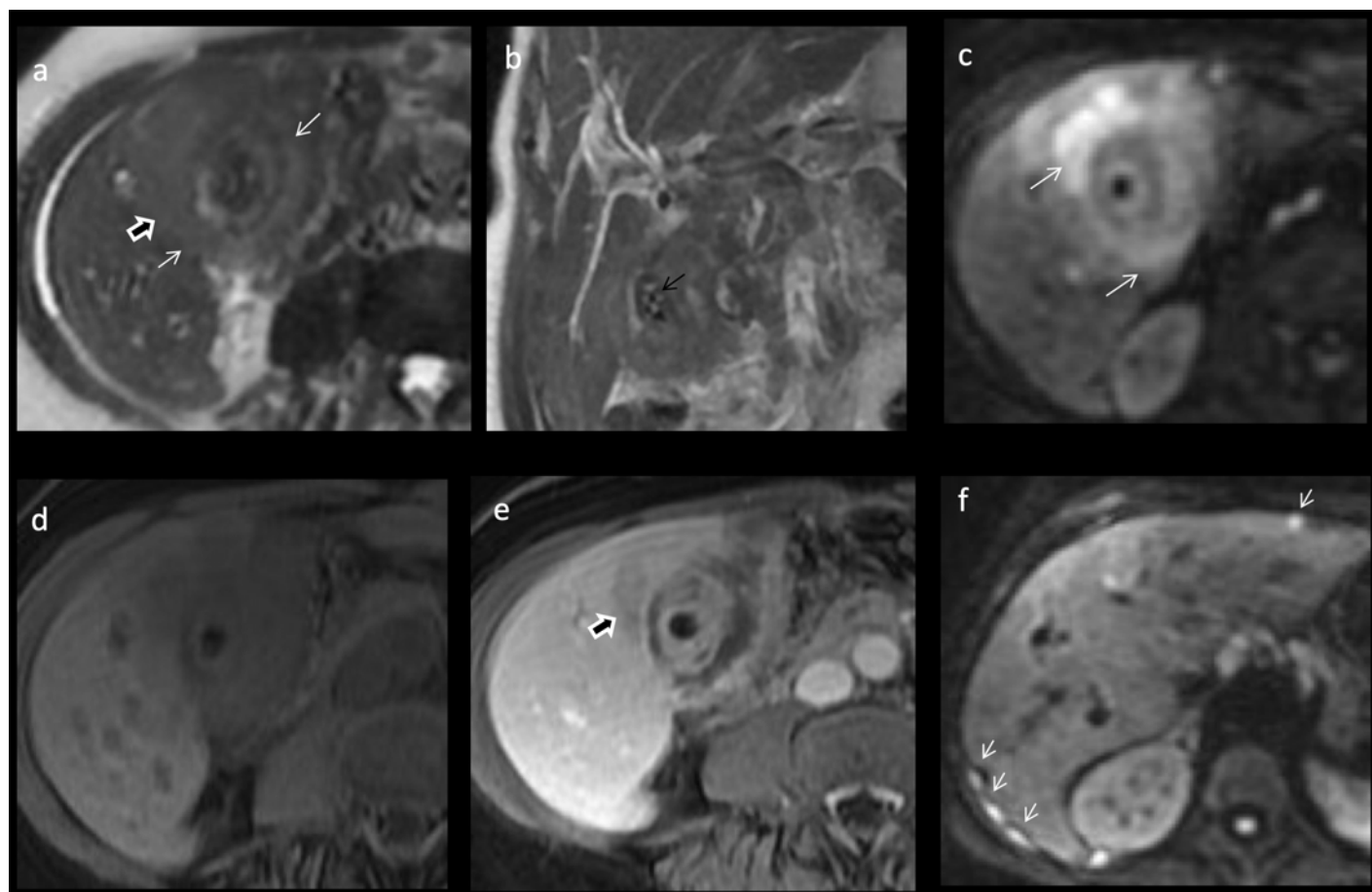


Figure 28-1. Gallbladder cancer radiological images.

- (a) axial e (b) coronal T2-weighted images show cholelithiasis (black arrow) and mural thickening (white arrows). Invasion of the hepatic parenchyma can be seen (open arrow).
- (c) Diffusion restriction helps differentiate malignancy from chronic inflammation. T1 fat-suppressed images.
- (d) before and (e) after gadolinium administration show heterogeneous enhancement, fat infiltration and liver invasion (open arrow).
- (f) Peritoneal metastases are seen on DWI.

(Images courtesy of Luiza Labrunie, MD, Oncology Radiologist at National Cancer Institute, Brazil).

Staging

Primary Tumor (pT) ⁽¹²⁾

Diagnosis of GBC is made in different clinical circumstances. Unexpected GBC may be found in between 0.4% to 1% of cholecystectomy

TX: Primary tumor cannot be assessed.

T0: No evidence of primary tumor.

Tis: Carcinoma *in situ*.

T1: Tumor invades lamina propria or muscular layer.

T1a: Tumor invades lamina propria.

T1b: Tumor invades muscular layer.

T2: Tumor invades the perimuscular connective tissue on the peritoneal side, without involvement of the serosa (visceral peritoneum) or tumor invades the perimuscular connective tissue on the hepatic side, with no extension into the liver.

T2a: Tumor invades the perimuscular connective tissue on the peritoneal side, without involvement of the serosa (visceral peritoneum).

T2b: Tumor invades the perimuscular connective tissue on the hepatic side, with no extension into the liver.

T3: Tumor perforates the serosa (visceral peritoneum) or directly invades the liver or one other adjacent organ or structure, such as the stomach, duodenum, colon, pancreas, omentum or extrahepatic bile ducts.

T4: Tumor invades the main portal vein or hepatic artery or invades two or more extrahepatic organs or structures.

Regional lymph nodes (pN) ⁽¹²⁾

NX: Regional lymph nodes cannot be assessed

N0: No regional lymph node metastasis.

N1: Metastasis in 1 - 3 regional lymph nodes.

N2: Metastasis in 4 or more regional lymph nodes.

Note: Regional lymph nodes include the common bile duct, hepatic artery, portal vein and cystic duct nodes.

Distant Metastasis (pM) ⁽¹²⁾

M0: No distant metastasis.

M1: Distant metastasis.

Stage Grouping ⁽¹²⁾

Table 28-1. Staging grouping			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2a	N0	M0
Stage IIB	T2b	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T1 - 3	N1	M0
Stage IVA	T4	N0 - 1	M0
Stage IVB	any T	N2	M0
	any T	any N	M1

Prognosis

The 5-year survival rate for gallbladder cancer is 5% and a median survival of 12 months. Survival in GBC, as for all other malignancies, is multifactorial and staging reflects it. Jaundiced patients usually reflect an advanced stage of disease and these patients experience half of the OS of those without it, as well as higher postoperative morbidity, bile leak and postoperative liver failure rates. ⁽¹³⁾

The 5-year survival rate for Stage 0 gallbladder cancer is 80%. Stage I 5-year survival rate is 50%. If the cancer has spread to the lymph nodes, the 5-year survival rate is between 7% and 8% and for Stage IV disease it is 4% or less. ⁽¹⁴⁾ Resectability is a condition for any hope of long term survival and most specifically negative margin (R0) resection in the absence of perineural invasion. Grade, lymph node metastasis and adjuvant chemotherapy are related with disease free survival (DFS). ⁽¹⁵⁾

Tumor located on hepatic side, advanced AJCC Cancer Stage and carcinoembryonic antigen (CEA) >98.91 U/ml were independent determinants of resectability in patients with GBC in a study conducted by Liu *et al.* ⁽¹⁶⁾ Neutrophil-lymphocyte ratio and elevated CEA have been significantly associated with worse OS. Neutrophil-lymphocyte ratio (NFR) seems to be a better prognostic factor than CEA in advanced (T3-T4) stage patients, while CEA is better for early (T1-T2) stages, early N0-1 and M0 stages. ⁽¹⁷⁾ Perioperative transfusion is another independent of OS and RFS after resection for GBC. ⁽¹⁸⁾

Studying CD8+ TILS density and the expression of PD-1, PD-L1, PD-L2 and CD 133 with immunohistochemistry in tumor specimens Lin *et al.* have concluded that PD-L1+ expression is related to worse OS and CD8high indicates better OS and PFS. ⁽¹⁹⁾

In the absence of an efficient survival prediction model for GBC Yifan *et al.* have proposed a nomogram-based prediction model composed of CA 19-9 and pathological characteristics that has a better predictive capacity compared with conventional tumor staging systems. ⁽²⁰⁾

Curative Treatment

Surgery is the only chance for cure in the early stages but only 20% of the cases are suitable for resection at presentation. Laparoscopic approach is an option in specialized centers for T1-T2 disease. In fact, laparoscopy helps avoiding futile laparotomies and should be the initial procedure under the suspicion of an advanced case.

Early T-stage (T1b-2) disease should include in bloc resection of adjacent liver parenchyma and liver pedicle lymphadenectomy. ⁽⁷⁾ The recommendation that at least 6 (six) lymph nodes should be resected has been validated and seems to improve survival for N0 GBC. Patients with preoperatively staged T3 or T4 N1 disease should be considered for clinical trials of neoadjuvant chemotherapy. ⁽²¹⁾

AJCC specialist panel consider that patients with N2 nodal metastases do not benefit from radical resection and should receive systemic and/or palliative treatments. Nevertheless, Chaudhary *et al.* have concluded that 1 to 3 13A positive node (superior retro pancreatic lymph node) does not worsen the prognosis in a T1/T2 GBC and should be treated as a N1 disease. ⁽²²⁾

Incidentally identified T1b, T2 or T3 cases in cholecystectomy specimens should undergo re-resection unless this is contraindicated by advanced disease or poor performance status. Re-resection should include complete portal lymphadenectomy and bile duct resection only when needed to achieve a negative margin (R0) resection. ⁽⁷⁾

A population based retrospective study has demonstrated that there is no benefit for reoperation for lymphadenectomy for T1a disease. ⁽²³⁾ Resection of bile duct for advanced GBC without biliary infiltration has not increased OS and DFS. ⁽²⁴⁾

R0 Hepatopancreatoduodenectomy is an acceptable indication for extensive extrahepatic biliary invasion in highly selected cases because it has been associated with 68% morbidity rate and variable postoperative death rate. Lee EC *et al.* have obtained a 25% survival rate for GBC patients.

Patients with preoperatively staged T3 or T4 N1 disease should be considered for clinical trials of neoadjuvant chemotherapy. ⁽²⁵⁾ Following R0 resection of T2-4 disease in N1 gallbladder cancer, patients should be considered for adjuvant systemic chemotherapy and/or chemoradiotherapy. ^(7, 26)

Adjuvant treatment with Capecitabine (BILCAP randomized study) aimed to determine whether capecitabine (Cape) improves overall survival (OS) compared to observation (Obs) following radical surgery.

Patients with completely resected cholangiocarcinoma (CCA) or gallbladder cancer, with adequate biliary drainage, no ongoing infection, adequate renal, hematological and liver function, and ECOG PS ≤ 2 , were randomized 1:1 to Cape (1250 mg/m² D1-14 every 21 days, for 8 cycles) or observation.

The 447 participants were randomized to Cape (n = 223) or Obs (n = 224) from 44 UK sites between 2006-2014. Primary site: 84 (19%) intrahepatic, 128 (28%) hilar, 156 (35%) extrahepatic CCA and 79 (18%) muscle-invasive gallbladder cancers. Resection margins: R0 in 279 (62%) and R1 in 168 (38%); 207 (46%) were node-negative. Follow up was at least 36m in > 80% of surviving patients. By ITT analysis (n = 447), median OS was 51m (95%CI 35, 59) for Cape and 36m (95%CI 30, 45) for Obs, HR 0.80 (95%CI 0.63, 1.04; p = 0.097). Median RFS was 25m (95%CI 19, 37) for Cape and 18m (95%CI 13, 28) for Obs. Grade 3-4 toxicity was less than anticipated. The researchers concluded that Cape improves OS in BTC when used as adjuvant and should become standard of care. ⁽²⁷⁾

Other publications support the use of adjuvant therapy for stage II and II GBC. ⁽²⁸⁾ Patients with preoperatively staged T3 or T4 N1 disease should be considered for clinical trials of neoadjuvant chemotherapy. ⁽²¹⁾

Advanced disease that responds to neoadjuvant chemotherapy and is treated with curative surgical resection may experience good survival (49 vs months). ^(22, 29)

The role of radiation therapy for advanced GBC is controversial.

Follow Up

Follow up should be performed with CT comprising the thorax and whole abdominal cavity and dosage of CA 19-9 and CEA every 3 months.

Systemic recurrence is more common than locoregional recurrence (78.5% vs 21.5%).²⁶ For recurrent cases

palliative strategies comprising radiation therapy, chemotherapy, immunotherapy and surgery is association or not may be planned on individual basis.⁽³⁰⁾ Other patients may only stand palliative measures such as biliary drainage, duodenal stenting and pain management.



Figure 28-2. Incidental finding of Gallbladder Cancer

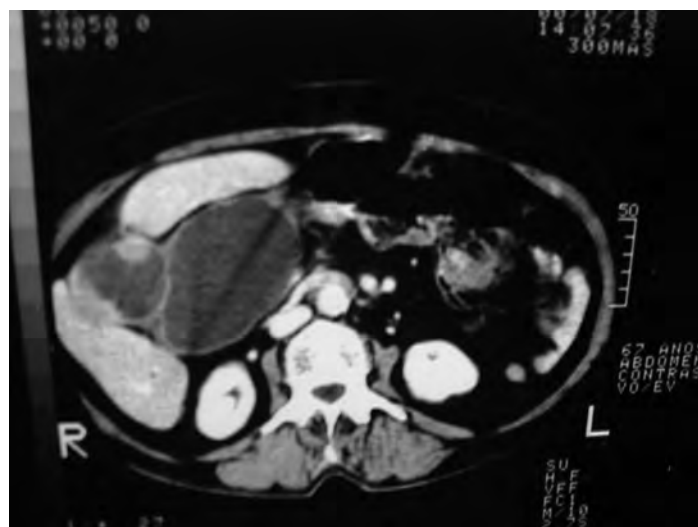


Figure 28-3. CT slice showing a contrast enhanced vegetation in the gallbladder wall.



Figure 28-4.A. Operative aspect of liver resection delimitation with involved stomach segment attached to the gallbladder.



Figure 28-4.B. Operative aspect of liver resection delimitation with involved stomach segment attached to the gallbladder.

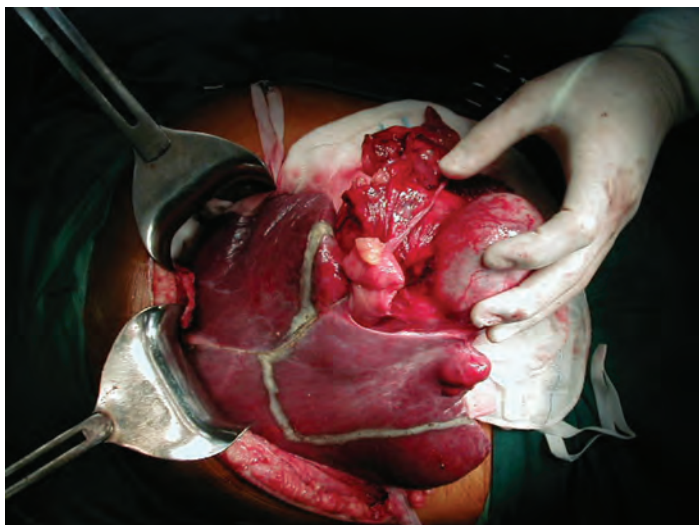


Figure 28-4.C. Operative aspect of liver resection delimitation with involved stomach segment attached to the gallbladder.

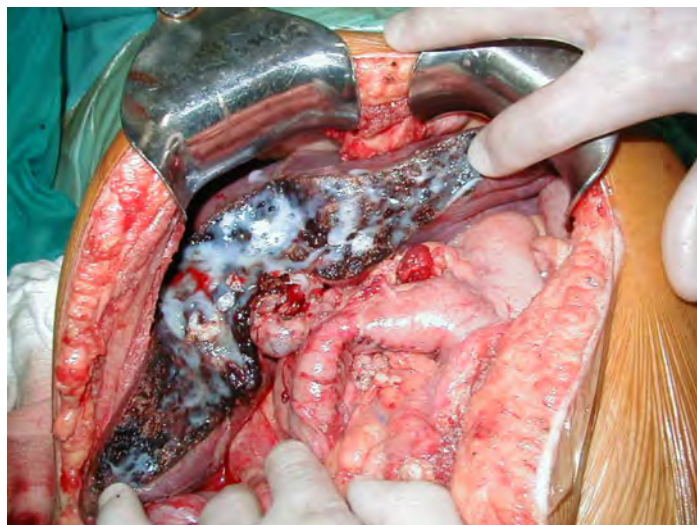


Figure 28-5. Final operative aspect of central hepatectomy plus atipic gastrectomy.



Figure 28-6. Open gallbladder specimen with malignant vegetation.

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Chapter 29

Cholangiocarcinoma

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Introduction

It is a rare malignancy originated from the biliary epithelium. It was first described by Durand-Fardel in 1840. This type of tumor can derive from any part of the biliary tract, and it has been classified according to its anatomical location. It is divided in intrahepatic, peri-hilar and extrahepatic. Intra-hepatic lesions are either peripheral mass-forming types that are located proximally to the second degrees bile ducts. Peri-hilar and distal tumors are periductal infiltrating lesions.

Peri-hilar lesions are located between the second degree bile ducts and the cystic duct and distal tumors are those encountered below the cystic junction and the ampulla of Vater.

Tumors at the biliary bifurcation or the hilar region was first described by Gerald Klatskin in 1965 and take its name nowadays. Peri-hilar lesions are the most common types, occurring in around 60-70% of cases (5-10% intrahepatic and 20-30% distal extrahepatic).

Surgical resection is the most effective form of treatment and the only chance for cure. However, many patients present with advanced disease at time of diagnosis. In cases where surgical resection is no longer possible, patients have 6 months to one-year survival and most die of hepatic failure or cholangitis because of biliary obstruction, although palliative measures.

The incidence in the United States is 1-2 cases per 100 people, with around 3,000 new cases annually. Clinical presentation uses to be at 60 years of age, with a male to female ratio of 1,5:1.

Biliary adenocarcinoma develops from premalignant and non-invasive lesions that occur as biliary tract dysplasia.

Two main types of precursors lesions have been proposed: flat or low-papillary dysplastic lesion, biliary intra-epithelial neoplasia (bilIN) and macroscopic lesion, the intraductal papillary neoplasm of the bile duct (IPN-B). Two other less common precursor lesions are: biliary mucinous cystic neoplasms (B-MCNSs) and intraductal tubular neoplasms (ITN-Bs).

Most part of these biliary tumors are adenocarcinomas (>90%). Other types are variants with signet cell ring, papillary and intestinal cells, clear cells, adeno-squamous and squamous cells. It is part of a group of slow growing, invasive type of tumors, with a potential of rapidly progression. They present a subepithelial tumoral extension and characteristically possess neural, perineural and lymphatic diffusion routes, which turns lymphonodal metastasis a common finding, while distant metastasis a rare finding.

There are 3 distinct morphological subtypes: sclerosing, nodular and papillary. Sclerosing types are predominant, 90% of the cases, and mostly they occur at the hilar region. They have firm consistency and generate an intense desmoplastic reaction, leading to technical difficulties during surgical resection, because of portal vein and hepatic artery tumoral invasion.

Nodular tumors consist of firm nodules that project inside the biliary ducts. A combined presentation of these two types is (nodular-sclerosing). In contrast, papillary subtype has a soft and frail consistency, and presents a well-defined base, occurring more commonly in the distal part of the biliary tree, and counts for less than 10% of all cholangiocarcinomas. It presents a great chance of surgical resection and a more favorable prognosis. ⁽¹⁻⁷⁾

Risk Factors

- Primary sclerosing cholangitis
- Ulcerative colitis
- Hepatolithiasis
- Bilio-enteric anastomosis
- Parasitary infestations – *Clonorchis sinensis*
- Bacterial infections – salmonella - typhoid fever carriers
- Congenic biliary cystic diseases – Caroli diseases and choledocal cysts
- Toxic compounds – torio dioxide and nitrosamines

Risk factors common characteristics are: biliary stasis, chronic inflammation due to ductal lithiasis and infection. ^(4,7,8)

Clinical Presentation

Most frequent clinical presentation is gradual and progressive icterus and pruritus. Other symptoms as fatigue, anorexia, mild right upper quadrant pain, weight loss, and sings of hepatic insufficiency may also be present. Hepatomegaly can be a finding in physical examination. Darker urine and clearer stool are also present, and they become more intense as total blood bilirubin levels rise. Fever, chills and biliary colics can be the initial symptoms in 10% of cases, but generally only occur in patients submitted to prior biliary manipulations. Generally, in tumors of the biliary confluence, the gallbladder is empty, but it can be palpable if there is tumoral extension to the cystic duct or in cases of distal tumors. Occasionally, it is found in asymptomatic patients are in clinical investigation of elevated blood levels of alkaline phosphatase or gamma-glutamy- transferase. However, most patients present with advanced disease, when surgical treatment is no longer possible. Most common tumor marker related to cholangiocarcinomas is CA19-9, but elevations of this tumor marker can also be seen with choledocholithiasis, cholangitis, pancreatic, gastrointestinal and gynecologic tumors.

Imaging Studies

Initially an ultra-sonography or a CT-scan tend to be the first imaging studies performed. In peri-hilar tumors, they will show a dilated intra-hepatic biliary tree, with non-dilated

gallbladder and distal bile duct. Distal cholangiocarcinoma will present with dilation of the entire biliary tree including the gallbladder. Ultra-sound can establish the level of the obstruction and exclude the presence of lithiasic biliary disease as the cause of obstruction. Multislice helical CT-scan shows the extent of the disease, identifies vascular invasion of portal or arterial branches that irrigate the liver, enlarged lymphonodes and possible distant metastasis. It can also calculate hepatic volumetry, which helps in the surgical strategy. Biliary anatomy and tumor extension are better evaluated by magnetic resonance studies. In cases of distal obstruction, the concomitant presence of main pancreatic duct obstruction favors a pancreatic tumor etiology. Endoscopic ultra-sound is a good option for loco-regional evaluation of these tumors, and still allows a fine-needle biopsy of the distal biliary lesions. More recently, a direct visualization of the biliary tree, using a very thin endoscope through ERCP can be very useful in cases of distal obstruction, when the diagnosis is not clear after the previous imaging studies. ^(9, 10)

Differential Diagnosis

- Choledocolithiasis
- Sclerosing cholangitis
- Hepatitis
- Mirizzi syndrome
- Hepatic metastasis
- Cholangiopathy or portal cavernoma
- Gallbladder cancer invading the biliary tree

Staging

A good pre-operative staging allows the surgeon to plan the best form of treatment for each patient. This treatment can vary from surgical resection of the tumor to just a palliative either endoscopic, percutaneous or even surgical drainage. The analysis of the pre-operative images allows the evaluation of the extent of biliary tumor, exclusion of distant metastases, the presence or not of vascular invasion, portal or arterial and the presence of lobar liver atrophy.

In non-resectable cases, a histopathological confirmation is mandatory for the beginning of palliative chemo or radiation therapy.

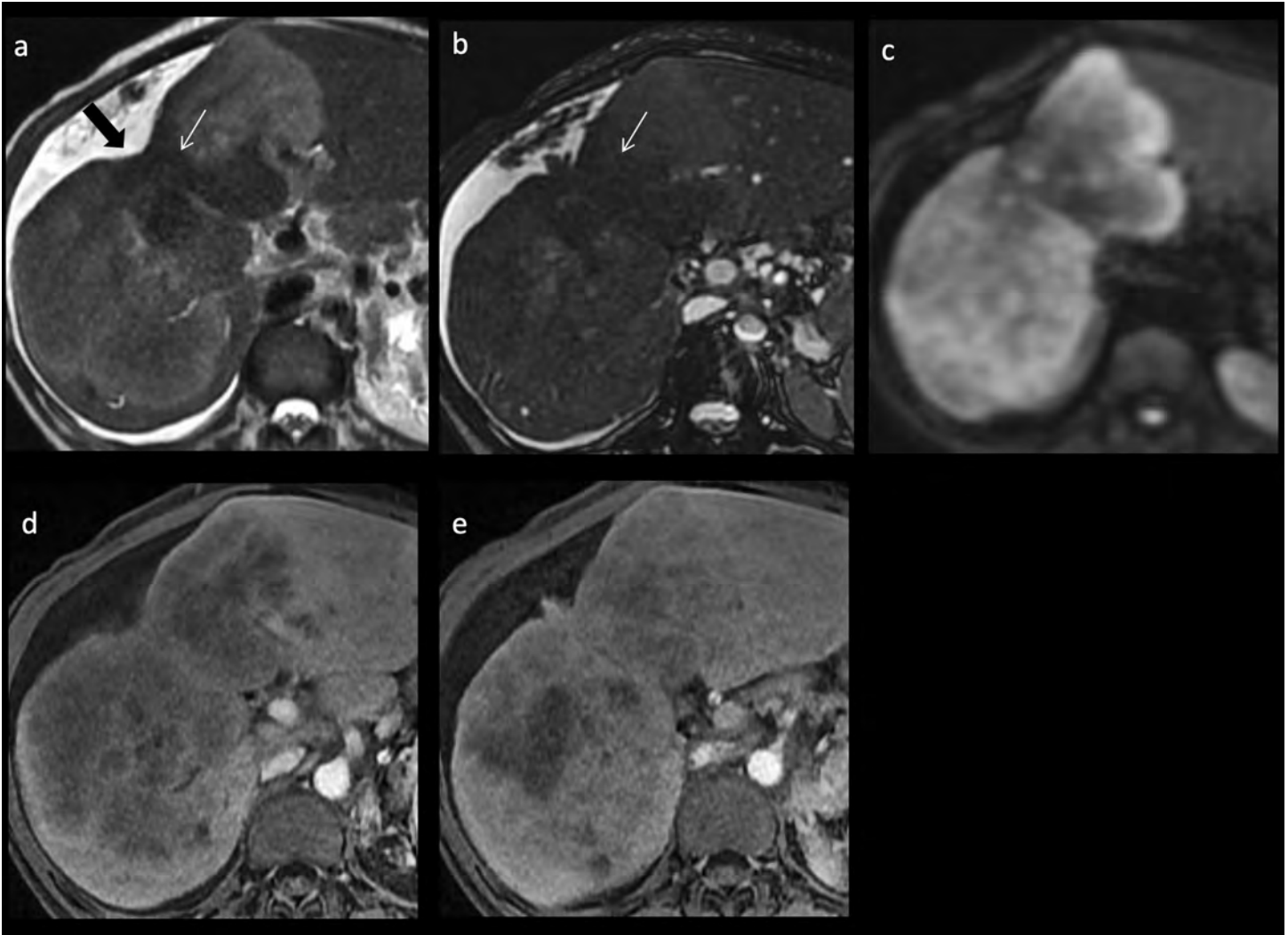


Figure 29-1. Cholangiocarcinoma. Large hepatic mass is:
 (a, b) slightly hyperintense on T2-weighted images with central hypointensity (white arrows) corresponding to fibrosis, associated with capsule retraction (black arrow).
 (c) Peripherally hyperintensity on DWI (“target” appearance) due to higher cellularity in the peripheral and central fibrosis. Gadolinium-enhanced T1- weighted images show,
 (d) heterogeneous minor peripheral enhancement on arterial phase and
 (e) gradual centripetal enhancement on delayed phase.
 (Images courtesy of Luiza Labrunie, MD, Oncologist Radiologist, National Cancer Institute, Brazil).

A biliary drainage is needed in all patients with dilated bile ducts. A complete excision of a Klatskin tumor will require an extended resection and usually it can only be safely done with previous proper biliary drainage and portal vein embolization.

Surgical Treatment

Surgical resection is the only potentially curable form of treatment for cholangiocarcinoma. With the improvement of surgical and anesthetic techniques and post-operative care, surgical mortality has reduced dramatically and

surgical results have improved along the last few decades. The decision for surgery should be taken in the context of a multidisciplinary team meeting, in a specialized multidisciplinary center for treatment of liver cancer. This meeting evaluation includes criterious evaluation of the patient's morbid conditions and performance status; revision of the imaging studies; evaluation of resectability and resection margins; the need for an hepatectomy and its extent; calculation of volumetry and the future liver remnant volume. Portal embolization may be necessary to induce hypertrophy of the remnant liver lobe, attaining a 30% volume for the liver remnant and therefore, decreasing the chance of post-operative liver failure. In cases of extended hepatectomies, it is mandatory to pre-operatively drain the biliary tree, since elevated bilirubin levels enhances liver suffering and impairs its regeneration. This type of biliary drainage is generally obtained through a percutaneous transhepatic biliary drainage (PTBD) and bile is sent for culture.

Intra-Hepatic Cholangiocarcinoma

Isolated hepatic resection with negative margins associated with hepato-celiac lymphadenectomy is enough.

Hilar Cholangiocarcinoma

It consists of a complex operation. The resection guideline was proposed by Bismuth and Corlette in 1975 (**Figure 29-2**) and is still followed nowadays. The association of hepatic parenchymal resection was proposed by Launois in 1979 and increased survival and resectability rates for these types of tumors. In 1982 Makuuchi introduced portal embolization as a form of hepatic failure prevention after major hepatectomies. Nimura proposed the concept of routine caudate lobe resection in 1990, in order to reduce tumoral recurrence after surgical resection.

Surgical exploration should be proposed to all patients considered potentially resectable by imaging studies. Laparoscopy can be proposed to exclude the presence of peritoneal carcinomatosis, since it is not so well visualized by pre-operative imaging studies, unless there is bulky peritoneal disease and ascites. Bile duct margins should always be evaluated by frozen section analysis.

For type I tumors, biliary resection associated with hepato-celiac lymphadenectomy with 'Roux-en-Y' reconstruction is indicated.

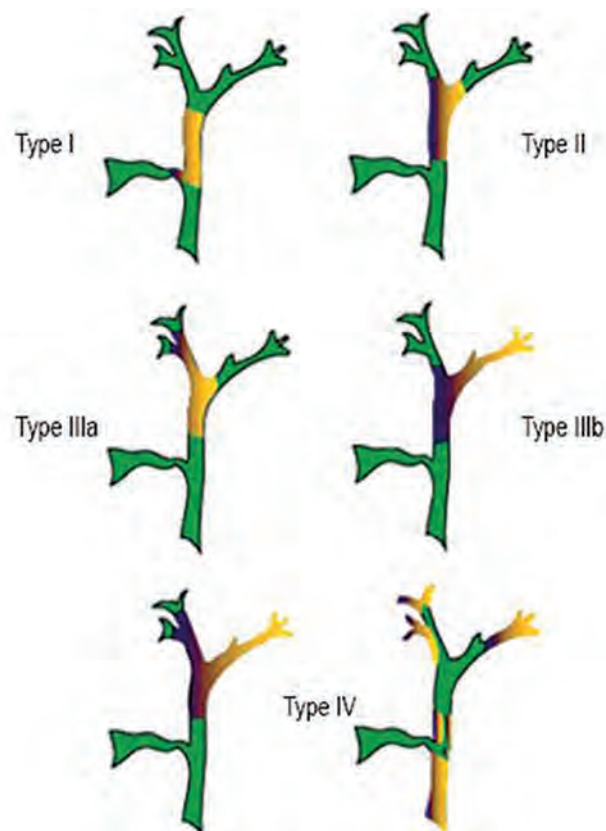


Figure 29-2. Bismuth-Corlette classification of perihilar cholangiocarcinomas. The yellow or purple areas represent the tumors. Green areas are normal.

Type I: Below the hepatic confluence.

Type II: involvement of the confluence. **Type IIIa and IIIb:** involvement of the confluence and the right lobe (a) or left lobe (b); and **Type IV:** Tumor in both hepatic lobes, multicentric.

(Image courtesy of Prof. Henri Bismuth).

For type II, biliary resection must be accompanied by liver parenchymal resection. Segments 4B and I must be included, because there can be tumor invasion to its biliary branches. Also, regional lymphadenectomy should be performed too. Biliary reconstruction is carried with a 'Roux-en-Y' anastomosis to the left and right hepatic ducts. Another option is to perform a right extended hepatectomy, including segments 4 and I, and thus performing a single bilio-enteric anastomosis, at the level of the left hepatic duct. In this case, a precedent PVE is demanded.

For types IIIa and IIIb, an extended right or extended left hepatectomy plus caudate lobe resection, followed by regional lymphadenectomy and 'Roux-en-Y' bilio-enteric anastomosis is indicated.

For type IV sparing segments II and III, radical resection may still be possible. If that is not the case, during laparotomy, a surgical palliation can be performed with an intra-hepatic bilio-enteric anastomosis at the bile duct of liver segment 3. However, a bilateral transhepatic external biliary drainage is the preferable choice.

Also, few patients without distant metastases can be candidates for multidisciplinary treatments including liver transplantation, in the context of formal clinical studies in specialized centers.

Distal Cholangiocarcinoma

Patients that normally do not present any surgical contraindications are submitted to pancreato-duodenectomy with regional lymphadenectomy. It is important to evaluate bile duct proximal margin by frozen section analysis. When surgical exploration reveals an irresectable case, surgical palliation must be made. Normally a hepaticojejunostomy in “Roux-en-Y” or “Omega” is performed and a gastric bypass. ^(1,11-19)

Palliative Treatment

This form of treatment is offered to patients with inoperable tumors and to those that cannot be submitted to surgical treatment due to poor clinical status. Palliative treatment consists mainly of biliary tree drainage. It can be performed either by endoscopy or percutaneous transhepatic under ultrasound or radioscopic guidance. Standard of care is the use of internal drainage, so the bile can flow to the digestive tract again. Stents can be either plastic or self-expansive metallic, but metallic are preferred over plastic ones for they have a longer patency and less episodes of cholangitis, they migrate less and have a lower rate of a secondary drainage, but they cost more. Plastic stents have a smaller diameter, occlude faster, and present a shorter patency interval, around 3 months. They are chosen when there is a short expectancy of life or when surgical decision is made, but bilirubin levels are too high for prompt operation. They are easier to remove than metallic stents. There is no consensus about the need of the use of multiple stents or just one. However, the drainage of more than 50% of the liver parenchyma promotes higher long term quality of life. When it's about patients with associated cholangitis, the drainage of all obstructed liver segments is beneficial. Surgical drainage of segment 3 duct is reserved for those patients taken to laparotomy with curative intent, but they judged non-operable at the operation. This form of drainage

resolves icterus in about 66% of patients. Radiotherapy has a limited role in cholangiocarcinoma patients. Gemcitabine based chemotherapy is used in adjuvant setting for R1 resections (or positive lymphnodes) or as palliation for R2 or unresectable patients. New forms of treatment consisting of dynamic phototherapy and radiofrequency ablation to reduce occlusion stents rates have been proposed. ⁽²⁰⁻²³⁾

Follow up

Post-operative follow-up is made with CT of the thorax and abdomen plus cholangio MRI and serum CA19-9 every 6 months in the first two years and then annually.

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Chapter 30

Hepatoblastoma

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Introduction

Hepatoblastoma is the most common malignant liver tumor and the third most common intra-abdominal neoplasm in children in Western countries, comprising approximately 1% of malignant neoplasms among children less than 20 years of age. The incidence rates of 8.7 and 5.1 cases per 1,000,000 children less than 1 year and 1–4 years of age. ^(1,2,3,4,5,6,7)

Overall, survival has significantly improved from 35 to 83 % over the last four decades due to advances in chemotherapy. ⁽¹⁾ Hepatoblastoma is a rare embryonal tumor of early childhood, with five histologic subtypes: pure fetal, embryonal, mixed epithelial, mesenchymal/macrotrabecular, and small cell undifferentiated - fetal carries the most favorable prognosis, while small cell undifferentiated the worst. ^(5,6)

Thus far, no environmental risk factors for HB have been described, but HB has been associated with prematurity or a low birth weight. ^(5,7) Medications such as furosemide, total parenteral nutrition, oxygen therapy, radiation, plasticizers and other toxins are postulated to play a role, but no hypothesis for the exact mechanisms is currently available. ⁽⁷⁾

Historically, four separate cooperative multicenter trial groups have undertaken the systematic treatment studies of this disease: the International Childhood Liver Tumor Strategy Group (SIOPEL); the Children's Oncology Group (COG), and its legacy groups the Children's Cancer Group (CCG) and the Pediatric Oncology Group (POG); the German Society for Pediatric Oncology and Haematology (GPOH); and the Japanese Study Group for Pediatric Liver Tumors (JPLT). ^(4,8)

These four groups (SIOPEL, COG, GPOH and JPLT) embarked on an effort to merge the data collected in the conduct of eight clinical trials into one database for analysis, creating the Children's Hepatic tumors International Collaboration (CHIC). ⁽⁴⁾

Diagnosis

Ultrasonography, chest radiography, and alpha-fetoprotein (aFP) levels in the blood were the first diagnostic tools used in all children with a suspicious abdominal mass. ⁽⁶⁾

The serum alpha-fetoprotein (AFP) level is elevated in 90% of children with hepatoblastoma and tumors that fail to express AFP at diagnosis are felt to be biologically more aggressive. ⁽⁶⁾

Ultrasound will identify the liver as the organ of origin; additional testing is aimed at distinguishing benign from malignant disease.

Abdominal CTscan, CTangiography, and/or MRI outline the anatomic extent of the tumor, clarify its relationship to the central venous structures, and evaluates for multicentricity. ⁽⁶⁾ CT has fallen from favor over the last decade because of its reliance on ionizing radiation. However, this modality still plays a role in the imaging assessment of pediatric liver tumors. ⁽⁹⁾ MRI has quickly become the cross-sectional modality of choice for the evaluation of pediatric liver masses. This is a result of several factors including its lack of ionizing radiation and superior soft-tissue contrast resolution. In addition, the advent of hepatocyte-specific MRI contrast agents has improved radiologists'

ability to identify and diagnose liver tumors. Currently, there are two hepatocyte-specific contrast agents on the market: gadoxetate disodium (Gd-EOB-DTPA, Eovist/Primovist; Bayer, Leverkusen, Germany) and gadopentetate dimeglumine (Gd-BOPTA, MultiHance; Bracco, Milan, Italy).⁽⁹⁾

Because the lungs are the most common site of metastasis in children with hepatoblastoma, a chest CT is required at diagnosis.⁽⁹⁾ Chest CT will show lung metastases at diagnosis in about 20%.⁽⁶⁾

Prior SIOPEL and COG protocols have recommended studies such as bone scan or brain MRI. These imaging studies are no longer recommended unless the child is symptomatic or there is an unexplained rise in the serum alpha-fetoprotein level.⁽⁹⁾

Diagnostic biopsy is strongly encouraged in all hepatoblastoma patients for the accurate pathological

diagnosis, including histological subtype, as well as for scientific purposes.^(1,10) Due to the risk of formation of adhesions between the tumor and the abdominal wall when an open biopsy is taken, a percutaneous, image-guided control biopsy (under ultrasound or computed tomography) and passing through normal liver tissue is recommended.⁽¹⁰⁾

Staging

COG Staging System (Table 30-1) is a surgico-pathologic staging (post-operative) while SIOPEL system (PRETEXT grouping and risk-based staging) is a pre-operative system based on radiological assessment.⁽⁶⁾

The traditional American staging system continues to be used by the children's oncology group (COG) and depends upon extent of surgery at the time of initial diagnosis.⁽⁶⁾

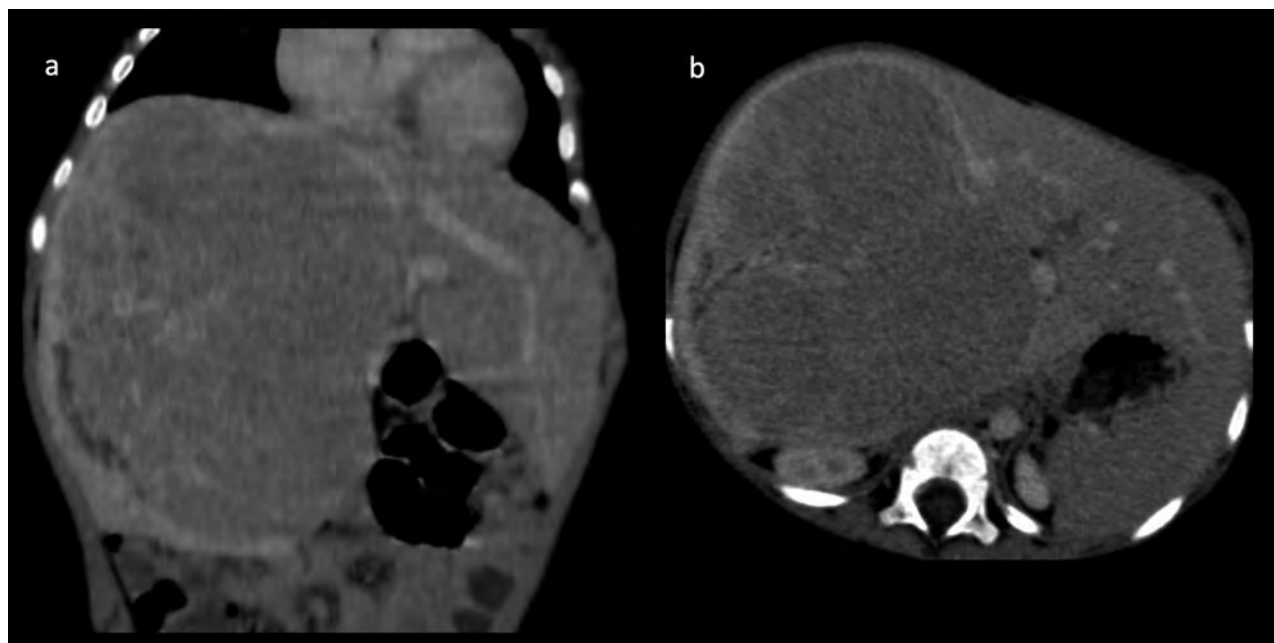


Figure 30-1. Hepatoblastoma. (a) Coronal and (b) axial contrast-enhanced CT images show large heterogeneous hepatic mass in the right lobe of a pediatric patient. (Images courtesy of Luiza Labrunie, MD, Oncologist Radiologist, National Cancer Institute, Brazil).

Table 30-1. COG staging system (Evan's staging) ^(6,8)

Stage I	complete gross resection at diagnosis with clear margins.
Stage II	complete gross resection at diagnosis with microscopic residual disease at the margins of resection.
Stage III	biopsy only at diagnosis, or, gross total resection with nodal involvement or tumor spill or incomplete resection with gross intra-hepatic disease.
Stage IV	metastatic disease at diagnosis.

The PRETEXT system was designed by the International Childhood Liver Tumor Strategy Group (SIOPEL) for staging and risk stratification of liver tumors. PRETEXT is used to describe tumor extent before any therapy and is based exclusively on imaging at diagnosis. ⁽¹¹⁾ PRETEXT Staging System divides the liver into four parts called

sectors. The left lobe of the liver consists of a lateral (Couinaud segments 2 and 3) and medial sector (segment 4), whereas the right lobe is divided into anterior (segments 5 and 8) and posterior sectors (segments 6 and 7). **(Figure 30-2)** Couinaud segment 1 is identical with the caudate lobe and is not included in this division. ^(6,9,11)

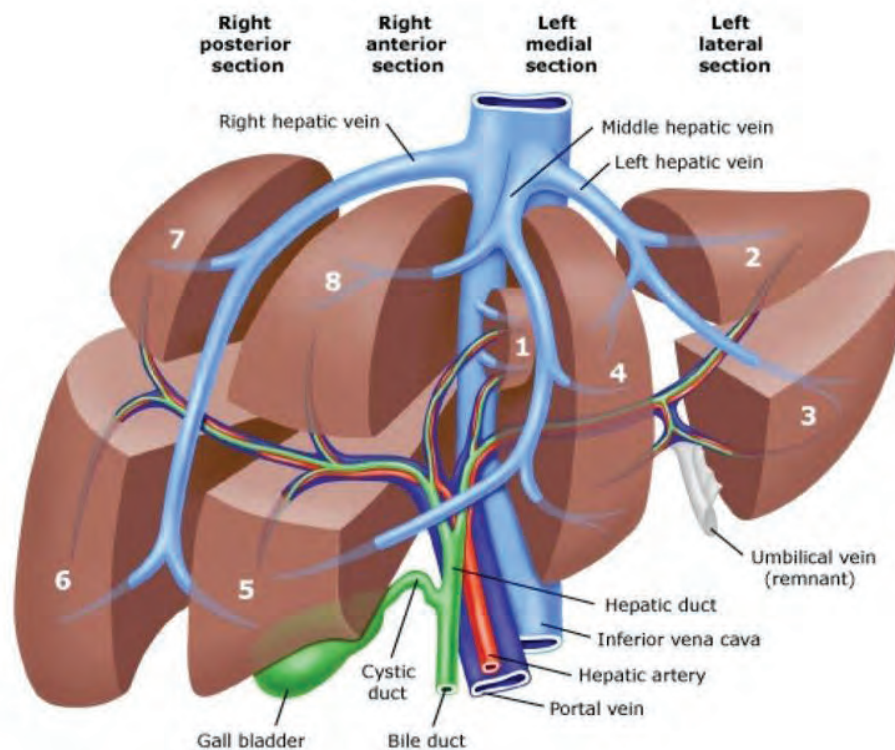


Figure 30-2. Schematic representations of the segmental anatomy of the liver. The numerals label Couinaud's segments 2 to 8. LPV:left portal vein. LPV:left portal vein. LHV:left hepatic vein. RHV:right hepatic vein.MHV:middle hepatic vein.LHV:left hepatic vein. ⁽¹¹⁾

International Society of Pediatric Oncology Liver Tumor Study Group (SIOPEL) has used two broad categories of risk stratification for several years: standard risk and high risk. ⁽⁶⁾ Standard risk tumors are PRETEXT I, II, or III. SIOPEL high-risk tumors are defined as tumors involving all four hepatic sectors (PRETEXT IV), or any tumor with metastasis (m), ingrowth of the vena cava(v), ingrowth of the portal vein (p) or contiguous extrahepatic disease (e), and tumors that fail to express AFP with AFP<100 at diagnosis. ⁽⁶⁾ (Figure 30-3)

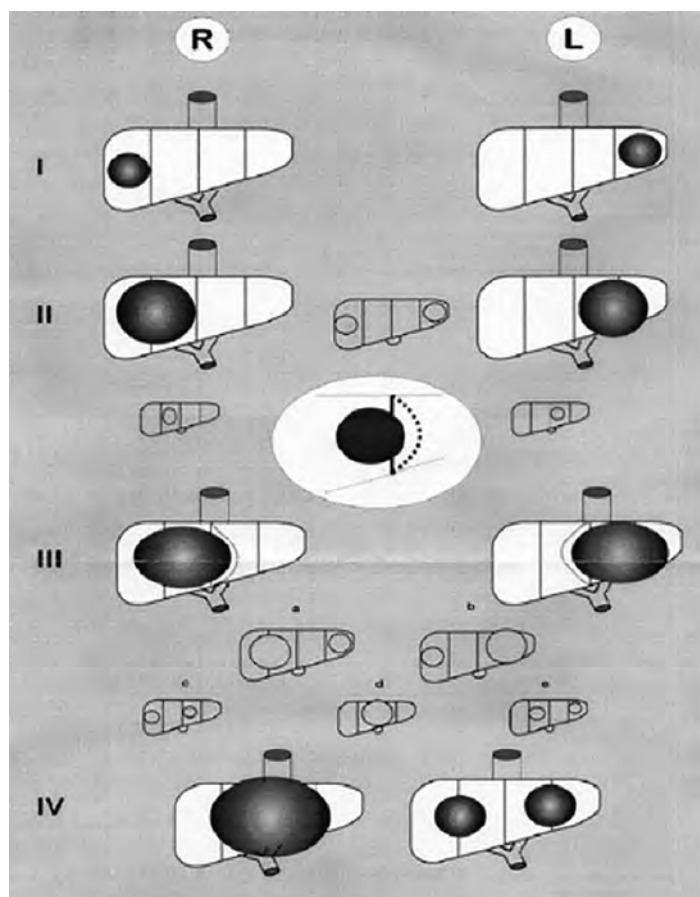


Figure 30-3. PRETEXT classification of liver tumors.

I - 3 contiguous sectors of liver tumor free, +V = invasion of all three hepatic veins. II - 2 contiguous sectors of liver tumor free, +P = invasion of main portal vein. III - 1 contiguous sector of liver tumor free, +E = invasion of extrahepatic organ. IV—No contiguous sector of liver tumor free, +M = distant metastatic disease. +C = caudate lobe. ⁽⁶⁾

Treatment

Surgical Treatment

Complete surgical resection of the primary lesion, either upfront or after neoadjuvant chemotherapy, is essential for cure. ^(1,2,6,10) Radical tumor resection can be either by conventional hepatic surgery (partial or total hepatectomy) or with orthotopic liver transplant. ^(6,10) Frequently, children with hepatoblastoma have unresectable tumors due to the involvement of multiple sectors of the liver. ^(3,8) In more than 60% of children with hepatoblastoma chemotherapy is necessary. Although neoadjuvant chemotherapy is associated with good results, some children of initially unresectable hepatoblastomas remain resistant to chemotherapy. ⁽³⁾

In the United States, the protocol of the current COG study AHEP 0731 recommends a primary resection for HB limited to PRETEXT I and II tumors with at least 1 cm of clear margin, whereas those tumors with larger extension (PRETEXT III, IV), vascular invasion or distant metastases are treated with neo-adjuvant chemotherapy. ^(6,9)

In contrast, the SIOPEL and GPOH group do not recommend upfront surgery. ^(6,8,9) This is followed in Europe, South America and most of Asia-Pacific region. These recommendations are based on the response rate of approximately 90% for these tumors to neo-adjuvant therapy, which not only makes them smaller and less risky to resect but potentially can also suppress occult micro-metastases without delay. Finally, the GPOH group observed that hepatic surgery alone with induction of liver regeneration may also promote the growth of residual tumor and metastases not pre-treated with chemotherapy by secretion of so-called liver growth factors. ⁽⁸⁾

If the tumor is not surgically resectable after four cycles, it is recommended that liver transplant is pursued instead of further chemotherapy. ^(2,6,10)

Chemotherapy

Surgery alone can cure very few patients with HB, mostly ones with the pure fetal HB variant. HB is a chemosensitive tumor and cisplatin is the backbone of the chemotherapy regimen. ⁽⁷⁾

All patients are treated with adjuvant chemotherapy except patients with a completely resected (Stage I) HB with pure fetal histology. Thus, the COG study AHEP 0731 stratifies patients into four different risk groups, reducing the intensity of chemotherapy in approximately 30% of patients. ⁽⁸⁾

Table 30-2. Current chemotherapy recommendations for the HB study groups

Study group	Risk group	Neo-adjuvant chemotherapy	Adjuvant chemotherapy
COG	Very low-risk Low risk Intermediate-risk High-risk	Nil Nil Doxo x 4-6 VCR-Irino x 2 + C5V-Doxo x 6	Nil C5V x 2 C5V-Doxo x 2
SIOPEL	Standard-risk High-risk	CDDP x 4 CDDP x 4 alternating with Carbo/Doxo x 3	CDDP x 2 CDDP x 1 alternating with Carbo/Doxo x 2
GPOH	Standard-risk High-risk	PLADO x 2-3 or IPA PLADO x 1 CDDP x 4 alternating with Carbo/Doxo x 3 or Carbo/Etoposide	CDDP x 1 alternating with Carbo/Doxo x 2
JPLT	PRETEXT I PRETEXT II PRETEXT III/IV or EVPH+ M+	– CITA x 2 CITA x 4 CITA x 4 + high dose Etoposide / Carbo / Melphalan +/- HACE	CITA x 4 (50% dose) CITA x 4 (50% dose) CITA x 2 CITA x 2

C5V Cisplatin + 5-fluorouracil + vincristine; CDDP Cisplatin; Carbo Carboplatin; Doxo Doxorubicin; PLADO Cisplatin + doxorubicin; CITA Cisplatin + pirarubicin; EVPHM Extrahepatic/venous involvement/portal vein invasion/tumor rupture/metastasis; IPA Ifosfamide/cisplatin/doxorubicin; HACE Hepatic artery chemo-embolisation; COG Children's Oncology Group; SIOPEL International Society of Pediatric Oncology – Liver Tumor Strategy Group; GPOH German Pediatric Hematology Oncology Group; JPLT Japanese Pediatric Liver Tumor Study Group; VCR Vincristine; Irino Irinotecan. ⁽⁸⁾

In current trials by COG (America), SIOPEL (Europe, South America), GPOH (German), and JPLT (Japan) chemotherapeutic agents used in combination with cisplatin have differed slightly. **Table 30-2** tabulates the current chemotherapy recommendations of the various HB study groups. ⁽⁸⁾

Liver Transplantation

A growing experience with liver transplantation has shown that liver transplant is a good treatment option in children with unresectable primary tumors and without demonstrable metastatic disease after neoadjuvant chemotherapy and pulmonary metastasectomy if necessary. ^(6,8) In large solitary, and especially multifocal, hepatoblastomas invading all four sectors of the liver transplantation has resulted in long-term disease free survival in up to 80% of children. ⁽⁶⁾ A recent analysis of data from the SIOPEL 1 study and a thorough review of the global experience have shown excellent results

with primary orthotopic liver transplant compared with those obtained by rescue transplant performed for relapse or incomplete tumor resection (87% versus 30% long-term, disease-free patient survival). ^(8,10) Therefore, it is worth re-emphasising the desirability of avoiding very difficult liver resections that carry a high probability of leaving residual tumor. ⁽¹⁰⁾

Recently, the study groups COG, SIOPEL, and GPOH have developed common guidelines for LTx in HB. These indications are:

1. Multifocal HB in all 4 liver sectors (PRETEXT IV).
2. Patients with solitary PRETEXT IV HB that are not clearly down staged to PRETEXT III.
3. HB with portal vein involvement.
4. HB with involvement of all 3 hepatic veins (V3).
5. Central HB (if a conventional resection does not seem feasible). ⁽⁸⁾

Pulmonary Metastases

The presence of lung metastases at diagnosis is not an absolute contraindication for partial liver resection or liver transplant because many lung metastases respond very well to chemotherapy and can disappear completely or become resectable by the end of pre-operative chemotherapy. Residual pulmonary disease should be removed and the primary tumor subsequently resected. ^(2,6,8) Not infrequently, the number of metastases detected manually can be higher than shown by imaging studies and therefore, open thoracotomy is preferred over thoracoscopic approach. ⁽⁸⁾

Alternative Therapies

When a difficult hepatic resection is anticipated or when orthotopic liver transplant has to be delayed, hepatic artery chemoembolisation (HACE) may be considered. There is very little experience of this technique in children, but HACE may induce a decrease in tumor size, even when the tumor has not responded to systemic chemotherapy. ^(8,10) Percutaneous tumor ablation with radiofrequency, ethanol injection, cryoablation, laser or microwave ablation, which are commonly applied in adults, are rarely indicated for HB. ⁽⁸⁾

Portal Vein Embolization / Portal Vein Ligation

Portal vein embolization (PVE) and portal vein ligation, which induces shrinkage of the embolized lobe and compensatory enlargement of the non-embolized lobe, has contributed to the improvement of postoperative outcomes in patients undergoing extensive liver resection. ^(3, 12)

Recently, this technique has been modified by performing a portal vein ligation with *in situ* splitting, which is named the Associating liver partition with portal vein ligation and staged hepatectomy (ALPPS) procedure. ⁽³⁾ ALPPS technique should only rarely be indicated for the treatment of liver tumors in children. ⁽³⁾

Prognosis

Data from the COG study, 9645, show 3-year event-free survival of 90% for Stage I–II, 50% for Stage III, and only 20% for Stage IV. In the European SIOPEL II 3-year survival in SIOPEL 2 for standard risk tumors was 90% and for high-risk tumors was 50%. ⁽⁶⁾

Previous cooperative group studies have identified such variables as PRETEXT, presence of metastatic disease, and very low serum AFP (<100 ng/ml) as poor prognostic factors. ⁽⁴⁾

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Chapter 31

Intraoperative Ultrasonography in Liver Surgery

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Mauro Monteiro, MD, PhD

Introduction

Ultrasonography has been used to obtain images of the liver for decades. ⁽¹⁾ Since 1956, when it was first used in medical practice, ultrasound proved to be a safe, practical, accurate and relatively inexpensive method for diagnosis of liver and bile duct injuries. Therefore, it is the first, and most often, the method of choice for identification and interpretation of hepatobiliary diseases. ⁽²⁾

The intraoperative ultrasound (IOUS) was first used in liver surgeries in 1977 by Makkuchi. ⁽³⁾ The acceptance of this new method by the surgical community was slow despite the reports of the potential benefit of its application. It was only with technological advances, increased accuracy of the technique and increased availability in the late eighties that the use of IOUS was really widespread. Since then, it has been considered critical and it is now firmly established as an instrument in liver surgery. It is the only real-time imaging modality available at the surgical center for identification of liver lesions. But for the precise use of intraoperative ultrasound, the surgeon needs to know the basic and advanced principles of ultrasonography and have in-depth knowledge of the three-dimensional anatomy of the liver.

The purposes of this chapter are: 1) to describe the intraoperative use of ultrasonography in liver surgery by explaining and detailing techniques and instruments and 2) to correlate the surgical anatomy examined by the method with the pathological findings during the surgery and its importance in the planning of the surgical approach.

Indication

Transcutaneous abdominal ultrasonography is limited in obtaining accurate images of the liver due to the interposition of the abdominal wall and the intestinal “window” loops. Placing the transducer directly on the liver eliminates these factors and allows the use of high frequency waves (5-10 MHz), which increases the quality of the images obtained.

USIO indications are extensive (**Table 31-1**) and include localization and characterization of known and concealed hepatic lesions, determining resectability and planning the approach based on the relation of the tumors to the intrahepatic anatomy, evaluating patency or vascular invasion, studying the bile ducts, guiding diagnostic punctures and therapeutic ablation, and staging of primary and secondary tumors of the liver. ^(4,5,6)

Table 31-1. Indications of IOUS

1. Determine new lesions not viewed on CT, MRI or PET-CT.
2. Measure, locate and relate lesions and anatomical structures.
3. Evaluate resection and delimit its extension.
4. Guide ablation and control its extent and effectiveness in real time.
5. Locate, differentiate and puncture or biopsy cysts, abscesses and solid tumors.
6. Identify and study the bile ducts (e.g., calculations, dilatations and stenoses).

Since the liver is the abdominal organ most affected by metastatic disease, ⁽⁷⁾ the technique is most suitable for this situation. Despite the advances in CT scanning, magnetic resonance imaging (MRI) and positron emission tomography (PET-CT) in the last decades, IOUS remains as the most sensitive method in the study of metastatic disease.

The IOUS accuracy is well established, with sensitivity of 93.8%, specificity of 94.4%, positive predictive value of 92%, and negative predictive value of 95.7%. ⁽⁸⁾ In a recent study involving 561 patients with malignant liver tumors, including primary and metastatic tumors, the IOUS sensitivity was 95.1%. ⁽⁹⁾ In another study comparing the intraoperative findings of the ultrasonography with the preoperative findings obtained by CT or MRI, USIO demonstrated superior ability to detect liver tumors in 418 patients. The IOUS was responsible for change of conduct in 69 (16.5%) patients, surgery was extended in 12.4% cases, more conservative in 1.7% and contraindicated in 2.4%. This led to the conclusion that IOUS should be routinely recommended in hepatectomies, even in the era of modern preoperative images. ⁽¹⁰⁾ Other series report a change in intraoperative management ranging from 5-30% of the cases. ^(11,12,13,14)

These findings may be justified by the fact that IOUS can accurately locate lesions smaller than 2 mm, with a sensitivity of 90%, which is not reached by CT or MRI for lesions of this size.

In primary liver disease, the IOUS also plays an important role. Particularly in hepatocellular carcinoma, where hepatic fibrosis and cirrhosis (frequently associated) make it difficult to palpate the liver parenchyma. In these cases, only 50-67% of the tumors smaller than 5 cm can be identified by inspection and palpation. ⁽¹⁵⁾ In addition, vascular involvement of the portal vein, hepatic veins, and ipsilateral or contralateral bile ducts can be easily identified by IOUS. ⁽¹⁶⁾ The radial growth of cholangiocarcinomas with involvement of the portal or bile branches can also be accessed by the technique to determine intraoperative behavior change.

Many procedures depend on the IOUS, and it is virtually impossible to perform them without using the method. The correct needle positioning for biopsy or core-biopsy is guided by ultrasound for impalpable tumors or for those deep in the parenchyma. Likewise, IOUS is indispensable for the ablation of lesions, either by ethanol injection, cryotherapy or radiofrequency. In these cases, it is possible to see the

success of the treatment in real time, with identification of the area of necrosis obtained.

Finally, the use of ultrasound has proven to be extremely useful in the diagnosis and treatment of liver damage. It is innocuous, simple and easy, and also reproducible multiple times during the surgery, without increasing the surgical time or exposing both the patient and the surgeon to radiation.

In addition, it can change the outcome of patients with malignant tumors. The data show increased survival in centers that use the method when compared to centers that do not use it routinely. ⁽¹⁷⁾ However, it is important to remember that the preoperative radiological study is indispensable to evaluate which patients with liver tumors (primary or secondary) can benefit from the surgery.

Basic Principles

Ultrasound scans use high frequency waves (mechanical vibrations) with alternating cycles of compression and rarefaction that travel through the tissues. ⁽¹⁸⁾ The waves are generated by piezoelectric crystals, designed in the format of translators, that aggregate the ultrasonic waves into bundles. The sound is then transmitted or reflected in its trajectory depending on the acoustic properties of the different tissues (acoustic impedance). The waves that get reflected back to the transducer are used to form the images. The depth of the refraction is calculated from the gap between the sending of the waves and the echo returned. To form images in real time, the impulses are repeated 20 to 30 times per second. The strength of the echoes depends on the impedance of the tissue at its interface. In soft tissues, such as the liver, collagen is responsible for the refraction of the waves. Adipose tissues are highly echogenic due to the abundance of fat/water interfaces. Liquid content (e.g. urine, blood, bile, collections and cystic lesions) are not echoed because there is no sound impedance during the transmission by the homogeneous fluid.

The frequencies mostly used in intraoperative ultrasonography are 5 to 7.5 MHz. The 7.5 MHz linear transducers (**Figure 31-1**) are the most applicable to hepatic surgery, because they give more detail of the intrahepatic structures while allowing the waves to penetrate the entire parenchyma. ⁽¹⁹⁾ When the liver has steatosis, cirrhosis or is simply large and dense, the 5 MHz transducer may be necessary since it has greater penetrance to scan the deeper portion of the organ.

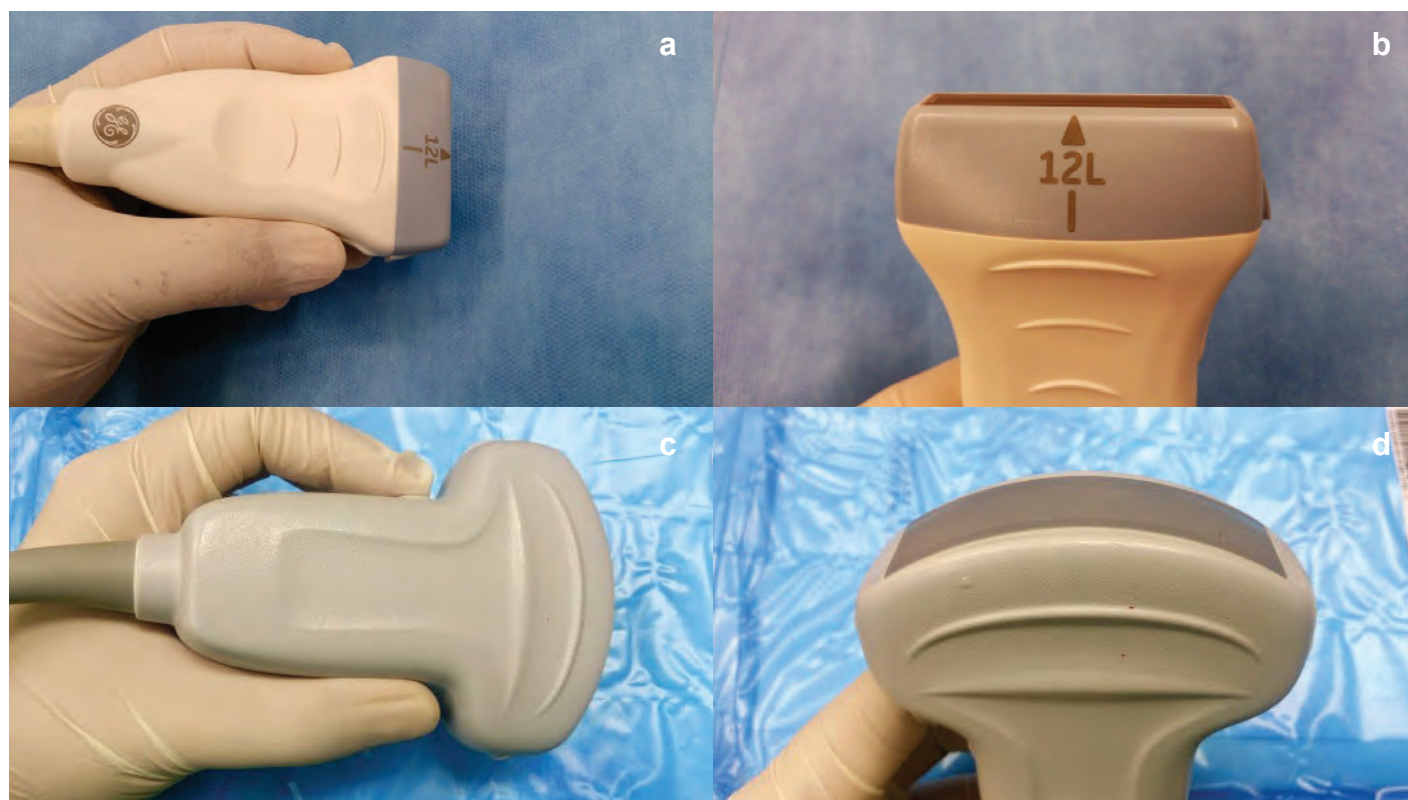


Figure 31-1. T-shaped linear transducer (A,B) and curved transducer (C,D).
Note the size difference between them.

Techniques and Systematization

It is important to mention that the IOUS must be performed by the surgeon responsible for the procedure rather than the assistant surgeon, radiologist or technician. This is because the information acquired during the examination requires interpretation to be best used in the elaboration of the surgical strategy. As previously mentioned, linear transducers facilitate the intraoperative liver study because they produce rectangular and more reliable images of both hepatic parenchyma and lesions. Because they are small and thin, they allow access to spaces that are often limited, such as the sub-diaphragmatic, subcostal and infrahepatic spaces (here, especially for the caudate lobe).

One of the most important points for success in intraoperative ultrasonography is the development of a systematized technique. To ensure an adequate and complete examination, the routine should always be performed exhaustively. This approach should be initiated by the identification of the anatomical structures and the hepatic segments. Once they are understood, the next step is to identify lesions previously studied in the preoperative period and their relation to the segmental anatomy. The final step is to look for undiagnosed injuries.

Techniques

Some techniques facilitate the intraoperative study of the liver. Knowing and understanding the applicability of each one of them can make a difference in the correct diagnosis. We can position the transducer in various directions on the liver and use an acoustic medium to aid visualization in some special conditions.

In contact scanning, the previously sterilized transducer is placed directly on the hepatic surface without any interposition of gel or liquid. This is the most commonly used method in IOUS. It is the best approach for the study of all segments of the liver, except for the small superficial lesions, as these may not be identified by this technique due to their proximity to the transducer. Beyond this condition, this technique is not properly employed in the cirrhotic liver, whose surface is irregular, making it difficult to slide the transducer. Added to this, and also to the roughness of the surface, the air from the external medium can fill the interface between the apparatus and the liver. For these cases and in some other conditions, it is possible to use acoustic window techniques. They basically consist of the interposition of a saline solution or gel between the transducer and the hepatic surface. This allows for better visualization of lesions and

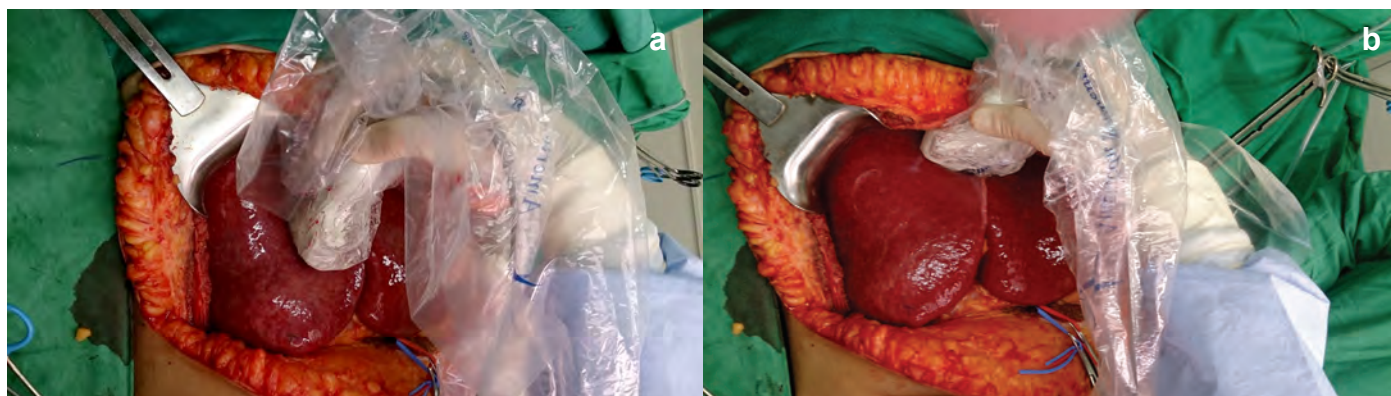


Figure 31-2. *A) Longitudinal scan. B) Transverse Scan.*

surface structures, as well as better scanning of uneven surfaces. To do this, we can immerse the liver in a saline solution or simply fill a sterile plastic bag with gel or saline solution. It is a simple technique that assists the applicability of the IOUS.

The position of the transducer in relation to the liver also varies according to the need of the study. And because ultrasound is dynamic, we can change the position of the transducer several times, creating different images almost simultaneously. Basically, there are two transducer orientations: transverse and longitudinal. Transverse scanning is the basic technique for intraoperative ultrasonography of the liver, in which the transducer is positioned transversely to the liver. It can be combined with transducer rotation or longitudinal and oblique scanning to evaluate structures or parenchymal changes in all planes. **(Figure 31-2)** Changing the orientation on a specific point (e.g. injury or anatomical structure) without removing the transducer on the hepatic surface generates a rotating image that generates a three-dimensional image in the surgeon's mind, allowing all axes to be evaluated. The transducer can be applied with different pressures on the hepatic parenchyma. Varying the force, pressuring or loosening the transducer help identify the lesion's consistency, the vascular permeability and visualize deeper structures or lesions.

Systematization

Systematizing the routine facilitates the performance and the understanding of the exam. It is important to know that complete liver scanning should be started prior to its mobilization and that a further liver scan should be repeated after mobilization. This practice minimizes false-positive findings (artifacts) that may result of the organ manipulation.

Evaluation should begin by identifying the vascularization of the liver, since the segmentation of the organ is defined by the hepatic veins and the portal pedicles. Firstly, the confluence of the hepatic veins with the vena cava should be found on the upper surface of the liver. Afterwards, each vein should be followed until its smaller branches. At this stage, the surgeon should be aware of anatomy variations and then identify the portal branches, follow them until their most peripheral portions and evaluate possible tumor invasions. Systematically, the entire parenchyma should be examined considering the preoperative findings, and then the new and previous lesions should be correlated with the segmental and vascular anatomy. Following a decision to proceed with the intervention of the organ, one should mobilize the liver and scan it again with special attention to the later segments that now can be better studied.

The study of hepatic vascularization begins with the identification of the hepatic veins on the anterior surface of the liver. The hepatic veins are located in the uppermost portion, more precisely on the diaphragmatic surface over the falciform ligament. At this point, its confluence with the vena cava can be visualized **(Figure 31-3)** and each vein can be traced to its periphery. It is important to emphasize that the transducer should be positioned perpendicularly to the direction of the veins, and one should not put too much pressure on the hepatic parenchyma at this moment, because the veins may collapse and are no longer be visible. Then, the transducer should be positioned longitudinally, and the three hepatic veins should be rescanned this way. It is possible to observe the full extent of the retrohepatic vena cava using the longitudinal technique.

Once it is done, one should start the transverse scanning of the lower surface of the liver to identify the portal triad. At this point, one should follow the right portal vein and study its division in the anterior branch (segments V and

VIII) and the posterior branch (segments VI and VII). Each branch sector is then scanned in search of its lower and upper sub-division. Afterwards, one should study the left portal vein that is located at the base of the umbilical fissure. Now it can be observed that the left portal vein ascends and bifurcates to the right and the left. The right branches go to segment IV and the left branches go to segment II (later) and III (previously).

After the study of the hepatic anatomy, one can then identify the previously accessed lesions (Tomography and/or Resonance) and search for lesions not yet diagnosed.

This routine (**Table 31-2**) allows the surgeon to decide on the approach of care of the liver in a safe and effective way.

Table 31-2. Steps

1. Scan the liver before mobilization.
2. Repeat the scan after mobilization.
3. Identify the hepatic veins.
3.1 At the junction with the vena cava.
3.2 Follow until the terminal branches.
3.3 Identify anatomical variations.
4. Identify portal structures.
4.1 Main trunks, right and left.
4.2 Follow each trunk until the segments.
5. Scan the entire parenchyma
5.1 Develop a standard routine (e.g. counterclockwise).
5.2 Identify all lesions.
5.3 Identify the correlation with anatomical structures.

Laparoscopic Ultrasonography

The role of IOUS in laparoscopy can be considered more important than in open surgery because the surgeon is not able to palpate the liver through this surgical access. Laparoscopic ultrasonography can be used as staging and evaluation methods for resectability both in preoperative and intraoperative settings of liver resection. It is a relatively new technique that combines the principles of high-resolution IOUS with laparoscopy using specially designed transducers for laparoscopic portals.

Reports of experiences with the method show encouraging results in the evaluation of potentially resectable tumors. ⁽²⁰⁾

As a preoperative investigation method, the surgeon uses laparoscopic ultrasonography to access hepatic tumors with indefinite surgical indication, thus sparing the patient from

unnecessary laparotomy. By combining the two techniques, laparoscopy and IOUS, the surgeon is able to detect any condition that contraindicates a surgical approach to the liver, such as: extrahepatic tumor dissemination, carcinomatosis, lymph node involvement, intrahepatic or multifocal dissemination. These conditions are considered factors of poor prognosis. ^(21, 22) The method can also be used in conjunction with laparoscopic procedures and resections.

In order to perform the USIO, a 7.5 MHz linear transducer with 9 mm in diameter and 35-50 cm in length (laparoscopic transducer) is passed through a 10 mm portal in both the umbilical scar and the right flank. During the pre-procedure, the optics and the transducer can freely change from portal depending on the hepatic segment being studied. Laparoscopic inspection of the whole peritoneal surface and omentum is performed. Any ascites should be aspirated, and the liquid should be submitted to oncotic cytology. Also, suspicious lymph nodes should be biopsied. The presence of liver cirrhosis should be documented, as well as capsular or extrahepatic involvement of the tumor. ⁽²³⁾

After the laparoscopic evaluation, the transducer is then positioned on the hepatic surface and the two images are shown on the screen in real time, both from laparoscopy and ultrasound, when the equipment allows. If this feature is not available, the surgeon should follow the procedure on the separate screens. Ultrasound examination then follows the same routine as described above.

Ultrasound Anatomy

Thorough knowledge of the anatomy of the liver is a prerequisite for modern liver surgery and consequently for the correct use of the IOUS.

Externally, the hepatic anatomy is defined by the ligaments and fissures that divide the liver into anatomical lobes: left, right, caudate and quadrate. On the diaphragmatic surface is the falciform ligament that divides the liver anatomically into left and right lobes. In the inferior or visceral surface, the venous ligament and the round ligament continue dividing the liver in these two great lobes. The quadrate lobe is delimited by the gallbladder, the hepatic hilum and the round ligament. In turn, the caudate lobe is demarcated by the vena cava, the hepatic hilum and the umbilical fissure. ⁽²⁴⁾

However, the classical description and simple external inspection of the liver does not reveal the anatomy of intrahepatic vascular and bile structures, which are obviously of paramount importance in liver surgery. IOUS

has the ability to combine the superficial anatomy of the liver with the ultrasonographic findings of the intrahepatic anatomy, accurately defining the hepatic segments.

It is important to remember that ultrasound produces two-dimensional images of the liver on a screen, so the surgeon should scan the entire organ systematically on at least two axes (transverse and longitudinal) to ensure that all parenchyma and liver structures are visualized.

Based on this, the surgeon must synthesize this information into two dimensions and mentally develop a three-dimensional map of the structural and functional anatomy of the liver. Needless to say, this requires extreme motor, spatial, and cognitive abilities.

For guidance, three planes in the central portion of the liver are used:

- The plane of the confluence of the hepatic veins. (**Figure 31-3**)
- The plane of the umbilical fissure, in the left branch of the portal vein. (**Figure 31-4**)
- The plane of the gallbladder.

Starting from this point, these three planes give access to a series of other parallel planes, which are elementary in the surgeon's mind and form the basis for the three-dimensional reconstruction of each patient's hepatic anatomy.

Texture and Echogenicity

The hepatic parenchyma has a uniform and homogeneous ultrasound image with a slightly brighter echogenicity

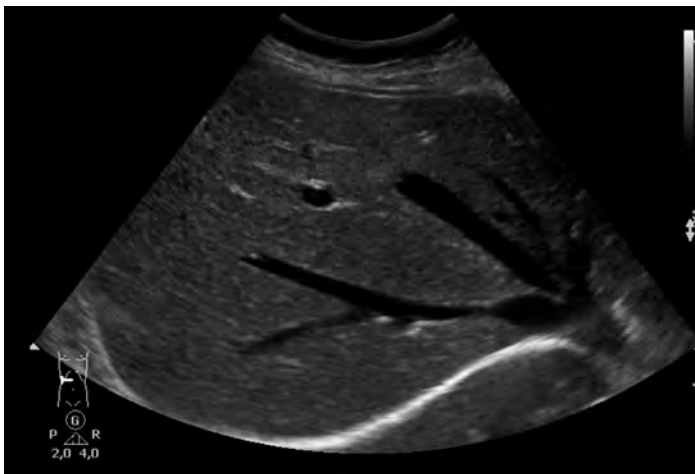


Figure 31-3. *Confluence of the hepatic veins with the vena cava.*

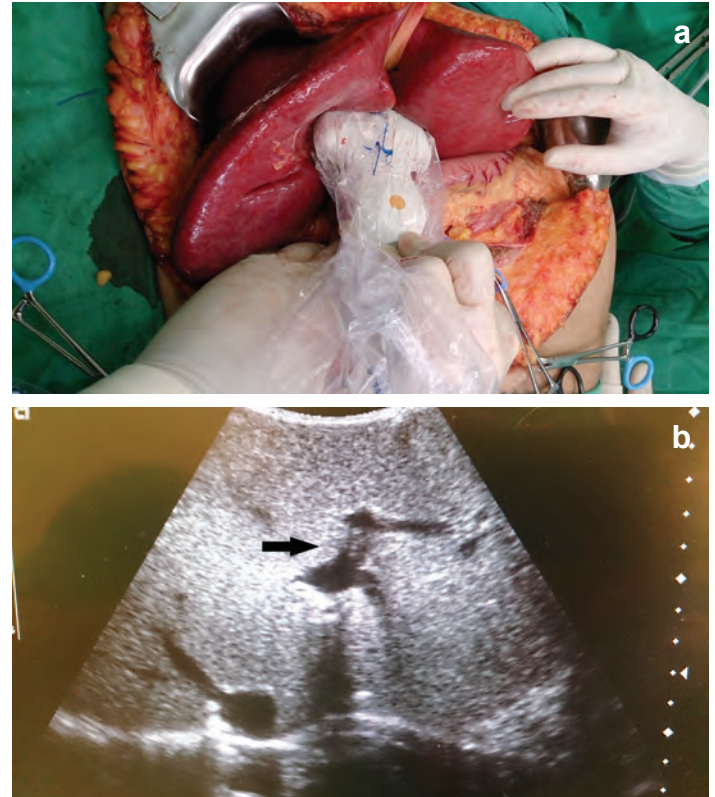


Figure 31-4. *A) Transducer in the plane of the umbilical fissure. B) Ultrasonographic image oblique.*

than the renal cortex. (**Figure 31-5**) But differences in echogenicity may be observed in cases of fibrosis, steatosis, or cirrhosis. The hepatic capsule and vascular walls are smooth, and the vascular architecture with its classical dichotomy is perceived harmoniously and in detail. The texture and echogenicity of normal hepatic parenchyma vary slightly among individuals with a healthy liver.

Hepatic Veins

The three hepatic veins are positioned between the hepatic segments. To identify them, the transducer is placed upon the upper surface of the liver, over the falciform ligament previously sectioned, and the confluence of the hepatic veins with the inferior vena cava is found. Afterwards, each vein is followed until its smaller branches. Their course through the parenchyma helps identify the lobes and segments of the liver. Their number and direction within the parenchyma may vary between individuals. The hepatic veins have a thinner and less echogenic wall (less bright) than the portal branches.

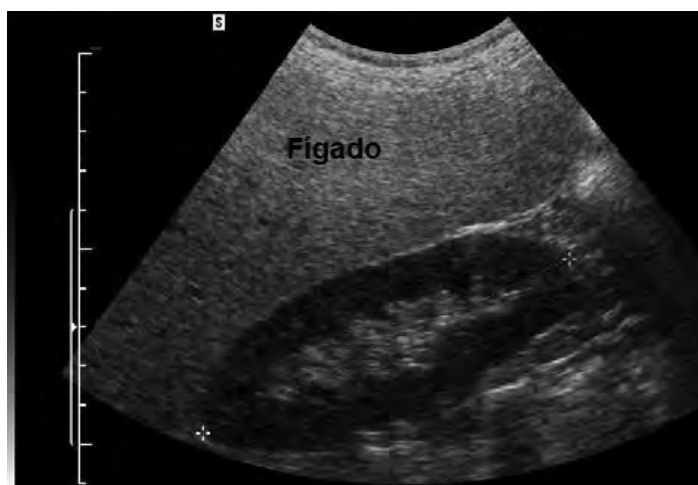


Figure 31-5. *Echogenicity of the normal hepatic parenchyma and the difference in echogenicity between the liver and the kidney (marking).*

Portal Vein

Formed by the confluence of the splenic vein and the superior mesenteric vein, the portal vein can be sonographically displayed by placing the transducer transversely on the lower border of the liver, but preferably the portal branches should be studied by the inferior (visceral) surface of the liver, over the hepatic hilum, with a transversal transducer or in the same way at the base of the Segment IV. The hepatic veins and the portal triad are differentiated by their ultrasonographic appearance. As soon as the portal triad enters the hepatic parenchyma, it becomes entrapped by the Glisson's capsule. This results in a higher echogenicity (brighter) edge in the IOUS. This feature helps differentiate the intrahepatic branches of both vascular structures. If there is still doubt, the venous branch itself may be traced back to its origin, which may be the confluence of the hepatic vein with the cava or the main branch of the portal vein.

In the intra-glissonian portion of the hepatic hilum, the portal vein bifurcates into right and left main branches. The right branch then divides into the anterior branch, vascularizing the segments V and VIII; and posterior branch, vascularizing the segments VI and VII. The left branch of the portal bifurcates into the lateral branch (segments II and III) and medial branch (segment IVa and IVb).

Hepatic Artery

It is an anechoic, small and rounded structure, usually located between the portal and bile branches in its intrahepatic

path. The common hepatic artery originates from the celiac trunk, and after giving rise to the gastroduodenal artery, it is called hepatic artery. Anatomical variations are frequent (up to 50% of patients), with the most common being the left hepatic artery from the left gastric artery. Another less common finding, however prevalent and of extreme importance, is the origin of the right hepatic artery in the superior mesenteric artery. Within the liver, the arterial branches run together to the branches of the portal vein and biliary tract, and often cannot be visualized or differentiated without the aid of a Doppler.

Bile Ducts

The bile ducts accompany the portal and arterial branches from the hepatic segments to the hilum where, even within the parenchyma, they form the right and left ducts, which join externally to form the hepatic duct. Sonographically, the bile duct presents itself as an anechoic canal, located anterior to the portal vein, and measures less than 2 mm in diameter in the absence of pathological dilatation.

IOUS Findings and Surgical Planning

IOUS is the most accurate imaging method for the identification and staging of liver tumors and in the surgical planning. Several types of lesions can be found in the liver, and based on their echogenicity, hepatic lesions can be characterized.⁽²⁵⁾ The echogenicity of the liver lesions is differentiated by the relation with the echogenicity of the surrounding liver parenchyma. They can be classified as hyperechoic (lighter and brighter), isoechoic (even grayish tone) or hypoechoic (darker and less shiny) when compared to the surrounding liver tissue. (Table 31-3)

Table 31-3. Common Liver Lesions

1. Cystic
1.1 Simple cyst, multiple or complex cysts.
1.2 Infected cyst
1.3 Cystic tumor
2. Solidas
2.1 Benign tumors
2.2 Malignant tumors
2.3 Regenerative nodes
2.4 Fatty infiltration

Some liver tumors may be heterogeneous, with different types of echogenicity. The shape of their borders and type of infiltration can also help differentiate these lesions. An ill-defined halo echo surrounding the lesion is more common in malignant tumors, whereas a well-delimited and hyperechogenic halo is characteristic of benign lesions. We may also find vascular or biliary invasion associated with tumor thrombi (cholangiocarcinoma and hepatocarcinoma). In contrast, benign lesions (adenomas and fatty infiltration) rarely have a mass effect on the vessels. Although USIO is excellent for differentiating cystic lesions from solid lesions, it is more difficult to determine whether these lesions are malignant or benign. The clinical diagnosis should be kept in mind to aid in the differential intraoperative diagnosis. However, in some cases, the diagnosis can only be made through biopsy. This difficulty may be even greater in cases of hepatic steatosis when the parenchyma infiltrated by fat becomes more echogenic.

Steatosis and Hepatic Cirrhosis

Hepatic steatosis is the most common liver disease. The sensitivity and specificity of the diagnosis by IOUS will depend on the experience of the surgeon. It is characterized, ultrasonographically, by increased echogenicity of the hepatic parenchyma. (**Figure 31-6**) This is due to ultrasonic attenuation and decreased intensity of ultrasound scattering by the fat-infiltrated parenchyma caused by absorption,

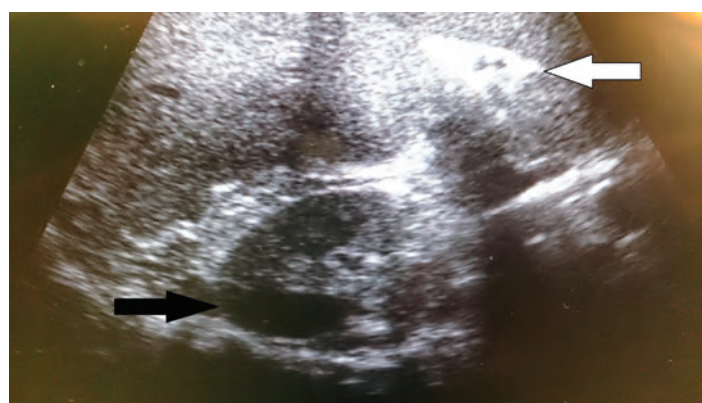


Figure 31-6. Sonographic signs that characterize hepatic steatosis include increased echogenicity, ultrasonic attenuation caused by absorption, dispersion and divergence of the bundle, and decreased details of the vascular anatomy. There is an increase in the difference in echogenicity between the liver (white arrow) and the kidney (black arrow).

dispersion and acoustic divergence of ultrasound waves. Attenuation decreases the detailed visualization of vascular architecture and may cause loss of deep liver visibility. The majority of patients with hepatic steatosis also present distinct hypoechogenic areas in the hepatic hilum. It is believed that the presence of these areas in the thread correspond to healthy parenchyma islands that were spared from fatty infiltration. ⁽²⁶⁾

Hepatic cirrhosis can be easily identified intraoperatively because of the macro nodular aspect of the liver surface. However, in cases of micro nodular cirrhosis, where macroscopic inspection may not show changes, IOUS may aid in its diagnosis. The presence of a parenchyma with heterogeneous echotexture (**Figure 31-7**), altered vascular architecture, collateral vascularization and reverse flow to Doppler-flowmetry may be signs of portal hypertension, corroborating to the diagnosis of cirrhosis.

Benign Liver Tumors

They are relatively uncommon except for the hemangioma, which is the most common benign tumor of the liver.

Most hemangiomas have a diameter smaller than 3 cm, are lobed and well-delimited, and are often located adjacent to the vessels, showing a texture rich in echogenicity and sometimes an increase in posterior acoustic echo due to the capillary vessels that form it.

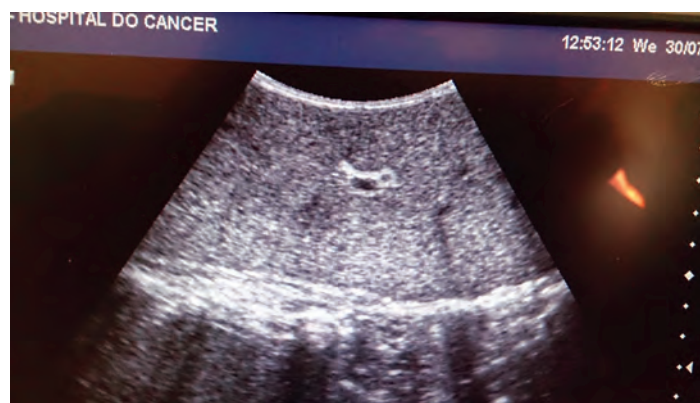


Figure 31-7. Liver with cirrhosis. Observe the areas with increased echogenicity (greater brightness) diffusely in the liver parenchyma.

In up to 10% of patients, the precise diagnosis cannot be obtained with imaging tests. For these patients, only the biopsy can differentiate the nature of the lesion, especially in cases of associated malignancies. Nodular focal hyperplasia, adenoma, regenerative nodules, and fatty infiltration are less common.

Hepatic cysts are frequently found on ultrasound. They are typically rounded, anechoic, smoothly delineated with refraction at the edges and a strong echo of the posterior wall. (**Table 31-4**) When these findings are present, the lesion is defined as a typical cyst; (**Figure 31-8**) when absent, they are considered atypical. Although most hepatic cystic lesions are simple hepatic cysts, the differential diagnosis can be complex.

Table 31-4. Characteristics of hepatic cysts

Anechoic (dark interior).
Demarcated borders.
Side acoustic shadow.
Later gain (lighter signal behind the lesion).



Figure 31-8. Typical hepatic cyst (arrow).

Hepatocellular Carcinoma

It is the most common primary malignant tumor of the liver. IOUS has become essential in the intraoperative management of these lesions. It is important in the detection of hidden lesions, satellite nodules and in the evaluation of resectability, particularly in cirrhotic patients when preoperative imaging fails to identify small lesions in the distorted liver. ⁽²⁷⁾ Some characteristic features of hepatocellular carcinoma (HCC), such as vascular invasion, are more easily identified by IOUS than by preoperative studies. ⁽²⁸⁾

There are two sub-types of HCC: nodular and diffuse, each one with different ultrasound characteristics. Nodular tumors are more common and present as single or multiple masses, but well-delimited. Diffuse tumors are difficult to delimit because they have imprecise and infiltrative limits that tend to mix with the surrounding parenchyma.

Usually small and hypoechoic, regenerative nodules are common in the cirrhotic liver and tend to be confused with HCC. Dysplastic nodules can be difficult to differentiate. When the diagnosis is not certain, the biopsy may be necessary for clarification.

Liver Metastases

In western countries, metastatic lesions are 10 to 20 times more common than primary malignant neoplasms of the liver. In the East, especially in China, HCC is the most commonly found solid tumor. Metastatic tumors may have a wide variety of shapes, ranging from microscopic lesions to giant masses over 20 cm in diameter. The echogenicity and echo patterns vary with the size of the tumors. Gastrointestinal metastases greater than 1 to 2 cm are often isoechoic to hyperechoic and surrounded by the hypoechoic halo. ⁽²⁹⁾ Distortion of neighboring structures may also be present as a result of the mass effect of the tumor. Although vascular or biliary invasion occasionally occur, these lesions tend to reject these structures, resulting in a displacement rather than invasion. The identification of invasion of these structures may change the surgical planning. When there is doubt about the nature of the lesion, biopsy becomes mandatory.

Hidden metastases are often detected by IOUS. Because preoperative imaging has evolved a lot in recent years, these occult lesions are often smaller than 1 cm and pose a challenge to the surgeon: they tend to be hypoechoic and lack the characteristics that help identify them as metastatic lesions. The identification of hidden lesions outside the resection plane changes the approach programmed in the preoperative period, so they must be clarified precisely. When there is doubt, biopsy should be performed.

Surgical Planning

The approach of liver lesions can be altered depending on the findings of the IOUS. Demonstration of a safe dissection plan between a portal branch or hepatic vein may allow for a resection that spares the parenchyma. On the contrary, if

a safe plan cannot be visualized or vascular involvement is present, it is necessary to change the strategy or even contraindicate the surgery.

Due to the high sensitivity of IOUS in identifying and characterizing new lesions, changes in the intraoperative approach are frequent. In the HCC, the IOUS allows for the detection of new lesions in 7% of the surgeries.⁽³⁰⁾ In an analysis related to hepatic metastases of colorectal origin, IOUS was superior in identifying these lesions with sensitivity of 95.2% versus 82.5% of CT and 84.9% of MR.⁽³¹⁾ Because of these advantages, IOUS is also essential in guiding liver resection and allows for the modification of the resection plane when necessary. The effectiveness and convenience of this approach reduces mortality to less than 4%^(32, 33) and, in some cases, up to 0% as shown in studies of large centers published in the last decade.^(34, 35)

In a prospective Italian study published in 2008 that evaluated patients who underwent liver resection using the IOUS, 21% of liver lesions were only discovered intraoperatively, and the surgery approach needed to be modified for all of these patients, especially in cases of HCC.⁽³⁶⁾

Due to the accuracy provided by IOUS, the preservation of parenchyma in hepatectomies can be increased. This applies particularly to patients with chronic hepatitis and cirrhosis who require minor resections to reduce the risk of postoperative liver failure, when the mortality rate is higher.^(37, 38)

In addition to the aforementioned properties, the IOUS can also aid in the identification of communicating veins between the three hepatic veins. For tumors involving the hepatic veins close to the hepatocaval confluence, liver resections are traditionally larger. The detection of communicating veins and their trajectory can allow dissection by the parenchyma to ensure its preservation. In fact, inadvertent ligation of these vessels may eliminate the benefits of sparing surgery and result in venous congestion in the remaining segments. A recent study published in 2010 was conducted prospectively to assess the role of IOUS in 21 patients with primary and metastatic tumors located at hepatic veins confluence. A higher than expected prevalence was found: 80% of the patients had communicating veins. In these patients, the surgical approach could be modified for minor resections and they experienced 0% mortality or morbidity.⁽³⁹⁾

For the above, the IOUS is undoubtedly considered to be extremely important in the practice of liver surgery. Therefore, the surgeon must master the technique to modify the surgical strategy whenever necessary.

Ultrasound Guided Interventions

The most frequently guided interventions by IOUS are fine needle aspiration (FNA) or core-biopsy of new lesions discovered intraoperatively. Core-biopsy is more appropriate for most solid lesions because histopathology is necessary to distinguish innumerable hepatic neoplasms. If the issue is the distinction between malignant or benign disease, especially in cases of liver metastases, FNA is almost always enough, since cytology may close the diagnosis. It is very important to note that, unlike FNA, the core-biopsy extends beyond the end point of the needle in the ultrasound. The moment the needle is triggered, its tip advances by 1.5 to 2 cm. This implies the need to correctly position the needle under IOUS guidance taking these extra centimeters into account, especially in lesions close to vascular and bile structures and in small lesions where the tissue sample acquired may not be the one desired. From the above, it can be inferred that the IOUS is essential in these cases.

Cystic content samples or therapeutic drains of cysts and abscesses are easily performed with the aid of ultrasonography, besides making it possible to obtain the post-puncture result immediately. Through the IOUS, it is possible to analyze the biopsied area, investigate any inadvertent accidents, ensure that the procedure was performed in the correct area and that aspiration resulted in the complete disappearance of the cystic lesion.

Similarly, the IOUS can be used to guide the catheterization of intra- and extrahepatic bile ducts in cholangiographies and external biliary drainage.

There are transducers that can be attached to the needle for the interventions. (**Figure 31-9**) The needle docking



Figure 31-9. Needle coupling system.

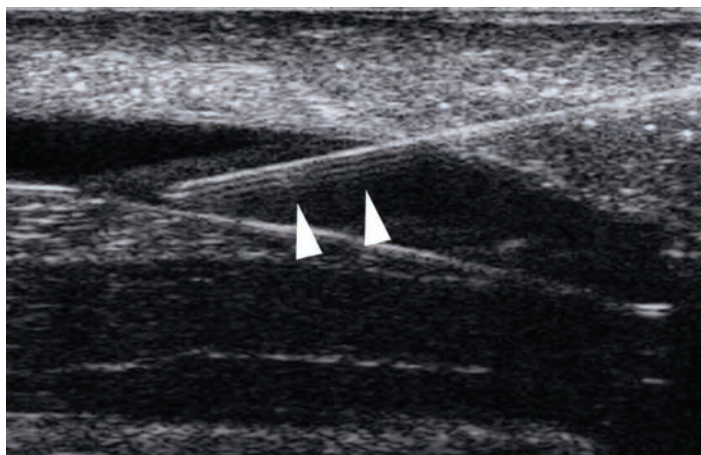


Figure 31-10. Needle in USIO. The arrows show the reverber artifacts.



Figure 31-11. Cryoablation Probe.

system makes learning easier, but increases the size of the transducer, preventing access to smaller spaces and limiting the variety of angles. In addition, some lesions require that the needle be positioned in an unusual way. In these situations, the surgeon should be familiar with free needle use, which is more difficult to master, but is more versatile and allows the surgeon to position the transducer and the needle independently. The key to mastering this technique is identifying the needle inside the hepatic parenchyma on the ultrasound screen and keeping it in the correct plane. To do this, place the needle in a plane parallel to the transducer and directly below it. A thin, hyperechoic line is visualized with posterior shadow and reverberation artifacts around it. **(Figure 31-10)** The transducer must follow the movement of the needle toward the desired point and its position should be changed whenever necessary to keep the tip at the center of the screen.

The IOUS is fundamental to locate liver lesions and correctly position the needles in biopsies, alcoholization, cryoablation and radio-ablation.

Ablation with ethanol is used in the treatment of HCC. Although most of the procedures are performed by percutaneous technique, new non-resectable lesions discovered intraoperatively can be addressed by ultrasound-guided alcoholization. In addition to guiding the positioning of the needle, the IOUS allows for real-time monitoring of the correct injection of ethanol into the lesion.

Ultrasound-guided cryoablation allows inserting the probe **(Figure 31-11)** for correct ablation, as well as monitoring the effectiveness of the method by visualizing the “iceball” immediately after the end of the procedure. **(Figure 31-**



Figure 31-12. Iceball on ultrasonography after cryoablation. Note that the result is a hypoechoic zone with a posterior shadow and an echogenic halo around it.

12) As soon as the tissue begins to freeze, an ablation zone starts to form and can be shown by IOUS. The area within the “iceball” is hypoechoic or anechoic, accompanied by posterior shadow. A precise transition zone seen on the ultrasound screen allows for the identification of the ablation area.

Thermal ablation, especially radiofrequency ablation, is a relatively new technique used in the treatment of lesions that cannot be resected. IOUS is essential for the success of this technique. ⁽⁴⁰⁾ As in other techniques, the radio ablation needle is ultrasonically guided to the lesion. **(Figure 31-13)** For a successful procedure, it is mandatory that the ablation zone covers the entire lesion. Therefore, the needle should

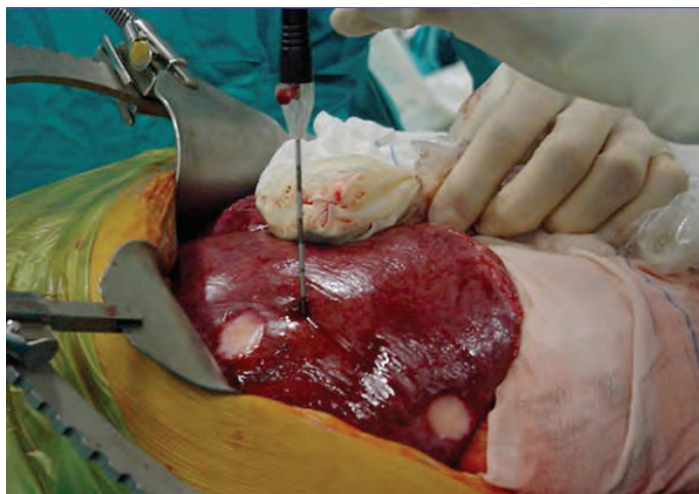


Figure 31-13. Radio-frequency ablation. Note the position of the transducer in relation to the needle penetrating the liver perpendicularly.

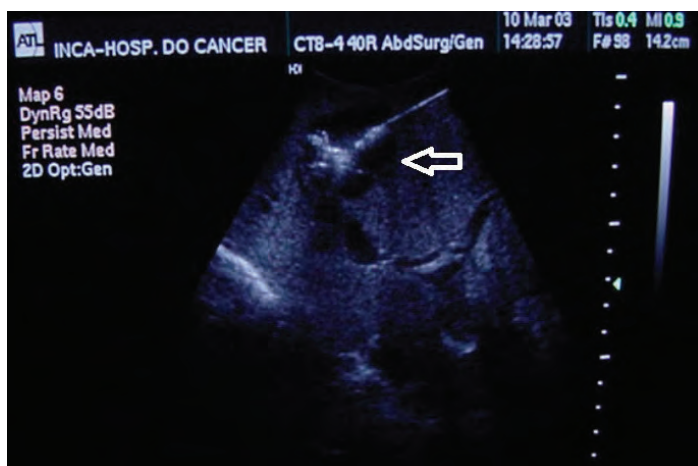


Figure 31-14. Ultrasound guided radio-ablation. Observe the tip of the needle in the lesion (black arrow). Note the formation of a hyperechoic zone during thermal action.

be correctly positioned because, unlike the other techniques, the ablation zone can no longer be visualized after the procedure has started. The thermal lesion generated by high-frequency radio waves dissipate air, making the area around the ablation hyperechoic and diffusely blurred, (**Figure 31-14**) so it becomes impossible to differentiate between the ablation area, the lesion and the hepatic parenchyma. Since positioning techniques vary depending on the needle, it is important to differentiate both types of needle: one is simple with just one tip and the other is retractable with a tip opening system.

Ultrasound Guided Resections

In addition to staging, IOUS is essential to guiding liver resections. It is almost impossible to correctly define the limits of tumors and hepatic segments without the ultrasound due to the existence of numerous anatomical variations. This is especially the case of cirrhotic patients whose liver has undergone an anarchic growth and hardened liver parenchyma hinders mobilization and palpation. The IOUS allows the three-dimensional reconstruction of the relationships between the tumor, the hepatic veins and the Glissonian pedicles. These pedicles are used as markers in the pathway definition of resections. Its location is essential in planning the surgical approach that should be individualized for each patient. The main advantage of ultrasound-guided resection is the modification of the traditional approach of hepatic parenchyma dissection, which involves dieresis in vertical planes to avoid tumor exposure. With IOUS, the relationships between dissection planes and tumor boundaries can be followed in real time, and the direction of section planes can be changed as needed. This approach has recently been redesigned by Torzilli, which he calls a radical but conservative approach, and should be used in liver surgery to improve outcomes. IOUS can also aid in traditional hepatic resections, allowing for more conservative behavior even in the most complex presentations.

A very practical and useful technique is anatomical ultrasound resection guided by ultrasound. It was initially described for tumors located in the left lobe of the liver⁽⁴¹⁾ and more recently extended for any segment,⁽⁴²⁾ including segment VIII and even for hepatic sectors.⁽⁴³⁾ It consists of the identification of the portal branches by the IOUS, followed by the compression of these branches between the fingers of the surgeon and the ultrasound transducer. The aim is to induce transient ischemia in the hepatic segment that has been compressed. This segment can then be demarcated with the electrocautery, the compression is discarded, and the resection can be started, as the surgeon knows in advance which and where is the portal branch to be connected. The great advantages of this technique are that it is easy, fast, non-invasive and reversible. This way, more parenchyma is preserved, and the intraoperative blood loss is reduced.

IOUS can be used to identify and mark the margin of resection of the lesions allowing a safe atypical hepatectomy. The resection margin can be accurately measured, and the hepatotomy line can be demarcated with electrocautery in parallel with the application of the transducer on the liver surface, with a real-time image of the lesion on the screen.

During the hepatotomy, the dissection line can be accessed countless times by the IOUS. Dissection plane is seen as a hyperechoic line, the result of air filling in the transected parenchyma. Echogenic materials, such as gases and metal instruments, can be applied in the section plane to increase the visualization of the hepatotomy line and confirm the distance of the lesion in relation to the planned resection. The intermittent use of the IOUS allows for the correction of the direction and depth of the hepatectomy whenever necessary, thus avoiding tumor exposure, preserving parenchyma and avoiding inadvertent vascular lesions.

Intraoperative contrast-enhanced ultrasound

The use of ultrasound contrast media, which consists of microbubbles of air or inert gases encapsulated by lipids or proteins, has opened up a new perspective in the IOUS. Because they are associated with lipid molecules, these gases have lower solubility than air, which results in increased acoustic impedance compared to adjacent tissues. ^(44, 45, 46) In addition, late images of the liver after 5 minutes of contrast injection can be obtained because hepatic macrophages (Kupffer cells) phagocytose the lipids containing the air microbubbles and so they remain for longer in the hepatic parenchyma. ⁽⁴⁷⁾

Contrast retention fundamentally depends on the normal amount of liver tissue and the type of vascularization of the lesion being studied. Therefore, it is much larger in hemangiomas and hepatocellular carcinomas, ^(48, 49) which are highly vascularized, and hypoechogenic in hepatic metastases, which are less vascular lesions. ⁽⁵⁰⁾

The use of contrast agents in the IOUS of liver surgeries is applied for different purposes. **(Table 31-5)** The characterization of a liver lesion begins as soon as some abnormality is identified. A good imaging method used to detect tumors should allow the examiner to differentiate between benign and malignant lesions. Ultrasound contrasted with arterial (early), portal and late phases considerably increases the characterization of liver tumors

when compared to conventional ultrasound, allowing for the differentiation of benign and malignant neoplasms in most patients.

Contrasted IOUS facilitates decision-making by the analysis of whether a liver lesion will require further investigation, reducing the number of unnecessary or invasive procedures (e.g. liver biopsy). A study comparing the findings of contrast-enhanced ultrasonography with the histopathological results showed that there is a low incidence of false positives, and that the lesions most associated with diagnostic doubt are mainly abscesses, fibrosis and focal nodular hyperplasia. ⁽⁵¹⁾

The correct diagnosis of hemangiomas is possible in 95% of the patients ⁽⁵²⁾ with the use of contrast. They are characterized by peripheral nodular increase of contrast uptake with centripetal filling. Exceptions are thrombosed hemangiomas and with areas of calcification, as these areas produce an iris-like signal and may be confused with metastatic lesions because they demonstrate absence of contrast filling in the arterial and portal phase.

Hepatocellular carcinoma is characteristically marked by abundant vascularization. It typically shows increased contrast uptake when compared to the adjacent tissue at an early stage where hepatic parenchyma has not yet been tested. In these tumors, we perceive a chaotic vascular pattern that represents a sign of neovascularization.

The use of contrast in the IOUS increased the accuracy of the detection of liver lesions, mainly of colorectal metastases. ^(53, 54) Recent studies demonstrate a 13-33% increase in the identification of these lesions when the contrast agent is used. ^(55, 56, 57)

Most of these lesions are poorly vascularized and show only peripheral arteries at the early stage (less than 15 seconds) after contrast agent injection, and often the only sign of contrast uptake is around the lesion (halo). In some cases, washout effect can be observed 2-5 minutes after the injection of the agent. False negatives are rarely found, while false positive findings should be excluded by puncture and histopathological analysis. ⁽⁵⁸⁾

Table 31-5. Applicability of Intraoperative contrast-enhanced ultrasound

Detecting liver tumors.
Characterizing tumors (benign versus malignant).
Monitoring the ablation area.
Viewing the hepatic vessels.
Analyzing the diffuse diseases of the liver (microscopic shunts).

Future Perspectives

Scientific advances have gained momentum over the years. The same did not happen with ultrasonography, which has remained practically unchanged since the beginning, except for improved equipment techniques and small advances when employed in clinical practice. In any case, it is incomparable to advances in other modalities of imaging

diagnosis, such as CT, MRI and PET-CT. Only with the recent introduction of contrast agents can ultrasonography take a step towards new horizons.

It seems the technique has reached its limit. But its combined use with other methods and its applicability in other fields of medicine prove to be inexhaustible.

In laparoscopy, the development of transducers capable of performing contrast-enhanced ultrasonography during minimally invasive procedures may overcome limitations still encountered with the laparoscopic technique. Some lesions cannot currently be interpreted with the aid of contrast during laparoscopy, increasing false positive indexes and thus exposing patients to unnecessary surgeries.⁽⁵⁹⁾ In robotic surgery, the incorporation of ultrasound into the robotic arm is meant to improve the results of this relatively new technique.

Developed in 1991, real-time 3D ultrasound is still being incorporated into clinical practice and its extension for intraoperative use promises gains for the surgeons, who will have a three-dimensional method never previously imagined for real-time use during resections hepatic diseases.⁽⁶⁰⁾

As we know, there is no limit to human inventiveness. And it will undoubtedly continue to exist in the development of imaging techniques to be used intraoperatively so that they can assist the surgeon in achieving the best possible result, which is safe surgery, without patient morbidities and reliable long-term results.

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Chapter 32

Interventional Radiology in Hepatobiliary Pathologies

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Introduction

Nowadays, Interventional Radiology (IR) plays a key role in the multidisciplinary approach to hepatobiliary diseases. Most of the patients diagnosed with hepatobiliary diseases will eventually be submitted to one or more IR procedure during the course of the disease, including image-guided biopsy for diagnosis and a sort of curative or palliative treatments. Our objective is to briefly describe some of these techniques and how they apply in the daily practice.

Percutaneous Biliary Drainage

Primary liver neoplasms, liver metastases, and pancreatic carcinomas will eventually evolve with biliary stenosis, obstruction or invasion, and biliary drainage may be indicated as a palliative treatment to reduce symptoms from cholestasis and pruritus or to reduce bilirubin levels to allow chemotherapy and/or surgery. Biliary drainage may also be indicated to treat postoperative stenosis or fistulas. ⁽¹⁾

Indications: ⁽²⁻³⁾

- Obstructive jaundice and/or cholangitis.
- Treatment of postoperative biliary stenosis and/or fistulas.

Contra-Indications:

- Coagulopathies.
- Large ascites (left-sided approach is preferable).
- Isolated bile segments.

Technique: ⁽²⁾

The procedure is usually performed under conscious sedation and local anesthesia. Intravenous antibiotic is routinely given to all patients. Fluoroscopy and ultrasound are used to guide biliary puncture and drainage.

There are three types of biliary drainage:

- a) external drainage;
- b) internal-external, and
- c) internal.

If a catheter cannot be advanced beyond the obstruction into the small bowel, then an external drainage catheter is placed above the obstruction point. When the stenosis is crossed, a multiside hole drainage catheter that allows bile to drain both externally into a bag and also internally into the small bowel is inserted into the biliary tree. Finally, a self-expanding metallic stent is a third option for drainage. The advantage of a stent is the ability to re-establish patency of the occluded duct(s), allowing for internal drainage of bile into the bowel without an external device. Since most metallic stents cannot be easily removed, surgeons often prefer that a metallic stent not be placed in patients who are candidates for resection. Furthermore, stent placement in high bile duct obstruction makes further percutaneous intervention more difficult, and stents should only be placed after all targeted segments have been drained. Recently, retrievable covered metallic stents are also being used and may minimize these issues. The metallic stent's patency is around 6 to 9 months. ^(4,5)

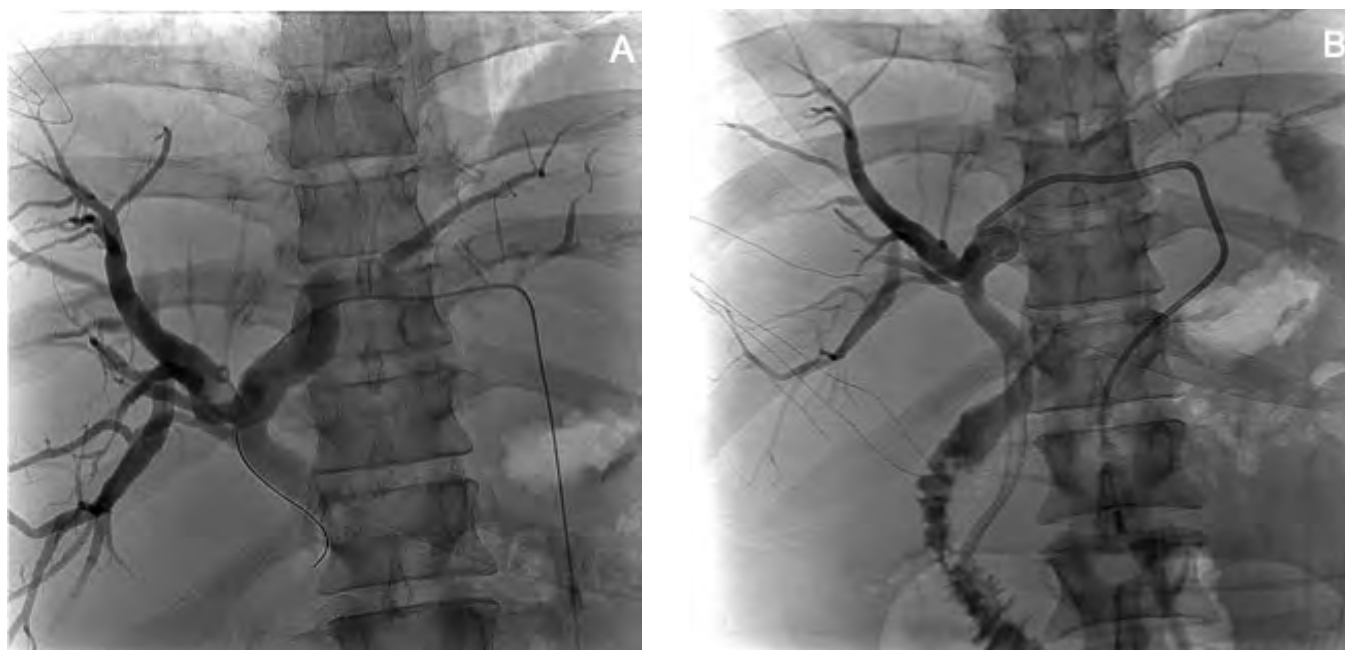


Figure 32-1. Male, 40 years old with pancreatic neuroendocrine tumor.

A) Cholangiography showing low bile duct obstruction, trespassed with guide wire.

B) Cholangiography after stent deployment, with good contrast passage to the duodenum.

Important to note that when the obstruction occurs below the confluence of right and left bile ducts, complete drainage of the entire biliary tree can be accomplished by a single, well-placed catheter or stent. However, in high obstructions, a single drainage catheter may not effectively drain the entire biliary tree. Though, two or more catheters or stents may be necessary.

Complications: ⁽⁶⁾

- Bleeding
- Sepsis
- Pancreatitis
- Bile leak around the catheter and catheter dislodging
- Stent migration and/or occlusion

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Chapter 33

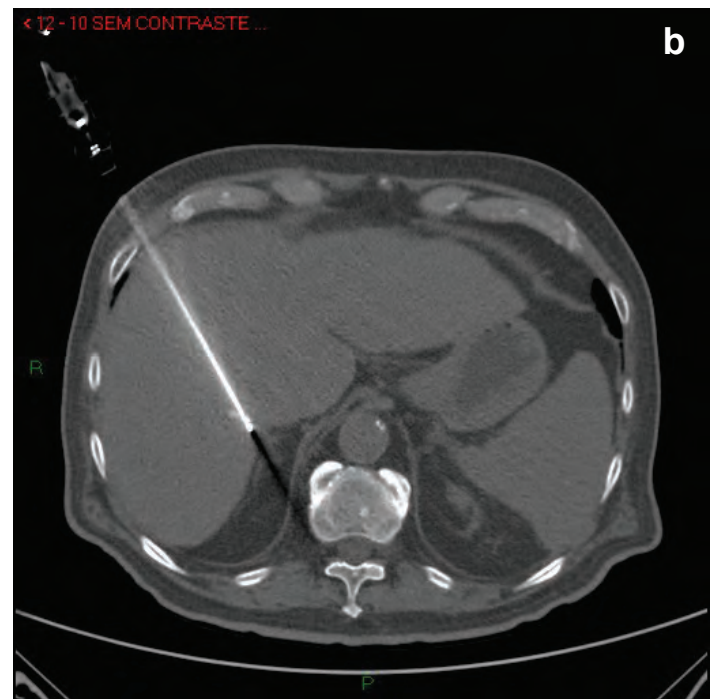
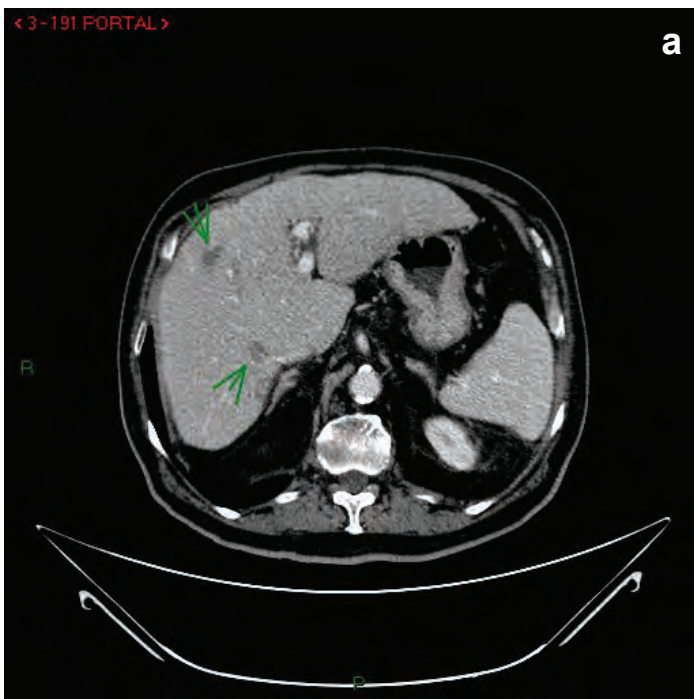
Interventional Radiology - Liver Thermal Ablation

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Liver thermal ablation (LTA) is a minimally invasive technique for treating primary and secondary malignant hepatic tumors. ⁽¹⁾ It can be used alone or in combination with liver resection. The best long term control is obtained when lesions are smaller than 3.0cm. ⁽²⁾ There are four main types of thermal ablation techniques: Cryoablation, Microwave Ablation (MWA), Radiofrequency Ablation (RFA), and Irreversible Electroporation. MWA and RFA are more frequently used. The choices for each technique will rely on the availability and operator experience. Imaging guidance is mandatory. Ultrasound, computed tomography, cone beam CT, and fusion imaging have been described to guide liver ablation. ⁽³⁾

Ablation is acknowledged to be one of the best treatment options for patients with early and very early stage hepatocellular carcinoma (HCC), according to a recent review of the Barcelona Clinic Liver Cancer classification. ⁽⁴⁾ RFA may also be used to treat hepatic metastases in non-surgical patients for tumor size, position, number of tumors or patients comorbidities. A recent randomized controlled trial has shown overall survival benefit when RFA was added to systemic chemotherapy in patients with colon-rectal liver metastases. ^(5,6)

In general, patients suitable for liver thermal ablation are those with up to 5 lesions, smaller than 3 cm. The



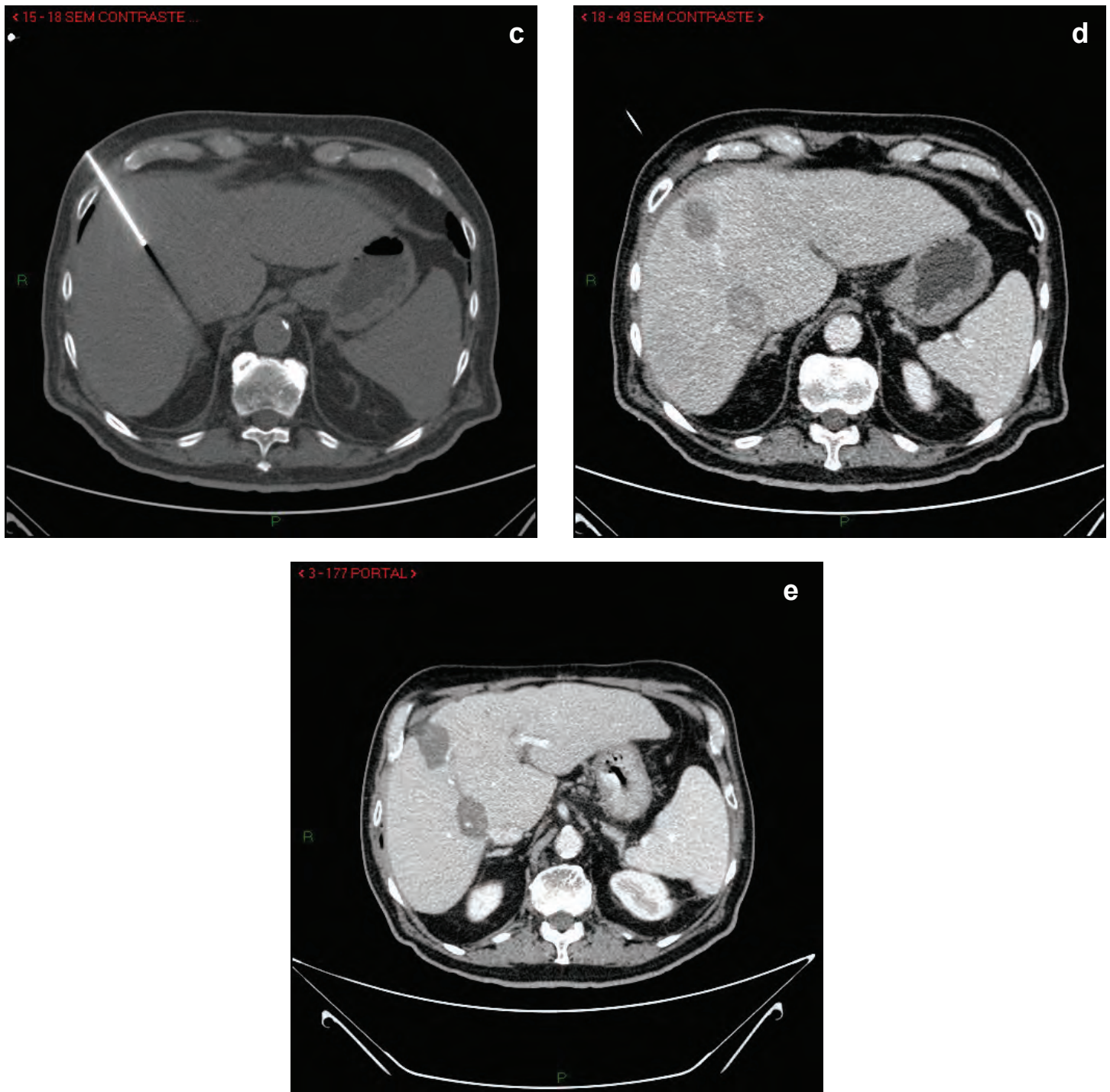


Figure 33-1. Radiofrequency ablation (RFA) of two small liver metastases from colorectal adenocarcinoma in a 79-year-old male.

(a) Pre-ablation portal-phase CT showing 2 hypovascular lesions (arrows).

(b, c) RFA needle positioning for ablation.

(d) Immediately post-ablation scan shows coagulative necrosis encompassing the entire lesion adequate margins.

(e) Follow-up CT 12 weeks later shows complete treatment with no signal of recurrences.

procedure is usually performed under general anesthesia with standard cardiac, pressure, and oxygen monitoring. The risks should be assessed before the procedure through a clinical evaluation by a multidisciplinary team, including an interventional radiologist, a hepatologist, an oncologist, a surgeon, and an anesthesiologist. The main contraindications to RFA are tumor located <1 cm from central biliary ducts (risk of delayed stenosis or bilomas); dilation of intra-hepatic bile ducts; anterior exophytic tumor (risk of tumor seeding); bilioenteric anastomosis; and untreatable coagulopathy. ^(2,3)

It is reported that the most common complication of percutaneous hepatic ablation is hemorrhage, ⁽⁷⁾ but major hemorrhage has been reported in less than 1% of cases. Abscess formation is more frequent in patients after biliary-enteric anastomosis or other manipulation such as stent placement or sphincterotomy. ⁽⁸⁾ Tract seeding rate remains under 1% of HCC ablated with straight electrodes. ⁽⁹⁾ Death is rare, at less than 1%. ⁽⁷⁾

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Chapter 34

Interventional Radiology - Portal Vein Embolization

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Hepatic resection plays a major role in the attempt of curative treatment of primary liver malignancies such as cholangiocarcinoma, hepatocellular carcinoma, and metastasis from colorectal cancer and other primary origins.

⁽¹⁾ Future liver remnant (FLR) predicts survival after major hepatectomy. Most hepatobiliary services admit an FLR of at least 25% in healthy livers. ⁽²⁾ In patients with hepatic cirrhosis ⁽³⁾ or previously exposed to intense systemic chemotherapy, larger FLR of 35% to 40% is required. ^(4,5)

The rationale is that portal vein embolization (PVE) of the aimed portal vein territory will diverge all blood flow containing trophic and growth factors to the FLR, inducing hypertrophy and allowing a safe future surgery. ⁽⁶⁾

Advances in hepatobiliary surgeries associated with more effective systemic chemotherapy have permitted the conversion of previously unresectable patients into surgical candidates. ⁽⁷⁻⁹⁾ PVE has been shown to be safe and effective in promoting FLR growth ^(2, 10) and is currently adopted in the preoperative scenario in many hepatobiliary units worldwide. ⁽¹¹⁾

Different access approaches and embolic materials have been described to perform PVE. Up to date, there is no definitive evidence of which one would be the best. ⁽¹²⁾ In our hospital, we use n-butyl-cyanoacrylate (NBCA) as the embolic agent because it is cheaper, the infusion time is faster, and some publications have suggested that it may be more efficient than other embolic agents. ^(10,13)

Before performing PVE, it is imperative to review all cross-section images. Ideally, the decision to proceed to PVE should be done by a multidisciplinary team, specially in difficult cases or when the surgery is unlikely to take place, whatever the reason.

Most teams wait 4-6 weeks before surgery to allow FLR hypertrophy. The absence of hypertrophy is uncommon, occurring in 10-20% of patients. ⁽¹⁴⁾ Major complications are rare, including liver abscess, cholangitis, portal vein thrombosis, and sub capsular hematoma. Minor complications including abdominal pain, fever, nausea are usually self-limited. No deaths have been reported in the literature so far. ⁽¹⁵⁻¹⁷⁾

Absolute contraindications for PVE:

1. Tumor substantially invading the portal vein, blocking the catheter passage;
2. Marked clinical portal hypertension;
3. Severe blood coagulation disorders (PT<60%, platelet count <50G/l).

Surgery With and Without PVE

In a recent publication of the interventional radiologists of our Liver Group – INCA - BRAZIL 50 non-cirrhotic consecutive patients were eligible to PVE, with primary or secondary liver cancer treatable by hepatectomy with a liver remnant (FLR) volume less than 25% or less than 40% in diseased livers. Colorectal liver metastases were the most frequent tumor and patients had been previously exposed to chemotherapy. As results FLR increased from 422 ml to 629 ml ($P < 0.001$) after PVE, corresponding to an increase of 52%. Kinetic growth rate was 2.98% / week. Resection finally occurred in 31 (62% of PVE) patients. Only one patient presented with liver insufficiency within 30 days after surgery. ⁽¹⁰⁾

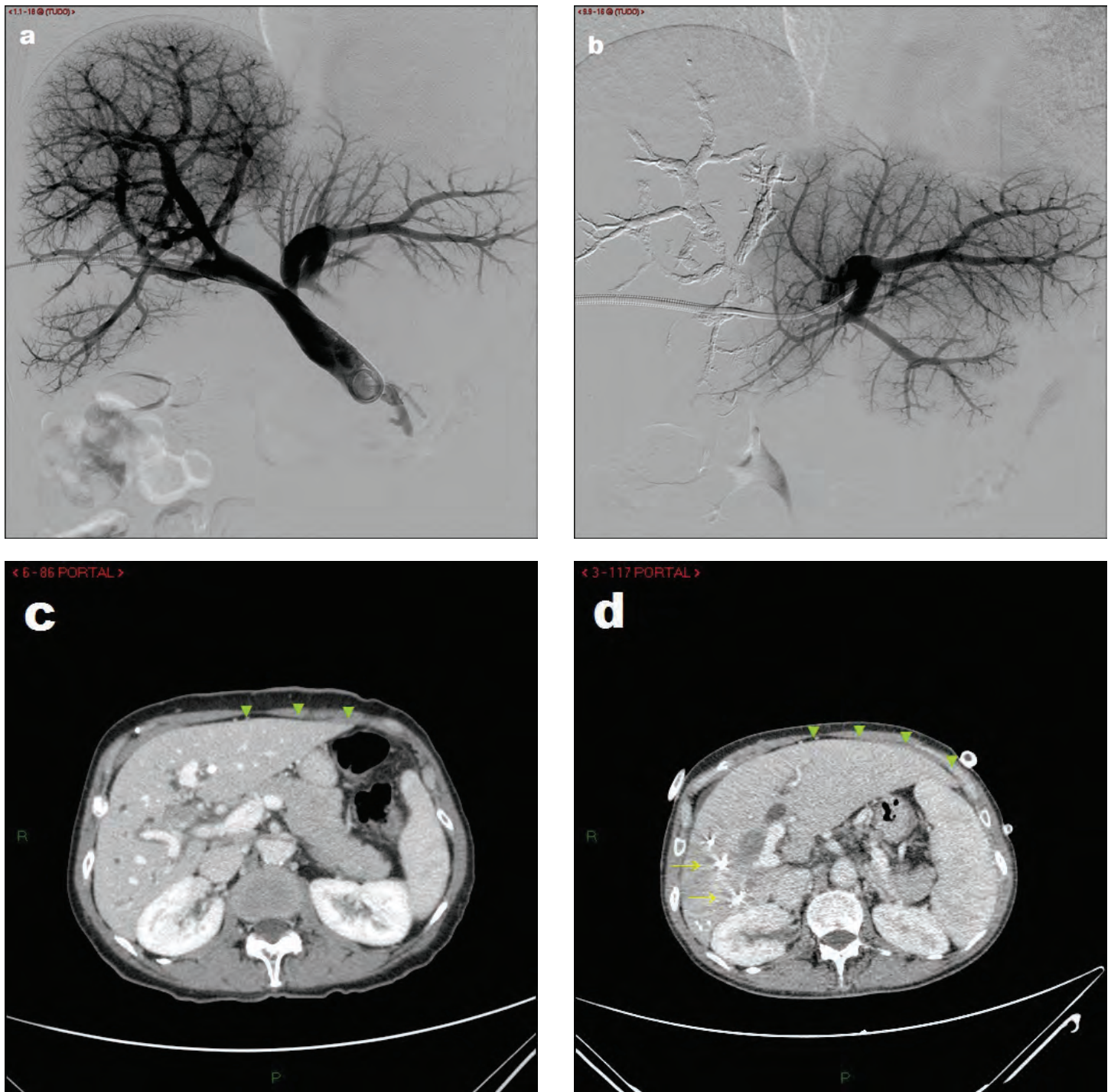


Figure 34-1. 66-year-old female with a large Cholangiocarcinoma, precluding major hepatectomy due to small FLR.

(a) Pre-embolization portography.

(b) Post-PVE portography showing Glue cast at the end of PVE in the right portal branches and demonstrating good flow to the left portal vein.

(c, d) Computed Tomography before and 30 days after PVE, respectively, showing glue at the right portal vein (arrows) and important hypertrophy of the left liver lobe (compare the arrowheads pre and post PVE).

In our earlier (2019) non-published data we have analyzed the survival curves of colorectal liver metastases resections with and without PVE. Patients with PVE (39 cases in 298) had a worst survival curve but no statistically significant difference could be demonstrated between our groups as in **Figure 34-2**.

A recent systematic review of perioperative and survival outcomes of liver resections with and without preoperative portal vein embolization for colorectal metastases by Ironside N et al identified 13 studies in which 539 patients had had PVE and 806 had not had N-PVE.

Following PVE 70% of patients proceed to liver resection. The postoperative morbidity was 42% after PVE, with a 10% risk of postoperative liver failure. Median overall survival, reported in all studies, was 38.9 months and 45.6 months (PVE and N-PVE respectively). The median disease free survival, reported in eight studies, was 15.7 (PVE) and 21.4 (N-PVE) months respectively. Tumor progression after PVE was the predominant reason for not proceeding to liver resection. ⁽¹⁸⁾

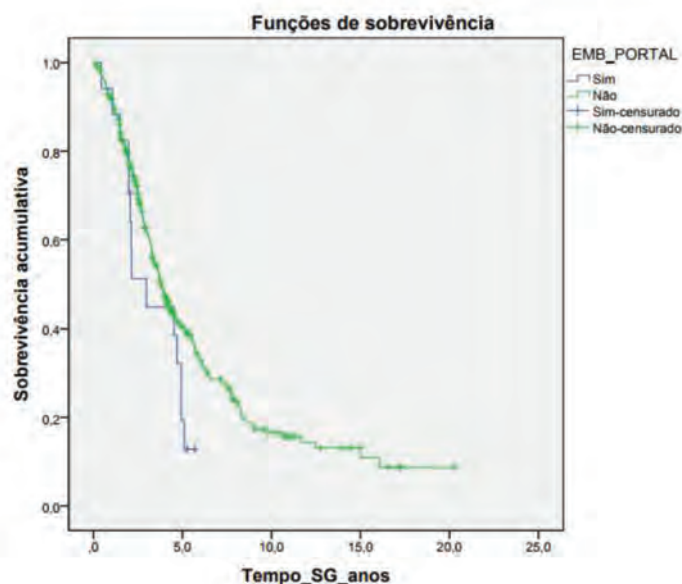


Figure 34-2. Survival Curves of patients with and without PVE, resected for colorectal cancer liver metastases in INCA-BRAZIL (2019).

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Chapter 35

Interventional Radiology - Loco Regional Therapies

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Introduction

The incidence of primary and metastatic liver cancer continues to increase and most patients are not surgical candidates. ^(1,2) In this scenario, minimally invasive techniques as a treatment option are becoming more common. Percutaneous interventions such as percutaneous ethanol injection (PEI), radiofrequency ablation (RFA) and microwave ablation (MWA) have been shown to be effective for the treatment of liver tumors. ⁽³⁻⁵⁾ Similarly, endovascular techniques such as intra-arterial chemotherapy (IAC), transarterial embolization (TAE), transarterial chemoembolization (TACE) and transarterial radioembolization (TARE) have shown clinical benefit in selected patients. ⁽⁶⁻¹⁰⁾

Endovascular Techniques

Transarterial therapy may effectively deliver highly concentrated doses of agents to the tumor, whereas sparing the surrounding hepatic parenchyma. ⁽¹¹⁾ Despite controversy and diversity, transarterial therapies have gained wide acceptance over the years and are currently considered as the mainstay therapy, especially for unresectable primary liver cancer. ⁽¹²⁾

Indications

Transarterial therapies are considered palliative options since long term tumor control is unlikely. TACE is the preferred treatment for intermediate stage BCLC hepatocellular

carcinomas ⁽¹³⁾ and has also successfully been employed for patients with carcinoid tumors, and other liver metastatic diseases. ⁽¹⁴⁻¹⁵⁾ Cholangiocarcinomas may be effectively treated with TACE, although only small uncontrolled studies have addressed this topic. ⁽¹⁶⁾ TARE improves local control for colorectal liver metastatic patients, but it has failed to show benefit in overall survival. ⁽¹⁷⁾

Predictors of outcome are related to tumor burden (tumor size, vascular invasion, and AFP levels), liver function (Child-Pugh, bilirubin, ascites), performance status (Karnofsky index, ECOG), and response to treatment. Thus, the best candidates are patients with preserved liver function and asymptomatic lesions without vascular invasion or extrahepatic spread. ⁽¹⁸⁾

Contra-Indications

End-stage liver disease, poor performance status, current systemic infection, total portal vein thrombosis, and replacement of more than 50% of liver parenchyma by tumors are contra-indications, although a superselective approach, as well as an adjustment of the chemotherapeutic dosage, may minimize liver damage in selected cases. ⁽¹⁸⁻²⁰⁾

Patients whose sphincter of Oddi function have been eliminated, that is, hepaticojejunostomy, sphincterotomy patients, or patients with percutaneous or internal biliary stents, are at high risk for developing a hepatic abscess after TACE. Stringent 24-hour bowel preparation and intravenous administration of broad-spectrum intravenous antibiotics before the procedure decrease the infection risks.

Technique

Regardless of the kind of technique implemented, a complete evaluation including clinical exams, laboratory tests, and imaging are mandatory to select patients to treatment. The type of treatment to be offered will rely mostly on availability, costs, and local experience.

Although radial arterial access is gaining favor, traditional femoral arterial access is likely still the preferred method at most institutions. Radial access certainly carries benefits, particularly with respect to patient comfort. ⁽²¹⁾

IAC

The tip of a port-catheter is placed inside the hepatic artery. Multiple drug schemes may be administered directly to tumor vessel, increasing drug concentration in the liver. ⁽²²⁾

TAE

Vascular embolization using liquids, particles, foam or calibrated microspheres in order to occlude tumor vascular supply and induce necrosis by ischemia.

TACE

Additional to embolization, a chemotherapeutic agent is used to improve tumor necrosis. A liquid agent (Lipiodol) or calibrated beads (Drug Eluting Beads) are used to carry the drug into tumor vessels. Liquid agent is not drug selective and may be mixed with a single or a combination of drugs. The most widely used single chemotherapeutic agent is doxorubicin and the combination of cisplatin, doxorubicin, and mitomycin C is the most common drug combination infused. On the other hand, drug eluting beads may be mixed with doxorubicin or irinotecan. ⁽²³⁾

TARE

Radioembolization, a form of intra-arterial brachytherapy (radiotherapy), is a technique where particles of glass or resin, incorporating the isotope Yttrium-90 (Y90), or more recently Holmium-166, are infused through a catheter directly into the hepatic arteries. Y90 is a pure beta emitter, decays to stable Zr-90 with a physical half-life of 64.1 hours and has a mean tissue penetration of 2.5 mm, and a maximum penetration of 10 mm. Given that radiation is embedded in the microspheres, the treatment planning is more complex and expansive. Important to note that due to the small size of the spheres, minimal embolization effect is expected with TARE.

As opposed to traditional whole liver external beam radiation to the liver, where doses are limited to 30 to 40 Gray (Gy), intra-arterial radiotherapy permits the application of higher doses to tumoral tissue with tolerable irradiation of normal liver parenchyma. Experience with this therapy has been shown to be effective for both primary and metastatic tumors. ⁽²⁴⁻²⁶⁾

Complications

Specially after TACE, patients may present the postembolization syndrome which manifests with pain, fever, nausea, fatigue, and elevated transaminases. These symptoms are usually self-limited. It is important to differentiate postembolization syndrome from other complications, such as liver abscess, gallbladder infarction, and septicemia. Complications resulting from nontarget embolization include necrosis in undesirable arterial beds. Liver failure in well-selected patients is extremely rare.

Radioembolization-induced liver disease (REILD) is a lethal complication after TARE, secondary to the microsphere deposition in nontumorous parenchyma. ^(6,27)

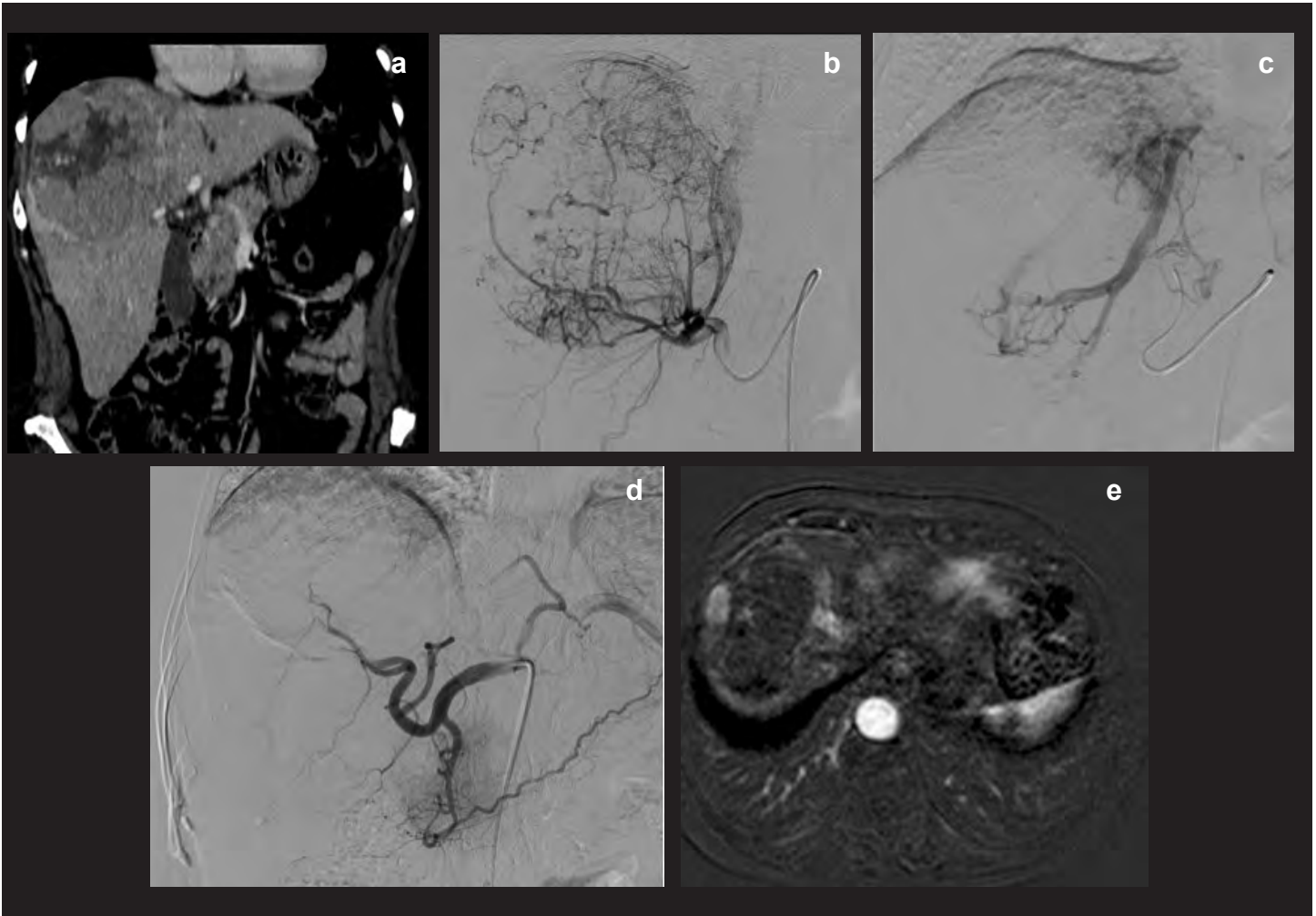


Figure 35-1. Female, 70 years old, with inoperable hepatocarcinoma (HCC)
(A) CT scan, portal phase, coronal plane, showing large HCC with wash-out.
(B) Angiography during first session of chemoembolization.
(C) After third session patient developed intra-tumoral arteriovenous fistula.
(D) Angiography after sixth session of chemoembolization (DEB-TACE)
 showing important tumor devascularization.
(E) Control MRI after sixth session - notice large avascular mass
 with small viable lesion on the tumor periphery.

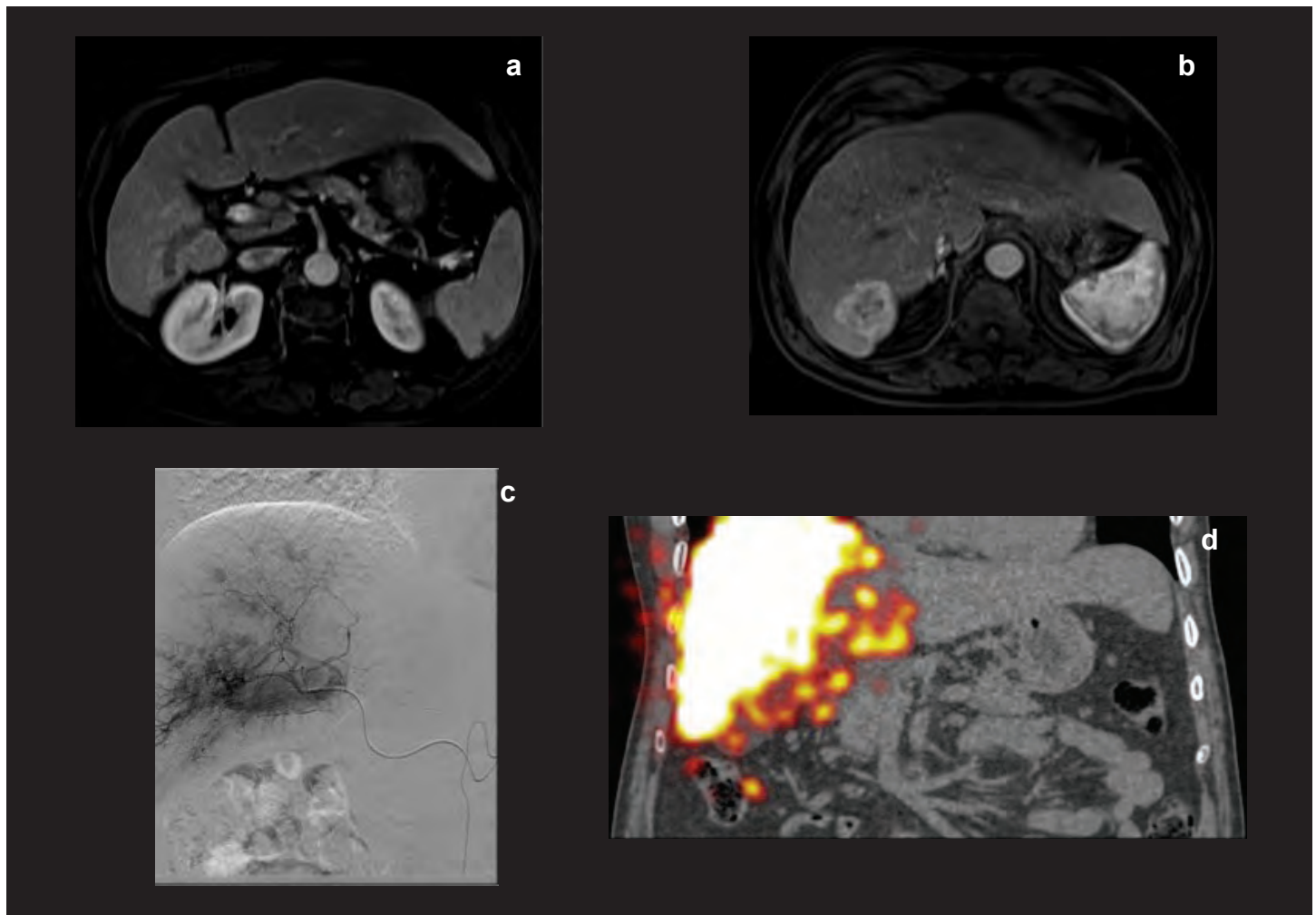


Figure 35-2. Male, 60 years old with unresectable HCC
(A, B) Pre-procedure MRI showing HCC with right portal vein invasion.
(C) Angiography before Y90 (SIRspheres) injection - notice tumoral thrombus opacification.
(D) PET-CT, coronal plane, after Y90 injection demonstrates high uptake on the right liver lobe.

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SECTION VIII
Urological Cancer

Chapter 36

Kidney Cancer

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Epidemiology

Renal cell carcinoma (RCC) represents the twelfth cause of death from cancer in the USA. Global statistics show an incidence of 4.8 new cases per 100,000 inhabitants. It occupies the twelfth place in incidence in the world, according to the sources of the Globocan the average age of diagnosis is 64 years. Male Predominance 2:1 (other sources speak 1.6 times more frequent). Peak incidence between 60 and 70 years. Its incidence in the last decades has increased 2 to 4% due to the greater use of imaging techniques. ⁽¹⁾

Etiology

Most of these carcinomas (80%) are sporadic. There is a direct relation with tobacco (causes 30% of cases), obesity (present in 30-40% of patients) and family history (2-5%); also, with hypertension, long-standing peritoneal dialysis (8 to 10 years), phenacetin consumption, increased age, diabetes mellitus (17%). In a lesser proportion, it is related to urban and occupational environments with exposure to industrial solvents (trichlorethylene), footwear and leather products, asbestos, cadmium, petroleum and gasoline. There is no strong association with alcohol consumption, dietary factors, oral contraceptives or use of analgesics.

The most important primary prevention for RCC is to eliminate smoking and avoid obesity. ⁽²⁾

Clinical

Many renal masses are asymptomatic until advanced stages of the disease, more than 50% of the RCC are detected incidentally by non-invasive imaging studies used to investigate non-specific symptoms or other abdominal

pathologies. The classic triad of flank pain, macroscopic hematuria and palpable mass is observed only in 6-10% of patients and correlates with aggressive histology or advanced disease. The bilateral presentation at the time of diagnosis is 1 to 5%. ⁽³⁾

Systemic Syndromes Associated with Renal Cancer: Paraneoplastic syndromes occur in approximately 30% of cases. These include: High erythrocytation in 55.5%, hypertension due to increased renin or compression of the renal artery, 37.5%, anemia 36.3%, cachexia, weight loss > 10%, occurs in advanced stages. 34.5%, fever of long evolution that can be isolated. 17.2%.

Stauffer syndrome: Reversible liver disease in the absence of liver metastases. It is manifested by elevated liver function test, fever, hepatic necrosis, which resolves after nephrectomy; its persistence or recurrence is a sign of poor prognosis, its incidence is approximately 14.4%.

Hypercalcemia that clinically manifests with osteotendinous hyperreflexia, fatigue, nausea. Its presence is a sign of very bad prognosis, considered in the Motzer criteria. It occurs in approximately 5 to 15%. ⁽⁴⁾

Diagnosis

It is based on the detection of a renal mass through imaging tests. The majority is identified by ultrasonography (USG), but the contrasted computer tomography (CT) is the diagnostic method of choice, since it shows the characteristic reinforcement (> 15 HU) of the tumor to the application of contrast agent (80% of the tumors are vascular and capture the contrast agent and only 20% are avascular) and the solidity of the tumor. ⁽²⁾ The CT also provides information on:

- The morphology and function of the contralateral kidney.
- The extension of the primary tumor with extrarenal dissemination.
- Venous involvement (thrombus, and number and position of arteries and veins).
- Lymph node involvement of loco-regional lymphatics.
- Extension to adrenal glands and liver.

Renal Biopsy

In contrast to other urological neoplasms (prostate, bladder, penis), where a histological diagnosis is necessary before proceeding with radical treatment, the use of percutaneous biopsies to determine the histology of a renal mass has been historically limited.

Traditionally, the indications for performing a percutaneous biopsy have been: Discard lymphoma, a renal abscess, or metastatic disease to the kidneys in the presence of a known extrarenal malignant tumor.

European guide recommends it in the following scenarios: ⁽²⁾

- For the histological diagnosis of radiologically indeterminate renal masses.
- To select patients with small renal masses (SRM) for surveillance approaches.
- To obtain histology before ablative treatments.
- In metastatic tumors to select white therapy.
- Confirm the diagnosis of a primary tumor in the presence of disseminated metastases of unresectable retroperitoneal tumors.

Fuhrman Grading

Dr. Susan Fuhrman created a histopathological grading for renal clear cell tumors, which she evaluates / assesses the size of the nucleus and the characteristics of the nucleoli. This grading has forecast correlation. The Fuhrman grading is one of the most important forecast variables in all stages of the RCC. The nuclear grade is a predictor of survival regardless of the pathological stage.

Applicable only for the clear cell histological subtype, it is not useful for the other subtypes (papillary and chromophobic mainly). ⁽⁵⁾

The most frequent Fuhrman nuclear grades are 2 and 3. Grade 4 is presented in slightly more than 10% and grade 1 in <10%. ⁽⁵⁾

Table 36-1. Fuhman Nuclear Grades				
Grade	Core Size	Nucleoli	Nuclear Contour	DFS* To 5 years
1	10µm	Absent or unclear	Uniform	89%
2	15µm	Small (visible 400x)	Irregular	65%
3	20µm	Prominent	Irregular	46%
4	>20µm	Prominent, Thick	Atypical	<46%

*DFS =Disease Free Survival

Histological Diagnosis

Renal cell carcinomas comprise a broad spectrum of histopathological entities described in the 2004 WHO classification and modified by the International Urological Pathology Society (ISUP) Classification in Vancouver.

There are three main types of RCC:

1. Clear cells (ccRCC),
2. Papillary (pRCC - Type I and II)
3. Chromophobe (chRCC)

The histological diagnosis includes, in addition to RCC, the evaluation of nuclear grade, sarcomatoid characteristics, vascular invasion, tumor necrosis and invasion of the collecting system and perirenal fat. ⁽⁶⁾

Sarcomatoid differentiation (may be fibrosarcoma, pleomorphic sarcoma). Its presence alone, regardless of the percentage of affectation, gives a poor prognosis. Survival with sarcomatoid inattention is from 4 to 9 months. With a 5-year survival from 15 to 22 months. The treatment with Sunitinb has presented modest results. The combination of gemcitabine and doxorubicin may be an option according to the European guidelines. Rhabdoid differentiation (similar to rhabdomyoblasts). ⁽⁶⁾

Family Syndromes and Renal Cell Carcinoma

Most RCCs are sporadic (80%), but hereditary predisposition causes 2 to 5% of cases, which may be multifocal or bilateral. Sporadic tumors have up to 50 to 60% chance of presenting mutations in the gene of the Von Hippel- Lindau

(VHL). And another 15 to 20% present hypermethylation of this gene. The VHL syndrome is associated with a 50% incidence of RCC, and it is associated with multiple and bilateral tumors up to 80%. The VHL gene helps maintain normal levels of HIF-1. ⁽⁷⁾

Table 36-2. Family Syndromes and Renal Cell Carcinoma

Syndrome	Genetics	Clinic	Characteristics
Von Hippel- Lindau	Loss of VHL gene function (chromo. 3p25-26) which is a tumor suppressor gene by deletions or mutations	Clear cell RCC Kidney cysts. Hemangioblastoma of the CNS. Retinal angiomas. Pheochromocytoma Pancreatic and epididymal cysts.	It is associated with almost 60% (80%) of sporadic cancers. Loss of VHL function leads to Fact activation. Hypoxia Inductor, including VEGF and platelet derivative (PDGFR), erythropoietin and other genes involved in tumor genesis. It is associated with multiple and bilateral tumors in 80%.
Hereditary papillary renal cell carcinoma	Mutations in the c-Met proto-oncogene (chromosome 7q34)	Papillary carcinoma type 1 It is related to other tumors: GI, melanoma.	It has an increased predisposition to form multiple and small bilateral tumors. Found at the end of life, with little predisposition to metastasize.
Leiomyomatosis and familial renal cell carcinoma	Fumarate hydratase gene of the Krebs cycle. (chromo. 1q42-43)	Papillary Carcinoma type 2 Cutaneous leiomyomas, Uterine leiomyomas, Kidney tumors in 20%	Development of large, unilateral, very aggressive tumors
Birt- Hogg- Dube	Loss of BHD1 gene function (chromosome 17p11.2)	Pulmonary Cysts Pneumothorax. Chromophobe Carcinoma and Oncocytoma Cutaneous Fibrofolliculomas	Increased risk to develop lung cysts and pneumothorax. Renal Subtype: Oncocytoma 30% of patients with BHD syndrome have chromophobe carcinoma.
Hereditary renal cell carcinoma	Mutations in Chromosome 3	Without other characteristics of the VHL gene	
Succinate dehydrogenase	It is associated with clear cell carcinoma and chromophobe		
Tuberous sclerosis	Triad: Epilepsy, mental retardation, sebaceous adenoma. Predisposes for the development of renal angiomyolipomas		

Histological Classification of Renal Cell Carcinoma

(Adenocarcinomas constitute more than 85% of renal cancers and originate from the epithelium of the proximal convoluted tubule of the cortex).⁽⁷⁾

There is a variety of kidney tumors, and about 15% are benign. All kidney injuries require an examination of malignant behavior.⁽⁷⁾

Table 36-3. Histological Classification of Renal Cell Carcinoma

Histology	Subtype	Genetic Factors	Characteristics
Conventional (70 - 80%)	Clear cells Granular Mixed	VHL gene mutations. Deletions of 3p Loss of 8p, 9p, 12q. Gain of 5q	Hypervascularity Aggressive behavior It can respond to immunotherapy. Family shape is the Sin. VHL. Coming from proximal or progenitor tubules. (+) antigens of RCC, CD-10 (+), Cytokeratins (+), PAS (+). It will give synchronous metastasis in 33% (one third) and 10 to 20% will have metachronic in the following 5 years. The prognosis is worse with metachronic than synchronous metastases.
CC Clear Cystic multilocular	Rare	Corresponds to <1% of conventional renal carcinomas	Clear cells. Well circumscribed mass of small or large cysts. Simple grade 1 cysts. No expansive nodules of tumor cells. Generally benign.
Chromofi (Papillar) (10 - 15%) (It is also known as Papillar RCC)	Type 1 (5%)	Mutations in the Protooncogen c-Met Loss of 14 and Y Gain of 12, 16, 20. Trisomy 7 and 17	Type 1: observed in Hereditary Papillary Carcinoma. Presents Basophilia and small nuclei, hypervascularized. Multicentricity (multifocal) frequent (30%). And bilateral more than the conventional RCC. Favorable forecast
The most frequent bilateral.	Type 2 (10%)	Mutations in the Fumarate Hydratase gene (in familial), and c-Met (sporadic)	Type 2: Worst prognosis, is observed in leiomyomatosis and renal cells. It has large nuclei. Frequent in acquired polycystic disease. It comes from proximal tubules, which are mixed with papillae. Presents microcalcifications and classic Psammoma Bodies
Chromophobe (3 - 5 %)	Type 1, Classic. Type 2, Eosinophilic	Loss of BHD gene function, Loss of chromosome 1, 2, 6, 10, 11, 13, 17, 21	Better prognosis than the conventional one. There are aggressive variants. It is observed in the Birt-Hogg-Dube (BHD) syndrome It comes from intercalated cells of the collecting tubule. Microscopically 2 variants: classical and eosinophilic. Positive for Hale Iron. Expression of c-Kit (+), PAS (-).

Cont...

Table 36-3. Histological Classification of Renal Cell Carcinoma

Histology	Subtype	Genetic Factors	Characteristics
Tubule Collector (Bellini tumor) (<1 %)	Medullary cell is a variant	Loss of chromosome 1, 6, 8, 11, 18, 21 and Y. Gain 7,12,17,20	It is the most aggressive RCC. Appearance in “fish meat”, wraps or compresses the structures of the hilum due to its central location (Infiltrating), presents with metastatic disease, poor prognosis.
Fusocellular Sarcomatoid	High grade variant of clear cell carcinoma or other subtypes, poor prognosis, overlaps and coexists with other types of carcinomas.		
Spinal carcinoma			
Not Classified (1%)	Little Defined		
RCC associated with Xp11.2 / TFE3 translocation (gene fusion)	Several mutations in chromosome Xp 11.2 resulting in a fusion in TFE3	Rare. Tumors well circumscribed. Tan yellow occurs in children or young adults, 40% of pediatric RCC, gives lymphatic metastasis. It presents as clear cell tumor with papillary structure. Immunohistochemical: TFE3 Nuclear	
RCC Post-Neuroblastoma	Rare. Well circumscribed tumor with solid and papillary structure. It occurs in children.		
Tubular mucinous and spindle cell carcinoma	Rare. Well circumscribed, pinkish white, located in the medulla. Combination of tubules and mucin and spindle cells. Favorable forecast		

Treatment of the RCC

The treatment of RCC can be divided, for its study, in stages or by the extension of the tumor in three large sections:

- Localized RCC
- Locally advanced RCC
- Metastatic RCC.

At each stage there are suggested management alternatives, so when the RCC is **located to the kidney** the management alternatives can be: partial nephrectomy (NP) or radical nephrectomy (NR) and even minimally invasive techniques such as radiofrequency ablation, cryosurgery, etc.

Cancer **locally advanced** it can be managed with nephrectomy plus lymphadenectomy in N + tumors, selective embolization of the renal artery, thrombus management in the venous system, etc.

In **metastatic stage**, cytoreduction nephrectomy, metas-

tastectomy, management with systemic white therapies, etc., are alternative management. Surgical treatment is the only curative therapeutic approach for RCC.

Surgical Treatment Options for RCC

Radical surgery (radical nephrectomy)

It consists of the resection of the kidney along with the fat, adrenal gland and the fascia, in addition to ganglionic dissection. This can be done by open, pure laparoscopic or assisted by robot.

Partial nephrectomy or tumoral enucleation

It consist of the partial resection of the kidney or the sole excision of the tumor, conserving with the rest of the renal unit. It is the ideal treatment option in peripheral tumors, generally < 4 cm. For T1 tumors, nephron sparing surgery should be performed whenever possible.

Table 36-4. 2017 TNM Classification System and TNM Supplement 2012 ⁽⁸⁾

T - Primary Tumor			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
T1	Tumor < 7 cm or less in greatest dimension, limited to the kidney		
	T1a	Tumor < 4 cm or less	
	T1b	Tumor> 4 cm but < 7 cm	
T2	Tumor > 7 cm in greatest dimension, limited to the kidney		
	T2a	Tumor > 7 cm but < 10 cm	
	T2b	Tumors > 10 cm, limited to the kidney	
T3	Tumor extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota fascia		
	T3a	Tumor grossly extends into the renal vein or its segmental (muscle-containing) branches, or tumor invades perirenal and / or renal sinus fat (peripelvic fat), but not beyond Gerota fascia	
	T3b	Tumor grossly extends into the vena cava below diaphragm	
	T3c	Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava	
T4	Tumor invades beyond Gerota fascia (including contiguous extension into the ipsilateral adrenal gland)		
N - Regional Lymph Nodes			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastasis in regional lymph node (s)		
M - Distant Metastasis			
M0	No distant metastasis		
M1	Distant metastasis		
TNM stage grouping			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage II	T3	N0	M0
	T1, T2, T3	N1	M0
Stage IV	T4	Any N	M0
	Any T	Any N	M1

A help desk for specific questions about TNM classification is available at <http://www.uicc.org/tnm>

Nephrectomy in metastatic disease

Some authorities recommend nephrectomy prior to medical treatment as it may improve the survival of patients with metastatic RCC. It has value in patients with synchronous metastases; the objective is cytoreduction in addition to palliation of hematuria, improvement of pain and reduction of paraneoplastic symptoms. ⁽²⁾

Indications for Nephron Preservation Surgery

Absolute indication: Unique kidney anatomically or functionally.

Relative indications: *Opposed kidney affected by a condition that may deteriorate its function in the future. Risk of developing a tumor in the contralateral kidney.* Multiple tumors, bilateral condition (chronic renal failure (CRF) or polycystic kidney).

Contraindications: Previous renal surgery, presence of thrombus in the vena cava, tumors of the middle renal portion, locally advanced tumor. ⁽²⁾

Techniques or Alternatives to Perform Radical Nephrectomy

Open vs Laparoscopic

There are no randomized controlled studies that have evaluated the oncological results of the Open Radical Nephrectomy vs laparoscopic. However, some studies have found:

- A significantly shorter hospital stays and less need for analgesics for open vs laparoscopic RN group.
- The length of hospital stay was also significantly shorter in the laparoscopic RN.
- There was no difference in the need for transfusions, but perioperative blood loss was lower in the laparoscopic arm.
- There were no differences in complications, but the operation time was significantly shorter in the open nephrectomy arm. The quality of postoperative life was similar.

In patients with T2 tumors, patients who underwent laparoscopic RN had less bleeding, less postoperative pain, less stay and convalescence compared to those who underwent open RN. And no significant differences were observed in the cancer specific survival (CSS), the

progression free survival (PFS) and the overall survival (OS) Level of Evidence (LE 2b). ⁽²⁾

Retroperitoneal vs Transperitoneal

On the best approach for nephrectomy: retroperitoneal or transperitoneal, the oncological results were similar in the two approaches

Assisted hand vs Standard pure laparoscopic RN

The assisted hand NR vs pure standard laparoscopic RN was compared in two studies found a similar OS, CSS and recurrence-free rates at 5 years.

The duration of surgery was significantly shorter in the hand-assisted approach, while hospital stay and time for activities were shorter for the standard laparoscopic RN.

Robotic-assisted laparoscopic vs Laparoscopic NR

The Robot-assisted laparoscopic NR vs laparoscopic NR was compared in a small study. Without finding differences in local recurrences, in port or in remote metastasis. ⁽⁹⁾

Adjuvant Therapy

Limited evidence for SUNITINIB!

Treatment of Locally Advanced RCC

Management of positive lymph nodes (cN+)

In the presence of clinically positive LNs (cN+), lymphadenectomy (LND) is always justified. However, the scope of the LND is controversial. ⁽⁹⁾

Management of RCC with tumor thrombus, venous involvement

The affection to the venous system, has been reported in the following percentages:

- 25% of renal tumors present thrombus in the renal vein.
- 8 to 12% of renal tumors present thrombus in the vena cava.
- 1 to 1.5% of kidney tumors will have thrombus to the atrium.

The invasion of the venous system is defined as a characteristic of RCC with intraluminal tumoral growth in the venous circulation, more frequent in the renal vein and in extreme cases this growth can extend to the inferior vena cava (IVC) with cephalic migration to the right atrium or beyond. ⁽¹⁰⁾

Types of Tumor Thrombus

Floating: thrombus that is free in the venous system, not adhered to the walls of the vein.

Adhered: thrombus that comes into contact with the walls of the renal vein or cava but does not infiltrate it.

Infiltrating: the most reliable sign of invasion of the vascular wall is to visualize the edge of the irregular tumoral thrombus attached to each side of the vascular wall that stands out with gadolinium. The tumor thrombus can invade the IVC wall directly (infiltrating) in up to 23% of patients, usually in the orifice of the renal vein. It is usually used in these cases repair or use of polytetrafluoroethylene replacement grafts. ⁽¹⁰⁾

Treatment of the Venous Affection of the Tumor Thrombo

The treatment indicated in patients with renal tumors with involvement of the venous system, is radical nephrectomy with tumor thrombectomy.

The surgery is performed with curative intent when there is no evidence of distant metastasis.

Or as an attempt to perform **cytoreduction**, followed by possible molecular white therapy, since one third of patients (33%) with vena cava involvement also have one or more synchronous metastatic lesions.

The precise staging and the exact definition of thrombus level are essential for correct surgical planning: the access or boarding site, the surgical technique and the need or not of extracorporeal circulation pump. The access and surgical technique depend on the level of involvement of the tumor thrombus. ⁽¹⁰⁾

Surgical Management

Aggressive surgical management (radical nephrectomy, IVC thrombectomy, lymph node dissection, and potential metastasectomy), with the level of the tumor thrombus dictating the surgical approach depending on whether the level of the thrombus affects: ⁽¹⁰⁾

1. The renal vein.
2. The infrahepatic vena cava. (triple clipping)
3. The vena cava retrohepatic (intrahepatic).
4. The suprahepatic vena cava.

5. The supradiaphragmatic vena cava.
6. The intra-auricular portion.

Metastatic Carcinoma

Between 20 and 30% of patients have metastases at the time of diagnosis and 10 to 20% of patients will develop metachronous metastases at 5 years.

Metastases appear in 20 to 40% of nephrectomized patients in localized disease. In advanced disease, the chances of survival at five years are less than 10%.

The median survival of patients with metastases is six to 18 months. The single nephrectomy produces a reversion of 5 to 7% of the metastases.

Brain metastases for renal tumors are less than 5%, but at autopsies it reaches up to 20%⁹.

Table 36-5. Sites of Metastasis ⁽⁷⁾	
Site	Percentage
Lung	75 - 80%
Soft parts	35%
Bones and liver	20%
Central Nervous System	8%

Prognostic Criteria for Metastatic Disease

Motzer (originals, 1999) or Memorial Sloan-Kettering Cancer Center (MSKCC) Criteria

These criteria were described by Motzer (Prognostic Criteria of the Memorial Sloan Kettering Cancer Center [MSKCC]) in 1999 before the advent of new molecular target therapies (antiangiogenic) when the use of interleukin and interferon were the only options available for treatment. All factors are pretreatment and are associated with lower overall survival. ⁽¹¹⁾

Motzer Criteria (modified 2002)

The original Motzer criteria were then modified, eliminating the absence of nephrectomy as a prognostic factor and including the time between diagnosis and treatment less than 1 year. Being as listed below. ⁽¹²⁾

Table 36-6. Motzer Criteria

Site	Percentage
Karnofsky PS	< 80
Time from diagnosis to treatment	<12 months
Hemoglobin	< Lower limit of the reference range of the laboratory
LDH	> 1.5 times at the upper limit of the laboratory
Serum calcium corrected *	> 10.0 mg/dL (2.4 mmol/L)

*Corrected calcium = $4 - \text{albumin} \times 0.8 + \text{Ca serum}$

According to these factors, the risk and survival are calculated:

There is an inversely proportional relationship between the number of risk factors and the prognosis, namely: “the greater the number of risk factors, the worse the prognosis of the patients”.⁽¹²⁾

Table 36-7. Proportional Relationship between Risk factors and Prognosis

Risk	Factors	Survival
Favorable (low)	No factors	30 months
Intermediate	1 or 2 factors	14 months
Poor (high)	3 or more factors	~ 5 months

IMDC Criteria validated by Dr. Heng (Mayo Clinic, 2009)

Since the criteria of the MSKCC (Motzer) was developed in the era of cytokines, the International Metastatic Renal Cancer Database Consortium (IMDC) established and validated a risk model to try to give an accurate prognosis to patients treated in the era of white therapies. Neutrophils and thrombocytosis have been added to the list of MSKCC risk factors, while lactate dehydrogenase (LDH) has been eliminated.^(13,14)

Four of the five adverse prognostic factors according to MSKCC were independent predictors of short survival:

- Low hemoglobin ($p < 0.0001$),
- High corrected calcium ($p < 0.0006$),
- Karnofsky lower than 80% ($p < 0.0001$),
- Time elapsed since diagnosis until treatment less than 1 year ($p < 0.01$).

In addition, the **neutrophil** count higher than the LSN ($p < 0.0001$) and **platelets** greater than the Normal Superior Level (NSL) ($p < 0.01$) were independent adverse prognostic factors.⁽¹³⁾

Clinical factors:

1. **Karnofsky:** Less than 80
2. **Time to treatment:** Less than 1 year.

Serum factors:

1. **Hemoglobin:** Below the normal value.
2. **Serum calcium:** Above the normal value.
3. **Neutrophils:** Above the normal value.
4. **Platelets:** Above the normal value.

Table 36-8. Survival risk factors

Risk	Factors	SG average	SV 2 years
Favorable	0	It was not reached	75 %
Intermediate	1-2	27 months	53%
Poor	3 or more	8.8 months	7%

Cytoreductive Nephrectomy (CN) in Metastatic RCC

Tumor resection is curative only if all tumor deposits are excised. This includes patients with the primary tumor in place and single- or oligo-metastatic resectable disease. For most patients with metastatic disease, CN is palliative and systemic treatments are necessary. In a Meta-analysis (MA) comparing CN+ immunotherapy vs. immunotherapy only, increased long-term survival was found in patients treated with CN. With the exception of a Randomized Controlled Trial (RCT) investigating the sequence of sunitinib and CN (EORTC 30073 SURTIME); only retrospective or single-arm prospective data for CN combined with targeting agents, such as sunitinib, sorafenib and others, are available. Based on retrospective data, CN has been recommended in mRCC patients with a good PS, large primary tumors and low metastatic volume. The randomized EORTC 30073 SURTIME Study revealed that the sequence of CN and sunitinib did not affect PFS (Hazard Ratio HR: [95% CI]: 0.88 [0.59-1.37], $p=0.569$). The trial accrued poorly and therefore results are mainly exploratory. However, in secondary endpoint analysis a strong overall survival (OS) benefit was observed in favor of the deferred CN approach in the Intention-To-Treat (ITT) population with a median OS of 32.4 (14.5-65.3) months in the deferred CN arm vs.

15.0 (9.3-29.5) months in the immediate CN arm (HR: [95% CI] 0.57 [0.34-0.95] $p=0.032$). The deferred CN approach appears to select out patients with inherent resistance to systemic therapy. This confirms previous findings from single-arm phase II studies. Moreover, deferred CN and surgery appears safe after sunitinib which supports the findings, with some caution, of the only available RCT. ⁽⁹⁾

Systemic Treatment of Metastatic RCC

1. Immunotherapy

Therapy with immunomodulatory cytokines: IL-2 and IFN- α . Immunotherapy generates a response of 5 to 25%.

Interleukin 2 (IL-2)

It increases the number of T cells and cytotoxicity mediated by T cells and natural killer (NK). Interleukin-2 (IL-2) has been used to treat metastatic kidney cancer since 1985, with response rates ranging from 7% to 27%. The clear cell RCC responds to immunotherapy. The high toxicity requires surveillance in intensive care (hypotension). Its usefulness is debatable today.

Interferon (IFN) - α

IFN- α has a response rate of 15.6%, along with a 25% decrease in the risk of progression and a modest (three to five months) survival benefit compared to placebo. The positive effect of IFN α corresponds to patients with metastatic RCC with clear cell histology, low risk according to the Motzer criteria and single pulmonary metastasis.

Immune system checkpoint blockers

Monoclonal antibodies against programmed death-1 (PD-1) or its ligand (PD-L1) have shown good efficacy and acceptable toxicity in patients with RCC.

These checkpoint blockers of immune control with specific monoclonal antibodies are:

- The T cell receptor inhibitor of programmed death-1 (PD-1) (in English: block the inhibitory T-cell receptor Programmed Death-1 (PD-1))
- The cytotoxic T lymphocyte associated antigen 4 (CTLA-4) (Cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) -signalling)

These aim to restore the immunity of tumor-specific T cells.

- The PD-1 are: pembrolizumab and nivolumab.
- The PD-L1 (ligand) are: atezolizumab and durvalumab,
- CTLA-4 are: ipilimumab.

Nivolumab

Nivolumab was evaluated in the CheckMate -025 study, a phase III, open-label, randomized trial of Nivolumab versus everolimus in patients previously treated with advanced or metastatic clear cell renal cell carcinoma.

2. Chemotherapy

Kidney cancer has classically been defined as chemoresistant. This is due to primary or intrinsic resistance by the expression of a membrane protein (glycoprotein P) encoded in the multidrug resistance gene (MDR-1) and described in 70% of the tumors.

Has been used: Vinblastine, 5-fluorouracil (5-FU), capecitabine and gemcitabine (response rates of 15 to 20%). Gemcitabine and adriamycin present response in sarcomatoid histological variety. Chemotherapy appears to be moderately effective only if 5-FU is combined with immunotherapeutics chemotherapy agents as monotherapy should not be considered effective in patients with metastatic renal cancer. And be emphatic that in clear cell cancer there is NO room for chemotherapy.

Inhibitors of Angiogenesis

The expression of the vascular endothelial growth factor VEGF is controlled by the von Hippel-Lindau protein (VHL). Mutations of the VHL gene increase the expression of VEGF that contributes to the development of the tumor. One of the first was thalidomide that generated many teratogenic effects.

Within clear cell RCC, the hypoxia-inducible factor (HIF) is overexpressed due to inactivation of the VHL gene (Von Hippel-Lindau), this inactivation results in overexpression of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), which promote neoangiogenesis. This process contributes substantially to the development and progression of the RCC. ⁽⁹⁾

Currently, there are several approved drugs for the treatment of metastatic renal cancer:

- Sorafenib (Nexavar ®)
- Sunitinib (Sutent ®)
- Pazopanib (Votrient ®)
- Axitinib (Inlyta ®)
- Cabozantinib (Cometriq®)
- Bevacizumab (Avastin ®) in combination with IFN- α
- Temsirolimus (Torisel ®)
- Everolimus (Afinitor ®)

Sorafenib

First inhibitor of Gene RAS, which also inhibits the vascular growth factor receptor (VGFR) and platelet-derived growth factor receptors (PDGF). Sorafenib is a multi-kinase inhibitor that reduces tumor cell proliferation in vitro. It inhibits tumor growth by reducing tumor angiogenesis. Sorafenib inhibits the activity of the targets present in the tumor cell (CRAF, BRAF, V600E BRAF, KIT and FLT-3) and in the tumor vasculature (CRAF, VEGFR-2, VEGFR-3 and PDGFR- β). The RAF kinases are serine / threonine kinases, while c-KIT, FLT-3, VEGFR-2, VEGFR-3 and PDGFR- β are tyrosine kinase receptors. The efficacy study was a phase 3, multicenter, randomized, double-blind, placebo-controlled study in 903 patients. I include patients with RCC and low or intermediate risk. The median PFS was 167 days (5.5 months) for Nexavar vs 84 days (2.8 months) with placebo ($p < 0.000001$). The median survival was 19.3 months with Nexavar vs 15.9 months for placebo ($p = 0.015$). Response rate of 36% as second line treatment after immunotherapy with cytokines.

Presentation: 200 mg tablets. Dose: 400 mg every 12 hours without stopping.

Adverse effects: hand-foot syndrome (6%), hypertension (5%), fatigue (4%), diarrhea (2%) and fever. ⁽¹⁵⁾

Sunitinib

It inhibits the tyrosine kinase of receptor 2 of VEGFR-2 and the platelet-derived growth factor receptor (PDGFR) B mainly. But it has also been identified that it inhibits multiple tyrosine kinase receptors (TKIs) that are involved

in tumor growth, neoangiogenesis and progression to cancer metastasis such as platelet-derived growth factor receptors (PDGFR α and PDGFR β), receptors for vascular endothelial growth factors (VEGFR1, VEGFR2 and VEGFR3), stem cell factor receptor (KIT), tyrosine kinase 3 Fms type (FLT3), colony stimulating factor (CSF-1R) , and the receptor of the neurotrophic factor derived from the glial cell line Neurotrophic Factor Receptor (RET). Indicated in the treatment of advanced / metastatic RCC, as the first line in patients with good prognosis. ⁽¹⁷⁾ Its efficacy was evaluated in a phase 3, randomized, multicenter, international study comparing it against IFN- α . 750 patients were randomized 1: 1. The main variable was PFS, observing a statistically significant advantage for sunitinib 47.3 weeks vs 22 for IFN- α ($p = < 0.001$). We also evaluated the objective response rate (ORR) that was in favor of sunitinib 46 vs 12.0%, $p < 0.001$. And the SG that was 114.6 weeks for sunitinib and 94.9 for IFN- α . ⁽¹⁶⁾

Dose: 50 mg a day, for four weeks and rest two weeks (4/2).

Adverse effects: Asthenia grade III-IV, hand-foot syndrome, neutropenia, thrombocytopenia, diarrhea, vomiting, HAS, hypothyroidism.

Axitinib

It is a potent and selective tyrosine kinase inhibitor of vascular endothelial growth factor (VEGFR) -1, VEGFR-2 and VEGFR-3 receptors. These receptors are involved in pathological angiogenesis, tumor growth and metastatic progression.

It is indicated in the treatment of patients with advanced RCC after failure to a previous treatment with sunitinib or cytokines. Its efficacy was reported in a phase 3, randomized, open and multicenter study. Patients (N = 723) with advanced RCC were randomized (1: 1) to receive axitinib (n = 361) or sorafenib (n = 362).

In the overall patient population and in the two main subgroups (previously treated with sunitinib and previously treated with cytokines) there was a statistically significant advantage of axitinib over sorafenib in terms of PFS (6.7 vs. 4.7 months, $p = < 0.0001$). However, with respect to OS, there were no significant differences ($p = 0.374$). The overall response rate (ORR) were 19.4 for axitinib vs 9.4 for sorafenib.

Presentation: 1 and 5 mg tablets. The recommended starting dose is 5 mg twice a day, but it can be adapted to the patient. The most frequent adverse reactions were diarrhea,

hypertension, fatigue, dysphonia, nausea, decreased appetite, and palmoplantar erythrodysesthesia syndrome (hand-foot syndrome), weight loss, asthenia, vomiting, and constipation.⁽¹⁸⁾

Cabozantinib

Cabozantinib is an oral inhibitor of tyrosine kinases, including MET, VEGF and AXL. Cabozantinib was investigated in a phase I study in patients resistant to mTOR inhibitors and VEGFR showing objective responses and control of the disease.

Based on these results, a randomized phase III trial (METEOR study, n = 658) investigated cabozantinib vs. everolimus in patients with ccRCC who had failed one or more therapies with anti-VEGF. Cabozantinib delayed PFS compared to everolimus in VEGF refractory disease by 42% (HR: 0.58 95% CI: 0.45 to 0.75) (NE: 1 B). The median progression-free survival was cabozantinib 7.4 months vs. 3.8 months for everolimus. The SG showed a strong tendency to favor cabozantinib (p = 0.005), however, a mature analysis of the SG is expected by the end of 2016. Grade 3 or 4 adverse effects were reported in 74% with cabozantinib and 65% with everolimus. Adverse events were treated with dose reductions; Doses were reduced in 60% of patients who received cabozantinib.⁽¹⁹⁾

Monoclonal Antibody Against VEG Circulating

Bevacizumab

Considered as the first line of treatment. This monoclonal antibody binds to circulating VEGF, blocking its action. Bevacizumab is a humanized monoclonal antibody produced by recombinant Deoxyribonucleic Acid (DNA) technology in Chinese hamster ovarian cells. Adverse effects: Hypertension, proteinuria and hemorrhages.

Inhibitors of the RAS/RAF Signaling Pathway

The Gene RAS / RAF kinase family signaling pathway stimulates changes in the transcription, metabolism and reorganization of the cytoskeleton, which influence cell replication and division. These proteins phosphorylate and activate a chain of proteins called RAF, MEK, ERK and MAP-kinase, which activate the hypoxia-inducing factor (HIF) 1 and produce the effects described intracellularly. There are no effective RAS inhibitors. Neither of the epidermal growth factor receptors (EGFR).

mTOR Inhibitors

Protein kinase, signal transducer, which regulates the progression of the cell cycle from G1 to S, through the pathway mediated by the PTEN suppressor oncogene, which in turn acts on AKT, which inhibits mTOR itself (mammalian target of rapamycin). PTEN dysfunction produces an increase in mTOR which in turn stimulates cell growth due to an increase in HIF-1.

Temsirolimus

First inhibitor of mTOR. It is a selective inhibitor of mTOR (target of rapamycin in mammalian cells). Temsirolimus binds to an intracellular protein (FKBP-12), and the protein / temsirolimus complex binds and inhibits the activity of mTOR, which controls cell division. Useful in carcinoma refractory to cytokines. Indicated in the first line treatment of adult patients with advanced RCC who present poor prognosis (> three prognostic risk factors). Presentation: 30 mg for IV application. Dose: 25 mg a week. Patients treated with 25 mg, the SG was 13.8 months; and the ORR was 5.6%. In combination with IFN it has an overall survival of 8.4 months, and 13% partial responses and 71% stabilization.

Moderate toxicity: weight loss, dyslipidemia, canker sores and mucosal inflammation, manic-depressive syndrome, anemia, neutropenia and thrombocytopenia. Effective in patients with poor prognosis according to Motzer criteria.⁽²⁰⁾

Everolimus

First mTOR for oral administration. It is a selective inhibitor of mTOR: a key serine-threonine kinase, whose activity is known to be deregulated in different human cancers. Everolimus binds to the intracellular protein FKBP-12, forming a complex that inhibits the activity of the mTOR 1 complex (mTORC1). It is therefore a potent inhibitor of the growth and proliferation of tumor cells, endothelial cells, fibroblasts and smooth muscle cells associated with angiogenesis.

Its safety and efficacy were approved with the RECORD-1 study, a phase 3, double-blind, international, multicenter, randomized study comparing 10 mg / day of everolimus against placebo in patients with metastatic RCC, with progression during or after previous treatment. with TKIs therapy (sunitinib, sorafenib, or both). In total, 416

patients with a 2:1 ratio were randomized to be treated with everolimus (n = 277) or placebo (n = 139).

Everolimus was superior to placebo in the PFS, with a statistically significant reduction of 67% in the risk of progression or death. Six-month PFS rates were 36% for everolimus treatment compared to 9% for placebo. Increase the PFS from 1.9 to 4.9 months. Improvement of quality of life, but not overall survival, since no statistically significant difference was observed (p = 0.177).

Indicated in patients with advanced RCC, in patients with failure to TKIs: sunitinib or sorafenib. Presentation: 2.5, 5 or 10 mg. Dose: 10 mg a day. Adverse effects: Pneumonitis (14%), infections by neutropenia (13%), stomatitis (3%), lymphopenia (15%), hyperglycemia (12%), hypercholesterolemia (3%), asthenia. ⁽²¹⁾

Inhibitors of the Epidermal Growth Factor Receptor

It has tyrosine kinase activity, activates stimulates the signaling pathways of RAF-kinase, P13K (phosphatidylinositol 3-kinase), AKT and mTOR. EGFR is overexpressed in 70% of renal cancers. It is inhibited by TKI monoclonal antibodies (tyrosine kinase inhibitors). Gefitinib and erlotinib, active in lung cancer, although in renal Ca its activity is lower. ABX-EGFR (colon) does not show activity in renal Ca.

Summary of Evidence and Recommendations about White Therapies in Metastatic RCC According to the European Guide ⁽⁹⁾

See **Table 36-9**.

Table 36-9. Summary of Evidences and Recommendations

Evidences	NE
TKIs VEGF increase the PFS and / or the SG in both as first and second line of treatment for metastatic clear cell RCC.	1b
Axitinib has shown efficacy and superiority in PFS as a second-line treatment after cytokine failure and anti-VEGF therapies compared to sorafenib.	1b
Sunitinib is more effective than IFN- α in patients without previous treatment.	1b
Bevacizumab plus IFN- α is more effective than IFN- α in low risk and intermediate risk patients without prior treatment.	1b
Pazopanib is superior to placebo in previously untreated mRCC patients and post-cytokine patients.	1b
Pazopanib is not inferior to sunitinib in patients with clear cell RCC.	1b
Monotherapy with temsirolimus prolongs OS compared with IFN- α in poor risk metastatic RCC.	1b
Nivolumab is superior to everolimus in terms of OS and adverse events in patients who have failed to one or two lines of treatment with anti-VEGF.	1b
Cabozantinib is superior to everolimus in terms of PFS in patients who did not respond to one or more lines of therapy with anti-VEGF.	1b
Everolimus prolongs PFS in patients who have previously failed or are intolerant of anti-VEGF therapy.	1b
Sorafenib has broad activity in a range of configurations in patients with clear cell renal cancer previously treated with cytokines or targeted therapies. It is lower than axitinib in patients previously treated with cytokines or sunitinib.	4
Both the mTOR inhibitors (everolimus and temsirolimus) and the targeted therapies VEGF (sunitinib or sorafenib) can be used in non-clear cell RCC.	3
No combination has been shown to be better than a single drug treatment.	1a

Cont...

Table 36-9. Summary of Evidences and Recommendations

Recommendations	GR
Systemic therapy for metastatic RCC should be based on white and immunological therapies.	A
Sunitinib and pazopanib are recommended as first line treatment for advanced / metastatic ccRCC.	A
Bevacizumab + IFN- α are recommended as first line treatment for advanced / metastatic RCC at favorable and intermediate risk of ccRCC.	A
Temsirolimus is recommended as a first line treatment in patients with unfavorable (poor) risk RCC.	A
Cabozantinib should be given to patients with ccRCC who progressed after one or two anti-VEGF treatment lines based on an PFS advantage over everolimus.	A
Nivolumab is highly recommended for patients who progressed ccRCC after one or two lines of anti-VEGF treatment based on an SG advantage over everolimus.	A
Axitinib can be administered as a second line treatment for metastatic renal cancer after cytokines or first line VEGF in which other drug products are not safe, tolerable or available.	A
Everolimus can be given to patients with ccRCC who have failed anti-VEGF therapy where other drug products are not safe, tolerable or available.	A
The sequencing of targeted agents is highly recommended.	A
Sunitinib or everolimus may be administered as first line therapy for metastatic renal cell cancer of unclear cells.	B

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Chapter 37

Bladder Cancer

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Bladder Cancer (BC) is the most common malignancy in the urinary tract.

Epidemiology

The age-standardized incidence rate in the world is 9 per 100,000 for men and 2 per 100,000 for women. The seventh most common cancer in men and the 17th in women, and 11th when both sexes are considered. Three times more frequent in men than in women. 3:1 ratio. ⁽¹⁾

The age-standardized mortality rate is 8 for men and 3 per 100,000 women. It represents the ninth cause of death in men, 3% of deaths among all cancers and 1.5% of deaths among all cancers in women. It happens at any age; the incidence increases proportionally with age. The median age is 70 years. The average age at diagnosis is: 69 years in men and 71 in women. In adolescents and young adults, it is less aggressive.

Presentation According to the Invasion

In 75-85% of patients with bladder cancer the disease is confined to the mucosa (stage Ta, Tis) or submucosa (stage T1).

Presentation: 75% non-invasive muscle, 20% invasive muscle, 5-10% metastatic.

The existence of synchronous tumors of the upper tract is 2.4% and tumors from the upper tract develops implants in the bladder is around 30 to 75%. ⁽²⁾

Risk Factors

Smoking

Tobacco smoking is the most important risk factor for BC, accounting for approximately 50% of cases (Level of Evidence: 3). Tobacco smoke contains aromatic amines and polycyclic aromatic hydrocarbons, which are renally excreted.

The cancer incidence is three to four times higher compared to those who do not smoke.

The bladder cancer incidence is directly related to the duration of smoking habit and the number of cigarettes smoked per day. The risk is also higher in people who start smoking at a young age or who are exposed to environmental tobacco smoke during childhood. ⁽³⁾

Occupational exposure to aromatic amines, polycyclic aromatic hydrocarbons and chlorinated hydrocarbons is the second most important risk factor for BC, accounting for about 10% of all cases. This type of occupational exposure occurs mainly in industrial plants, which process paint, dye, metal and petroleum products. ⁽⁴⁾

It is also related with the presence of chronic cystitis and other infections, radiotherapy and chemotherapy (cyclophosphamide). ⁽⁵⁾

Clinical

It is presented as a **painless hematuria** (most important finding: 80-85%). Rarely there are symptoms of bladder irritation (20%) with dysuria, urgency and frequency

(suspicion of Tis and tumors that invade the trigone or bladder neck). Symptoms such as pelvic pain suggest advanced disease.

Diagnosis

Ultrasound has been used as the initial tool in the evaluation of the urinary tract. It allows observing lesions on the bladder wall in the form of intravesical filling defects. On the other hand, **urotomography** can identify filling defects as well as being useful for identifying small tumors and for evaluation of the upper urinary tract, and / or abdominal pathology (metastatic visceral or lymph node involvement). It must be done prior to the transurethral resection of bladder tumor (TURBT). Useful to identify depth and extravesical metastasis and lymph node staging in invasive muscle tumors; as well as in the follow-up of patients after neoadjuvant chemotherapy or cystectomy.

Urinary Cytology

Examination of the exfoliated cells of bladder tumors. Standard non-invasive marker with high specificity, but low sensitivity for Ta, G1 and T1 tumors. It presents high sensitivity in high grade tumors, but low in the low grade. The interpretation of cytology is dependent on the examiner. Specificity > 90% (83 to 99.7%) and sensitivity of 20 to 53%. Sensitivity is low (12%) in low grade tumors and 75 to 80% in high grade tumors, as well as *in situ* carcinoma. Sensitivity for Tis detection ranges from 28 to 100%.⁽⁴⁾

Diagnostic and Staging Procedures

Cystoscopy

White light cystoscopy is the standard in the diagnosis of bladder cancer. The flexible is as convenient as the rigid one. It has an excellent sensitivity and specificity for papillary tumors, but scarce for Tis. Blue light cystoscopy following the intravenous injection of porphyrin dye: hexaminolevulinate (HLA) or 5-amino-levulinic acid (ALA) can identify lesions that with white or conventional light would not detect particularly Tis lesions. With blue light 25 to 35% more cases are identified. During the cystoscopy a careful description of the findings should be made: site, size, number, and appearance (papillary or solid) of tumors, as well as a description of mucosal abnormalities. The use of a bladder diagram is recommended.

The diagnosis of papillary bladder cancer depends ultimately on the cystoscopy and the histological study of the resected tissue. Tis is diagnosed by a combination of cystoscopy, urine cytology, and histological evaluation of multiple bladder biopsies.

Endoscopic transurethral resection (TURBT)

This procedure is considered both diagnostic and potentially therapeutic. Deep resection of the injury is recommended for adequate staging. It is recommended to perform random biopsies (bladder mapping) in case of positive cytologies and absence of visible tumor. It should include detrusor resection and visualization of perivesical fat. TURBT depends on the size of the tumor: tumors smaller than 1 cm must be removed in a block containing the entire tumor as well as a considerable sample of bladder wall. Tumors larger than 1 cm should be extracted in separate fractions including the exophytic part of the same, the wall below the tumor including the detrusor and the angles of the resected areas. The cauterization should be reduced as much as possible to avoid tissue destruction. The risk of understaging in samples without muscle is 64% vs. 30% with muscle.

TURBT for restaging (Re-resection)

The significant risk of residual tumor after the initial TURBT of a Ta or T1 tumor has been demonstrated. Persistent disease after TURBT of T1 tumors has been observed in 33-53%, after TURBT of T1/High Grade (HG) tumors (G3) in 41.4%.

In addition, the risk of a non-accurate staging in the initial resection is latent. The probability that a T1 tumor has been understaged and muscle invasion is detected in a second resection ranges from 4 to 25%. This risk has increased up to 50% in some series. Because the treatment of a tumor Ta, T1 (HG) and T2 is completely different, the correct staging is important. It has been shown that a second TURBT can increase recurrence-free survival.

A **second resection** is recommended when:

1. After an incomplete TURBT.
2. In the absence of muscle in the sample (except TaG1 or primary Tis).
3. In all T1 tumors.
4. In all G3 (except primary Tis).
5. Also in multiple or large volume tumors.

The interval between both surgeries is recommended to be from 2 to 6 weeks and include the previous resection site.

The restaging with TURBT is now the management standard for high grade Ta and T1 tumors. It must be done in a scheduled manner: A delay > 3 months compromises the prognosis. Also indicated in bladder preservation protocol in patients with invasive tumors. ⁽⁴⁾

Tumor Markers

Together, they have sensitivity of 64 to 80% and specificity of 71 to 95%. Positive predictive value (PPV) from 49 to

84% and negative (NPV) from 79 to 95%. The presence of false positives is frequent, but the false negatives are rare. All are superior to cytology for sensitivity, but inferior to specificity. They do not replace cystoscopy in the diagnosis or therapeutic decision making and therapeutic decisions should not be made based on the only tumor markers.

Useful in the early detection of bladder cancer and to evaluate the response to treatment and tumor recurrence. Some pathologies (such as lithiasis, infections, BCGitis, etc.) can increase false positive results and decrease the specificity. ^(6, 7)

Figure 37-1. Summary of urinal markers.

Markers (or specific tests)	General sensitivity (%)	General specificity (%)	Sensitivity for high grade tumors (%)	Cutoff point of the test	NE
UroVysion (FISH)	30-86	63-95	66-70	No	2b
Microsatellite analysis	58-92	73-100	90-92	No	1b
Immunocyt/uCyt +	52-100	63-79	62-92	No	2a
Nuclear matrix Protein 22	47-100	55-98	75-92	Yes	2a
BTA STAT test	29-83	56-86	62-91	Yes	3
BTA TRAK test	53-91	28-83	74-77	No	3
Cytokeratins	12-88	73-95	33-100	No	3

BTA = bladder tumor antigen.

Figure 37-2. Growth patterns.

Pattern	Features
Papillary	It is the most frequent form of presentation (70%), has good prognosis.
Sessile drops or infiltrating nodular	It occurs in 10% and usually have a bad prognosis.
Mixed	With papillary and solid characters at the same time, it represents approximately 20% of presentations of bladder cancer.
Flat	In situ, non-papillary, non-infiltrating, limited to the mucosa.

Adverse Histology in Bladder Cancer

1. Cancer *in situ* (Tis)

It appears as a velvety focus of erythematous mucosa. Limited to the urothelium. It is almost always multifocal. It can be asymptomatic or produce frequent urination, urgency and dysuria. It appears in 10 to 60% of superficial tumors (60% in T1G3). It presents positive urinary cytology in 80 to 90% of patients with Tis.

Between 40 and 83% (> 50% according to the UAE guidelines 2010, 54% the European 2016) progress to invasive muscular cancer. Deletions or mutations of P53 and RB are seen, so it is a high grade (anaplastic) carcinoma confined to the urothelium, but with a nonpapillary flat configuration.

It is possible to distinguish between primary Tis (without previous or simultaneous papillary tumors), secondary Tis (with a history of papillary tumors) and simultaneous Tis (in the presence of papillary tumors).

Intravesical immunotherapy with BCG (induction and maintenance) is superior to intravesical chemotherapy to increase the complete remission rate and the general percentage of patients remaining tumor free.

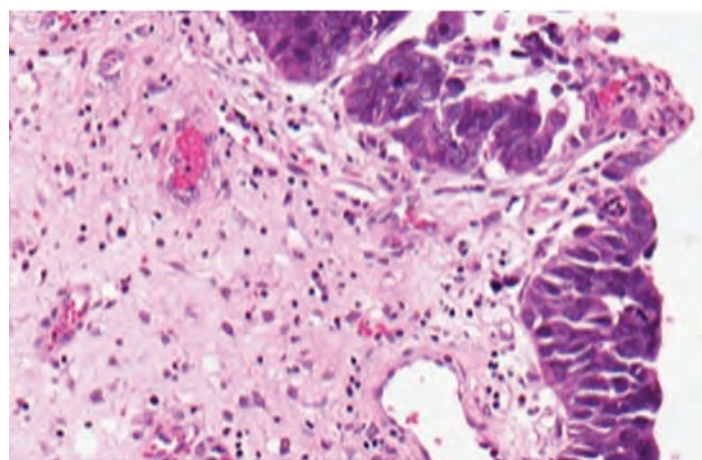


Figure 37-3. Carcinoma *in situ* “Flat Tumor” showing the lack of cell maturation of all the thickness of the urothelium with large and hyperchromatic and irregular nuclei without crossing the basement membrane.

Early radical cystectomy (at the time of diagnosis) provides excellent disease-free survival but may be an excessive treatment in 50% of patients.

The response to intravesical treatment with BCG or chemotherapy is an important prognostic factor for progression and subsequent death related to bladder cancer. Approximately 10-20% of patients with complete response eventually progress to muscle-invasive disease, compared to 66% of non-responders (LE: 2a).⁽⁴⁾

2. Squamous cell carcinoma (SCC)

When we speak of squamous or epidermoid carcinoma, we refer to those non-bilharzian. It represents 3 to 7% of bladder cancers in the US, America, Europe (non-bilharziatics). And up to 80% of bladder tumors are SCC in endemic regions of infection by *Schistosoma haematobium* (Egypt, Sudan, Saudi Arabia, South Africa).

They are caused by persistent (chronic) irritation from stones, catheters, chronic infections, bladder irritation after BCG, cyclophosphamide, or bladder diverticula. And in quadriplegic patients with suprapubic probes or permanent catheterization or intermittent. Up to 80% of paraplegics with chronic infections or permanent catheters experience flaky changes of the bladder, and about 5% develop SCC.

Leukoplakia: also called keratinized squamous metaplasia is a premalignant condition for the development of SCC. The keratinization of metaplasia is indicative of a high probability of malignancy, since 21% will progress to carcinoma versus 5% without keratinization. For the treatment of SCC, the recommendation of radical surgery is clear. Validated adjuvant treatment modalities are absent, with only sporadic reports of favorable prognosis after radiotherapy or chemotherapy, or both.

3. Bladder adenocarcinoma

Bladder adenocarcinomas represent between 0.5 and 2% of malignant bladder tumors. Regarding its origin, there has been much speculation, since the urothelium lacks glandular epithelium, and several theories are described; thus we would have the adenocarcinomas that originate from urachal remains, those originating from mesonephric remains present in the bladder base and those originating from pluripotent cells included in the transitional epithelium; some authors also consider the origin from metaplastic changes of the transitional cells themselves, so that the von-

Brunn glands, constituted by submucosal invagination of the urothelium itself, or glandular cystitis, could be considered as premalignant lesions.

It is divided into 3 types:

1. Primary bladder adenocarcinoma.
2. Adenocarcinoma of the Urachus.
3. Metastatic adenocarcinoma.

Due to their location, they are classified as urachal (30%) and non-urachal (70%). The first (urachal) are characterized by their location in vesical dome, epicenter in the thickness of the bladder wall (not in the mucosa that must be intact or ulcerated), absence of intestinal metaplasia or glandular cystitis, persistence of urachal remains, presence of suprapubic mass and no other primary tumor focus being the most common anatomopathological strain, the mucinous adenocarcinoma.

The non-urachal are classified from the anatomopathological point of view in mucinous, enteric, ring cells, clear cells, mixed and unspecified. The latter are the most frequent and those of ring cells the most aggressive, although curiously, there are series report cases of ring cells have had a favorable evolution remaining disease-free after 7 and 10 years of follow-up.

Primary bladder adenocarcinoma (or non-urachal) represents from 0.5 to 2% of bladder tumors. It initially presents as asymptomatic disease. In some patients only presents with irritative symptoms and hematuria in advanced stages.

Bladder adenocarcinoma is characterized by growing towards the thickness of the wall causing late clinical manifestations, this delays the diagnosis being detected in advanced stage and thus, despite the treatment, it usually has a very bad prognosis.

It is associated with a history of inflammation or infection in the long term, by response to irritation. It usually occurs at the base or dome of the bladder.

It is frequently found in cases of bladder exstrophy (90% of the cancers found in bladder exstrophy are adenocarcinomas).

Regardless of the various histological patterns, there is evidence of cystic and glandular cystitis or surface glandular metaplasia of the urothelium, are predisposing lesions.

The adenocarcinoma of the urachus has a Worldwide incidence is 0.17 to 0.34% of all bladder cancers. It predominates in men with a 1.8:1 ratio; the average age is 50 years.

The first extension studies, the cystoscopy with a biopsy or bladder transurethral resection It is usually the first invasive diagnostic-therapeutic measure, with which very often a solid-appearing tumor located in the bladder dome is observed.

Due to its characteristic location, it has been stated that: "The histological confirmation of adenocarcinoma in the vesical dome is equivalent to urachal carcinoma until proven otherwise." ⁽⁹⁾

Diagnostic Criteria

Classical criteria for diagnosis were originally proposed by Wheeler, in 1954, to differentiate bladder adenocarcinomas of urachal origin from primary bladders:

- a) Tumor located in the bladder dome.
- b) Presence of urachal persistence.
- c) Absence of cystitis cystica and glandular cystitis.
- d) Well-defined demarcation between the tumor and the superficial epithelium of the bladder.
- e) Urachal remnant with tumor or growth of the tumor in the bladder with extension to the Retzius space, to the anterior abdominal wall or to the umbilical scar.
- f) No evidence of a primary tumor outside the bladder.

Staging

Regarding the staging of urachal tumors, the TNM for bladder cancer staging does not apply to urachal tumors because these appear from outside the bladder and grow inwards in second place, and in some cases, they cannot invade the bladder at all. Three systems have been published:

Classification of Sheldon

This classification proposed by Dr. Sheldon in 1984 is the most used. ⁽⁸⁾

Figure 37-4. Classification of Sheldon.

Stage	Description
Stage I	Tumor confined to the urachal mucosa.
Stage II	Invasion confined to the urachus.
Stage III a	Tumor with local extension to the bladder.
Stage III b	Tumor with extension to the abdominal wall.
Stage III c	Tumor with invasion of the peritoneum.
Stage III d	Tumor with extension to another organ different from the bladder.
Stage IV a	Tumor with invasion of lymph nodes
Stage IV b	Tumor with distant metastasis

Surgical Treatment

The treatment is surgery, the discussion and controversy revolve around the extension of the same: radical cystectomy

en bloc and urinary derivation (preferably orthotopic) or partial cystectomy with broad extension *en bloc* including vesical dome, urachal ligament, posterior fascia of the rectum and umbilical scar. In addition to pelvic lymphadenectomy from the hypogastric ganglia and obturators to the region of the common iliac.

Radical cystectomy (with *en bloc* resection of the urachus and umbilical scar) with urinary diversion has been proposed as the treatment of choice for patients with disseminated disease or with a clinical stage superior to IIIa of Sheldon, reporting good local control and survival over 5 years. When partial cystectomy is performed, negative surgical margins should be at least 2 cm, transoperative study and freezing cuts. The laparoscopic approach has been described.

Other Non-uroteral Bladder Cancers ^(4,5)

Figure 37-5. Other Non-Urolateral Bladder Cancers.

Type	Description
Carcinosarcoma	Highly malignant, weird. It contains epithelial elements (epithelial cells, CCT, adenocarcinoma) and mesenchymal (chondrosarcoma and osteosarcoma). It causes macroscopic hematuria. It has a bad prognosis.
Metastatic carcinoma	Prostate, ovary, uterus, colon, rectum, lung, breast, kidney, stomach, melanoma, lymphoma, leukemia; 1 to 5% of bladder tumors
Neurofibroma	Benign tumor with origin in Schwann cells.
Pheochromocytoma	Less than 1%, grows from paraganglionic cells. Hormonally active (hypertension, syncope). TURBT is contraindicated.
Primary lymphoma	Submucosal follicles (second most common type).
Angiosarcoma and Hemangioma	Extremely rare, they debut with macroscopic hematuria, their metastases are very fast.
Leiomyosarcoma	The most common mesenchymal, aggressive treatment should be used, survival of 62%.
Rhabdomyosarcoma	Common in children, produces polypoid lesions, loss of chromosome 11p, has an unfavorable prognosis.
Other sarcomas	Liposarcoma, chondrosarcoma, osteosarcoma.

Carcinoma of Transitional Cells

It represents 90% of bladder cancers. It is characterized by the high number of layers with papillary folds of the mucosa. Loss of cellular polarity. Characteristics: maturation of abnormal cells from the basal layer to the surface.

Increased nucleus-cytoplasm ratio, prominent nucleoli, chromatin condensation, increased mitosis number.

The invasion of the muscularis mucosa and the interior of the lamina propria can be confused with invasion of the detrusor muscle.

According to its degree of differentiation before it was classified in grade 1, 2 and 3, now it is classified in low and high grade. The difference between low and high grade histologically lies in the architecture and organization of cells, the size and shape of the nucleus, mitosis and nucleoli, among other characteristics. And clinically in the degree of aggressiveness in terms of tumor recurrence and progression: Ta low grade: relapse 50 - 70% and progress 5%, while a T1 high grade: relapse 80% and progress 50% at 3 years.

WHO Graduation of 1973 and 2004

In 2004, the WHO and the International Society of Urological Pathology published a new histological classification of urothelial carcinomas which provides a different patient stratification between individual categories compared to the older 1973 WHO classification. Recently an update of the 2004 WHO grading classification was published. ⁽⁴⁾

Comparison WHO 1973–2016

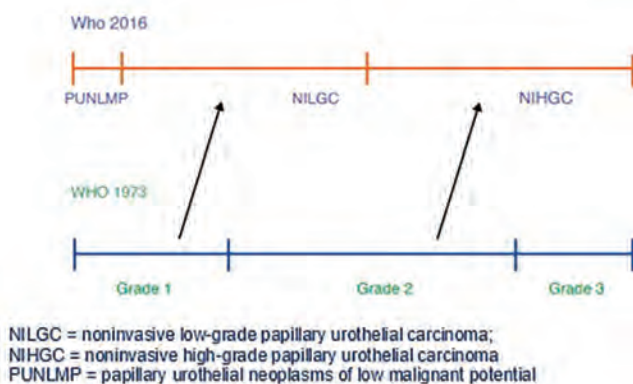


Figure 37-6. 2004-2016 WHO Grading Classification.

TNM of Bladder

Figure 37-7. 2017 TNM classification of urinary bladder cancer. ⁽¹⁰⁾

T - Primary Tumor		
TX	Primary tumor cannot be assessed	
T0	No evidence of primary tumor	
Ta	Non-invasive papillary carcinoma	
Tis	Urothelial Carcinoma in situ: 'flat tumor'	
T1	Tumor invades subepithelial connective tissue	
T2	Tumor invades muscle	
	T2a	Tumor invades superficial muscle (inner half)
	T2b	Tumor invades deep muscle (outer half)
T3	Tumor invades perivesical tissue	
	T3a	Microscopically
	T3b	Macroscopically (extravesical mass)
T4	Tumor invades any of the following: pros- tate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall	
	T4a	Tumor invades prostate stroma, sem- inal vesicles, uterus or vagina
	T4b	Tumor invades pelvic wall or ab- dominal wall
N - Regional lymph nodes		
NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)	
N2	Metastasis in multiple regional lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)	
N3	Metastasis in common iliac lymph node(s)	
M - Distant metastasis		
M0	No distant metastasis	
	M1a	Non-regional lymph nodes
	M1b	Other distant metastases

Natural Evolution

The 60 to 70% of the reports of transitional cell pathology are well or moderately differentiated, superficial and papillary. Most develop recurrences, of these 16 to 25% with higher grade tumors. 10 to 20% of cases with superficial papillary develop metastatic invasive cancer.

On the other hand, 30 to 40% is represented by high grade tumors. Of these more than 50% invade the muscular layer of the bladder (muscle invaders). A considerable portion of patients with low grade tumors eventually develop high grade recurrences. High grade, completely resected lesions often recur as low grade or in the same bladder, low and high grade lesions coincide.⁽⁵⁾

Non-Muscle-Invasive Bladder Cancer (NMIBC) (TA, T1, AND Tis)

Definition of non-muscle-invasive bladder cancer

Traditionally known as superficial cancers of the bladder; now as non-invasive muscle. Currently, the term “superficial bladder cancer” should no longer be used. If it is a papillary tumor confined to the mucosa, it is classified as Ta stage. Tumors that have invaded the lamina propria are classified as stage T1.

Ta and T1 tumors can be eliminated by transurethral resection of the bladder (TURBT) and are therefore grouped under the title of NMIBC. Also included in this item are flat, high grade tumors that are limited to the mucosa, and those classified as Tis.

However, molecular biology techniques and clinical experience have shown the highly malignant potential of T1 and Tis lesions due to their high rates of recurrence and progression. For which, whenever the term NMIBC is used, the tumor stage and grade should be specified.⁽⁴⁾

- **Ta.** Tumors confined to the urothelium, have papillary configuration in the exophytic part and do not penetrate from the urothelium to the lamina propria or the detrusor muscle.
- **T1.** They are generated from the urothelium, but penetrate the basement membrane that separates the urothelium from the deeper layers. They invade the lamina propria but not deep enough to reach the detrusor.

- **Tis.** It is by definition a high grade (anaplastic) carcinoma entrusted to the urothelium, but with a non-papillary, flat configuration. It has a high risk (> 50%) of progression to invasive muscle. It can be local or diffuse. They can be distinguished:

- **Primary Tis** (without previous or simultaneous papillary tumors)
- **Secondary Tis** (with a history of papillary tumors)
- **Simultaneous Tis** (with presence of papillary tumors)

Approximately 70 to 85% of patients with bladder cancer have mucosal confinement (Ta status, Tis) or submucosa (T1 stage). Of these, 70% are presented as Ta, 20% as T1 and 10% as Tis. Of all cancers, no muscle invaders, 50 to 70% will recur and from 10 to 20% will progress to invasive disease of the muscularis propria.

Intravesical Therapies for Bladder Cancer

BCG Considered immunotherapy. It generates an inflammatory response in the host, acts through the release of cytokines. It can be combined with interferons.

Interferons. They act by activating lymphocytes, releasing cytokines, stimulating phagocytes, with antiproliferative and antiangiogenic action. The most used is IFN- α . More active in doses of at least 100 million units; The optimal dose and the administration schedule have not yet been determined. IFN as a single agent is more expensive and less effective than intravesical BCG or chemotherapy in the eradication of residual disease, the prevention of papillary recurrence and in the treatment of Tis.

Thiotepa Non-specific alkylating agent; generates cross-links with nucleic acids. Decreases recurrence Systemic side effects (occur due to its low molecular weight [189 kDa]).

Mitomycin C. Antibiotic. Alkylating agent (334 kDa) that inhibits DNA synthesis. Useful to reduce tumor progression (38%) and recurrence. It is not as effective as BCG, but it is a good option because it has fewer side effects (septicemia).

Doxorubicin (adriamycin), Epirubicin, Valrubicin. Anthracycline of 580 kDa. Antibiotic that acts through the union of DNA base pairs, the inhibition of topoisomerase II and the inhibition of protein synthesis. Useful in the

prevention of recurrence, but not in progression. Side effects: Chemical cystitis and reduction of the capacity of the bladder.

Gemcitabine Analog of deoxycytidine; inhibits DNA synthesis. Intravesical is safe. It is administered weekly or twice a week for six to eight cycles. Minimum systemic absorption. Useful in reducing recurrence from 39 to 70%.

Hemocianin of the Californian limpet (KLH). It contains copper. It is a non-specific immune stimulant, it can be more effective than MMC in short series. Although it is less effective than BCG, KLH is much less toxic and may have a role as an alternative biological response modifier. ⁽¹¹⁾

Bacillus Calmette–Guérin (BCG)

Non-specific immune stimulant. It acts by binding to the urothelial cell through binding sites to the fibronectin from where it generates an immune response. It elicits a local host immune response against tumor cells, by the release of IL-1, IL-2 and tumor necrosis factor (TNF).

Five meta-analyses have confirmed that BCG after TURBT is superior to TURBT alone or TURBT + chemotherapy to prevent recurrence of non-muscle-invasive tumors. Three recent randomized prospective studies of intermediate and high risk tumors have been conducted. BCG was compared with epirubicin + interferon, MMC, or epirubicin alone. All these studies have confirmed the superiority of BCG for the prevention of tumor recurrence, both in high and intermediate risk tumors.

- BCG has greater efficacy against Tis and recurrence than intravesical chemotherapy, but side effects are more frequent.
- In the treatment of Tis, the initial tumor-free response rate is up to 80%. 50% experience a lasting response to four years. At 10 years, only 30% remain free of progression or recurrence.
- BCG subsequent to TURBT is superior to TURBT alone or TURBT plus chemotherapy in the prevention of recurrences of TaT1 tumors with moderate / high risk.
- BCG can effectively treat residual papillary tumors but does not replace surgical resection. BCG is superior to intravesical chemotherapy for the initial management of high grade Ta and T1 tumors.
- BCG is not recommended for patients with low risk disease due to its side effects.
- BCG has been shown to delay or reduce the progression to high grade tumors.
- The optimal dose and the treatment scheme with BCG are not determined. At least one year of maintenance with BCG is required to have superiority over mitomycin C in the prevention of recurrence or progression.
- IFN alpha has not shown benefits compared to BCG for primary treatment, but it seems to work well in combination, especially for salvage.

Dose and Current Valid Schemes

Scheme with greater acceptance is the one suggested by Lamm and the Southwest Oncology Group (SWOG):

- **Induction scheme:** this scheme consists of 6 weekly instillations according to the empirical scheme proposed by morales in 1976.
- **Maintenance scheme** (necessary for optimal efficiency): 3 weekly applications at 3, 6, 12, 18, 24, 30 and 36 months. For a total of 27 instillations.

If it is decided to give only one year of maintenance, the three weekly doses are given at 3, 6, 9 and 12 months.

This full-dose schedule for 3 years of maintenance reduces the recurrence rate compared to one year of discharge, but not in intermediate risk patients.

Different maintenance programs have been used, ranging from a total of 10 instillations in 8 weeks to 27 doses for more than 3 years. There is no ideal maintenance plan with BCG. But most studies conclude that a maintenance period of at least one year is required to obtain the superiority of BCG over CMM in the prevention of recurrence or progression.

The optimal number of induction instillations and the frequency and duration of optimal maintenance instillations remain unknown. However, in an RCT of 1,355 patients, the EORTC has shown that when BCG is administered at full dose it offers a major benefit. ⁽¹²⁾

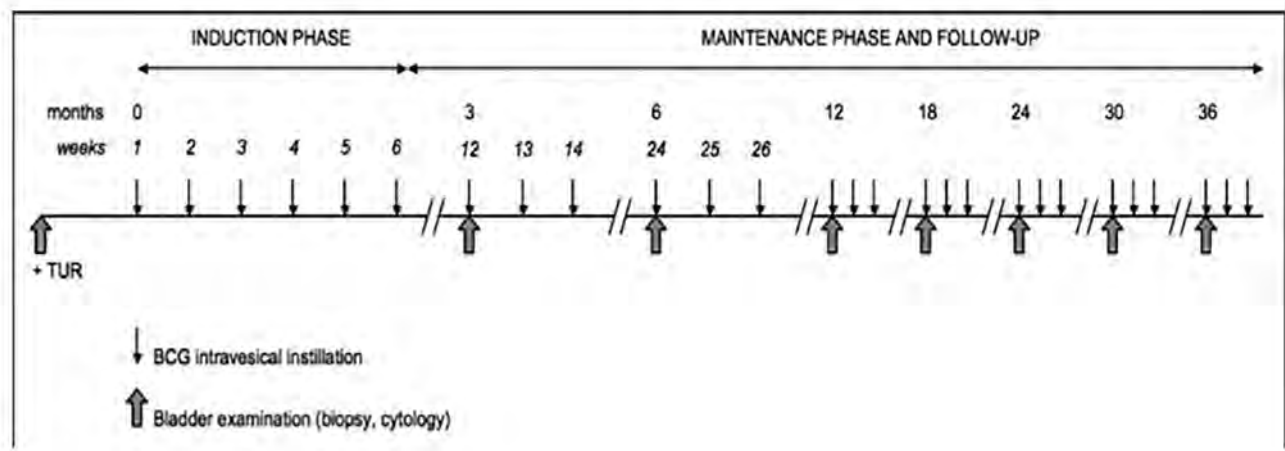


Figure 37-8. Regime recommended by the European and American guidelines.

Invasive and Metastatic Muscle Bladder Cancer (T2, T3, T4)

- 1. **Presentation with infiltrating tumors.** They have a high grade of anaplasia. They are aggressive behavior. They have a rapid infiltration process. Despite the radical treatment used, survival at two years is around 50%.
- 2. **Previous history of superficial tumor (15-20%).** Patients with recurrences that progress in histological grade and/or stage.

The incidence of tumors of the upper urinary tract is low (1.8%) but increases (to 7.5%) in tumors located in the trigone and in those multiple and high risk.

Figure 37-9. Prognostic factors.	
Lymphatic Propagation (Occurs before the hematogenous)	Lymphatic Propagation (Occurs before the hematogenous)
• Obturator: 74% • External iliac nodes: 65% • Presacral nodes: 25% • Regional common iliac: 20% • Paravesical: 16%	• Liver: 38% • Lung: 36% • Bone: 27% • Kidney glands: 21% • Intestine: 13%

Radical Cystectomy

Radical cystectomy: is the usual treatment for patients with muscle-invasive bladder cancer (MIBC) but only represents significant survival in 50% of cases.

However, the recent interest in the quality of life (QoL) of patients has promoted the trend towards treatment modalities that preserve the bladder, such as radio and / or chemotherapy.

Functional status and age influence the choice of primary treatment, as well as the type of urinary diversion, cystectomy is reserved for young patients without concomitant disease and with a better functional status.

One study identified that patients aged > 80 years have an increase in postoperative morbidity, but not in mortality. Although some patients underwent a neobladder procedure successfully, the majority of patients were treated with an ileal conduit. ⁽⁵⁾

Time to cystectomy and delay in its completion. It has been reported that a delay of radical cystectomy >3 months in three US centers is not associated with a worse clinical outcome. However, the analysis of T2 tumors showed a statistically significant survival benefit if patients underwent surgery within 90 days of diagnosis. A study based on US population, analyzed patients who underwent a cystectomy and concluded that a delay of more than 12 weeks has a negative impact on the results and should be avoided. ⁽⁴⁾

Indications for Cystectomy

1. Main: Muscle-invasive bladder cancer (T2-T4a, N0-NX, M0).
2. Other: Non-invasive high grade (G3 T1 and Tis resistant to BCG) and the extensive papillary that can not be controlled with conservative measures.
3. Still in controversy: (early cystectomy) in patients with p53 mutations with T1 high grade tumors.

Indications for Partial Cystectomy

1. Single tumor in a mobile part of the bladder.
2. Tumor in the dome and absence of previous multifocal lesions.
3. With the possibility of free oncological resection margins (2cm).
4. No associated Tis.

Rescue Cystectomy

1. Non-responders to non-surgical therapies or relapse after conservative treatment of the bladder.
2. Carcinoma of non-transitional cells, since these tumors generally do not respond well to chemotherapy and radiotherapy.

Contraindications to Cystectomy

1. Comorbid conditions of the patient.
2. Patients not willing to accept the surgical risks.

Complications of Cystectomy

1. Global in 25%. Mortality 1-2%.
2. Related to pre-existing disorders (comorbidities).
3. By extirpation of the bladder and adjacent structures (rectal injury <1%, vascular).
4. For the use of intestinal segments:
 - o Intestinal obstruction: 4 to 10%, <10% require reoperation.
 - o Stenosis of the uretero-enteric anastomosis (3%).
 - o Infections
 - o Metabolic disorders, lithiasis, depression, etc.

The 5-year survival after cystectomy is around 50%. The percentage of presentation of the second primary in the prostate, that is, prostate cancer in the surgical piece of the cystoprostatectomy is 28% (UAE guide: 25 to 46%). Radical cystectomy presents a percentage of local recurrence of approximately 10 to 20%. The risk of recurrence in the urethra if the cystoprostatectomy reported prostatic invasion in the stroma is 18%, in the 12% conduits and 5% in the urothelium. The life expectancy at 5 years is 65% for T2, 30% for T3 and 20% for N1.

Partial Cystectomy

The indications for partial cystectomy are:

1. Single tumor in a mobile part of the bladder.
2. Tumor in a diverticulum.
3. Small tumor (<2 cm) isolated, invasive away from the trigone.
4. Tumor not associated with carcinoma *in situ*.
5. Absence of previous multifocal lesions.

That there remains a functional bladder after resection of the tumor with 2 cm of free margin. In patients who undergo radical or partial cystectomy with positive nodes, positive margins, high grade or pathological T3, adjuvant therapy with chemo and radiotherapy should be considered. ⁽⁴⁾

Cystectomy for Non-Invasive Muscle

It is reasonable to propose an immediate radical cystectomy to those patients with non-invasive muscle who are at higher risk of progression. These are the patients with the following characteristics:

1. T1 tumors multiple and/or large (> 3 cm). High grade tumors (G3).
2. High grade T1 tumors with concomitant Tis.
3. Recurrent high grade T1 tumors. And T1 with early recurrence.
4. T1 high grade tumors with Tis in prostatic urethra.
5. Micropapillary variant of urothelial carcinoma.
6. Patients with failure to BCG (progression or recurrence).
7. Hematuria refractory to large volume tumors.
8. Surgically unresectable tumors by TURBT.

The potential benefit of radical cystectomy must be weighed against risk and impact on quality of life. The delay of radical cystectomy could lead to decreased survival.

In patients in whom radical cystectomy is performed at the time of the pathological non-muscle-invasive disease of 5 years, the rate of disease-free survival is greater than 80%.⁽⁴⁾

Pelvic Lymphadenectomy (LDP)

Pelvic lymph node dissection is the most accurate method for lymph node staging (N) and has a direct impact on oncological control and survival, therefore, it is considered a staging and treatment surgery. Lymphadenectomy is mandatory in invasive muscle bladder cancer and indicated whenever a cystectomy is performed.

Ganglionic Landing Sites in Bladder Cancer

Bladder cancer presents a landing with very diffuse ganglionic affectation, which is why templates have been made with areas or areas determined of lymph node involvement, the most frequent being the internal distal iliac areas (21%), the external proximal (20%) and the distal obturator fossa (18%). And the areas of least involvement are above the junction of the ureter over the common iliac with only 4% and in the area above the bifurcation of the bifurcation of the aorta (4%).⁽¹³⁾

Urinary Derivations

When the bladder is removed due to cancer or some other condition it is necessary to redirect the flow of urine to the outside, for this various forms and techniques have been devised, among which include, contingent and noncontinent heterotopic urinary diversions, orthotopic urinary diversions.

The European guide maintains that from an anatomical point of view, three alternatives are currently used after cystectomy:⁽⁴⁾

- **Abdominal bypass:** ureterocutaneostomy, ileal conduit or colon duct, and various forms of contingent bags.
- **Urethral bypass:** includes various forms of gastrointestinal bags attached to the urethra as a continent, orthotopic urinary diversion (neobladder, orthotopic bladder replacement).

- **Rectosigmoid shunts:** as the ureterorectomy (ileum).

The different types of segments of the intestinal tract have been used to reconstruct the urinary tract, including the stomach, ileum, colon and appendix.

Several studies have compared certain appearance of the quality of life, as the sexual function, the urinary continence and the body image, in the different alternatives of urinary diversions. However, more research is needed in the pre-operative setting of the tumor and the functional status, the socioeconomic condition, and the time interval to primary surgery.⁽⁴⁾

Types of urinary diversions⁽⁴⁾

When the bladder is removed due to cancer or some other condition it is necessary to redirect the flow of urine to the outside, for this purpose various forms and techniques have been devised, among which include:

- Heterotopic urinary diversions
 - No continents
 - Continents
- Orthotopic urinary diversions

Metastatic Disease

Half of patients with MIBC will experience relapse after CR, depending on the pathological stage of the primary tumor and the condition of the lymph nodes. Local recurrence occurs in 30% of relapses, while distant metastases are more common.

From 10 to 15% of patients are already metastatic at the time of diagnosis. Before the development of chemotherapy, patients with metastatic urothelial cancer rarely had a median survival that exceeded 3-6 months.⁽⁴⁾

Prognostic Factors in MIBC

The independent prognostic factors of survival in multiple studies are the Karnofsky performance (PS) of <80% and presence of visceral metastases.

For refractory patients, or who progress shortly after platinum-based chemotherapy schemes, four prognostic groups have been established, based on three adverse factors that have developed in patients treated with vinflunine and validated in a set of independent data:⁽⁴⁾

- Hb <10 g / dl
- Presence of liver metastases
- ECOG PS >1

Chemotherapy for Bladder Cancer

Chemotherapy schemes and schedules. ⁽¹⁴⁾

- **Cisplatin/gemcitabine:** This combination is considered the standard in first line management for most patients. Compared with M-VAC, no statistically significant difference was found. In complete pathological response rates (by CR or Cystoscopy) 31% for MVAC vs. 25%. Overall survival was similar in both arms: 14 months for GC and 15 for MVAC ($p = 0.66$ not significant). Progression free survival (PFS): 7.7 months GC and 8.3 months for MVAC (HR 1.09).
- But they differ in adverse effects and toxicity which is greater for MVAC than for GC.
- **MVAC:** Classic scheme used for many years, increasingly used less because of its high toxicity.
- **Cisplatin / gemcitabine plus paclitaxel:** has offered good results in adjuvant therapy, improving disease free survival.
- **Carboplatin:** It should be used in patients with renal failure. But it should not be considered equivalent to cisplatin.

Neoadjuvant Chemotherapy in Bladder Cancer

Reduces the risk of mortality from 10 to 13% with an absolute improvement of 5% to 5 years. 3 cycles are normally used: MVAC, CMV, CG. ⁽¹⁶⁾

Advantages:

1. It is administered when the expected load of micrometastasis is low.
2. Chemosensitivity in vivo is demonstrated.
3. It is better tolerated before than after cystectomy.
4. It can improve the pathological state (pT0) of the ganglia and surgical margins.

Disadvantages:

1. There may be a poor staging of the real one. By CT or MRI (70% is real) which could imply an overtreatment.

2. Cystectomy differs and compromise the outcome in a patient not sensitive to chemotherapy. ⁽¹⁵⁾

Adjuvant Chemotherapy

Useful in patients with the following scenarios: Patients after radical or partial cystectomy classified in stages II with lymphovascular invasion and / or positive margin and / or T2b.

Stage III or IV (T3a-T4 and / or N + and M0) regardless of the status of the vascular invasion or the surgical margin.

In these patients, 5-year survival after radical cystectomy is only 25% to 35% in the best scenario. Generates an overall survival of 8 - 10%.

Adjuvant Chemotherapy has been recommended for high risk patients, in an effort to delay recurrence and prolong survival. However, there are not enough data in favor of systemic use.

Advantages:

1. The chemotherapy is given after the exact pathologic staging.
2. Excessive treatment is avoided in patients with low risk of microscopic metastasis.
3. The definitive treatment is not stopped, especially in patients not sensitive to chemotherapy.

Inconvenient:

1. It is necessary to wait for recovery time and delay the start of chemotherapy.

The results of the randomized studies of adjuvant chemotherapy, all small and of low statistical power, are controversial.

The largest retrospective series with 3,947 patients: The adjuvant chemotherapy was associated with a better survival ($p = 0.017$). Improvement in the **risk of progression of the disease** with greater benefit of adjuvant chemotherapy in the subgroups of greater. With 32% at 5 years the probability of cancer-specific survival, in patients with advanced pathological status ($\geq T3$) and lymph node involvement. Being useful in patients with high risk of recurrence including:

- Extravesical disease.
- Advanced pathological stage ($\geq pT3$).

- Positive margins after CR.
- Lymph node involvement
- With lymphovascular invasion.

Multimodal Strategy for Vesical Preservation (Trimodal Therapy)

It consists of multimodal strategies that combine TURBT, chemotherapy and radiation, with the aim of preserving the bladder, in patients who are not candidates or who do not accept surgery.

TURBT and XRT try to achieve local control of the tumor. While the Qt (MCV or C5-FU, G- as radiosensibilizer) attempts to eradicate micrometastasis

The multimodal therapy of bladder preservation, also called trimodal therapy, for which there are many and different treatment protocols, however, the central point of success is the correct selection of candidates for this treatment modality.

Components of trimodal therapy

1. **Transurethral resection of bladder:** You must initially proceed to the aggressive TURBT.
2. **Radiotherapy:** Four weeks later, RT is started in the total dose of 40 Gy for 4 weeks (1.8 to 2 Gy per day)
3. **Chemotherapy:** concomitantly with Rt Cisplatin, 70 mg / m² IV, during 2 h, D1 and D22.

If there is a complete clinical response, the patient begins the consolidation phase with the third dose of cisplatin, 70 mg/m² IV, with additional dose of Rt of 20 Gy (1.8 to 2 Gy per day).

If it recurs or progresses, radical cystectomy should be performed. Approximately one quarter to one third of patients require a cystectomy. ⁽¹⁷⁾

Principles of Radiotherapy ⁽¹⁸⁾

External Radiotherapy ERT is not appropriate for patients with recurrent T1 - T1 or diffuse Tis. XRT has good results in patients without hydronephrosis. It can be used in medically inoperable patients or for palliation. Precede the XRT with a wide TURBT of the tumor when possible and safe. The combination of XRT and Chemotherapy is recommended to reduce the cytotoxicity of the tumor.

Treat the bladder with or without lymph nodes with 40 - 45 Gy and increase to a total dose of 64 - 66 Gy, excluding normal areas of the bladder if possible. Consider low doses of Rt before partial resection in muscle invasive tumors.

Immunotherapy in Bladder Cancer

Up to 50 percent of patients with advanced urothelial carcinoma are not candidates for cisplatin-based chemotherapy because of age or comorbidity (e.g., impaired renal function, neuropathy, heart failure). Although comparative phase III data are not available for first-line immunotherapy in this setting, a phase II study supports its use and tolerability. ⁽¹⁹⁾

Pembrolizumab

The Pembrolizumab (a programmed cell death-1 protein (PD-1)/PD-1 ligand (PD-L1) checkpoint inhibitors) prolongs overall survival in patients with metastatic urothelial carcinoma who have progressed during or after platinum-based chemotherapy.

In the phase II KEYNOTE-052 study, 370 patients with advanced urothelial carcinoma who were not eligible for a cisplatin-based regimen were treated with pembrolizumab (200 mg every three weeks for up to two years). At a median follow-up of 9.5 months, the objective response rate, the primary endpoint of the study, was 29% for the entire cohort, including 7% complete responses and 22% partial responses. The median duration of response had not been reached at the time of analysis. Response rates were consistent across all major subgroups. The objective response rate was higher in patients with PD-L1 expression >10%, but responses also were observed in those with PD-L1 expression <10%.

The KEYNOTE-045 trial ⁽²⁰⁾ is a randomized, pivotal, phase III study evaluating pembrolizumab monotherapy compared to investigator-choice chemotherapy (paclitaxel, docetaxel, vinflunine) in the treatment of patients with metastatic or locally advanced or unresectable urothelial cancer that has recurred or progressed following platinum-based chemotherapy. The co-primary endpoints are overall survival and progression-free survival; secondary endpoints are overall response rate, duration of response, and safety.

The study randomized 542 patients to receive pembrolizumab (200 mg every 3 weeks) or investigator's choice of paclitaxel (175 mg/m² every 3 weeks), docetaxel (75 mg/m² every 3 weeks), or vinflunine (320 mg/m² every 3 weeks).

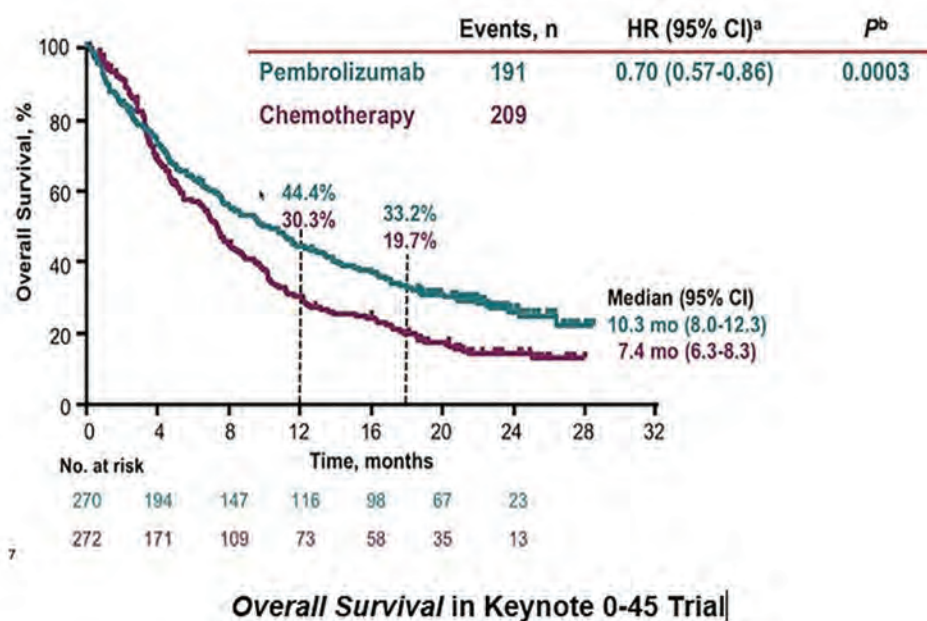


Figure 37-10. KEYNOTE-045 Study. Overall Survival – Updated Analysis.

The median follow-up was 22.5 months in both arms. The median OS was significantly longer with pembrolizumab compared to chemotherapy in the overall patient population. Median OS was 10.3 with pembrolizumab compared to 7.4 months with chemotherapy, hazard ratio [HR] 0.70 ($p = 0.0003$).

Similar progression-free survival (PFS) was observed between the treatments; median PFS was 2.1 versus 3.3 months with pembrolizumab versus chemotherapy, respectively, HR 0.96 ($p = 0.32$).

The objective response rate (ORR) was nearly doubled with pembrolizumab; ORR was 21.1% (95% confidence interval [CI] 16.4, 26.5) with pembrolizumab versus 11.0% (95% CI 7.6, 15.4) with chemotherapy. The responses with pembrolizumab were more durable than with chemotherapy; the median response duration of response was not reached (range 1.6+ to 24.6+ months) versus 4.4 months (range 1.4+ to 24.0+ months).

Fewer patients experienced treatment-related adverse events (TRAEs) with pembrolizumab compared with chemotherapy. The incidence of TRAEs any grade was 62.0% versus 90.6%, and the incidence of grade > 3 TRAEs was 16.5% versus 50.2%, respectively.

The PD-L1 inhibitor pembrolizumab continued to demonstrate a survival benefit compared to chemotherapy among patients with advanced urothelial carcinoma.

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Chapter 38

Testicular Cancer

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Epidemiology

Testicular cancer is the most common neoplasm in males of reproductive age from 15 to 35 years; 95% of testicular tumors originate in the germ cells and 5% are from the gonadal stroma. At the time of diagnosis, 1-2% of cases are bilateral, and the predominant histology is germ cell tumor (90-95% of cases). They occupy 1% of neoplasms in men and 5% of urological tumors in general.

It presents 3 peaks of important incidence; in childhood, in the ages of 25 to 40 years and to 60 years. Seminoma is the most common and is infrequent in patients younger than 10 years or older than 60; with a peak incidence between 35 and 39 years. ⁽¹⁾

Risk Factors

The most important risk factor is cryptorchidism, which is associated to 2% of cases. Other factors that have been found associated are those related to viral orchitis due to measles and exposure of the mother during gestation to diethylstilbestrol. Klinefelter syndrome is associated with primary mediastinal germ cell tumor. ⁽²⁾

Laterality

Testicular neoplasms are slightly more frequent in the right testicle (57%) than in the left testis (43%); 2 to 3% of tumors are bilateral and can occur simultaneously (synchronous) or successively (metachronous). Most of the bilateral ones are metachronic. Of the bilateral tumors, seminoma is the most frequent.

Clinical

- The usual presentation is a nodule or painless swelling of a gonad.
- 30-40% refers to dull pain. Acute presentation of pain is uncommon unless it coexists with epididymitis or tumor bleeding.
- Feeling of heaviness in hypogastrium, anal region or scrotum.
- In about 20% of cases, the first symptom is scrotal pain, and up to 27% of patients with testicular cancer may have local pain.
- Growth of a previously atrophic testicle.
- Sterility.
- Gynecomastia appears in 7% and is common in non-seminomatous tumors due to endocrine manifestations.
- In 10% of cases the initial manifestations are due to metastasis. ⁽³⁾
 - **Pulmonary** (dyspnea cough). For pulmonary metastases.
 - **Gastrointestinal** (anorexia, nausea, vomiting, hemorrhage). For metastasis to retroperitoneum.
 - **Low back pain.** By retroperitoneal involvement by compression of the psoas and nerve roots.
 - **Bone pain.** By metastasis to bone.
 - **CNS and peripheral involvement.** By cerebral or medullary involvement of nerve roots.
 - **Retroperitoneal** (edema of lower or upper limbs). Obstruction of the vena cava or iliac (obstructive thrombus).
 - **Identify supraclavicular nodes.**

Diagnosis

Clinic and exploration: complete physical examination (palpation), pain. Investigate symptoms of metastasis.

Tumor markers: Mandatory before and after treatment: alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG) beta subunit, Lactic Acid Dehydrogenase (LDH); Placental alkaline phosphatase (PAP) and gamma-glutamyltranspeptidase (GTP) may also be ordered.

Testicular USG: Mandatory in every patient. Perform it before clinical suspicion or normal scrotal palpation. It informs about the tumoral appearance, distinguishes masses of testicular and non-testicular origin, solid or cystic. In addition, it reveals particular characteristics of some tumor types. 90% sensitivity. It also values reactive hydrocele.

Abdominal-pelvic and lateral thorax XR: Compulsory. Identify pulmonary metastases. Perform it always in seminoma.

Abdominal-pelvic CT: mandatory. Recommended to all patients. Identify retroperitoneal and / or visceral lymph node metastasis. In addition, it provides information on the size and characteristics of metastatic lesions and the involvement of other structures. It displaced to intravenous urography and lymphangiography.

Chest CT: only if the radiography presents suspicious images. Always in non-seminomatous. Identifies lesions usually in the base and periphery of the lung.

Brain CT/MR: only if there are positive or retroperitoneal metastases. According to protocol.

Magnetic resonance (MR): It should be done when CT is not conclusive, especially in the skull. Request it when there is significant tumor load in thorax or with tumor markers in stage S3.

Positron Emission Tomography-Computed Tomography (PET-CT): It can be performed as a follow-up of residual masses greater than 3 cm post-chemotherapy in seminoma (performed approximately at 6 or more weeks). It evaluates the viability of the tumor, it is considered positive or viable generally greater than 3 (some centers consider it 2.5) units SUV max (Standard Uptake Value).

PET-CT with 18 Fluorodeoxyglucose (18FDG)-PET has a high negative predictive value in patients with residual masses after treatment of seminoma, but false-positive results can be a problem and scans should not be performed < 2 months after chemotherapy. In patients with > 3 cm

residuals, FDG-PET should be performed in order to obtain more information about the viability of these residues. In patients with < 3 cm residuals, the use of FDG-PET is optional.

Tumor Markers (TM)

Useful from the clinical point of view for the diagnosis, staging and monitoring of the therapeutic response in patients with germ cell neoplasms. They can be useful as a prognostic index. However, negative markers do not exclude the diagnosis of a germ cell tumor. ⁽⁴⁾

In general, there is an increase in TM in 51% of cases of testicular cancer. Alpha-fetoprotein increases in 50-70% of patients with non-seminomatous tumors, and an increase in hCG is seen in 40-60% of patients with Non-Seminomatous Germ Cell Tumor (NSGCT).

About 90% of non-seminomatous tumors debut with an increase of one or two of the markers. Up to 30% of seminomas can present or develop hCG elevation during the course of the disease.

LDH is a less specific marker, and its concentration is proportional to the volume of the tumor. Its level may be elevated in 80% of patients with advanced testicular cancer. ⁽¹⁾

Alpha-fetoprotein (AFP) Produced by cells of the yolk sac, but also in the liver. 70,000 D glycoprotein Half life: 5 to 7 days. Useful to assess response to treatment. Normal value: depending on the laboratory (7, 10, 15 ng/ml). It rises in 50 to 70% of all testicular cancers, never in pure seminoma or choriocarcinoma. Present in embryonic carcinoma, teratocarcinoma, yolk sac. ⁽⁴⁾

Beta - hGC. It originates in syncytiotrophoblast cells. Polypeptide chains of 38,000 Daltons. Half life: 2 to 3 days (24 hrs. and even up to 36 hours). Detectable also in other neoplasias: Liver, pancreas, stomach, lung, breast, kidney and bladder; marijuana smokers (delta-9-tetrahydrocannabinol). Normal value: < 0.1 mIU/mL. It is elevated in all testicular cancers and only in 10% of pure seminomas. 100% choriocarcinoma. Embryonic carcinoma 40 to 60%. ⁽⁴⁾

LDH. Weight of 134,000 D. Marker of tissue destruction: elevated in 80% of advanced tumors. It is directly related to the tumor size. Greater utility in surveillance. There are 5 forms, the 1 is the one that rises more frequently in the GCT. It may be the only biochemical alteration in 10% of patients with non-seminomatous tumors. ⁽⁴⁾

Other Markers PAP: Placental alkaline phosphatase, can be elevated in pure seminoma. Almost 40% of cases of advanced disease have high levels of PAP. GTP is a hepatocellular enzyme that usually occurs in benign diseases or liver neoplasms NSE: Specific neuron enolase. GTCM-2: Surface anti-proteoglycan antibody. ⁽⁴⁾

Table 38-1. Main Testicular Tumors and Tumor Markers

Tumor	<i>hGC-B</i>	AFP
Pure Seminoma	25 %	0 %
Choriocarcinoma	100 %	0%
Embryonal Carcinoma	80 %	75 %
Teratoma	25 %	37 %

Usefulness of Markers

Prior to orchiectomy, a determination of markers should always be made, which should be repeated seven to 10 days after it, especially when they have tested positive. Between 50 and 70% of patients with non-seminomatous tumors have high levels of AFP and about 40 to 60% elevation of hCG.

The detection of high AFP strongly suggests a non-seminomatous component. The persistence of high tumor markers after orchiectomy indicates the presence of metastatic disease (micro or macroscopically), however, its normalization does not exclude it. During the chemotherapy the markers must decline; if they persist elevated the prognosis of the patient is unfavorable. ⁽⁵⁾

Cellular Classification of Testicular Cancer

The following histological classification of malignant testicular germ cell tumors (testicular cancer) reflects that used by the WHO. Less than 50% of malignant testicular germ cell tumors have a single cell type, of which approximately 50% are seminomas. The rest has more than one cell type and the relative proportions of each cell type must be specified. The cell type of these tumors is important to calculate the risk of metastasis and the response to chemotherapy. Polyembryoma has an unusual growth pattern and is sometimes classified as an individual histological type, although it would be better to consider it as a mixed tumor. ⁽⁶⁾

Table 38-2. Intratubular Germ Cell Neoplasia, Not Classified

1. Germ cell tumors (96%).

Tumor of pure germinative cells (that presents a single type of cell) malignant:

1. Seminoma (35-50).
2. Embryonic carcinoma (25%).
3. Teratoma (5%)
4. Choriocarcinoma
5. Tumor of the yolk sac.

Mixed germ cell tumor (showing more than one histological pattern) malignant:

1. Embryonic carcinoma and teratoma, with or without seminoma.
2. Embryonal carcinoma and tumor of the yolk sac, with or without seminoma.
3. Embryonic carcinoma and seminoma.
4. Tumor of the yolk sac and teratoma, with or without seminoma.
5. Choriocarcinoma and any other element.

Polyembryoma (mixed).

2. Tumors of the gonadal stroma (2%).

- I) Leydig's tumor
- II) Sertoli tumor
- III) Gonadoblastoma.

3. Metastasis

Germ Cell Tumors

Seminomatous

Seminoma:

- **Classic:** seminoma occurs in 40% of the Germ Cell Tumors (GCT). The age of presentation is between 30 and 40 years of age. Rare in <10 years or > 60. It has elements of the syncytiotrophoblast in 10 to 15% which explains the production of beta hCG. AFP never rises in pure seminoma. It is the most common of all germ cell tumors. 82-85% of seminomas. Homogeneous character in ultrasound, solitary, large, well defined. It contains uniform cells with clear cytoplasm, spherical and hyperchromatic nuclei. 70% debut in stage I. 15% have metastases to regional lymphatics and 5-10% have distal lymph nodes or visceral metastases.
- **Spermatocytic:** It represents 2 to 12% of seminomas, it does not present Cis. Composed of cells of variable size with pigmented cytoplasm, spherical nucleolus with chromatin. Bilateral presentation more than the classic one. Slow-growing tumor; rarely metastasizes (only one case has been reported) and practically healing occurs with orchiectomy, so it has a very good prognosis.

Non-Seminomatous ⁽²⁾

- **Embryonic Carcinoma (EC):** represents 20 to 25% of the GCT. It elevates beta hCG not by EC cells, but by those of syncytiotrophoblast that may be present in the stroma. HCG does not rise in pure EC, because it does not contain syncytium cells. The elevation of AFP is rare in the pure and is due to the presence of elements of the yolk sac. It is characterized by hemorrhage, necrosis and undifferentiated cells. It is round, small (testicle of almost normal size), hard and irregular, of rapid growth; It is spread via lymphatic and hematogenous to distal viscera (lung, liver). More than 60% have metastases at the time of diagnosis. Pain is frequent Good response to treatment
- **Teratoma: There are different types:** 1. Mature. 2. Immature. 3. With malignant transformation. Represents 5 to 10% of the GCT. Elevates AFP in 20 to 25% of cases, although it generally does not elevate markers. Tumor composed of two or more layers of embryonic germ cells that can be mature and immature, with a cribriform appearance (pierced with holes or perforated). Large, multilocular, non-homogeneous to the touch, it can contain tissue of any kind. It is found in residual or recurrent masses after chemotherapy, with a cystic appearance to both tomography and lumpectomy. It is the least aggressive of the germinal. 30% relapse after orchiectomy. Clinical: Enlarged testis with cystic and solid components. May develop teratoma syndrome in retroperitoneal expansion, with accelerated and voluminous growth. Classically it is resistant to chemotherapy and radiotherapy (RT). ⁽²⁾
- **Endodermal sinus tumors** (From the Yolk sac): represents 1 to 2% of the GCT. It can occur in childhood. They are the largest AFP producers (90%). Variable characteristics at the time of diagnosis they have considerable size. They appear combined with other histological types in young adults, 25% develop hydrocele. Treatment: Inguinal radical orchiectomy.
- **Choriocarcinoma:** it represents about 1% of the GCT. Elevates hCG-B by 99%. AFP never rises in choriocarcinoma. It is a very aggressive behavior tumor, besides being the most metastatic. It presents preferably hematogenous spread. It manifests with hemorrhage, frequent necrosis, testicle of small or normal size, poor prognosis. It is the most aggressive of the germinal. It may appear pure or with more than one histological type. It contains elements of syncytium and cytotrophoblast. Metastasis to lung, liver and brain

even to the gastrointestinal tract; It usually debuts with metastatic manifestations. Small tumor and can even be self-consumed (burned out, Burned). Responds to chemotherapy although patients debut with advanced stages usually. ⁽²⁾

- **Mixed:** they represent from 25 to 30% of the GCT. They raise both AFP and hCG. Tumors with more than one histological grade. The most frequent is the one that contains EC, seminoma, yolk sac tumor, teratoma and syncytiotrophoblast. ⁽²⁾

Tumors of Non-Germinal Cells

Mesenchymal Tumors of the Sexual Cord Stroma:

- **From the Leydig cells:** the most frequent It represents 1 to 3% of testicular tumors. It is characterized by increased secretion of estrogen by tumor cells. No association with cryptorchidism. In prepubertal (> 5 years): Isosexual precocity (secondary characters). Increase in testosterone production of urinary 17-ketosteroids. In adults: Testicular nodule with or without endocrine manifestations (gynecomastia and hypogonadism, erectile dysfunction, decreased libido). Thrombotic phenomena Elevates AFP and hCG. Histopathologically eosinophilic cytoplasm with lipid vacuoles of brownish pigmentation (Reinke crystals). Generally benign, 10% malignant. Treatment: Radical inguinal orchiectomy plus chemotherapy. ⁽²⁾
- **Sertoli cells** (Androblastoma, Gonadal Stromal Tumor or Sertoli Mesenchymal): are infrequent. They represent <1% of testicular tumors. Generally benign, 10% malignant. From 1 to 20 cm, with uniform consistency and cystic formations. They originate from the primitive gonadal mesenchyme. They contain epithelial components similar to Sertoli cells. The secretory material that forms the Call-Exner bodies can be found inside the tubules. Pain and gynecomastia (due to estrogen production) in up to 1/3 of patients and sexual impotence. Treatment: radical inguinal orchiectomy, chemotherapy, radiation therapy and hormonal therapy.

Mixed Tumors: Germinal and Stromal Cells

- **Gonadoblastoma:** it occurs in patients with gonadal dysgenesis (probability 25%), with a female phenotype and signs of virilization. Unilateral or bilateral solid tumor, microscopic, spherical, smooth, soft and fleshy,

firm, with calcifications. Three factors: 1. Gonadal dysgenesis, 2. Potentially malignant cells, 3. Endocrine dysfunction: androgen production (virilization).

- Histopathologically three elements: Sertoli cells, interstitial tissue, germ cells (teratoma, choriocarcinoma, yolk sac tumor) between the tubules. It can progress from in situ to the invasive germinoma (seminoma) known as gonadoblastoma with germinoma. 80% female phenotype: Small breasts, hypoplastic internal genitalia.

Debuts with amenorrhea and/or tumor in the epigastrium. The rest (20%, male) presents cryptorchidism, hypospadias and female internal genitalia, gynecomastia, dysgenetic testes. Chromosome patterns XY, X0, X0 / XY.

Treatment: Radical orchiectomy. Contralateral gonadectomy in dysgenesis. Forecast: Good in general.

- Of Mesenchymal Origin:** benign fibroma, angioma, neurofibroma leiomyoma.

Malignant Mesothelioma of the Tunica Vaginalis

- It can affect any part of the pleural membrane, peritoneum or tunica vaginalis. It covers 5% of all mesotheliomas. There are <80 cases described.

Clear risk factor: Exposure to asbestos. Etiopathogenesis: Presence of HLA W27 antigen, chromosomal abnormalities, previous RT, viral infections, testicular trauma.

Clinical: Painless scrotal swelling, associated with reactive hydrocele (an incidental finding during hydrocele surgery). Three subgroups: Epithelial (50-75%), mesenchymal (8%), mixed (25-35%). Treatment: radical orchiectomy with block excision of the scar of the previous hydrocelectomy and surrounding tissue. Little response to chemotherapy, radiotherapy presents complete remission at 12 months that reaches 50%. Global Forecast: Unfavorable (average survival: 23 months).⁽²⁾

Lymphatic Drainage of the Testicle

It is important to know the lymphatic drainage of the testicle because it is the main route of dissemination of the tumors and occasionally it can be ordered, that is, to follow the primary sites of lymphatic spread in the metastases.

Right tumors: The ganglionic relays on this side follow the following order of frequency: Interaortocaval (3), precaval (2), paracaval (1). Drainage is carried out from right to left and is presented from 10 to 15%.

Left tumors: For the left side is the following order: para-aortic (5) and pre-aortic (4). The spread from left to right is very rare approximately <5%.⁽⁷⁾

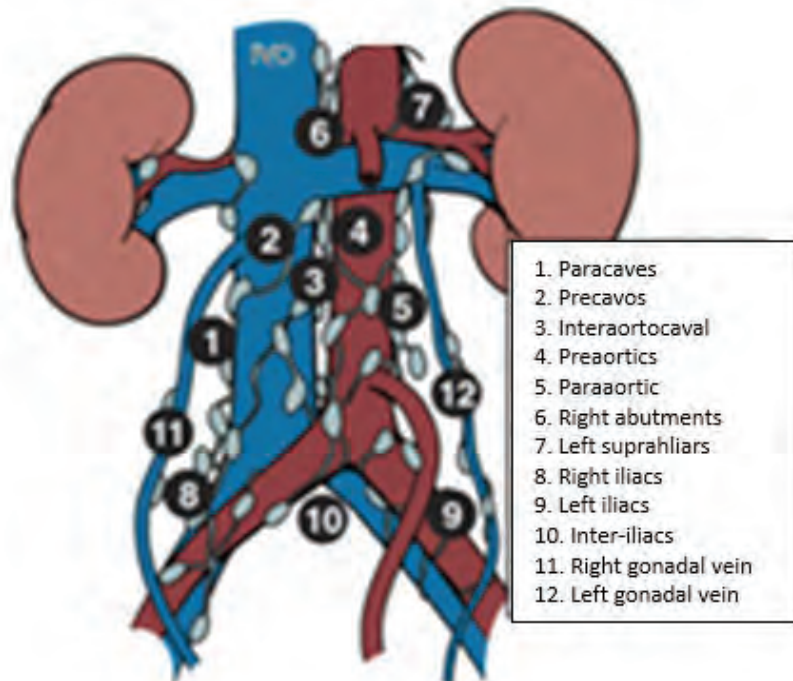


Figure 38-1. Lymphatic Drainage of the Testicle..

Table 38-3. TNM Classification for Testicular Cancer (UICC, 2017, 8th ed.) ⁽⁸⁾

pT - Primary Tumor ¹			
pTX	Primary tumor cannot be assessed (see note 1)		
pT0	No evidence of primary tumor (e.g. histological scar in testis)		
pTis	Intratubular germ cell neoplasia (carcinoma <i>in situ</i>)		
pT1	Tumor limited to testis and epididymis without vascular/lymphatic invasion; tumor may invade tunica albuginea but not tunica vaginalis*		
pT2	Tumor limited to testis and epididymis with vascular/lymphatic invasion, or tumor extending through tunica albuginea with involvement of tunica vaginalis		
pT3	Tumor invades spermatic cord with or without vascular/lymphatic invasion		
pT4	Tumor invades scrotum with or without vascular/lymphatic invasion		
N - Regional lymph nodes - Clinical			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastasis with a lymph node mass 2 cm or less in greatest dimension or multiple lymph nodes, none more than 2 cm in greatest dimension		
N2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence of extranodal extension of tumor		
N3	Metastasis with a lymph node mass more than 5 cm in greatest dimension		
Pn - Regional Lymph Nodes - Pathological			
pNX	Regional lymph nodes cannot be assessed		
pN0	No regional lymph node metastasis		
pN1	Metastasis with a lymph node mass 2 cm or less in greatest dimension and 5 or fewer positive nodes, none more than 2 cm in greatest dimension		
pN2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence of extranodal extension of tumor		
pN3	Metastasis with a lymph node mass more than 5 cm in greatest dimension		
M - Distant Metastasis			
MX	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		
	M1a Non-regional lymph node (s) or lung metastasis		
	M1b Distant metastasis other than non-regional lymph nodes and lung		
S - Serum Tumor Markers			
SX	Serum marker studies not available or not performed		
S0	Serum marker study levels within normal limits		
	LDH (U/l)	hCG (mIU/mL)	AFP (ng/mL)
S1	<1.5 x N and	< 5,000 and	< 1,000
S2	1.5-10 x N or	5,000-50,000 or	1,000-10,000
S3	> 10 x N or	> 50,000 or	> 10,000

N= indicates the upper limit of normal for the LDH assay. LDH= lactate dehydrogenase; hCG= human chorionic gonadotrophin; AFP =alpha-fetoprotein.

*AJCC subdivides T1 by T1a and T1b depending on size no greater than 3 cm or greater than 3 cm in greatest dimension.

1 Except for pTis and pT4, where radical orchidectomy is not always necessary for classification purposes, the extent of the primary tumor is classified after radical orchidectomy; see pT. In other circumstances, TX is used if no radical orchidectomy has been performed.

According to the 2009 TNM Classification, Stage I Testicular Cancer includes the following substages:

Table 38-4. 2009 TNM Classification.

Stage grouping				
Stage 0	pTis	N0	M0	S0
Stage I	pT1-T4	N0	M0	SX
Stage IA	pT1	N0	M0	S0
Stage IB	pT2 - pT4	N0	M0	S0
Stage IS	Any patient/TX	N0	M0	S1-3
Stage II	Any patient/TX	N1-N3	M0	SX
Stage IIA	Any patient/TX	N1	M0	S0
	Any patient/TX	N1	M0	S1
Stage IIB	Any patient/TX	N2	M0	S0
	Any patient/TX	N2	M0	S1
Stage II	Any patient/TX	N3	M0	S0
	Any patient/TX	N3	M0	S1
Stage III	Any patient/TX	Any N	M1a	SX
Stage IIIA	Any patient/TX	Any N	M1a	S0
	Any patient/TX	Any N	M1a	S1
Stage IIIB	Any patient/TX	N1-N3	M0	S2
	Any patient/TX	Any N	M1a	S2
Stage IIIC	Any patient/TX	N1-N3	M0	S3
	Any patient/TX	Any N	M1a	S3
	Any patient/TX	Any N	M1b	Any S
Stage IA:	patients have primary tumors limited to the testis and epididymis, with no evidence of microscopic vascular or lymphatic invasion by tumor cells on microscopy, no sign of metastases on clinical examination or imaging, and post-orchietomy serum tumor marker levels within normal limits. Marker decline in patients with CS I disease should be assessed until normalization.			
Stage IB:	patients have a more locally invasive primary tumor, but no sign of metastatic disease.			
Stage IS:	patients have persistently elevated (and usually increasing) serum tumor marker levels after orchietomy, indicating subclinical metastatic disease (or possibly a second germ cell tumor in the remaining testis).			

In large population-based patient series, 75-80% of seminoma patients, and about 55% of patients with NSGCT cancer have stage I disease at diagnosis. True stage IS (persistently elevated or increasing serum marker levels after orchietomy) is found in about 5% of non-seminoma patients.

In 1997, the IGCCCG defined a prognostic factor-based

staging system for metastatic testis tumors based on identification of clinically independent adverse factors. This staging system has been incorporated into the TNM Classification and uses histology, location of the primary tumor, location of metastases and pre-chemotherapy marker levels in serum as prognostic factors to categorize patients into 'good', 'intermediate' or 'poor' prognosis.

**Table 38-5. Prognostic-based Staging System for Metastatic Germ Cell Cancer ⁽⁹⁾
(International Germ Cell Cancer Collaborative Group) ***

Good-prognosis group	
<i>Non-seminoma (56% of cases)</i> 5-year PFS 89% 5-year survival 92%	<i>All of the following criteria:</i> • Testis/retro-peritoneal primary • No non-pulmonary visceral metastases • AFP < 1,000 ng/mL • hCG < 5,000 IU/L (1,000 ng/mL) • LDH <1.5 x ULN
<i>Seminoma (90% of cases)</i> 5-year PFS 82% 5-year survival 86%	<i>All of the following criteria:</i> • Any primary site • No non-pulmonary visceral metastases • Normal AFP • Any hCG • Any LDH
Intermediate-prognosis group	
<i>Non-seminoma (28% of cases)</i> 5-year PFS 75% 5-year survival 80%	<i>Any of the following criteria:</i> • Testis/retro-peritoneal primary • No non-pulmonary visceral metastases • AFP 1,000 - 10,000 ng / mL or • hCG 5,000 - 50,000 IU / L or • LDH 1.5 - 10 x ULN
<i>Seminoma (10% of cases)</i> 5-year PFS 67% 5-year survival 72%	<i>All of the following criteria:</i> • Any primary site • Non-pulmonary visceral metastases • Normal AFP • Any hCG • Any LDH
Poor-prognosis group	
<i>Non-seminoma (16% of cases)</i> 5-year PFS 41% 5-year survival 48%	<i>Any of the following criteria:</i> • Mediastinal primary • Non-pulmonary visceral metastases • AFP > 10,000 ng/mL or • hCG > 50,000 IU/L (10,000 ng/mL) or • LDH > 10 x ULN
<i>Seminoma</i>	No patients classified as poor prognosis

*Pre-chemotherapy serum tumor markers should be assessed immediately prior to the administration of chemotherapy (same day). PFS = progression-free survival; AFP = alpha-fetoprotein; hCG = human chorionic gonadotrophin; LDH = lactate dehydrogenase.

Clinical Stages ^(2,4)

Stage I (Limited to the testicle)

Cancer is limited to the testicle. Invasion of the scrotal wall by the tumor. The invasion of the tunica albuginea of the epididymis or the spermatic cord does not change the stage but does increase the risk of retroperitoneal lymph node involvement and the risk of recurrence.

- **Stage 1A:** patients have primary tumors limited to the testis and the epididymis, without evidence of microvascular lymphatic invasion or by tumor cells in microscopy, no trace of metastases after clinical examination or imaging, and the levels of serum tumor markers after orchiectomy within normal limits. The decrease in markers in patients with clinical stage I disease should be evaluated until normalization.
- **Stage 1B:** patients have a more locally invasive primary tumor, but no sign of metastatic disease.
- **Stage 1S:** patients have persistently elevated (and usually lower to higher) levels of serum tumor markers after orchiectomy, indicating subclinical metastatic disease (or possibly a second germ cell tumor in the remaining testis).

Stage II (Retroperitoneal lymph node involvement)

It includes the testicle and the retroperitoneal or para-aortic lymph nodes usually in the region of the kidney. The risk of recurrence increases if there are more than five nodes involved, if the size of one or more of these nodes is > 2 cm or if there is extranodal adipose involvement.

Stage II bulky disease describes patients with large retroperitoneal nodes (> 5 cm) that require primary chemotherapy and have a worse prognosis.

Stage III (Supradiaphragmatic extension)

It involves spreading beyond the retroperitoneal ganglia based on physical examination, radiographs or blood tests. It is subdivided into:

- **Stage III not bulky:** Metastases limited to the lymph nodes and the lung without a mass > 2 cm.

- **Voluminous stage III:** It includes extensive retroperitoneal lymph node involvement, in addition to pulmonary nodes or spread to other organs such as liver or brain.

Treatment

Testicular cancer is a model of curable disease.

Treatment Options

- **Radical orchiectomy.**
- **Retroperitoneal lymphadenectomy (RPL),** as adjuvant in non-seminomatous ECI, only option in mature teratoma (which is chemotherapy and radiotherapy resistant) in the face of evidence of retroperitoneal activity.
- **Chemotherapy,** option in seminomatous and non-seminomatous, as adjuvant in ECI, in advanced or metastatic disease.
- **Radiotherapy,** option for seminomatous tumors, adjuvant in ECI, or after chemotherapy.
- **Metastasectomy** at different levels: retroperitoneal, pulmonary, cerebral, etc.

Orchiectomy

1. **Inguinal radical orchiectomy:** it is the standard treatment and it consists of the *en bloc* resection of the testicle, the tunica albuginea and the spermatic cord. It provides 100% local control in organ-confined, with minimal morbidity and mortality in reference centers. In case of previous scrotal violation (biopsy, puncture or trans-scrotal orchiectomy) hemiscrotectomy is recommended simultaneously with retroperitoneal lymphadenectomy.
2. **Conservative surgery (lumpectomy):** can be considered in bilateral synchronous or metachronous tumors and in monorchid patients with normal testosterone levels when the tumor volume does not exceed 30% of the testicle. The enucleation is carried out together with a small margin of adjacent parenchyma. In 82% of bilateral tumors there is Tin, so all patients should be treated with adjuvant radiotherapy

(20 Gy) after surgery. Radiation can cause testosterone deficiency and infertility, so it can be delayed in young patients.

3. Conducting a contralateral biopsy to rule out or confirm the presence of carcinoma *in situ* (TIN) must agree with the patient. Contralateral biopsy is recommended in “high risk” patients (testicular volume < 12 ml, history of cryptorchidism and age less than 40 years).

Retroperitoneal Lymphadenectomy (RPL)

It can be done with conservation of sympathetic chains to prevent ejaculatory disorders and laparoscopy. In Europe it is used for the treatment of post-chemotherapy non-seminomatous residual masses. In the USA it precedes the chemotherapy in patients with non-seminomatous tumors in stage IB or IIA with negative markers.

The inferior mesenteric artery being established as the lower limit, ejaculation is conserved in a high percentage of cases. The suprahilar dissection can surely be omitted and the unilateral lymphadenectomy performed with minimal risks of stage I metastasis.

In the dissection of the para-aortic region, special attention should be paid to the postganglionic sympathetic fibers of the hypogastric plexus, since they directly affect postoperative ejaculation and fertility.

Complications of RPL⁽¹⁰⁾

- **Chylous ascites:** it is presented from 2 to 7%. It usually resolves with conservative management (low-fat diet, diuretic, total parenteral nutrition or paracentesis).
- **Pulmonary failure:** solves usually with pulmonary physiotherapy. It usually occurs in patients previously treated with bleomycin.
- **Renovascular damage:** has declined as a result of infrahilar dissection.
- **Intestinal injury:** usually of small intestine, or long-term intestinal occlusion.
- **Other complications:** atelectasis, surgical wound infection, retrograde ejaculation or infertility (hypogastric plexus dissection), prolonged ileus.

Treatment of GCT Seminoma Stage I

1. Radical orchiectomy

Only with orchiectomy 80% of patients will be cured, the rest (15-20%) will have recurrence due to retroperitoneal subclinical metastases, which will be highly chemoradiosensitive. With tumor size > 4 cm and invasion of rete testis recurred 32%, without any of these risk factors only 12%.

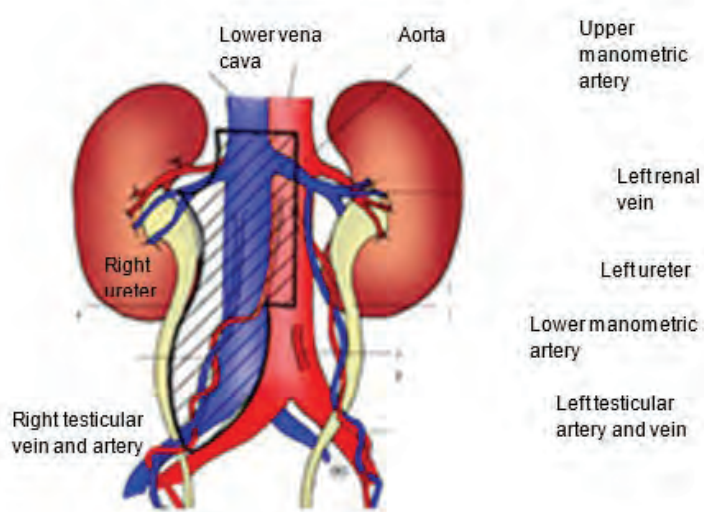


Figure 38-2. Template for RPL for right testicle.

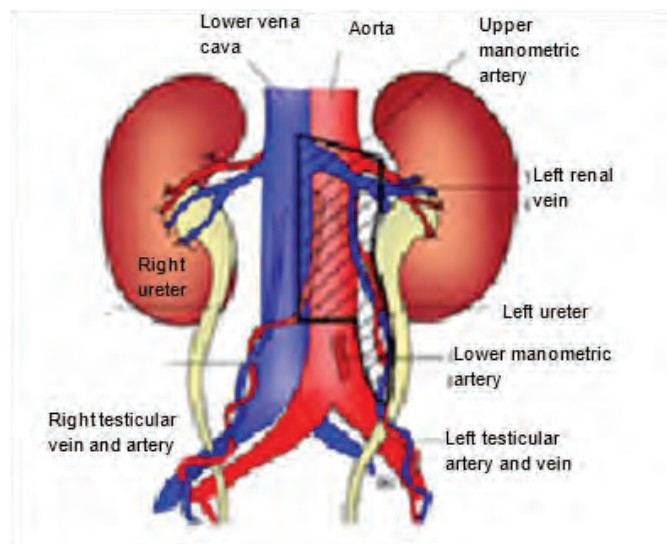


Figure 38-3. Template for RPL for left testicle.

2. Post-orchietomy treatment options

- **Expectant Surveillance:** Option when there are no risk factors and strict monitoring can be carried out. Of the 15-20% who relapse after orchietomy, 70% can be treated with rescue RT. Only 20% of those treated as such recur and need, therefore chemotherapy rescue. Cancer-specific survival with this policy is 97-100%.
- **Prophylactic Chemotherapy:** With 1-2 cycles of Carboplatin, recurrences are reduced to 1-3%, which is why chemotherapy after orchietomy is an alternative to observation and prophylactic Radiotherapy when there are risk factors or follow-up is going to be difficult.
- **Prophylactic RT:** With 20-24 Gy on the para-aortic or hockey stick chains (para-aortic + ipsilateral iliac), recurrence is reduced to 1-3%. It is a cheap option with late side effects < 2% in patients with risk factors.

A carboplatin cycle (AVC 7) is not inferior to Rt in the adjuvant treatment of classic stage I seminoma and also offers less late toxicity, risks of CVD and second neoplasms.

Treatment of Non-Seminomatous GCT Stage I

1. Orchietomy

Excluding IS-stage cases, up to 30% of these patients will relapse if only the testicle is removed. 80% will do it in the 1st year, 12% in the 2nd year, 6% in the 3rd year and 2% in successive years. The best predictor of recurrence is the presence of vascular invasion in the primary tumor (no invasion, i.e. pT1, recur 15-20% and with invasion, pT2-4, 50%). 35% have normal markers at the time of recurrence. The other factor of poor prognosis is the presence of > 50% of embryonic carcinoma lineage.

The overall relapse of these tumors after surveillance is 28%, after retroperitoneal lymphadenectomy of 12% and after adjuvant chemotherapy with Bleomycin Etoposide and Cisplatin (BEP) (3-4 cycles) of 3%. Note that in NSGCT SI radiotherapy has no indication.

2. Post-orchietomy Treatment Options

Expectant Surveillance

Valid option in low risk patients. With this option, 15% of low risk tumors fall, in which case the next alternative will be chemotherapy or RPL, of which only 1% will relapse.

High risk surveillance has a relapse of up to 50%, therefore, it is not a good option. This relapse will have to be managed with 3-4 cycles of BEP.

Not indicated in stage IS, in which the first option is the chemotherapy with 3-4 cycles of Bleomycin, Etoposide and Cisplatin (BEP) and the alternative is the RPL.

Prophylactic Chemotherapy

In high risk patients (with vascular invasion) or with difficult follow-up or who do not want to assume the risk of follow-up. With 2 cycles of BEP the recurrence rate drops to 2-3%. There is a risk of mature teratoma after chemotherapy and also of late chemo-resistant recurrence. In this case, RPL of the residual mass is indicated. There is also the alternative of giving a BEP cycle for low risk patients.

Retroperitoneal lymphadenectomy (RPL)

Alternative to chemotherapy in patients with high risk or with difficult follow-up, or who do not want to assume risk. It can be done with conservation of sympathetic chains to prevent ejaculatory disorders and laparoscopy. The risk of recurrence after this surgery is 7% (and some studies up to 10-15%), somewhat higher than prophylactic chemotherapy.

If the pathological anatomy is positive, chemotherapy is recommended with 2 cycles of BEP (some literatures sustain up to 3-4 cycles), then lowering the risk of recurrence to 2%.⁽¹¹⁾

Radiotherapy has no utility or indication in non-seminomatous germ cell tumors.

Prognostic Factors for Hidden Metastatic Disease

These factors identified in the orchietomy pathology report help predict the risk of recurrence in testicular tumors initially staged as stage I.

For Seminoma:

- Tumor size (> 4 cm)
- The invasion of rete testis (Haller ducts)
- Lymphovascular infiltration
- Age over 34 years
- Beta HGC > 200 IU / L pretreatment

Patients with tumors <4 cm and without invasion of the *rete testis*, can be subjected to vigilant observation. And even with one of the two factors. Those with tumors > 4 cm and invasion of the *rete testis*, adjuvant chemotherapy with carboplatin, AUC 7 (depending on creatinine clearance of 12 or 24 h), for 1 or 2 cycles, every 3 weeks (as first option) is recommended, or para-aortic RT 20 Gy (as a second option).

In a prospective study on risk of recall, tumor > 4 cm and invasion of the *rete testis* were the 2 most important risk factors for recurrence. Patients with no or only one of these factors presented a 12 to 15% risk of recurrence. While those with two factors had 30% recurrence.

For Non-Seminoma:

- a) Lymphatic / vascular invasion or peritumoral invasion
- b) Percentage of embryonal carcinoma > 50%
- c) Proliferation rate greater than 70%
- d) Size > 4 cm
- e) AFP > 10,000

For patients with non-seminomatous LRP testicular cancer, adjuvant chemotherapy and vigilant observation are the alternatives of complementary treatment after orchiectomy in ECI. These behaviors depend on two anatomopathological criteria: vascular invasion and amount of embryonal carcinoma present in the primary tumor.

Patients with absence of vascular invasion and predominance of embryonal carcinoma can be monitored because the probability of lymph node involvement is 16%. Patients with vascular invasion who were subjected to observation, the recurrence rate was 41.7%.

The presence of one or two risk factors (vascular invasion or predominance of embryonal carcinoma) is indicative to give chemotherapy with BEP for 1 or 2 cycles (many centers prefer 2 cycles when both factors are present). Nerve-sparing RPL represents a good alternative. The probability of lymph node involvement in patients under surveillance is 30% in patients with a risk factor, and 62% with both.

Patient with risk factors treated with 2 cycles of BEP, one of BEP or observation have disease-free survival of 100, 96.5 and 58.3% respectively. ⁽¹²⁾ If these risk factors occur, it is important to treat patients with adjuvant options: chemotherapy, RT or RPL depending on the histopathological lineage.

Low Volume Metastatic Tumor (Stages IIA / B)

Seminoma IIA / B

In this group of patients with lymph node metastases <5 cm in their maximum transverse diameter (IIA and IIB) the standard treatment is RT in hockey stick or also called dog-leg (para-aortic and pelvic: ipsilateral iliac) 30 Gy for IIA and 36 Gy for the IIB. In stage IIB the alternative is chemotherapy with 3 cycles BEP or 4 cycles of EP showing complete responses of 83% and SLP and SG rates in 5 years of 90 and 95%, respectively.

No seminoma IIA / B or Clinical Stage II in which the RPL is positive for metastasis.

The standard treatment is chemotherapy with 2-3 cycles of BEP or EP followed by RPL if there is residual mass. But in the NSGCT IIA with negative markers you can:

- **Observation:** reevaluation at 6 weeks. If the adenopathies decrease in size they are probably of non-malignant origin and should be monitored; if the lesions are equal or grow, RPL should be performed (if the histopathological result shows mature teratoma, nothing should be done, if there is a malignant tumor, chemotherapy should be performed with 2 cycles of BEP).
- **Primary RPL** with preservation of sympathetic chains: if the histopathological report is positive for tumor, it should be continued with 2 cycles of BEP.

The risk of recurrence depends on the number of positive lymph nodes and the size of the larger lymph node. In patients with lymph nodes <2 cm and <5 metastatic nodes and without extracapsular invasion, the risk of recurrence is less than 35%. ⁽¹²⁾

Advanced Metastatic Tumors (Stages IIC, IIIA/B/C)

Presence of metastases in non-regional (mediastinal, supraclavicular) or visceral (lung, bone, liver and brain) lymph nodes. The treatment of choice is primary chemotherapy with 3-4 cycles of BEP.

Seminoma EC III

Based on the prognostic classification of the IGCCCG.

- **Low risk:** BEP x 3 or Etoposide and Cisplatin (EP) x 4.
- **Intermediate risk:** BEP x 4 or VIP with G-CsF of support (in those who cannot suffer any form of pulmonary toxicity induced by the bleomycin).

In relation to the post-treatment behavior of the primary, the same comments made in the cases in Clinical Stage IIC are valid.

Non-seminoma Clinical Stage (CS) III

The standard treatment depends on the prognostic classification of the IGCCCG:

- **Low risk:** BEP x 3 (first option) or EP x 4 (second option).
- **Intermediate or high risk:** BEP x 4. As an alternative, consider exclusively, in individuals with intermediate risk, the scheme T-BEP x 4 cycles (with G-CsF prophylactic).

After finishing chemotherapy if there is a residual radiological image, surgery will be indicated whenever resectability is feasible.

Generally, in primary testicular and retroperitoneal tumors, residual mass resection should be performed only if the markers are normal. And in case the pathological result reveals residual disease in activity, we recommend 2 to 4 additional cycles of EP or Paclitaxel Ifosfamide and Cisplatin (TIP).

When there is residual disease in the abdomen and thorax, the MSKCC group recommends that the resection should be made first in the abdomen and then in the thorax. If there is necrosis / fibrosis in the anatomopathological evaluation of the abdomen, the histological concordance of the thoracic injury varies from 73 to 90% and, in these cases, the monitored observation can be considered. The data of concordance between retroperitoneal and extraretroperitoneal tumors (thorax) by type of residual mass are: 83% fibrosis, 42% teratoma, and 47% viable tumor.

And when only one side is explored and necrotic nodules are found, we recommend only the observation of the contralateral hemithorax. In the same way, when a mature teratoma and / or viable tumor is found on one side, the other should necessarily be operated.⁽¹²⁾

And in general terms for EC III and prognostic factors, the following is recommended:

Table 38-6. EC III and Prognostic Factors

Group of good prognosis of the IGCCCG:
• 3 cycles of BEP or 4 of EP if the Bleomycin is contraindicated
Interim forecast group of the IGCCCG:
• 4 cycles of BEP.
IGCCCG poor forecast group:
• 4 cycles of BEP or clinical trial in reference center.

Restaging After Primary Chemotherapy and Rescue Treatment

After primary chemotherapy, it must be re-staged with image tests and markers. We can find several possibilities:

1. Markers decreasing and tumor stable or in regression:

- **If there is no residual mass:** follow-up.
- **If residual mass of a seminoma remains:** It should not be resected at the beginning, it is controlled with imaging techniques and markers, if the tumor is less than 3 cm by CT it is monitored, if it is greater than 3 cm a PET / CT can be performed (6 or more weeks after the chemotherapy is completed)) to differentiate active tumor fibrosis in the residual mass.

If there is progression of the mass with positive tumor markers, rescue chemotherapy is indicated with 4 cycles of PEI / VIP (Cisplatin, Etoposide, Ifosfamide), TIP (Paclitaxel, Ifosfamide, Cisplatin) or VeIP (Vinblastine, Ifosfamide, Cisplatin),

If the markers are negative and mass is viable by PET / CT (with SUV max units > 2.5-3), a new cycle or other chemotherapy line can be indicated or sent to RT and re-evaluated or retroperitoneal tumorectomy of the residual mass is also indicated.

- **If residual mass remains of a non-seminoma:** RPL should be performed even if the markers have normalized. The risk of residual tumor is 10%, 40% mature teratoma and 50% necrosis-fibrosis. (Another reference considers 20% viable tumor, 20 to 30% mature teratoma and 30 to 40% Necrosis or fibrosis).

Neither the PET nor any prognostic model is able to predict the tumor activity of the residual mass. The chemotherapy of consolidation after the resection of the mass is only indicated after incomplete resection of immature teratoma or viable carcinoma, but not in case of complete resection of a tumor that occupies <10% of the mass, neither in mature teratomas nor in fibrosis/necrosis.

In mature teratoma, special care should be taken in monitoring for the risk of developing an expanding teratoma syndrome.

2. Markers decreasing but progression metastasis:

RPL with conservation of sympathetic chains if possible.

3. Markers growing after 2 cycles of BEP:

Rescue chemotherapy with 4 cycles of PEI / VIP, TIP or VeIP or clinical trials. With increasing markers the RPL is not indicated. ⁽¹²⁾

Residual Masses After Chemotherapy in Non-Seminoma.

In general, after BEP induction chemotherapy, only 10% of residual masses contain viable cancer, 50% contain mature teratoma, and 40% contain fibrotic necrotic tissue. Until now, no imaging tests, including PET or a prognostic model, are able to predict the histological differentiation of residual non-seminoma tumor. Therefore, resection of residual tumor is mandatory in all patients with residual disease > 1 cm. ⁽¹⁾

Histology of residual retroperitoneal masses post-chemotherapy of NSGCT after first line:

- Necrosis: 40 – 50%
- Mature Teratoma: 35 – 40%
- Viable tumor: 10 – 15%

Approximately 15% of retroperitoneal lymphadenectomy in CS I will have mature teratoma in the histopathological report. The 91% of the retroperitoneal ganglia reported with mature teratoma was not a component of the primary tumor in the testicle.

A testicle with a primary tumor composed of teratoma will have a teratoma in the lymph node metastases. The histological discrepancy between retroperitoneal and extra-retroperitoneal histology is from 8 to 30%. The necrosis in the pathology report of a liver biopsy is sufficient to indicate no further liver resections. ⁽¹⁾

Late Recurrences

After 2 years of first line treatment. A complete resection of all lesions should be attempted. If it is not technically feasible, at least biopsy should be performed, and rescue chemotherapy should be initiated according to the pathological anatomy. If the patient responds to the rescue chemotherapy, secondary surgery should be performed if possible, and RT if it is not possible. ⁽¹²⁾

Schemes of Chemotherapy

First Regimes

Some schools consider only the first line the scheme with BEP and VIP consider it second line, this scheme is based on the NCCN guidelines, and we adapt it with the data from the Clinical Oncology Manual (MOC) for solid tumors. ⁽¹²⁾

Table 38-7. Schemes of Chemotherapy – First Regimes

Scheme	Description
BEP	• Bleomycin 30 units IV weekly, on days 2, 9, 16 (or 1, 8, 15). • Cisplatin, 20 mg/m² in 1000 mL Physiological Solution (SF), with 200 mL of mannitol 20% IV, for 2 hrs. From day (D) 1 to D5. • Etoposide, 100 mg/m² in 500 mL SF IV, from D1 to D5. Hydrate aggressively with at least 1.5 L of SF before and after cisplatin. Use granulocyte colony stimulating factor (G-CSF) in the case of previous RT. Repeat every 3 weeks (21 days)
EP: BEP without Bleomycin.	• Etoposide, 100 mg/m² in 500 mL SF IV, from D1 to D5. • Cisplatin, 20 mg/m² in 1000 mL Physiological Solution (SF), with 200 mL of mannitol 20% IV, for 2 hrs. From day (D) 1 to D5. Repeat every 3 weeks (21 days)
VIP	• Etoposide, 75 mg/m² IV, from D1 to D5, and G-CSF in the dose of 5 mcg/kg/day SC until the granulocytes exceed 10,000/mm³. • Ifosfamide, 1200 mg/m² IV, from D1 to D5 • Cisplatin, 20 mg/m² IV, for 1 h, from D1 to D5, • Mesna, 400 mg/m² IV, 30 min before, 4 and 8 h after ifosfamide). Repeat every 3 weeks.

Second Line Regimes ⁽¹²⁾

Table 38-8. Schemes of Chemotherapy – Second Regimes

Scheme	Description
VeIP	• Vinblastine, 0.11 mg / kg IV, D1 and D2. • Cisplatin, 20 mg/m² IV, for 1 h, from D1 to D5, • Ifosfamide, 1200 mg/m² IV, from D1 to D5 • Mesna, 400 mg/m² IV, 30 min before, 4 and 8 h after Ifosfamide. Repeat every 3 weeks.
TIP: (T: Taxane)	• Paclitaxel, 250 mg/m² in 1000 mL of SF IV, in continuous infusion through 24 h, the D1. • Ifosfamide, 1200 (1500) mg/m² IV, for 1 h, from D2 to D6. • Cisplatin, 20 mg/m² IV, for 1 h, from D2 to D6, • Mesna, 400 mg/m² IV, 30 min before, 4 and 8 h after each cycle of Ifosfamide, and G-CSF in the dose of 5 mcg/kg/day SC until the granulocytes exceed 10000/mm³. Repeat every 3 weeks.
T-BEP	• Paclitaxel (Taxano), 175 mg/m², in infusion of 3 h the D1, • Followed by BEP starting the D1.

Table 38-9. Schemes of Chemotherapy - Predominantly Palliative Regimens

Scheme	Description
GemOx	Gemcitabine , 1000 mg/m ² IV, D1 and D8. Oxaliplatin , 130 mg/m ² IV, D1 (after Gemcitabine, infused in 2 h), every 21 days.
GOP	Gemcitabine , 800 mg/m ² IV. Paclitaxel , 80 mg/m ² IV, both D1 and D8. Oxaliplatin , 130 mg/m ² IV, D1, every 3 weeks.
Gemcitabine / Paclitaxel	Paclitaxel , 110 mg/m ² IV, for 1 h. Gemcitabine , 1000 mg/m ² IV, for 30 min, both D1, D8 and D15, every 28 days.
Irinotecan / Cisplatin	Irinotecan , 100 to 150 mg/m ² IV, D1 and D15 (or 200 to 300 mg/m ² IV, each 4 weeks). Cisplatin , 20 mg/m ² /day IV, from D1 to D5, every 4 weeks.
Oxaliplatin / Bevacizumab	Oxaliplatin , 85 mg/m ² IV. Bevacizumab , 10 mg/kg IV, every 2 weeks.
Epirubicin / Cisplatin	Epirubicin , 90 mg/m ² IV, D1. Cisplatin , 20 mg/m ² IV, from D1 to D5. Every 3 weeks.
Etoposide	Etoposide oral, 50 mg/m ² /day, for 21 days, every 4 weeks.
Thalidomide	Thalidomide , 200 to 600 mg/day.

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Chapter 39

Prostate Cancer

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General Information

The incidence of prostate cancer (PC) is growing proportionally to the age of man, which is a health problem, especially in developed countries that represent a greater proportion of elderly men.

PC is the second most diagnosed cancer around the world in men. A systematic review assessed autopsy studies finding PC prevalence in men under 30 years of age 5% (CI 95%: 3-8%), increasing in an odds ratio (OR) of 1.7 per decade, to a prevalence of 59% (48-71%) in older than 79 years. ⁽¹⁾

The estimation of new cases at 2018 is projected from 164,690; Which is equivalent to 9.5% of all cancers and 19% of the new cases of cancer in men.

The age group of dominant presentation ages are 65 to 74 years with an average age at the diagnosis of 66 years. ⁽²⁾

PC is an androgen-dependent cancer and androgens are the main regulators of their growth and activity. It represents a highly potential distance metastatic with predominance to bone.

In the biology of advanced cancer in approximately 50% of the tumors, there are mutations in the androgen gene receptor, which generates a “*sui generis*” behavior, causing modifications in the own androgenic receptor, increasing its expression, sensibility and number, thus generating a rapid and lethal progression of the tumor even in environments of minimal concentrations of androgens, a condition known as “castration-resistant PCa” ⁽³⁾ final stage of disease.

Risk Factors

The most important are: the age, with a directly proportional risk; ⁽⁴⁾ the family history, where the number of affected members, the age of onset and the degree of kinship are the most important determinants; ⁽⁵⁾ genetic factors have identified the HPC1 (Hereditary prostate cancer-1), and recently BRCA-2 or Lynch syndrome (mutations in the germinal line in MLH1, MSH2, MSH6 or PMS2) among the principals, ⁽⁶⁾ as well as exogenous and environmental factors, where the diet stand out, obesity, excessive carbohydrate consumption, tobacco, alcohol and African descent.

Diagnosis

The elements to consider the PC staging include the digital rectal exam (DRE), the prostate specific antigen (PSA) and its variables: Total PSA, free PSA, PSA density, PSA elevation (historic), Gleason score obtained from the prostate biopsy, as well as extension studies including computed tomography (CT) for the identification of lymph nodes (LN) and/or visceral metastases, and a bone scan for the detection of metastasis.

Prostate biopsy is not for all men with high PSA score. Consider: digital rectal examination, family history, ethnicity, prostate volume and risk prediction models before undergoing a prostate biopsy. Life expectancy should be considered as well.

Stage and Grade

The Gleason Score is a grading system which is based on the architectural pattern of the prostate gland. Nowadays it starts at 6 (or 3+3) and this is the lowest score. The Gleason score includes the main degree or most extensive pattern (primary pattern), plus the second most common pattern (secondary pattern).⁽⁹⁾

Based on the above elements, three clinical stages are integrated:⁽⁷⁾

1. Localized prostate cancer.
2. Locally advanced prostate cancer.
3. Metastatic prostate cancer.

Each of these stages with prognostic characteristics, survival measures, clinical data and specific treatment alternatives.

The definitive diagnosis is based on the confirmation of adenocarcinoma by histopathological report in the samples of the prostate biopsy guided by ultrasound or in the fragments of the surgical piece obtained by Transurethral Resection of the Prostate (TURP).

The histologically predominant type is adenocarcinoma. Other rare types are ductal, neuroendocrine, sarcoma, among others. Prostate biopsy provides information on the Gleason score and the extent of the tumor. The model of sextant is no longer considered adequate, being better to take 10-12 samples in addition to those ecographically suspicious areas.⁽⁸⁾

The indications for prostate biopsy for early detection of Prostate Cancer are mainly three:

- a) Abnormal or suspicious rectal digital exam.
- b) PSA greater than 10 ng/ml.
- c) PSA free percentage less than 10%.

Multiparametric Magnetic Resonance Imaging (mpMRI)

The use of mpMRI has shown promising results in diagnosis, location, risk stratification and clinically significant PCa staging. It has also opened opportunities for focal treatment of PCa.

Combinations of T2 weighted images (T2-weighted imaging), diffusion images, perfusion (enhanced dynamic

contrast images) and spectroscopic images have been used in the evaluation of PCa with mpMRI, but the morphological evaluation of T2 and functional evaluation by diffusion images remain the pillar for the diagnosis of PCa in the multiparametric magnetic resonance.

The mpMRI combines the following evaluations:

- Morphological evaluation of the T2-weighted imaging (T2WI).
- The diffusion-weighted image (Diffusion-Weighted Imaging (DWI)).
- The Dynamic Contrast-Enhanced (DCE) perfusion image.
- The spectroscopic image (MRSI).

The mpMRI has been widely studied in recent years. In particular, the parameters of T2WI and DWI have shown considerable promise in the detection, location, risk stratification and staging of prostate cancer.⁽¹⁰⁾

The mpMRI can be performed with endorectal coil in 1.5 tesla (1.5T) equipment, or without it when a 3 tesla (3T) equipment is available.

The criteria of suspicious of PCa with multiparametric MRI are lesions in the peripheral gland with the following characteristics:

- Lesions with low signal in T2 (T2-WI).
- A ADC (apparent diffusion coefficient): <1.1 (units: $1 \times 10^{-3} \text{ mm}^2/\text{s}$) in the diffusion.
- Pathological perfusion (DCE): early and intense uptake and contrast washing.
- Score 3 or more in spectroscopy (MRSI).

T2-weighted images (T2WI) remain the most useful method for local staging when a mpMRI is performed. The 1.5 T (Tesla) mpMRI has a good specificity but low sensitivity to detect PCa in T3 stages.

The data evaluated from a meta-analysis showed a sensitivity and specificity of 0.57 and 0.91 to identify extracapsular extension (ECE), 0.58 and 0.96 for invasion to seminal vesicles, and in general for the global detection of the T3 stage of 0.61 and 0.88 respectively.⁽¹¹⁾

The evidence supports the implementation of mpMRI in various aspects of the management of PCa as:⁽¹²⁾

- First, the mpMRI helps to detect poorly differentiated tumors (Gleason ≥ 7). The mpMRI has been incorporated into the MRI-TRUS fusion-directed biopsy protocols, which has led to an increase in the diagnosis of high-grade cancers with fewer biopsy cores, while reducing the detection of low-grade and insignificant cancers.
- Second, mpMRI helps in the detection of extracapsular extension with very low negative predictive values in patients with low-risk PCa. The results of the mpMRI can outline the decision making regarding performing surgery with nerve preservation or not.
- Third, it can also be useful in the detection of pelvic lymph nodes.
- Finally, the mpMRI is superior to conventional bone scan and the radiographs directed to the detection of bone metastases, with a sensitivity of 98% to 100% and a specificity of 98% to 100%.

The European Guidelines ⁽¹²⁾ maintains with respect to the mpMRI that the correlation that exists between the pathology report of radical prostatectomy pieces with the results of the mpMRI when associating the T2-weighted image (T2-WI) with at least one functional imaging technique (DWI, DCE, H1 spectroscopy) has a good sensitivity for the detection and localization of significant cancers with Gleason Scores ≥ 7 and strongly recommends “performing mpMRI images before repeating a biopsy when clinical suspicion of PCa persists despite previous negative biopsies”.

PI-RADS Score:

Because the evaluation of the mpMRI images can be subjective, the European Society of Urogenital Radiology

(ESUR) proposed a numerical system for the interpretation of the mpMRI images called the Data and Reporting System Prostate Imaging, or PI-RADS for its acronym in English (Prostate Imaging and Reporting Archiving Data System), for the detection of Pca ⁽¹⁰⁾

The PI-RADS system, recently updated in its version 2 (PI-RADS v2), is designed to improve the detection of focal lesions, location, characterization and risk stratification in patients with suspicious prostate cancer and consists of the numerical technical recommendation for the interpretation of images. PI-RADS uses a scale of 1-5 to report the general probability of detecting a clinically significant PCa in a biopsy (defined for this system as: Gleason ≥ 7 and / or volume ≥ 0.5 cc, and / or extra prostatic extension (EPE)).

The PI-RAD evaluation in mpMRI is limited to patients who have not received prior treatment and should not be used for staging, evaluation of treatment outcome, recurrence or progression during follow-up.

The assignment of a PI-RADS assessment category is based only on the findings of the mpMRI does not incorporate other factors such as PSA, digital rectal examination, and clinical history.

Although the biopsy should be considered for PIRADS 4 or 5, but not for PIRADS 1 or 2, the PI-RADS v2 system does not include management recommendations and must take into considerations other factors in addition to the mpMRI findings, which includes clinical and laboratory aspects.

Therefore, for findings with the PIRADS 2 or 3 Evaluation Category, the biopsy may or may not be appropriate, depending on factors other than those of a single mpMRI. ⁽¹⁰⁾

Table 39-1. PIRADS Classification

PI-RADS Classification	Definition	Total T2+DWI+DCE score	Total T2+DWI+DCE +MRS score
I	Most probably benign	3-4	4-5
II	Probably benign	5-6	6-8
III	Indeterminate	7-9	9-12
IV	Probably malignant	10-12	13-15
V	Most probably malignant	13-15	17-20

Urinary and Blood Biomarkers

There are currently several urinary and blood biomarkers that can support the possibility of identifying high-risk tumors, or that can be used to predict positivity in repeated biopsies, including: PCA-3, the 4K Score, the PHI index, ConfirmMDx (an epigenetic test based on biopsied tissue); the SelecMDx for Prostate Cancer, a reverse transcription PCR assay (RT-PCR); Pro Marxk, Polaris, Decipher®, Oncotype Dx Prostate cancer; and some indexes such as MiPS (Michigan Prostate Score), the Stockholm Multiplex-3 algorithm (STHLM-3), the Score Rotterdam Prostate Cancer Risk calculator or genetic tests such as the Oncotype Dx® Prostate Cancer. ⁽¹³⁾

Conventional imaging studies for staging are bone scintigraphy, computed tomography (CT) or magnetic resonance imaging (MRI). However, today with the advances in technology the term “new generation of imaging studies” has been used.

Next Generation Imaging Techniques

The evolution and development of novel next generation imaging (NGI) techniques will affect diagnostic and therapeutic decision-making. Clinicians must navigate when and which NGI techniques to use and how to adjust treatment strategies based upon their results, oftentimes in the absence of correlative therapeutic data. Therefore, guidance is needed based on best available information and current clinical experience.

The RADAR III Group recommends NGI techniques for select patients suspected of disease progression based on laboratory (biomarker) values, comorbidities, and symptoms. Currently, ¹⁸F-fluciclovine, ⁶⁸Gallium (Ga) PSMA PET/CT and ¹⁸F-sodium fluoride (¹⁸F NaF) PET/CT are the NGI agents with a favorable combination of availability, specificity, and sensitivity. There is ongoing research for additional NGI technologies, which may offer improved diagnostic accuracy and therapeutic options. As NGI techniques evolve and presumably result in improved global accessibility, clinician’s ability to detect micrometastases may be enhanced for both decision-making and patient outcomes. ⁽¹⁴⁾

Prostate Specific Antigen (PSA)

Biochemically, PSA is a seric protease, a 34 kD glycoprotein. It is encoded in the gene located on chromosome 19

(19q13.41). PSA expression is strongly influenced by androgens. The half-life of the PSA is 2.2 to 3.2 days. Its clearance is 10 half-lives.

The PSA in the circulation can be forming complexes (it represents 85% of the serum PSA) or in free form (remaining 15%). We found it circulating together with proteins, it does so mainly to the ACT (alpha-1 anti-chymotrypsin) and forms the PSA-ACT complex, the most common (60 to 90%).

Digital Rectal Examination (DRE)

PC is in the peripheral area and can be detected by digit rectal exam (DRE) when the volume is 0.2 ml or greater. PC is detected by suspicious rectal exam only, regardless of the PSA level, in about 18% of all patients. A suspicious DRE in patients with a PSA of up to 2 ng / ml has a positive predictive value of 30.5% for PC. A suspicious DRE is a strong indication of prostate biopsy, as it is predictive for the identification of aggressive PC (Gleason > 7). ⁽³⁾

Staging of Prostate Cancer

The staging of patients with PC is essential and important aspect to determine the extent of the disease, its aggressiveness, and thereby define the best treatment options and thus be able to determine the prognosis of the patients. PC is staged by the classification proposed by the American Joint Committee on Cancer (AJCC) known as TNM (Tumor, Nodes, Metastasis), 8th ed., 2017. ⁽¹⁵⁾ (Table 39-2)

Treatment

Treatment decisions or strategies fall into three main scenarios: ⁽¹⁶⁾

1. When the prostate cancer is localized. The treatments offered to patients are with curative intent and are outlined according to the risk group of each patient: very low, low, intermediate (favorable intermediate, unfavorable intermediate), high and very high risk. Groups are based on their definition at the APE level, the degree of Gleason and the characteristics of the prostate to the rectal exam.

Treatment alternatives can be active surveillance, radical surgery in any of its modalities: pure laparoscopic, open or Robot-assisted; radiotherapy, cryotherapy or focal therapies such as cryotherapy or HIFU.

Table 39-2. Definitions for T, N, M
American Joint Committee on Cancer (AJCC) TNM Staging System for Prostate Cancer
(8th edition, 2017)

Clinical T (cT)		
T		Primary Tumor
TX		Primary Tumor cannot be assessed
T0		No evidence of primary tumor
T1		Clinically inapparent tumor that it not palpable
	T1a	Tumor incidental histologic finding in 5% or less of tissue resected
	T1b	Tumor incidental histologic finding in more than 5% of tissue resected
	T1c	Tumor identified by needle biopsy found in one or both sides, but not palpable
T2		Tumor is palpable and confined within prostate
	T2a	Tumor involves one-half of one side or less
	T2b	Tumor involves more than one-half of one side but not both sides
	T2c	Tumor involves both sides
T3		Extraprostatic tumor that is not fixed or does not invade adjacent structures
	T3a	Extraprostatic extension (unilateral or bilateral)
	T3b	Tumor invades seminal vesicle(s)
T4		Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, ad/or pelvic wall
Pathological T (pT)		
T		Primary Tumor
T2		Organ confined
T3		Extraprostatic extension
	T3a	Extraprostatic extension (unilateral or bilateral) or microscopic invasion of the bladder neck
	T3b	Tumor invades seminal vesicle(s)
T4		Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall

* Note: There is no pathologic T1 classification

** Note: Positive surgical margin should be indicated by an R1 descriptor; indicating residual microscopic disease

N		Regional Lymph Nodes
NX		Regional lymph nodes cannot be assessed
N0		No positive regional nodes
N1		Metastases in regional node(s)
M		Distant Metastasis
M0		No distant metastasis
M1		Distant metastasis
	M1a	Non-regional lymph node(s)
	M1b	Bone(s)
	M1c	Other site(s) with or without bone disease

* Note: When more than one site of metastasis is present, the most advanced category is used, M1c is most advanced.

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The original source for this information is the AJCC Cancer Staging Manual, 8th edition published by Springer International Publishing.

There are treatment modalities for patients with a disease called oligometastasis and they can obtain a benefit of curative intent with radical treatments.

2. The metastatic prostate cancer. Whose main site of impact of the metastases is bone and lymph nodes are susceptible to hormonal management with androgen suppression therapy or also called hormonal blockage, which consists in the suppression of testosterone by the testicles which are the main source of androgens (testosterone). In this scenario the use of LHRH analogues, LHRH antagonists and antiandrogens or orchiectomy are the medications of choice, and the treatments are intended to control, but not to eradicate the disease.
3. Once this metastatic prostate cancer has become Castrate-resistant prostate cancer (CRPC) after hormonal manipulation. For many years the only treatment option was represented by docetaxel-based chemotherapy. However, from 2010 until our days, the therapeutic decision in this lethal stage of the disease, with the new medications available, are based on the functional status of the patient and the characteristics of the tumor. In this scenario, the following alternatives are currently available on the market: chemotherapy with docetaxel and cabazitaxel, the latest generation hormonal agents such as abiraterone or enzalutamide, immunotherapy with Sipuleucel-T, and an alpha emitting radiopharmaceutical: Ra-223.

In the process of transition to castration resistance, a stage also known as “progression”, hormonal manipulations traditionally called second line can, under certain circumstances, be indicated. In this scenario the changes of antiandrogens, the withdrawal of antiandrogen, are useful. The use of corticosteroids with prednisone, ketoconazole, low doses of diethyl ethylbestrol, etc., with very variable success and utility rates.

Deferred Treatment

Many men are detected by screening with localized prostate cancer, some of these will not benefit from definitive treatment and 45% of them are candidates for deferred treatment. There are two different strategies for conservative or deferred treatment whose objective is to reduce over treatment. Expectant attitude in which conservative management is carried out until the development of local symptoms or systemic progression, at this time the patient would be a

candidate for palliative treatment with TUR, hormone therapy or Radiotherapy for metastatic lesions, in order to maintain the quality of life. Active surveillance that includes an active decision of not to treat the patient immediately and follow him closely with surveillance and start active treatment at the beginning of the progression. It aims to achieve the correct synchronization for curative treatment, instead of postponing the application of palliative care.

Several series have applied rigorous criteria to include patients under active surveillance: clinically confined PC (T1-T2), Gleason score <7 (for most studies), PSA <10-15 ng / ml. Low volume in biopsies (for example, number of positive cores and maximum cancer involvement in cores) ⁽³⁾

Low tumor volume in biopsies is defined by a low number of cylinders involved and a low tumor length in each cylinder involved.

Radical Prostatectomy (RP)

It consists of the total removal of the gland between the urethra and the bladder, and the resection of both seminal vesicles with enough surrounding tissue to obtain negative margins. Depending on risk factors, perform lymphadenectomy (bilateral pelvic lymph node dissection).

The goal in RP is the eradication of the disease, with preservation of urinary continence and sexual potency (erectile function) whenever possible.

There is no age limit for RP and this procedure should not be denied due to age alone.

RP is the only localized prostate cancer treatment that has shown a benefit in cancer-specific survival, compared to conservative approaches; In addition, the surgical experience has reduced the rate of complications and improved the results.

Options for Performing Radical Prostatectomy (RP)

1. Retropubic Radical Prostatectomy (RRP), the most commonly used, allows lymphadenectomy.
2. Perineal Prostatectomy (PP).
3. Minimally Invasive Laparoscopic Radical Prostatectomy (LRP).
4. Robot-Assisted Radical Prostatectomy (RARP).

Robot-assisted laparoscopic prostatectomy (RARP) is displacing retropubic radical prostatectomy (RRP), as the most commonly used surgical approach for clinically located PC in the United States, and it is being used more and more in Europe and all over the world.

This trend has occurred despite the lack of high-quality studies to support the superiority of the RARP. A recent systematic review showed that robotic surgery had lower perioperative morbidity and a lower risk of positive surgical margins compared to laparoscopic prostatectomy, although there was considerable methodological uncertainty. There were no differences in urinary incontinence at 12 months and there was insufficient evidence to draw conclusions about the differences in erectile dysfunction.⁽¹⁷⁾

A recent prospective, randomized, non-randomized study in 14 centers with patients undergoing RP with both RARP and open retropubic RP (RRP), which showed no difference in positive surgical margin rates. At 12 months, continence rates did not differ, but erectile dysfunction rates were significantly different with 70.4% after RARP and 74.7% after RRP.⁽¹⁸⁾

Currently, there are no studies comparing the different surgical modalities, as well as the long-term results that allow the comparison between specific cancer mortality or overall mortality.

What seems clear is that the concentration centers for RP have lower complication rates and better success rates.

Radiotherapy

Intensity modulated radiotherapy (IMRT), with or without Image-Guided Radiation Therapy (IGRT), is the gold standard for external radiotherapy. There have been no randomized studies comparing radical prostatectomy (RP) with external radiotherapy (ERT) or localized PC brachytherapy. However, the consensus of the National Institutes of Health (NIH) established in 1988 remains valid: the ERT obtains the same results in terms of long-term survival as surgery. In addition, ERT provides a quality of life at least as good as the achieved with surgery. The radiation acts on the DNA that is inside the cells producing small fractures. These “fractures” prevent cancer cells from growing and dividing, and often cause them to die. Normal nearby cells may also be affected by radiation, but most recover and return to normal function.

Utility of Radiation Therapy in Prostate Cancer

The usefulness of radiotherapy in the context of prostate cancer is as follows:

1. As a definitive treatment. Used to treat localized prostate cancer that is still only in the prostate gland, when used with this indication is often called “radical radiotherapy.” The cure rates with radiotherapy in patients with localized cancer are very similar to the results of radical prostatectomy.
2. As rescue treatment. Used in this way, when the cancer was not completely removed in radical surgery, that is, if after the surgery positive margins reported by the pathologist were obtained, if cancer was reported in the seminal vesicles or in the lymph nodes. Or when the cancer comes back (recurs) sometime after surgery in the prostate area (also called a “surgical bed”).
3. As palliative treatment. Used this way, when the cancer is advanced and has spread to other parts of the body, it is usually used to reduce the size of the tumor and provide relief from pain caused by the invasion of the cancer to the bones.

Types of Radiotherapy for Prostate Cancer

Radiation to treat prostate cancer can be applied from a device outside the body, called external radiation or external beam radiotherapy.

The four current forms of external radiotherapy are:

- Three-dimensional Conformal Radiotherapy (3D-CRT).
- Intensity Modulated Radiation Therapy (IMRT).
- “Conformal” Radiotherapy with proton rays.
- Stereotactic Body Radiotherapy (Cyber Knife).
- Applied with the introduction of radioactive materials placed directly in the tumor, called Brachytherapy or Internal Radiation, where the most commonly used radioactive elements are Iodine-125 and Palladium-103. Applied in low dose rate (LDR) mode of radiation or with high dose rate (HDR).

Focal Therapies for Prostate Cancer

During the last two decades, there has been a trend towards an earlier diagnosis of PC as a result of greater public and

professional awareness, which leads to the adoption of varied screening strategies. The effect of this has been to identify men at an earlier stage with smaller tumors that occupy only 5-10% of the prostate volume, with an increasingly large propensity for unifocal or unilateral disease. Most of the focal therapies to date have been achieved with ablative technologies: cryotherapy, HIFU, photodynamic therapy, electrovaporation and focal RT through brachytherapy or the CyberKnife Robotic Radiosurgery System Technology. The main objective of focal therapy is the ablation of tumors selectively, limiting toxicity by respecting the neurovascular bundles, the sphincter and the urethra. ⁽³⁾

Metastatic Prostate Cancer

Metastatic Prostate Cancer (mPC) is usually a debilitating disease. In developed countries only 7 to 22% of patients debut with metastatic disease. However, in some Latin American countries these figures can reach 50 or 60%. The treatment of PC at this stage (metastatic) is palliative.

In about 80% of these patients, hormonal therapy or androgen deprivation therapy (ADT) provides an improvement in symptoms and a reduction in serum PSA levels, but over time, all patients eventually become refractory to hormonal treatment, scenario known as castration resistant.

The median survival of patients with newly diagnosed metastases is at least 42 months, but the M1 population is very heterogeneous.

Several prognostic factors that have an impact on survival have been identified, including: the number and location of bone metastases, skeletal-related events (ERE), the presence of visceral metastases, the Gleason score, the presence or absence of pain or symptoms related to cancer, functional status (FS, ECOG, Karnofsky), initial PSA, alkaline phosphatase, among others, but none of them has been validated in direct comparison.

In clinical trials, the number and location of bone metastases and the presence of visceral lesions are the most commonly used prognostic factors. ⁽³⁾

Androgen deprivation therapy (ADT) through hormonal blockade is the treatment for these patients. Treatment strategies include the following options:

- Simple bilateral orchiectomy.
- LHRH analogues with or without antiandrogen 7 or more days prior to avoid the flare effect of overstimulation of testosterone.

- LHRH agonist plus continuous antiandrogen.
- LHRH antagonists.
- Observation (only for patients with M0 disease).

This testosterone block may be accompanied by the administration of antiandrogens, oral medications, which compete with testosterone and Dihydrotestosterone at the level of the androgen receptor inside the prostate cell, promoting its apoptosis and inhibiting the growth of PC. The most important are bicalutamide, flutamide and nilutamide. Recently two new antiandrogens of last generation have been approved that are useful in the case of castration resistance: Enzalutamide and Apalutamide.

Androgen deprivation therapy (ADT) for prostate cancer represents one of the most effective systemic palliative treatments known for solid tumors.

Surgical or medical castration is considered the “gold standard” in ADT and involves the elimination of the source of testicular androgens, which decreases serum testosterone and induces a state of hypogonadism.

The castration level is <50 ng / dL (1.7 nmol / L), which was defined more than 40 years ago, when testosterone tests were limited. Current methods have shown that the average value after surgical castration is 15 ng / dL. Therefore, a more appropriate level is defined as <20 ng / dL (1 nmol / L). ⁽³⁾

Recently treatment alternatives for metastatic patients with high tumor burden or high risk have been proposed as a better strategy with significant impact on global survival and progression-free survival.

- A. Chemotherapy (Docetaxel) plus ADT. The first source of evidence of its usefulness was obtained from the CHARTED ⁽¹⁹⁾ studies, directed by Dr. Swenin, where assigned men with metastatic, hormone-sensitive prostate cancer to receive either ADT plus docetaxel (at a dose of 75 mg per square meter of body-surface area every 3 weeks for six cycles) or ADT alone. The primary objective was to test the hypothesis that the median overall survival would be 33.3% longer among patients receiving docetaxel added to ADT early during therapy than among patients receiving ADT alone.

A total of 790 patients (median age, 63 years) underwent randomization. After a median follow-up of 28.9 months, the median overall survival was 13.6 months longer with ADT plus docetaxel (combination therapy) than with ADT alone (57.6 months vs. 44.0 months; HR for death in the combination group, 0.61; 95% CI, 0.47 to 0.80; P<0.001).

When subgroups were analyzed, patients with high metastatic volume, defined as 4 or more bone metastases, with at least one metastatic lesion beyond the pelvis or spine (extra axial) or visceral metastases, overall survival was observed in this group of almost 17 months (HR 0.60; $p = 0.0006$).

The median time to biochemical, symptomatic, or radiographic progression was 20.2 months in the combination group, as compared with 11.7 months in the ADT-alone group (HR, 0.61; 95% CI, 0.51 to 0.72; $P < 0.001$). The rate of a prostate-specific antigen level of less than 0.2 ng per milliliter at 12 months was 27.7% in the combination group versus 16.8% in the ADT-alone group ($P < 0.001$). In the combination group, the rate of grade 3 or 4 febrile neutropenia was 6.2%, the rate of grade 3 or 4 infection with neutropenia was 2.3%, and the rate of grade 3 sensory neuropathy and of grade 3 motor neuropathy was 0.5%.

Six cycles of docetaxel at the beginning of ADT for metastatic prostate cancer resulted in significantly longer overall survival than that with ADT alone.

Docetaxel offered no benefit in patients without metastases or low volume metastatic, as its similar study European GETUG-AFU-15.

- B.** High metastatic volume, defined as 4 or more bone metastases, with at least one metastatic lesion beyond the pelvis or spine (extra axial) or visceral metastases:

The STAMPEDE ⁽²⁰⁾ a multi-stage multi-arm trial evaluated in one of its arms the impact of chemotherapy plus ADT in hormone-native metastatic patients. In the study the standard of care was hormone therapy for at least 2 years; Stratified randomization (via minimization) allocated men 2:1:1:1 to standard of care only (SOC-only; control), standard of care plus zoledronic acid (SOC+ZA), standard of care plus docetaxel (SOC + Doc), or standard of care with both zoledronic acid and docetaxel (SOC + ZA + Doc).

There were 2,962 men randomly assigned. Median age was 65 years (IQR 60–71); 1,817 (61%) men had M+ disease, 448 (15%) had N+/X M0, and 697 (24%) had N0M0; 165 (6%) men were previously treated with local therapy, and median PSA was 65 ng/mL (IQR 23–184). Median follow-up was 43 months (IQR 30–60).

There were 415 deaths in the control group (347 [84%] prostate cancer). Median overall survival was

71 months (IQR 32 to not reached) for SOC-only, not reached (32 to not reached) for SOC + ZA (HR 0.94, 95% CI 0.79–1.11; $p = 0.450$), 81 months (41 to not reached) for SOC + Doc (0.78, 0.66–0.93; $p = 0.006$), and 76 months (39 to not reached) for SOC + ZA + Doc (0.82, 0.69–0.97; $p = 0.022$). There was no evidence of heterogeneity in treatment effect (for any of the treatments) across prespecified subsets. Grade 3–5 adverse events were reported for 399 (32%) patients receiving SOC, 197 (32%) receiving SOC+ZA, 288 (52%) receiving SOC+Doc, and 269 (52%) receiving SOC + ZA + Doc.

The study concluded that zoledronic acid showed no evidence of survival improvement and should not be part of standard of care for this population. Docetaxel chemotherapy, given at the time of long-term hormone therapy initiation, showed evidence of improved survival accompanied by an increase in adverse events. Docetaxel treatment should become part of standard of care for adequately fit men commencing long-term hormone therapy.

- C.** Abiraterone (1000 mg plus prednisone 5mg daily) plus ADT continues in patients recently debuting with high-risk sensitive hormone prostate cancer. (high risk: Gleason Score 8 or higher, visceral metastasis).

STAMPEDE ABIRATERONE

The study ⁽²¹⁾ included a total of 1,917 assigned 1:1 for ADT plus AA / P vs. Only ADT. The primary objective was overall survival and the intermediate primary outcome was survival without failure (treatment failure was defined as radiological, clinical or PSA progression or death from prostate cancer).

A total of 52% of the patients had metastatic disease, 20% had non-metastatic disease with positive or indeterminate nodes, and 28% had non-metastatic disease with negative nodes; 95% had a newly diagnosed disease. The median follow-up was 40 months. There were 184 deaths in the combination group compared to 262 in the ADT group alone (HR, 0.63, 95% CI, 0.52 to 0.76, $p < 0.001$); the risk ratio was 0.75 in patients with non-metastatic disease and 0.61 in those with metastatic disease. There were 248 treatment failure events in the combination group compared to 535 in the ADT group alone (HR, 0.29, 95% CI, 0.25 to 0.34; $p < 0.001$); the risk ratio was 0.21 in patients with non-metastatic disease and 0.31 in those with metastatic

disease. Adverse events of grade 3 to 5 occurred in 47% of patients in the combination group (9 grade 5 events) and in 33% of patients in the ADT group alone (3 grade 5 events). Concluding that men with locally advanced or metastatic prostate cancer, ADT plus abiraterone and prednisolone were associated with significantly higher overall survival rates and no failure than ADT alone.

D. LATITUDE TRIAL

In the phase 3 **LATITUDE trial**,⁽²²⁾ researchers randomly assigned 1,199 patients to receive androgen-deprivation therapy plus abiraterone 100 mg once daily and prednisone 5 mg once daily or androgen-deprivation therapy plus 2 placebos. The primary endpoints were OS and radiographic PFS.

At a mean follow-up of 30.4 months, 406 patients had died. The median OS was significantly longer for the abiraterone arm vs the placebo arm (not reached vs 34.7 months, respectively; HR, 0.62; 95% CI, 0.51-0.76; $P < .001$).

Patients in the abiraterone group had a median radiographic PFS of 33.0 months vs 14.8 months in the placebo group. (HR for disease progression or death, 0.47; 95% CI, 0.39 to 0.55; $P < 0.001$). Significantly better results were observed at all secondary endpoints in the abiraterone group, including time to pain progression, subsequent therapy for prostate cancer, chemotherapy onset and PSA progression ($p < 0.001$ for all comparisons), together with symptomatic skeletal events ($P = 0.009$).

The results led to study unblinding, allowing patients receiving placebo to cross over to the abiraterone arm.

Grade 3 to 4 hypokalemia and hypertension were the most frequently reported adverse events (AEs), which occurred more frequently in the study group.

The authors concluded that “the addition of abiraterone plus prednisone to androgen-deprivation therapy was associated with longer overall survival (OS) and longer radiographic progression-free survival (PFS) than was androgen-deprivation therapy alone.”

Newly diagnosed patients with metastatic, castration-sensitive prostate cancer may have significantly prolonged (OS) and radiographic (PFS) when treated with abiraterone, prednisone, and androgen-deprivation therapy, according to a study published in *The New England Journal of Medicine*.

E. Recently a meta-analysis has been published that directly compares both treatment options:⁽²³⁾

Abiraterone acetate/androgen deprivation therapy combination versus docetaxel/androgen deprivation therapy combination in advanced hormone-sensitive prostate cancer: a network meta-analysis on safety and efficacy, by Kassem *et al*.

A major, yet precisely studied, shift has occurred in treatment of advanced hormone-sensitive prostate cancer (HSPC) by addition of docetaxel to androgen deprivation therapy (ADT) in the first line. Recently, two landmark trials showed that abiraterone acetate (AA) can be an effective alternative along with ADT in the same setting. We implemented a network meta-analysis to compare safety and efficacy of both combinations.

The trial evaluates the efficacy endpoints including (PFS) and (OS) and safety endpoints (including treatment related deaths and selected adverse events) were assessed.

Twenty relevant studies were retrieved and assessed for eligibility. Of those trials, eight were found potentially eligible. Inconsistent reporting of efficacy outcomes limited our analysis to M1 HSPC. The pooled hazard ratios of OS and PFS of the direct comparison of abiraterone acetate plus ADT versus ADT were 0.63(95%CI:0.545-0.717) and 0.38 (95%CI:0.34-0.43), respectively. Meanwhile, in the trials of docetaxel plus ADT the pooled hazard ratio (HR) of OS and PFS were 0.75 (95%CI:0.65-0.86) and 0.634 (95%CI:0.57-0.70), respectively. The indirect comparison showed that HR of OS and PFS in DOC+ADT in comparison to AA+ADT was 1.2 (95%CI:0.98-1.46) and 1.65 (1.40-1.94) respectively. The pooled RR of treatment-related mortality in docetaxel+ADT versus AA+ADT was 1.438 (95%CI:0.508-4.075).

Conclusion: Patients with mHSPC who received abiraterone acetate with ADT had better PFS and less toxicity compared to those receiving docetaxel with ADT. A trend towards superior OS and less treatment-related deaths was also observed, yet statistically non-significant. In view of lacking clear OS advantage, the choice between docetaxel and AA should include a discussion with the patient about potential toxicities and impact on quality of life of each regimen.

Castrate-Resistant Prostate Cancer (CRPC):

Prostate cancer (PC) is an androgen dependent disease that initially responds to hormonal manipulation with androgen deprivation therapies (ADT). For most patients with metastatic prostate cancer, this therapy can produce dramatic improvement of symptoms and an objective response in disease control (for approximately 24 to 36 months, and rare in more patients), but invariably prostate cancer stops responding to this androgenic suppression and progresses, evolving towards a lethal PC phenotype called “castrate resistant” a scenario in which PC continues to progress, even in an environment of concentrations minimum circulating androgens (testosterone), leading the patient in a short time to a fatal outcome.

Compared to hormone-sensitive prostate cancer, the prognosis for patients with CRPC is poor and survival is reduced. In clinical trials, the median survival of patients varies between 9 and 30 months. ⁽²⁴⁾

Definition of Castrate-Resistant Prostate Cancer:

The definition of castration-resistant CRPC includes as a basic premise the confirmation of testosterone values at “castration” levels, in addition to the biochemical progression by PSA or the radiographic progression documented by bone scintigraphy, CT-scan or some other modality of image.

Definition must include the following aspects:

Serum levels of castration of testosterone (<50 ng / dL or <1.7 nmol / L) plus any of the following:

1. **Biochemical progression:** Three consecutive increases of PSA, one week apart, giving rise of two increases over 50% with respect to nadir, with an PSA > 2 ng/mL.
2. **Radiographic progression:** The appearance of new lesions, the appearance of two or more new lesions in bone scintigraphy or an increase in soft tissue lesions using the RECIST criteria (Response Evaluation Criteria in Solid Tumors, version 1.1).

The only symptomatic progression should be questioned and subjected to further investigation, this is not enough to diagnose CRPC. ⁽³⁾

Castrate-Resistant Non-Metastatic Prostate Cancer (CRPCM0)

This scenario of patients, in which the progression of PSA, despite showing levels of castration of testosterone, and also have no evidence of metastasis demonstrable by any imaging method, represents a clinical challenge for treatment and follow-up.

These are patients who have debuted with a localized CP, which is why they underwent curative treatment (usually RP or RT), in their surveillance, biochemical relapse is identical, they undergo ADT with or without some other local control therapy, and after a while they begin with elevated PSA, despite continuing testosterone levels in castration parameters, all of the above without any evidence of distant metastatic activity through image studies.

In these patients with CRPC and without detectable clinical metastases, the baseline PSA level, the PSA velocity and PSA doubling time (PSA-DT) have been directly associated with time until the appearance of the first metastasis, bone metastasis-free survival and overall survival. ⁽³⁾

There are currently two treatment strategies for CRPC-M0 patients

1. Apalutamide: (SPARTAN) ⁽²⁵⁾

Apalutamide, a competitive inhibitor of the androgen receptor, is under development for the treatment of prostate cancer. We evaluated the efficacy of apalutamide in men with nonmetastatic castration-resistant prostate cancer who were at high risk for the development of metastasis.

We conducted a double-blind, placebo-controlled, phase 3 trial involving men with nonmetastatic castration-resistant prostate cancer and a prostate-specific antigen doubling time of 10 months or less. Patients were randomly assigned, in a 2:1 ratio, to receive apalutamide (240 mg per day) or placebo. All the patients continued to receive androgen-deprivation therapy. The primary end point was metastasis-free survival, which was defined as the time from randomization to the first detection of distant metastasis on imaging or death.

A total of 1,207 men underwent randomization (806 to the apalutamide group and 401 to the placebo group). In the planned primary analysis, which was performed

after 378 events had occurred, median metastasis-free survival was 40.5 months in the apalutamide group as compared with 16.2 months in the placebo group (hazard ratio for metastasis or death, 0.28; 95% confidence interval [CI], 0.23 to 0.35; $P < 0.001$). Time to symptomatic progression was significantly longer with apalutamide than with placebo (hazard ratio, 0.45; 95% CI, 0.32 to 0.63; $P < 0.001$). The rate of adverse events leading to discontinuation of the trial regimen was 10.6% in the apalutamide group and 7.0% in the placebo group. The following adverse events occurred at a higher rate with apalutamide than with placebo: rash (23.8% vs. 5.5%), hypothyroidism (8.1% vs. 2.0%), and fracture (11.7% vs. 6.5%).

Among men with nonmetastatic castration-resistant prostate cancer, metastasis-free survival and time to symptomatic progression were significantly longer with apalutamide than with placebo.

2. Enzalutamide: (PROSPER)⁽²⁶⁾

Men with nonmetastatic, castration-resistant prostate cancer and a rapidly rising prostate-specific antigen (PSA) level are at high risk for metastasis. that enzalutamide, which prolongs overall survival among patients with metastatic, castration-resistant prostate cancer, would delay metastasis in men with nonmetastatic, castration-resistant prostate cancer and a rapidly rising PSA level.

In this double-blind, phase 3 trial, we randomly assigned, in a 2:1 ratio, men with nonmetastatic, castration-resistant prostate cancer and a PSA doubling time of 10 months or less who were continuing androgen-deprivation therapy to receive enzalutamide (at a dose of 160 mg) or placebo once daily. The primary end point was metastasis-free survival (defined as the time from randomization to radiographic progression or as the time to death without radiographic progression).

A total of 1,401 patients (median PSA doubling time, 3.7 months) underwent randomization. As of June 28, 2017, a total of 219 of 933 patients (23%) in the enzalutamide group had metastasis or had died, as compared with 228 of 468 (49%) in the placebo group. The median metastasis-free survival was 36.6 months in the enzalutamide group versus 14.7 months in the placebo group (hazard ratio for metastasis or death, 0.29; 95% confidence interval, 0.24 to 0.35; $P < 0.001$). The time to the first use of a subsequent antineoplastic

therapy was longer with enzalutamide treatment than with placebo (39.6 vs. 17.7 months; hazard ratio, 0.21; $P < 0.001$; such therapy was used in 15% vs. 48% of patients) as was the time to PSA progression (37.2 vs. 3.9 months; hazard ratio, 0.07; $P < 0.001$; progression occurred in 22% vs. 69% of patients). At the first interim analysis of overall survival, 103 patients (11%) receiving enzalutamide and 62 (13%) receiving placebo had died. Adverse events of grade 3 or higher occurred in 31% of the patients receiving enzalutamide, as compared with 23% of those receiving placebo.

Among men with nonmetastatic, castration-resistant prostate cancer with a rapidly rising PSA level, enzalutamide treatment led to a clinically meaningful and significant 71% lower risk of metastasis or death than placebo. Adverse events were consistent with the established safety profile of enzalutamide.

Metastatic Castrate-Resistant Prostate Cancer (CRPCM1)

Almost a third of patients who underwent for local treatment PC will experience a relapse and most will receive androgen deprivation therapy (ADT). Patients treated with ADT eventually become resistant, developing CRPC, which can also be metastatic. For years, Docetaxel was the only treatment option for these patients, however, now there is a wide variety of new agents that can help the remission and survival of these patients.

Improvements in quality of life, cancer-specific survival and PFS are the objectives, however, the gold standard remains to be OS.

- a. **Docetaxel:** From the taxane family, it acts by stimulating tubulin assembly in stable microtubules, inhibiting depolymerization. It is the first chemotherapeutic with an improvement in survival, this Benefit has been observed in patients with advanced castrate resistant prostate cancer with acceptable toxicity. Considered the first option in CRPC. Mechanism of action: Disruption of microtubular function by protein binding. Dose: 75 mg / m² every three weeks. Presentation of 40 mg / mL. Last generation cytostatic, second generation taxane, has shown in several studies PSA decreases in 38 to 48% of cases with a median survival between 9 and 18 months and acceptable toxicity. Docetaxel is not contraindicated among the patients age.⁽²⁷⁾
- b. **Cabazitaxel:** Is a semi-synthetic taxane that is strong against cell lines and resistant to taxane-sensitive.

Cytotoxic anticancer of the taxane family, indicated in combination with prednisone, for the treatment of patients with metastatic castrate resistant prostate cancer previously treated with docetaxel. It acts as a microtubule inhibitor. The efficacy and safety of cabazitaxel in combination with prednisone were evaluated in phase III of the worldwide TROPIC study (N = 755) of PC with CRPCM1 after Docetaxel. Patients were randomized in two arms: 1. Cabazitaxel (25 mg / m² IV) + Prednisone (10 mg / day VO) every three weeks for a maximum of 10 cycles; and 2. Mitoxantrone (12 mg / m²) + equal dose of prednisone and same cycles.

Cabazitaxel (25mg / m², IV) plus prednisone was associated with a 2.4-month OS advantage (15.1 vs. 12.7 months, p <0.0001).⁽²⁸⁾

Androgen Receptor Targeting Drugs in Castration-Resistant Prostate Cancer

a. Abiraterone: Is a selective irreversible inhibitor of CYP17. CYP17 catalyses the rate limiting step in the formation of testosterone; thus, blocking CYP17 reduces stimulation of the androgen receptors which therefore lessens growth and proliferation of the tumor cells. CYP17 is also responsible for glucocorticoid production, so prednisone is given to counteract.

The mechanism of action is threefold. It is a potent, competitive binder of androgens at the level of the Androgen Receptor (AR). It prevents the translocation of the androgen receptor from the cytoplasm to the nucleus. Within the nucleus, it inhibits androgen receptor binding to chromosomal DNA, which prevents further transcription of tumor genes.

The mechanism of Abiraterone results in decreased proliferation of tumor cells, tumor cell death and reduce tumor volume.

The efficacy and safety of Abiraterone in the treatment of CaPRC has been evaluated in two large scenarios where it has proven its statistically significant efficacy in both global survival and progression-free survival:

After failure with docetaxel treatment: **COU-AA 301**.

Prior to treatment with docetaxel: **COU-AA 302**.

COU-AA 301 (AFTER DOCETAXEL)⁽²⁹⁾

The study conducted by Bono *et al.* and published in 2011, evaluated 1,158 patients with mCRPC previously treated with Docetaxel. Inclusion criteria were: patient previously treated with docetaxel. ECOG 0-2. Biochemical progression of PSA or radiological with or without progression of PSA (due to metastatic lesions in the bone or ganglionic or soft tissue scintigraphy). Patients were randomized 2: 1 to receive Abiraterone Acetate 1000 mg daily + prednisone 5mg twice daily (n 797) versus daily placebo + Prednisone 5mg twice daily (n 398). Demonstrated an improvement in overall survival (OS) in almost 4 months (14.8 vs. 10.9 months) (p <0.001), with a progression-free survival of 5.6 versus 3.6 months.

The secondary endpoints were:

- PSA progression (10.2 vs. 6.6 months, p <0.001)
- Progression-free survival (5.6 months versus 3.6 months, p <0.001)
- PSA response rate (29% vs 6%, P <0.001)

Adverse events were those related to mineralocorticoids, including fluid retention, hypertension and hypokalemia, more frequent in the abiraterone group than placebo.

After the publication of these results, Dr. Fazazi in 2012, reported new results with a follow-up to 20.2 months where there was a considerable increase in overall survival, which increased from 3.8 to 4.6 months, with a reduction in 26% risk of death (HR = 0.74).

COU-AA 302 (BEFORE DOCETAXEL)⁽³⁰⁾

The first results of the use of abiraterone in the pre docetaxel environment were recently published in 2013 by Ryan *et al.*, in which 1,082 CRPC patients without previous chemotherapy, followed by 22.2 months, were randomized to Abiraterone and placebo, both combined with prednisone. Inclusion criteria were patients not treated before with docetaxel. ECOG 0-1. PSA or radiographic progression of the disease. Asymptomatic or with moderate symptoms, without visceral metastases.

The final results reported an improvement in the overall survival of 5.2 months (35.3 vs. 30.1 months). In addition, the results showed almost a doubling of the radiological free survival progression from 8.3 to 16.5 months (p <0.0001) with 57% of reduction.

In addition to a significant increase in the meantime to chemotherapy (Docetaxel) with 26.5 months versus 16.8 months with placebo plus prednisone, it increased in time until the progression of PSA which was 11.1 months for Abiraterone versus 5.6 months for prednisone, as well as a significant increase in the average time to the use of an opioid for pain related to PC, with respect to which, the study reports for the Abiraterone arm “NR” (not reached, that is, that in the whole study did not require opiates for pain management), as can be seen in the following table of the results of the main and secondary points of the study. ⁽³¹⁾

Regarding the safety profile of Abiraterone, the incidence of adverse effects was similar in both branches, both for the heading of all adverse effects (for all grades: 99 vs. 99% and for grade 3 and 4 (60 vs. 61%) respectively for the group treated with abiraterone against those managed with more predictable placebo, the same was observed for serious adverse events in which no statistical difference was found.

Abiraterone presented manageable and well tolerated adverse effects, even in elderly patients, and were consistent with the properties of the medication. Therefore, abiraterone can be considered as a safe and effective medicine in the patient with CRPC.

b. Enzalutamide: Formerly called MDV3100 is a drug that targets multiple stages in the Androgen Receptor signaling pathway (AR), which is the main growth point of PC.

It is a second-generation antiandrogen that blocks the transfer of the androgen receptor to the nucleus. It slows tumor growth and induces cell death through three routes of action:

1. Blocks the binding of testosterone (androgens) to the androgen receptor (AR).
2. Prevents AR internalization to the nucleus of the tumor cell (nuclear translocation).
3. Inhibits DNA binding.

The dose of enzalutamide is 160 mg (4 tablets) per day, orally that does not require the concomitant use of corticosteroids.

Regarding studies related to enzalutamide and its benefit in the survival of patients and other clinical benefits, they have been evaluated in two large studies: one using the drug before chemotherapy (pre-docetaxel) and another post docetaxel:

AFFIRM (AFTER DOCETAXEL) ⁽³²⁾

Published in 2012, the clinical benefit of post-Docetaxel enzalutamide was confirmed in the phase III study called AFFIRM (n = 1,199) in patients with castrate-resistant metastatic prostate cancer (mCRPC) after docetaxel. The article was published in the New England under the name of “Increased Survival with Enzalutamide in Prostate Cancer after Chemotherapy.”

The main objective of the study was to assess whether enzalutamide was able to prolong survival in patients with castration-resistant PC after chemotherapy (Docetaxel).

This was a double-blind, placebo-controlled study, including 1,199 patients with CRPC after chemotherapy. They were randomized 2: 1, to receive enzalutamide orally 160 mg daily (800 patients) or placebo (399 patients). The primary objective of the study was OS.

The study was discontinued after an interim analysis planned at the time of 520 deaths. Enzalutamide achieved a global survival (OS) of 4.8 months against placebo: the median overall survival was 18.4 months in the enzalutamide arm versus 13.6 months for placebo (with a risk of death in the enzalutamide group of 0.63, CI 95 %, 0.53 to 0.75; with a p <0.001).

The superiority of enzalutamide over placebo was also evident in all secondary endpoints:

- PSA reduction by 50% or more (54% vs. 2%, p <0.001).
- Response rate of soft tissues (nodes and liver) (29% vs 4%, p <0.001).
- Response rate in quality of life (43% vs 18%, p <0.001).
- The time to PSA progression (8.3 vs. 3.0 months; p <0.001).
- Radiographic progression-free survival (8.3 vs. 2.9 months; HR 0.40, p <0.001)
- The time until the first skeletal-related event (16.7 vs. 13.3 months; HR 0.69, p <0.001).

Concluding that enzalutamide significantly prolongs the survival of patients with metastatic CRPC after chemotherapy.

PREVAIL (Chemotherapy-naïve) ⁽³³⁾

The PREVAIL study (Enzalutamide in Metastatic Prostate Cancer before Chemotherapy) phase III evaluates

enzalutamide in the pre-docetaxel scenario, the primary objectives of the study were overall survival and radiographic progression-free survival.

The study included 1,717 patients, 872 in the Enzalutamide group and 845 for the placebo group; both groups of similar demographic characteristics.

1. Overall Survival (OS)

The median overall survival was 32.4 months in the enzalutamide group and 30.2 months in the placebo group, with a baseline benefit of 2.2 months. The effect of enzalutamide treatment on overall survival was consistent in all subgroups of the study.

To assess overall survival, the average during follow-up was 22 months. Finding that in the enzalutamide group there were fewer deaths (241 of 872 patients [28%]) than in the placebo group (299 of 845 patients [35%]). Enzalutamide treatment, compared with placebo, provided a 29% decrease in the risk of death (HR = 0.71, 95% CI, 0.60-0.84, $P < 0.001$).

2. Radiographic Progression-Free survival (rPFS).

Regarding the radiographic progression-free survival at 12 months follow-up, the radiographic progression-free survival rates were 65% in the Enzalutamide group and 14% in the placebo group.

Enzalutamide treatment, compared with placebo, resulted in an 81% reduction in the risk of radiographic progression or death ($p < 0.001$). The beneficial effect of enzalutamide treatment on radiographic progression-free survival was present in all subgroups analyzed.

The benefit of Enzalutamide was observed in all secondary assessment criteria, including:

- The time to start cytotoxic chemotherapy (Docetaxel), which was 28.0 months for the enzalutamide group compared to 10.8 months for the placebo group (RR 0.35).
- The time until the first skeletal-related event which occurred in 278 patients (32%) for enzalutamide versus 309 patients (37%) in the placebo group, with an average of approximately 31 months in each of the groups (RR 0.72).
- The complete or partial response in soft tissues (59% vs. 5%).
- The time to PSA progression (HR 0.17).
- The decrease in a rate of less than 50% of the PSA (78% vs. 3%).

All secondary benefits were purchased by obtaining a ($p < 0.001$) statistically significant.

So we can conclude with the article that in patients with asymptomatic metastatic PC or with minimal symptomatology who have not received chemotherapy (Docetaxel), oral enzalutamide can provide a significant decrease in the risk of radiographic progression and death, as well as the need for Cytotoxic chemotherapy, with an appropriate safety profile and adverse effects. Positioning itself as a drug capable of reducing the deterioration in the quality of life of patients and providing positive results in overall survival.

c. Immunotherapy for Prostate Cancer

SIPULEUCEL-T

Available since 2010 as the first approved immunotherapy for any malignancy. FDA approved Sipuleucel-T for the treatment of mCRPC.

It is an autologous cellular immunological agent, is thought to work through APCs to stimulate T-cell immune response targeted against prostatic acid phosphatase (PAP), an antigen that is highly expressed in most prostate cancer patients.

The randomized phase III IMPACT⁽³⁴⁾ trial (N = 512) in asymptomatic or minimally symptomatic mCRPC, conducted by Dr. Kantoff, showed improvement in OS of 4.1 months (from 21.7 to 25.8 months) ($P = 0.03$) what constitutes a reduction of the risk of death of 22%. This improvement persisted at 3 years ($P = 0.02$).

Patients with lower PSA seem to benefit more than patients with advanced disease. The best candidates for this agent are patients with mCRPC and indolent symptoms, more than those with rapid progressive disease. Adverse effects are chills, pyrexia and headache. It is indicated in patients with metastatic CRPC when it exists: a good physical status (ECOG 0-1). Life expectancy > 6 months. No liver metastases and no or minimal symptoms. The drawback is the high cost of the product.

d. Bone-Targeting Radiopharmaceuticals

As already mentioned, bone metastasis-oriented therapies fall into two categories:

1. Resorption inhibitors (Ac. Zoledronic, Denosumab), which delay skeletal related events (SRE) to metastases.
2. Radiopharmaceuticals that are divided into two:
 - Beta emitters (samarium-153, strontium-89), palliation of pain, with high myelosuppression and renal excretion.
 - Alpha emitters: Ra 223 represents a unique and different option to improve survival and have fewer adverse effects in CRPC patients with bone metastases.

STRONTIUM-89:

Sr-89 is a β -emitting radionuclide approved in Europe for intravenous injection to treat painful bone metastases. In a palliative context, disseminated bone metastases can be treated using Sr-89 with or without external radiotherapy.

Due to the chemical similarity between strontium and calcium, Sr-89 is preferentially incorporated into the skeleton in areas of rapid bone formation, such as bone metastatic sites. This allows a concentrated administration of the radioactive dose to the immediate areas of the lesions.

SAMARIUM-153:

Sm-153 is a β -emitting radionuclide approved in Europe for intravenous injection to treat painful bone metastases. In a palliative context, disseminated bone metastases can be treated using Sm-153 with or without external beam radiotherapy.

Sm-153 is administered together with a bone-directed agent, chelated with phosphonate called leixidronam (ethylenediamine tetramethylene phosphonate [EDMT]), which aims at Sm-153 regions of bone formation, such as bone metastatic sites.

In other tissues of the body, the radiopharmaceutical is rapidly excreted through the kidneys, keeping global radioactive exposure low.

RADIUM-223 (Ra-223)

Radiopharmaceutical with action on bone metastases, which also has benefit in global survival. Ra-223 is an alpha emitter, which selectively targets bone metastases with alpha particles. Radium-223 dichloride (radio-223) is a specific alpha emitter that selectively binds to areas of increased bone turnover in bone metastases and emits high-energy alpha particles of short range ($<100\ \mu\text{m}$). Acts as a mimetic calcium to the bones, the Radium-223 joins in the newly formed bone stroma, especially in the osteoblastic or metastatic microenvironment.

The radiation of high-energy alpha particles induces breaks mainly from the double strand of DNA that results in a potent and highly localized cytotoxic effect in the areas of action. This short effect of alpha particles also means that the toxic effects on adjacent healthy tissue and in particular the bone marrow can be minimal, corroborating its safety profile and low myelosuppression.

Its efficacy and safety were evaluated in a study published in the New England Journal of Medicine by dr. With the name “Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer”,⁽³⁵⁾ the study compared the effects of Ra-223 against placebo, in addition to the best level of care, in patients with CRPC and bone metastases.

The double-blind, randomized, placebo-controlled study randomized 921 patients who had received, or were not eligible to receive, or rejected docetaxel. They were randomized in a 2:1 ratio, to receive six injections of radium-223 (50 kBq / Kg IV dose) or placebo; The injection was given every 4 weeks. In addition, all patients received the best level of care. The primary goal was overall survival. The main criteria for assessing secondary efficacy included the time to the first symptomatic skeletal event and several biochemical endpoints.

In the intermediate analysis, which involved 809 patients, radium-223, compared with placebo, significantly improved overall survival (median of 14 months versus 11.2 months (HR 0.70; 95% CI 0.55 to 0.88; $p = 0.002$). The updated analysis involving 921 patients confirmed that radio-223 survival benefit (median of 14.9 months versus 11.3 months; (HR 0.70, 95% CI 0.58 to 0.83; $p < 0.001$). Evaluations of the main secondary objectives also showed a benefit for radio-223, compared to placebo:

SER were lower, and the time until the first ERE was significantly delayed in 5.8 months ($p = 0.00046$).

- Prevention of spinal compression 3% vs 6% for placebo, $p = 0.016$.
- The time to PSA progression improved with a $p = 0.0001$.

Concluding the clear benefit of radium-223 in the overall survival of patients with metastatic CRPC:

- Significantly prolong overall survival ($p = 0.00185$).
- Extend the time to the first SER ($p = 0.00046$).
- Prolong skeletal related events, spinal compression, and pathological bone fracture, in addition to being well tolerated.

There is also a benefit in survival used both before and after treatment with chemotherapy with Docetaxel (both with a statistically significant p), with a benefit greater than 4.6 months in the pre-docetaxel scenario (Ra-223: 16.1 months against 11.5 months in the placebo arm).⁽³⁶⁾

Conclusion

With many agents approved for mCRPC, practitioners will see an increased use of abiraterone, enzalutamide, and radium-223 along with older medications such as docetaxel, cabazitaxel, and sipuleucel-T. Abiraterone, enzalutamide, and radium-223 have all been proven to extend survival in patients with or without previous chemotherapy.

Like all medications used in the treatment of cancer, these medications have distinct adverse effects that will need to be monitored and managed. Of the three agents, only enzalutamide presents a risk of seizure, albeit small, and therefore, should be avoided in those with lower threshold. Both abiraterone and enzalutamide (before chemotherapy) can increase risks of hypertension. Abiraterone can also increase risks in cardiovascular effects (e.g., arrhythmia, heart failure).

Complete blood count and infection should be monitored in patients who are taking enzalutamide and radium-223 because of drug-related neutropenia, thrombocytopenia, and myelosuppression.

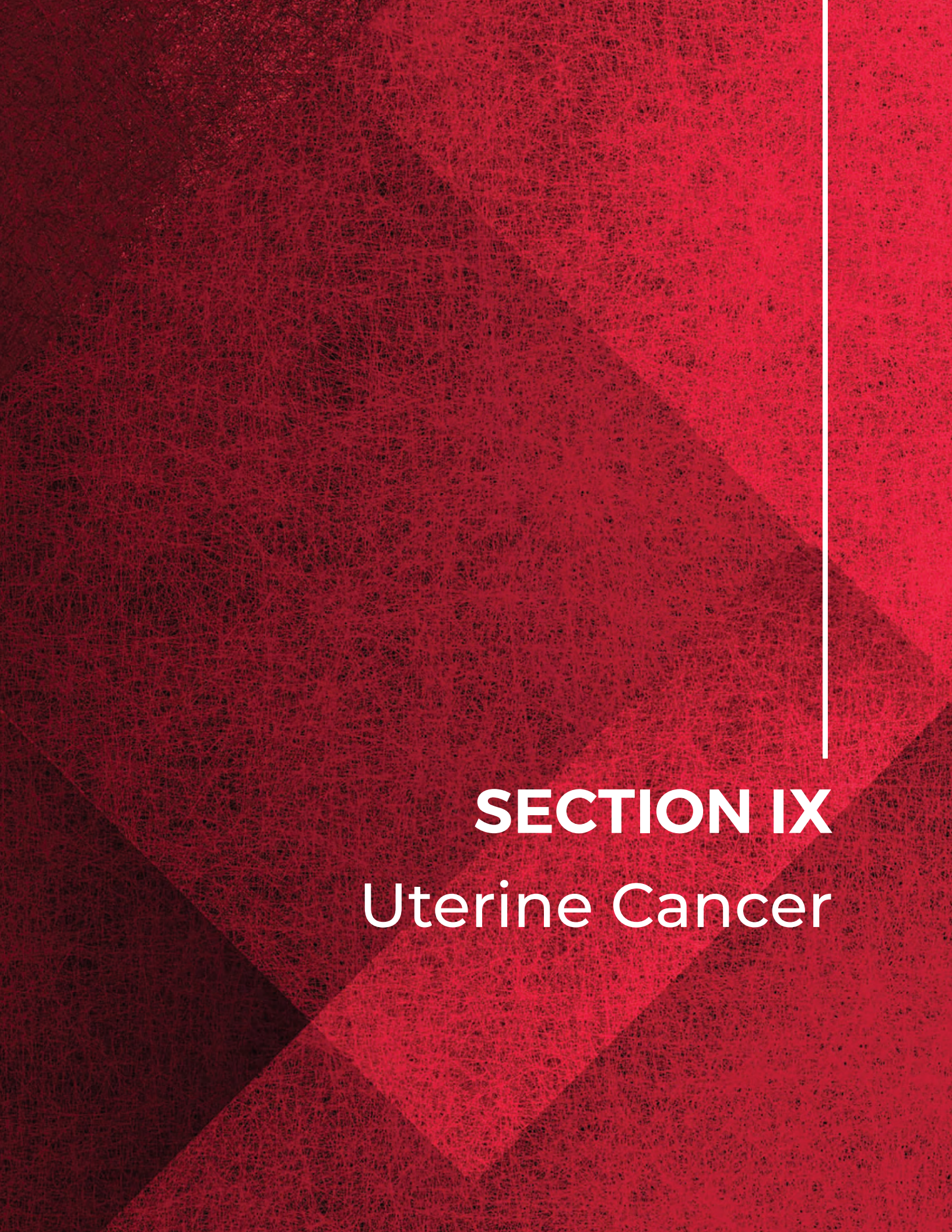
Patients on radium-223 who experience severe nausea/vomiting and diarrhea should be monitored for fluid and electrolytes because of higher dehydration risk. Patients with a history of liver dysfunction may want to avoid abiraterone and enzalutamide, since both agents can cause an increase in liver functions.

The three most used drugs involved in the treatment of mCRPC, have no direct comparisons between them, no face to face trials have been conducted. Therefore, no preference can be given to any one drug, and pharmacists should be familiar with the adverse reactions, drug interactions, and recommended safety monitoring for all of these drugs.

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SECTION IX

Uterine Cancer

Chapter 40

Endometrial Polyps

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Introduction

Endometrial polyps represent the localized growth of endometrial glands and stromal around a vessel, focal, which may occur anywhere in the uterine cavity. The proportion of glands, stromal and blood vessels will define their appearance. Endometrial polyps may have features such as: being soft or cystic or firm and fibrous; sessile or pedicle; single or multiple and of various sizes; from small polyps that do not alter the uterine anatomy to large polyps that occupy the entire endometrial cavity. Most endometrial polyps are detected in asymptomatic women during imaging, especially transvaginal ultrasonography (TVS). However, their final diagnosis is histological and should be done on the specimen completely removed, usually by hysteroscopy. ⁽¹⁻³⁾

Goals

The objectives of this chapter are:

- To enable specialists to recognize the prevalence, etiology, natural history, diagnosis and treatment of endometrial polyps.

After reading this chapter, the reader is expected to be able to:

- Understand the prevalence and etiology of endometrial polyps in the various phases of life.
- Recognize the histological characteristics of endometrial polyps.

- Understand spontaneous regression rates, as well as complications: infertility, abnormal uterine bleeding, and potential association with malignancy of endometrial polyps.
- Identify endometrial polyps in symptomatic and asymptomatic women at pre and post menopause according to different imaging methods.
- Select the diagnostic method that is most appropriate for each woman and the different scenario.
- Conduct women with endometrial polyps with the most up-to-date drug and surgical techniques.

Epidemiology

It is difficult to determine the exact prevalence of endometrial polyps in the female population without abnormal uterine bleeding (AUB). Many asymptomatic polyps are found on routine exams, especially TVS, hysterosonography, and hysteroscopy. Thus, the prevalence of endometrial polyps is directly related to the accuracy of detection methods. When comparing hysterosonography with TVS, hysterosonography presents a better accuracy in the diagnosis of endometrial polyps. TVS has a sensitivity of 71% (IC95% 58-82) and a specificity of 60% (IC95% 47-72) ⁽³⁾ of saline solution. In a meta-analysis and systematic review, it was concluded that the sensitivity and specificity of hysterosonography for detection of endometrial polyps were 93% (95% CI 89-96) and 81% (CI 95% 76-86), respectively. ⁽⁴⁾ Asymptomatic polyps are detected incidentally in about 12% of women in menacne and up to 16% of women in infertility research

without AUB. ^(5,9) In asymptomatic menopausal women, the prevalence of polyps varies from 13 to 16%. However, the prevalence of polyps may reach more than 30% in pre and postmenopausal women with AUB. ⁽⁴⁾

The etiology of polyps remains controversial and the mechanisms involved in their development remains uncertain. As they are often positive for estrogen and progesterone receptors, it is possible that these hormones have a role in their pathophysiology. Although genetic modifications have recently been extensively studied, the appearance of polyps seems to depend on the combination of several mutations. ⁽¹⁾ In addition, the penetrance of these genetic changes is possibly dependent on external factors such as metabolic, drug and environmental factors. Studies describe a significant relationship between the presence of polyps and diabetes mellitus, obesity, systemic arterial hypertension, late menopause, advanced age, hormone receptors and weak agonists of estrogens (e.g. Tamoxifen), hormone therapy, inflammatory processes and endometritis. ⁽³⁾

Histological characteristics of endometrial polyps

Endometrial polyps are considered as hyperplastic growth of the stromal and endometrial glands, in a mixture of large blood vessels covered by fibrous stromal and various glandular spaces. The morphological diversity of the endometrial polyps is related to the type of endometrium in which it originates, and the polyps can vary from atrophic to hyperplastic or with carcinomatous degeneration. ⁽⁶⁾ Many classifications are used to categorize endometrial polyps, such as adenomatous, cystic, fibrous, vascular, inflammatory, and fibromyomatous polyps. Other classification includes: hyperplastic polyps, atrophic, functional, adenomyomatous or pseudo polyps. Chronic endometrial inflammation, erosion and endometrial vascular dilatation are often found in women with endometrial polyps. Larger polyps may develop ischemic necrosis as a consequence of intermittent torsion and thrombosis. ^(1,7,8)

Natural history: Spontaneous regression, complications and evolution for malignancy

The spontaneous regression of endometrial polyps was described in several authors; however, all published series included a small number of cases. In the study by Wong *et al.* (2016) there was no factor associated with spontaneous

regression of polyps. ⁽²⁾ However, although most endometrial polyps are benign, there is a tendency for them to dry out. In clinical practice, endometrial polyps may be related to infertility in women in pre menopause, abnormal uterine bleeding and evolution to malignancy. ⁽¹⁾

In relation to infertility it is believed that intrauterine abnormalities, such as polyps, may interfere with sperm transport and / or implantation of embryos in the endometrial cavity. The lack of response to progesterone stimulation, as well as the induction to local inflammatory reactions and the inhibition of natural killers induced by polyps, render the endometrium less receptive to implantation of the embryo. Conservative treatment of small asymptomatic polyps in menacne is adequate, but resection in infertile women may increase spontaneous conception rates or assisted reproduction procedures. ⁽⁹⁾

Although a recent Cochrane meta-analysis did not find randomized clinical trials comparing fertility rates after removal of hysteroscopy from endometrial polyps, we conclude that removal of hysteroscopy from polyps in sub fertile women is commonly performed in clinical practice, considering the low risk and low cost of procedure. ⁽¹⁰⁾ However, the management of small polyps in infertile women should be individualized according to polyp size, location, response to ovarian stimulation, number and quality of embryos, and the history of embryo transfer success. ⁽⁹⁾

Another complication often associated with endometrial polyps is abnormal uterine bleeding (AUB) in pre or post menopause. AUB in menacne may be related to functional or morphological disorders, which led the International Federation of Gynecology and Obstetrics (FIGO) in 2011 to define a new bleeding classification system for these women. Nine categories that make up the PALM-COEIN system are: polyps, adenomyosis, leiomyoma, malignancy or hyperplasia, coagulopathies, ovulation, endometrium, iatrogenic and non-classifiable alterations. ⁽¹¹⁾ In a retrospective study including nearly 500 women with AUB, 20% of endometrial polyps were identified. ⁽¹²⁾ The bleeding associated with endometrial polyps is still not well understood. It is believed that endometrial, inflammatory or angiogenesis changes may be involved.

In a systematic review of observational studies, the prevalence of atypical hyperplasia in endometrial polyps ranged from 0.2 to 23.8%. ⁽¹³⁾ Atypical endometrial hyperplasia is described in up to 6.7%, and the prevalence

of cancer in endometrial polyps varies from 0.5 to 3%, according to the population studied. ⁽¹⁾ Menopause and abnormal uterine bleeding are the major risk factors for endometrial carcinoma, although they may be found in endometrial polyps in pre and postmenopausal, asymptomatic women. The risk of malignancy increases with age, polyp size and use of tamoxifen. In a histological evaluation of 390 hysteroscopy polyps resected in Brazilian women over 40 years old, 93% were benign, and 14% (49 cases) were associated with atypical hyperplasia. Among the 7% (28 cases) of polyps considered as a pre-malignant and / or malignant lesion, 20 were endometrial carcinoma and 8 atypical hyperplasia. Only postmenopausal age and bleeding were significantly relevant with the risk of malignancy. However, 4 malignant or premalignant lesions were found in asymptomatic women. ⁽¹⁴⁾

Diagnosis

Patients with endometrial polyps may present with abnormal uterine bleeding, however, the vast majority of polyps are detected through TVS exams in asymptomatic women. ⁽¹⁴⁾ TVS is a noninvasive test, well accepted by most women, with minimal discomfort and used on a large scale.

At the TVS, the endometrial polyp appears as a hyper echogenic lesion with regular contours, and a hyper echoic halo around the uterine cavity. Cystic images can be visualized inside the polyp and the same may show echography signs of focal endometrial thickening, without too many specifications. In women in menacne, TVS should preferably be performed in the proliferative phase of the menstrual cycle. ⁽¹⁵⁾

The TVS report should describe the presence, size, and number of polyps. As previously seen, the size of the polyp is related to the risk of malignancy, whereas the small polyps often present spontaneous resolution. ⁽¹⁴⁾ The sensitivity and specificity of the TVS vary and there are few studies with large groups of women, which makes it difficult to compare the data. Doppler can demonstrate the presence of a central vessel and increase sensitivity in the detection of polyps in women with or without symptoms. However, there is no evidence that Power Doppler or conventional Doppler help differentiate hyperplasia or malignancy in polyps. Thus, it should not replace histological evaluation after complete resection. Saline hysterosonography can identify small polyps, which were not visualized in gray scale.

The disadvantage of hysterosonography is that it does not replace histological examination; the learning curve is slow and causes discomfort to the patient due to fluid loss or pain during the examination. Studies with 3-D TVS evidenced a small increase in accuracy when compared to conventional TVS. However, this increase in accuracy is similar to that of hysterosonography. ⁽¹⁵⁾

Fragmenting or cureting biopsy

Both fragment biopsy and curettage have low accuracy in the detection of endometrial polyps, although they have an excellent specificity. ⁽¹⁹⁾

Hysteroscopy-guided biopsy

Hysteroscopy-guided biopsy is currently the gold standard for the diagnosis of endometrial polyps because it has greater sensitivity and specificity. Hysteroscopy may be diagnostic or surgical. Diagnostic hysteroscopy only allows a subjective assessment of lesion characteristics, with low sensitivity and specificity, as compared to hysteroscopy resection. One of the limitations of diagnostic hysteroscopy is that the description of the lesion size, as well as its morphological characteristics are subjective and examiner dependent. Thus, polyps should be biopsies, even when they do not have malignant characteristics. Although it has to be performed under anesthesia, thus leading to a greater risk and cost of the procedure, surgical hysteroscopy has the advantage of visualizing the whole endometrial cavity and removing all polyps in a single procedure / moment. It may also help in the diagnosis / treatment of other endometrial pathologies (e.g. fibroma). The choice between diagnostic (outpatient and low cost) hysteroscopy and surgical (hospital and costly) hysteroscopy depends on the technical conditions, the choice of the woman and the medical capacity. The rate of complications in hysteroscopy is small, however, higher than TVS and saline hysterosonography. It is important to emphasize that it is easier to visually identify a polyp in the woman in the menopause than in the menacne; in menopause small focal lesions are prominent in the atrophic endometrium. ⁽¹⁵⁾ Another important factor is the equipment used to perform hysteroscopy: although flexible hysteroscopy is more comfortable for the patient, retrospective studies have shown a decrease in accuracy when compared to rigid hysteroscopy. ⁽¹⁶⁾



Figure 40-1. *Hysteroscopic view of endometrial polyps*

Other diagnostic exams such as hysterosalpingography, computed tomography and nuclear magnetic resonance are not justified for the diagnosis of endometrial polyps due to the high cost and low accuracy when compared to TVS.

Conduct

Considering the high prevalence of incidental findings of endometrial polyps in asymptomatic women in menopause, expectant treatment in lesions smaller than 10 mm can be considered, since most present spontaneous regression.^(1,7,13) Likewise, asymptomatic polyps in menopausal women are rarely malignant and, therefore, expectant management may be appropriate, as long as it is shared with the woman.⁽¹³⁾ In these cases, the complete polyp removal can be considered as excessive treatment, which, although it is a minor surgical risk, requires anesthesia and brings a cost that must be considered.⁽⁷⁾ However, in contemporary gynecological practice, in women with infertility, subfertility, or even to rule out neoplasia, the surgical removal of endometrial polyps is widespread. It is important to note that, in women with bleeding, expectant behavior does not apply, either in pre or post menopause.

Medication treatment

It can be performed with the use of levonorgestrel intrauterine device (L-IUD). Although GnRH has been used in the past, before hysteroscopy resection, its cost and side effects do not justify its use.^(1,7,13)

Polypectomy

Electrosurgical hysteroscopy (mono or bipolar) polyp removal is a safe procedure, both for diagnosis and for treatment. It is the most widely used method for the removal of endometrial polyps. It allows for a complete histological evaluation and is performed safely in most services. It is important to emphasize that the polyp should be removed whole (without fragmentation) and with safety margin, either the pedicle or sessile polyp because, if there is a malignant transformation, it is located at the base / pedicle of the lesion. Occasionally, after hysteroscopy polyp removal, curettage may be used to rule out endometrial hyperplasia or occult endometrial cancer.⁽⁷⁾ The excision of the endometrial polyps by techniques that use electro-surgery is very effective in reducing uterine bleeding and improving the quality of life.

The use of curettage and forceps has lost its place in current gynecological practice. Recently, the excision of endometrial polyps by MyoSure™ or TruClear™ has been the subject of publications, with results not yet completely consensual.

However, the impact of polyp removal on the recurrence of menopausal uterine bleeding has not been proven. As up to 8% of menopausal women with endometrial polyps associated with bleeding have atypical hyperplasia or carcinoma, the removal of polyps should be performed on recurrence with bleeding. The etiology of persistent bleeding after polyp removal in menopausal women is controversial but should always be valued. ⁽¹⁷⁾

Radical treatment

The hysterectomy guarantees that there will be no recurrence of the polyp and prevents an endometrial carcinoma, however it presents as a complex surgical procedure, with high cost and greater morbidity. It should be used with caution and after discussion with the woman evaluating risk / benefit. There is no study comparing hysteroscopy polyp removal and hysterectomy.

Follow-up

After hysteroscopy polyp removal, histologically confirmed recurrence of polyps ranges from 2.5 - 3.7% in a maximum follow - up of 9 years. ⁽¹⁸⁾ Regarding uterine bleeding, the procedure presents resolution in 75 - 100% of the cases. Since uterine bleeding in postmenopausal women represents the greatest risk for malignant and premalignant disease, a new evaluation is important in these cases. ⁽¹⁵⁾

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Chapter 41

Ovarian Cancer Surgery

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Introduction

Epithelial ovarian cancer (EOC) is one of the major causes of mortality among women. This is partly because of its highly sub-clinic nature, lack of reliable screening techniques and non-availability of effective biomarkers.

Patients with early-stage disease are often asymptomatic, and 60-70% most will present with advanced disease (stage III or IV) at diagnosis. Despite the sensitivity of EOC to several chemotherapeutic agents, particularly taxanes and platinum compounds, only 20% to 41% of patients presenting with stage III or IV disease remain alive 5 years after diagnosis.⁽¹⁾

Over the last two decades, 7 high income countries (Australia, Canada, Denmark, Ireland, New Zealand, Norway, and the UK) had significant improvement in overall survival (5.9% to 12%) for EOC patients,⁽²⁾ probably due to major health care reforms and technological advances, with better diagnosis and treatment plans. Although EOC is a disease mainly related to more developed countries, there is a significant tumor burden among populous developing countries such as India and China.

Histology and Biological Behavior

Ovarian cancer (OC) encompasses a heterogeneous group of malignancies differentiated by cell/site of origin, pathologic grade, risk factors, prognosis, and treatment.⁽¹⁾ Epithelial cancers are most common among women of all racial/ethnic groups, accounting for 90% of all cases. Epithelial cancers are classified by tumor cell histology as serous (52%), endometrioid (10%), mucinous (6%), or clear cell (6%), with one-quarter classified as more rare or unspecified subtypes.^(3,4)

Surgery plays a significant role in the multidisciplinary approach of ovarian cancer patients, with overall survival (OS) impact and disease morbidity reduction. Most of EOC patients will require at least one timely surgical procedure for diagnosis and extent of disease evaluation, staging, cytoreduction or palliation.

Epidemiology

In 2018, there were approximately 22,240 new cases of ovarian cancer diagnosed and 14,070 ovarian cancer deaths in the United States.⁽¹⁾ It is a malignant disease which accounts for 2.5% of all malignancies among females but 5% of female cancer deaths because of low survival rates, largely driven by late stage diagnoses. Ovarian cancer accounts for an estimated 239,000 new cases and 152,000 deaths worldwide annually.

A woman's lifetime risk of developing OC is 1 in 75, and her chance of dying of the disease is 1 in 1004. The disease typically presents at late stage when the 5-year relative survival rate is only 29%. Few cases (15%) are diagnosed with localized tumor (stage 1) when the 5-year survival rate is 92%.⁴ Strikingly, the overall 5-year relative survival rate generally ranges between 30%–40% across the globe and has seen only very modest increases (2%–4%) since 1995.

Histology

The term ovarian cancer subsumes a heterogeneous group of malignant tumors that differ with respect to essential features of etiology, pathogenesis, prognosis, pathology, and molecular pathology.^(5,6)

One of the main objectives of developing a molecular classification of epithelial ovarian cancer that reflects the underlying pathogenesis of the disease is to facilitate individualized treatment selection.

Ovarian cancers are classified into three main histologic groups: epithelial tumors, sex cord-stromal tumors, and germ cell tumors.⁽⁷⁾ Epithelial tumors are believed to originate from the surface epithelium of the ovary.⁽⁸⁾

There are four main subtypes of epithelial tumors: serous, mucinous, endometrioid, and clear cell adenocarcinomas.^(1,8)

Sex cord-stromal tumors originate in granulosa or thecal cells, or other stromal cells. Germ cell tumors are formed by cells that are believed to be derived from primordial germ cells, and they include the subtypes dysgerminomas, teratomas, and yolk sac tumors, among other subtypes.⁽⁸⁾ Several histologic-specific ovarian cancer incidence studies are published in the peer-reviewed literature, and most are based on populations in the United States.

In a 2003 publication, Goodman *et al.* reported that 91.9% of ovarian tumors were epithelial, 1.2% were sex cord-stromal, and 1.9% were germ cell.

Serous adenocarcinoma was the most incident epithelial subtype, accounting for 37.7% of all ovarian tumors.⁽⁹⁾ These United States data are consistent with those from the Netherlands, where 89% of all ovarian cancer diagnoses were reported to be epithelial tumors.⁽¹⁰⁾

Ovarian cancer has been divided into epithelial and non-ep-

ithelial groups for many years, but recent work has enabled finer subdivision of epithelial ovarian cancers into different groups according to a combination of morphological and clinical characteristics.

The new WHO classification takes into account the recent findings on the origin, pathogenesis, and prognosis of different ovarian cancer subtypes.

Type I epithelial tumors include low-grade serous, endometrioid, clear cell, mucinous and transitional cell (Brenner) carcinomas. They often present at an early stage, may arise from borderline ovarian tumors or endometriosis and typically have a good prognosis.

Type II epithelial tumors comprise high-grade serous carcinoma, undifferentiated carcinomas and malignant mixed mesodermal tumors. They account for around 75% of epithelial ovarian cancers, typically present at an advanced stage and have a poor prognosis.⁽¹¹⁾ Distinct molecular pathways that influence chemosensitivity, the pattern of metastasis and the probability of survival are far different from each histological group.

The main molecular genetic feature that separates type I from type II tumors is the relative genetic stability (as reflected by global DNA copy number changes) of type I tumors compared with the marked chromosomal instability of type II tumors.

In addition, ubiquitous TP53 mutations characterize type II tumors, in contrast to their infrequency in type I tumors.⁽¹²⁾ The other important differences are the shown in **Figure 41-1**.

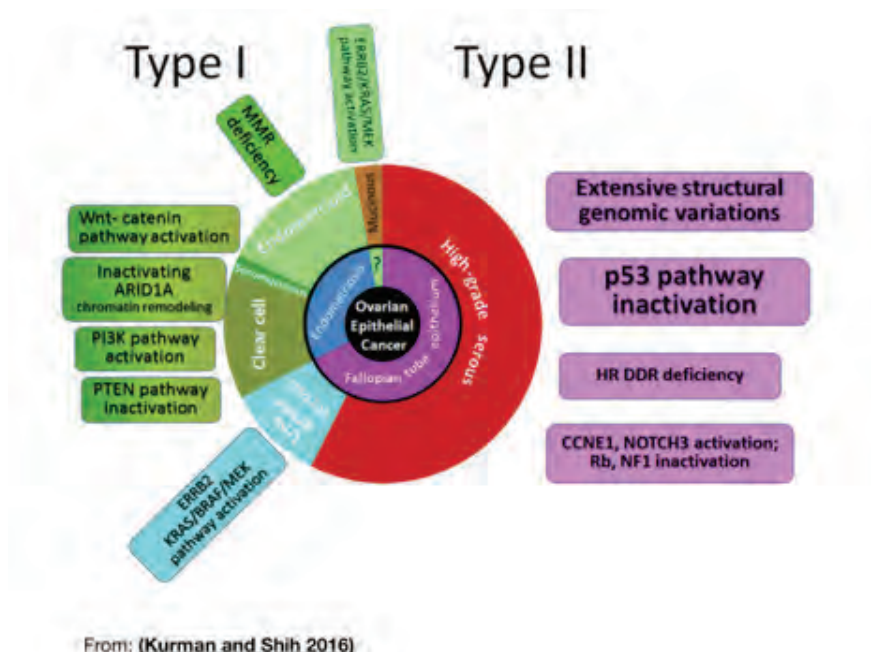


Figure 41-1. The revised dualistic model in the pathogenesis of ovarian cancer.

Early stage EOC

Patients with initial high grade serous (HGS) EOC should be surgically staged for extra ovarian disease spread. ⁽¹³⁾ Rates of upstaging after surgical staging may range from 10% to 30%, depending on risk factors as lymph vascular space invasion (LVSI), capsular involvement, histology, etc. Most frequent sites of metastasis are peritoneal, contralateral ovary, and lymph nodes, followed by systemic spread.

A complete surgical staging for early stage EOC, following contra lateral salpingo oophorectomy and total hysterectomy (in a non-fertility sparing approach), should include: inspection and palpation of all peritoneal surfaces, biopsies of any suspicious lesions for metastases, biopsies or removal of any adhesions surrounding the (area of the) primary tumor, peritoneal washing, infracolic omentectomy, blind biopsies of right hemi-diaphragm, of right and left paracolic gutter, of pelvic sidewalls, of ovarian fossa, of bladder peritoneum, and of *cul-de-sac* Iliac and paraaortic lymph node dissection. ^(13,14)

Based on the ACTION Trial, including 448 early stage EOC patients randomized to receive or not adjuvant platinum based therapy. Among patients in the observation arm, optimal staging was associated with a statistically significant improvement in overall and recurrence-free survival (HR = 2.31 [95% CI = 1.08 to 4.96]; P = .03 and HR = 1.82 [95% CI = 1.02 to 3.24] P = .04, respectively). No such association was observed in the chemotherapy arm. In the non-optimally staged patients, adjuvant chemotherapy was associated with statistically significant improvements in overall and recurrence-free survival (HR = 1.75 [95% CI = 1.04 to 2.95]; P = .03 and HR = 1.78 [95% CI = 1.15 to 2.77]; P = .009, respectively).

In the optimally staged patients, no benefit of adjuvant chemotherapy was observed. ⁽¹⁴⁾ The lack of knowledge of EOC behavior or lack of adequate training in surgical staging were related to incomplete staging (66%), even in a multicentric trial addressing comprehensive staging. High volume centers included more patients completely staged when compared to low volume centers (37% versus 21%, p<0.04). ⁽¹⁵⁾

Minimally invasive surgery (MIS) for early stage EOC was evaluated in a meta-analysis including 3,065 patients, 1,450 undergoing laparoscopy and 1,615 laparotomic surgical staging. Upstaging and rupture rates were similar in both groups. Laparoscopy was associated with shorter hospital stay, lower estimated blood loss and postoperative complications, and lower time to adjuvant therapy, with comparable overall survival. ⁽¹⁶⁾

In summary, early stage EOC should be completely staged, in referral centers, by specialized surgeons. Complete surgical staging for early stage EOC can be safely performed by MIS. This leads to better OS and disease-free survival (DFS), significant upstaging rates with adequate subsequent management, and potential reduction in useless adjuvant chemotherapy. ⁽¹³⁻¹⁶⁾

Advanced Stage Disease

Unfortunately, more than 80% of HGS EOC are detected in stages III or IV. Mostly due to the lack of specific symptoms, that are not considered by the patient or even by the attending physician. Surgery has a significant impact on overall survival for advanced stages HGS EOC patients. ⁽¹³⁾ A complete resection of all macroscopic tumors is the single most important therapeutic approach in this setting. Extensive cytoreductive procedures may be required to achieve complete removal of all lesions, mainly in the upper abdomen. ⁽¹⁷⁾ Many strategies coordinating systemic therapy, peritoneal chemotherapy, and immunotherapy have been associated to a complete cytoreductive surgery with promising results.

Peritoneal Extension Evaluation

Radiological clear contraindications to PDS are related to the surgical team experience. Most criteria are relative, but as a common sense, the following should be carefully described and evaluated: ⁽¹⁸⁾

- Massive mesenteric infiltration and retraction with segmental small bowel sub-occlusions.
- Massive porta hepatis or hepatic round ligament deep infiltration.
- Liver or lung parenchymal multiple metastases.
- Omental cake with clear infiltration of the lesser and major gastric curvatures, along with transverse colon (demanding total gastrectomy with *en bloc* transverse colectomy).

The limitations in accurately correlating relatively low-resolution imaging in a surface-spreading disease with wide variation in the amount and location of intraperitoneal dissemination only obvious by direct inspection has led the preoperative laparoscopy to another level of importance.

Peritoneal cancer index (PCI) has been used in assessing the extent of the peritoneal spread in intra-abdominal and intrapelvic malignant tumors. It gives valuable information about the exact distribution of seeding and tumor volume, representing in detail the extent of the peritoneal spread. **(Figure 41-2)** Survival has reliably and consistently been predicted by using PCI for ovarian cancer. In addition, the preoperative evaluation of PCI with CT-scan has been proved to be very helpful in carefully selecting patients for complete cytoreduction. ^(19,20)

The PCI quantitatively combines the distribution of tumor throughout 13 abdominopelvic regions with a lesion size score. The lesion size (LS) score is determined after complete inspection of all parietal and visceral peritoneal surfaces within the abdominopelvic regions. The PCI is calculated by adding the scores of all 13 regions together with a maximum score of 39 (13×3). **(Figure 41-3)**

It is likely that a PCI around 10 is of prognostic significance for any intra-abdominal and intra-pelvic malignant tumor with peritoneal spread. ⁽¹⁹⁻²¹⁾

Even though a complete or near-complete cytoreduction has been performed and standard treatment with systemic chemotherapy has been used patients with PCI>10 are not expected to have prolonged survival and are likely to consist a high-risk group. Intraperitoneal chemotherapy (either hyperthermic intraoperative or early postoperative) may be an alternative for this subgroup of patients.

Experienced centers that offer CT scan with extent of carcinomatosis evaluation provide good accuracy to predict cytoreductive surgery. With a cutoff index >20, accuracy was 85%, sensitivity 97%, specificity 40%, negative predictive value 76%, and positive predictive value 93%, after evaluating 80 consecutive EOC cases. ⁽²²⁾ When CT scan was compared to MRI and surgical PCI, in 36 patients, MRI was superior to CT scan. ⁽²³⁾

Basically, visualization of disease distribution is used, on the spot, to triage patients towards PDS or NAC with the intent of avoiding unnecessarily morbid, suboptimal laparotomies that have no clinical benefit.

Fagotti *et al.* tested this principle in a pilot study of advanced ovarian cancer patients. Based on their findings, diagnostic laparoscopy seemed a more effective method for triaging patients than existing tools. ⁽²⁴⁾ These data led to the development of the predictive index value (PIV), a system devised to provide an objective score. In essence, the lower the PIV score, the higher the likelihood of achieving primary debulking to R0.



Figure 41-2A. Laparoscopic PCI evaluation, omental implants, total PCI= 22.



Figure 41-2B. After decision for cytoreductive surgery, laparotomic view.



Figure 41-2C. Final view, after complete debulking surgery.

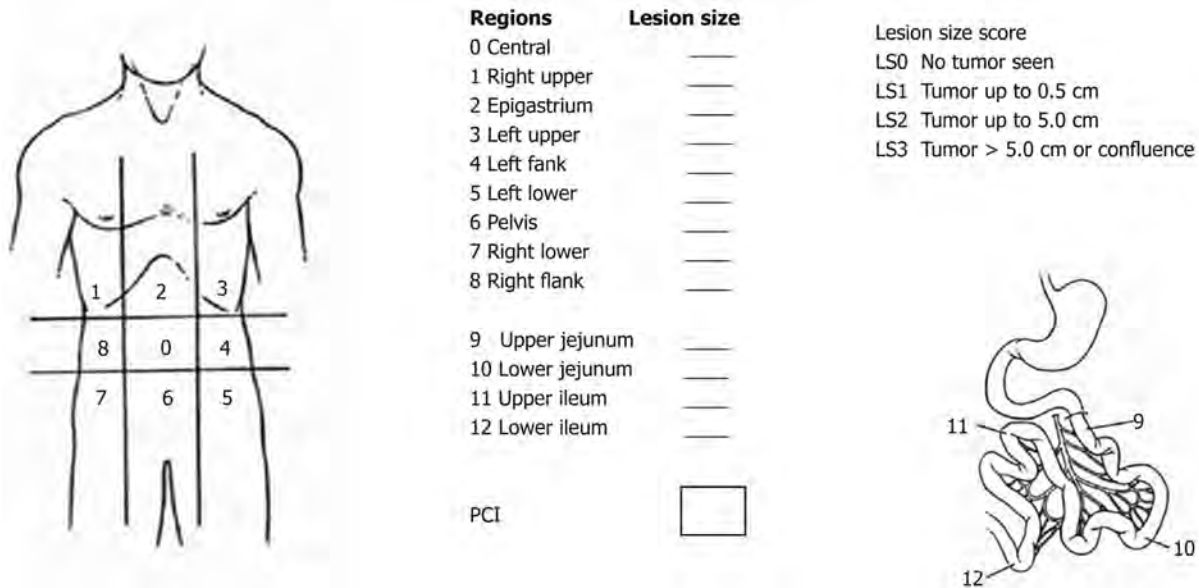


Figure 41-3. PCI according to Sugarbaker et al.

Table 4-1. Fagotti Score for peritoneal carcinomatosis.

Laparoscopic feature	Score	
	0	2
Peritoneal carcinomatosis	Carcinomatosis involving a limited area (along the paracolic gutter or the pelvic peritoneum) and surgically removable by peritonectomy	Unresectable massive peritoneal involvement with a miliary pattern of distribution
Diaphragmatic involvement	No infiltrating carcinomatosis and no nodules confluent with most of diaphragmatic surface	Widespread infiltrating carcinomatosis or nodules confluent with most of the diaphragmatic surface
Mesenteric involvement	No large infiltrating nodules and no involvement of the root of the mesentery (i.e., movement of intestinal segments is not limited)	Large infiltrating nodules or involvement of the root of the mesentery indicated by limited movement of intestinal segments
Omental involvement	No tumor diffusion observed along the omentum up to the greater curvature of the stomach	Tumor diffusion observed along the omentum up to the greater curvature of the stomach
Bowel infiltration	No bowel resection assumed and no miliary carcinomatosis observed on the bowel ansae	Bowel resection assumed or miliary carcinomatosis observed on the ansae
Stomach infiltration	No obvious neoplastic involvement of the gastric wall	Obvious neoplastic involvement of the gastric wall
Liver metastases	No surface lesions	Any surface lesion
A value of 0 or 2 is assigned depending on whether disease is present in these locations. If patients score ≥ 8 , optimal cytoreduction is very unlikely. If they score < 8 , they are considered candidates for cytoreductive surgery.		

Extensive Surgery Training and Implementation

Institutions that implemented an optimal and/or complete cytoreduction concept, with specific programs for upper abdominal surgical approaches observed significant improvement in radicality and consequent improvement in overall survival.⁽¹⁷⁾

Referral centers that concentrate large case volume, with high-volume surgeons, offer larger rates of hysterectomy and cytoreductive procedures. Mortality rate is 69% lower in procedures performed by high volume surgeons, and complete/optimal cytoreductive procedures are more likely to be achieved in high volume hospitals, with lower hospital stay and lower costs.⁽²⁵⁾

According to Brazilian Society of Surgical Oncology (BSSO) consensus, patient selection for surgery should be based on a combination of performance status (PS), tumor burden and surgical complexity.⁽²⁶⁾ (Table 41-2)

Narasimhulu *et al.*, in a recent paper considering women at high risk of surgical mortality / morbidity, purpose and evidence-based triage algorithm to decide between prima-

Table 41-2. Summarizes initial surgical indications for advanced EOC.
ECOG PS0-1, and potentially resectable disease, with few or no organs to be resected: staging laparoscopy followed by cytoreductive procedure, under a single anaesthetic procedure.
ECOG PS0-1, and high tumour load: staging laparoscopy. The multidisciplinary team then provides details regarding organs to be spared or resected, and morbidity and mortality in PDS versus IDS.
ECOG PS2 or higher, and medically fit for general anaesthesia: staging laparoscopy followed by neoadjuvant strategy.
Medically unfit for general anesthesia: image guided percutaneous biopsy, followed by neoadjuvant strategy.

ry debulking surgery (PDS) and neoadjuvant chemotherapy followed by interval debulking surgery (NACT/IDS) for advanced epithelial ovarian cancer (EOC).⁽²⁷⁾ The algorithm was associated with reduced 90-day mortality after PDS and improved oncologic outcomes. The Mayo triage algorithm to predict surgical M/M after PDS. (Figure 41-4)

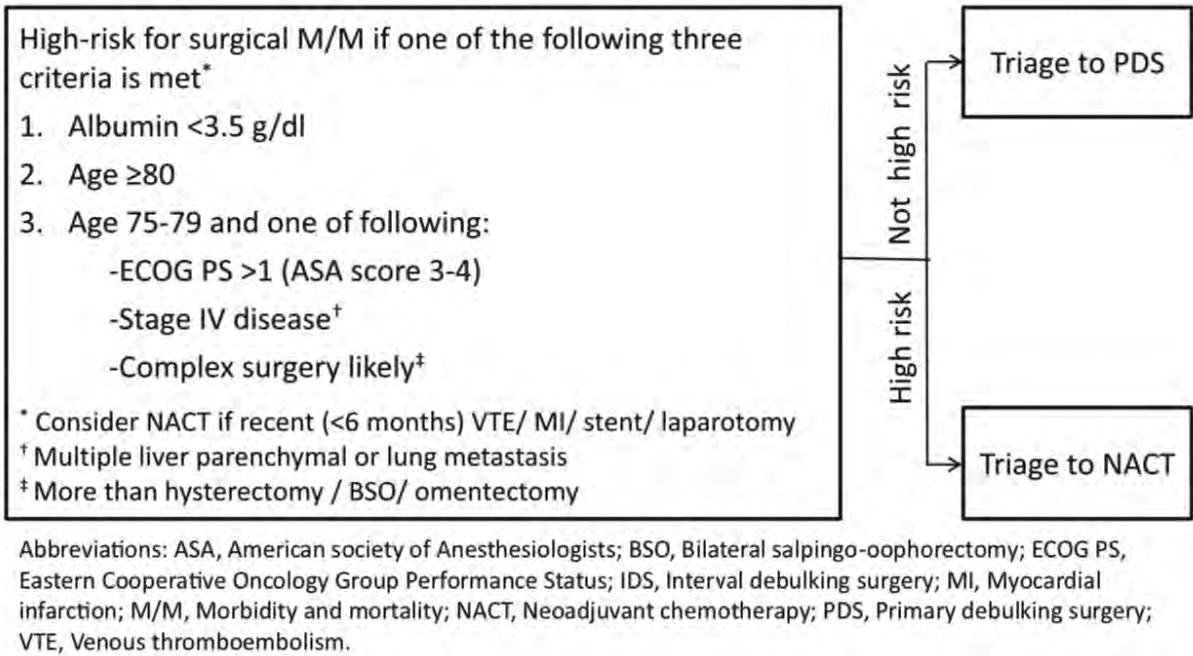


Figure 41-4. The Mayo triage algorithm to predict surgical M/M after PDS.

Lymph Node Management

Initial Stage

Patients with early stage EOC should undergo comprehensive para-aortic and pelvic lymph node staging, especially if HGS EOC. ACTION trial is the randomized controlled trial (RCT) study that included 448 early stage EOC patients, from 40 different centers, randomized for adjuvant chemotherapy versus observation after recommended complete staging. Completely staged patients with para-aortic or pelvic lymph node sampling, had superior 5years DFS (79% vs 61%, $p=0.03$) and OS (89% vs 71%, $p=0.01$).⁽²⁸⁾

In the era of tailoring adjuvant therapy, adequately staged low risk initial EOC should undergo observation, stage IA grade 3, IB grade 3, clear cell, IC, and completely resected stage II EOC patients would benefit from receiving only 3 cycles of adjuvant carboplatin/paclitaxel chemotherapy, with same oncological outcomes, and less toxicity when compared to standard 6 cycles.⁽²⁹⁾ On the other hand, stage I high grade serous would present superior recurrence free survival when receiving 6 cycles of adjuvant carboplatin and paclitaxel (83% vs 60%, $p=0.007$), based on an exploratory analysis of 98 patients.⁽³⁰⁾ Furthermore, stage III EOC patients (i.e. pT1 pN1 cM0) would be referred for 6 platinum-based adjuvant cycles plus maintenance with PARP inhibitors.

Advanced Disease

A total of 647 stage IIB to IV EOC patients at LION trial were randomized intraoperatively to observation versus systematic lymphadenectomy after complete cytoreductive surgery. Systematic lymphadenectomy increased surgical time (340 vs. 280 minutes, $p<0.001$), median blood loss (650 vs. 500 ml, $p<0.001$), transfusions rates (63.7% vs. 56.0%, $p=0.005$), infections requiring antibiotics (25.8% vs 18.6%, $p=0.03$), rate of reoperations (12.4% vs 6.5%, $p=0.01$), and mortality (3.1% vs 0.9%, $p=0.049$). The median overall survival and progression-free survival were 65.5 and 25.5 months in the lymphadenectomy group and 69.2 and 25.5 months in the no-lymphadenectomy group.

After LION trial, patients with normal lymph nodes at the preoperative imaging, selected for upfront PDS, should undergo a complete peritoneal cytoreduction attempt, without lymphadenectomy.

When suspicious lymph nodes are observed at preoperative imaging and/or during surgery, all nodes should be removed, as part of the debulking procedure.

Primary Versus Interval Debulking Surgery

Primary cytoreductive surgery (PCS) is the traditional surgical approach to EOC patients with good (PS). When feasible and complete/optimal, PCS has a significant better OS (37.3 vs 32.1 months, $p<0.001$) when compared to interval debulking surgery (IDS), probably due to higher tumor burden and worse PS at the diagnosis, for patients selected to IDS.⁽³¹⁾ Different series correlate a worse and earlier recurrence profile associated to NACT and IDS when compared to PDS. This effect could be related to a platinum resistance behavior and TP53 K351N or HGF/c-Met axis mutations.⁽³²⁻³⁴⁾

IDS has the potential of cost-reducing when compared to PDS, but with a lower OS rate. IDS could be the best cost-effective approach for patients over 65 years-old, with worse PS, and higher tumor burden.^(35,36)

Two large RCT demonstrated comparable low OS and DFS for patients undergoing PDS versus NACT followed by IDS.

The first RCT compared PDS with adjuvant CT versus NACT and IDS (EORTC 55971), and was published by Vergote *et al.* Patients with EOC stage IIIC or IV, with high volume of disease, and PS 0-2, were randomized to primary debulking surgery followed by adjuvant chemotherapy versus neoadjuvant chemotherapy, interval debulking surgery, followed by completion chemotherapy. Median OS (29 and 30 months) and median PFS (12 months) was similar in both arms. The strongest independent predictors of prolonged survival, in descending order, were complete cytoreductive surgery ($P<0.001$); stage IIIC disease ($P=0.001$); small tumor size before randomization ($P=0.001$); endometrioid histologic type, followed in descending order by serous, mixed, undifferentiated, mucinous, and clear-cell types ($P=0.005$); and younger age ($P=0.005$). The residual tumor size was 1 cm or smaller after primary debulking surgery in 41.6% of patients and after interval debulking surgery in 80.6% of patients.⁽³⁷⁾

The second RCT to compare PDS with adjuvant CT versus NACT and IDS in advanced EOC was CHORUS trial, with very similar design, achievements/limitations, and results. A total of 552 eligible stage III and IV EOC patients were recruited, in of 87 institutions from the UK and New Zealand, to upfront surgery followed by 6 cycles of chemotherapy, or 3 cycles, surgery and completion of chemotherapy. Severe adverse events and deaths within 28 days after surgery were more common in the primary-surgery group (24% vs 14%, $p=0.0007$, and 6% vs <1%, $p=0.001$, respectively). Median

operative time was 120 minutes in both arms. Complete or optimal debulking was obtained in 41% and 76%, with a median OS of 22.6 months in the primary-surgery group versus 24.1 months in primary chemotherapy, respectively (HR 0.87 (95% CI 0.72–1.05), with comparable DFS ($p=0.2923$)).⁽³⁸⁾

A peer-protocol pooled analysis of both EORTC 55971 and CHORUS trial included 1,220 patients, 612 were allocated into the upfront debulking arm, and 608 to the neoadjuvant therapy arm. 68% were stage IIIC and 19% stage IV. Median follow up was 7.6 years. Median OS for EORTC and CHORUS was significantly different, at 30.2 months and 23.6 months, respectively. Women with stage IV disease had significantly better outcomes with neoadjuvant chemotherapy compared with upfront debulking surgery (median overall survival 24.3 months and 21.2 months).⁽³⁹⁾

Strong criticism regarding the lack of radicality, centers heterogeneity, with high rates of low complexity procedures, and low volume centers accrual, was associated to CHORUS and EORTC 55971 trials. In order to compare PDS and IDS in high volume accredited centers, there is an ongoing new study, including European institutions (TRUST trial).⁽⁴⁰⁾

Hyperthermic Intraperitoneal Chemotherapy - HIPEC

Due to the lack of specific clinical symptoms and the characteristic of spreading to the abdominal cavity, most of EOC have spread to peritoneum by the time of preliminary diagnosis. The natural feature of EOC provided a perfect opportunity to develop the local therapy. A systematic review showed that intraperitoneal (IP) chemotherapy prolonged survival time and reduced the risk of death. After every cycle of IP chemotherapy finished, the risk of death decreased by 12%.⁽⁶⁾

Recently, to evaluate the impact of two different intraperitoneal (IP) chemotherapy regimens on progression-free survival (PFS) among women with newly diagnosed advanced ovarian carcinoma, 1560 women were randomly assigned to six cycles of IV paclitaxel 80mg/m² once per week with intravenous (IV) carboplatin versus IV paclitaxel 80mg/m² once per week with IP carboplatin versus once every 3 weeks IV paclitaxel 135 mg/m² over 3 hours day 1, IP cisplatin 75 mg/m² day 2, and IP paclitaxel 60 mg/m² day 8 (IP cisplatin). All participants received bevacizumab 15 mg/kg IV every 3 weeks in cycles 2 to 22.

The median PFS duration was 24.9 months in the IV carboplatin arm, 27.4 months in the IP carboplatin arm, and 26.2 months in the IP cisplatin arm. For the subgroup of 1,380 patients with stage II/III and residual disease of 1 cm or less, median PFS was 26.9 (IV-carboplatin), 28.7 (IP-carboplatin), and 27.8 months (IP cisplatin), respectively. Median PFS for patients with stage II/III and no residual disease was 35.9, 38.8, and 35.5 months, respectively. Median overall survival for all enrolled was 75.5, 78.9, and 72.9 months, respectively, and median overall survival for stage II/III with no gross residual disease was 98.8 months, 104.8 months, and not reached. The results clearly show that compared with the IV carboplatin reference arm, the duration of PFS was not significantly increased with either IP regimen when combined with bevacizumab and was better tolerated than IP cisplatin.⁽⁴¹⁾

Rationale for using hyperthermic conditions when delivering intraperitoneal chemotherapy is multifactorial. Clinical hyperthermia is defined as the use of temperatures of 41° C and higher.

In contrast to IP chemotherapy without hyperthermia condition, HIPEC had following advantages:

- 1) Direct impairment against cancer cells.
- 2) Enhancement of the cytotoxicity of chemotherapy.
- 3) Inhibition of angiogenesis.
- 4) Improvement in denaturation of proteins.
- 5) Great tolerance without additional adverse effect.

To date, there is increasing evidence that the combination of complete cytoreductive surgery and HIPEC enhances the prognosis of ovarian cancer significantly.

The outcomes of the trial by van Driel *et al.* are encouraging, but questions remain about how to apply these results in everyday clinical practice.⁽⁴²⁾

Eligible patients had newly diagnosed stage III epithelial ovarian, fallopian tube, or peritoneal cancer and were referred for neoadjuvant chemotherapy because of extensive abdominal disease or incomplete cytoreductive surgery (one or more residual tumors measuring >1 cm in diameter). Eligibility criteria also including performance status score of 0 to 2, normal blood counts, and adequate renal function.

At the time of surgery, patients were randomly assigned in a 1:1 ratio to undergo interval cytoreductive surgery with HIPEC (surgery-plus-HIPEC group) or without HIPEC (surgery group). HIPEC was administered at the end of the cytoreductive surgical procedure. Perfusion with cisplatin

at a dose of 100 mg per square meter was then initiated. The procedure took 120 minutes in total.

A total of 245 women were randomized between April 2007 and April 2016. The median follow-up at the time of recurrence-free survival analysis was 4.7 years. Recurrence-free survival events occurred in 81% of the HIPEC group vs 89% of the control group; median recurrence-free survival was 14.2 months vs 10.7 months, respectively (hazard ratio [HR] 0.66, $P = 0.003$). Death occurred in 50% of the hyperthermic intraperitoneal chemotherapy group vs 62% of the control group; median overall survival was 45.7 vs 33.9 months (HR 0.67, $P = 0.02$).

Among the patients who underwent bowel resection, a colostomy or ileostomy was performed more commonly among patients in the surgery-plus-HIPEC group (21 of 29 patients [72%]) than among those in the surgery group (13 of 30 patients [43%]) ($P = 0.04$).

First, with the extensive reported experience with HIPEC in select single center or multicenter trials, it is reasonable to conclude the procedure can be successfully undertaken by well-trained surgical/gynecologic oncologists and at institutions experienced in the approach. However, clinical trials have limited external validity, and while providing evidence regarding efficacy (i.e., the effect of the intervention under highly selected conditions), they generally do not provide evidence of effectiveness (i.e., the benefit to the general population of patients with the disease).

However, whether the same results can be reproduced at centers at which surgeons do not have as much expertise in administering HIPEC remains to be seen. New confirmatory clinical trials of HIPEC are needed before it can be recommended as a common treatment strategy.

Brazilian Society of Surgical Oncology established minimum standards for EOC surgery, in a consensus report, adjusting international guidelines to a middle-income country, with adequate resources in most referral centers. Strong recommendations for high volume center referral, multidisciplinary approaches, specific complex surgical procedures technique, genetic counseling and maximum effort towards a complete cytoreduction were reinforced.⁽²⁶⁾

Quality of Life (QOL) after Treatment

After EOC treatment, 1360 patients were evaluated for QOL, with an internet based cross-sectional questionnaire. Recurrent patients accounted for 31%. Most patients were

obese (59%) and physically inactive (35%), and these two factors were highly correlated to poorer QOL scores and higher symptom burden across a range of domains.⁽⁴³⁾

All professionals related to EOC survivorship approaches should recommend healthy diet and regular exercises in order to improve QOL after treatment.

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Chapter 42

Cervical Cancer

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- The cervical cancer is a public health problem, is the fourth most frequent cancer in women. Approximately 90% of deaths from cervical cancer, occurred in low-middle income countries.
- It is a disease with a long evolution. The high mortality rate from cervical cancer globally could be reduced through a comprehensive action that includes prevention, early diagnosis, effective screening and timely and effective treatment.
- Vaccines protect against common cancer-causing types of human papilloma virus and can significantly reduce the risk of cervical cancer.
- Complementary strategies for comprehensive cervical cancer prevention and control, and highlights the need for collaboration across programs, organizations and partners.
- Comprehensive cervical cancer control includes primary prevention (vaccination against Human Papilloma Virus), secondary prevention (screening and treatment of pre-cancerous lesions), tertiary prevention (diagnosis and treatment of invasive cervical cancer) and palliative care.
- Screening and treatment of pre-cancer lesions in women of 30 years and more is a cost-effective way to prevent cervical cancer.
- Cervical cancer can be cured if diagnosed at an early stage.

Introduction

The cervical cancer is a global public health issue. In 2018 were reported 490,000 new cases. Is the fourth most prevalent cancer and the fourth leading cause of cancer death in women worldwide, with an estimated 530,000 new cases and 270,000 deaths every year. ⁽¹⁾ Approximately 90% of deaths from cervical cancer occurred in low-middle income countries.

The persistent infection by human papilloma virus (HPV) is an important factor for the disease development. There are other factors such as smoking, sexually transmitted diseases, use of oral contraceptive methods and earlier beginning of sexual activity. ⁽²⁾

The cervical cancer is a long evolution disease, which allows an excellent opportunity of earlier detection and an effective treatment in the first detected injuries (precancerous, dysplasia or both).

The Pap smear is used as an earlier detection test for the cervical cancer. It is a cheaper, simple and highly effective method that reduce the evolution of dysplastic injuries to carcinoma because it allows the patients to be treated and cured up to 100% when the disease is diagnosed in an earlier clinical stage.

The infection's biological behavior of the Asian-American type HPV16 has greater oncology aggressiveness than the one reported for European type HPV16. HPV 16 and 18 account for approximately 70% of cervix cancer.

There is evidence that the improvements in socioeconomic conditions and implementation of early detection programs have significantly impacted in the slowdown and reduction of the cervical cancer death rate.

Prevention

Primary prevention begins with HPV vaccination of girls aged 9-14 years, before they become sexually active.

Other recommended preventive interventions for boys and girls as appropriate are:

- education about safe sexual practices, including delayed start of sexual activity;
- promotion and provision of condoms for those already engaged in sexual activity;
- warnings about tobacco use, which often starts during adolescence, and which is an important risk factor for cervical and other cancers; and
- male circumcision.

Women who are sexually active should be screened for abnormal cervical cells and pre-cancerous lesions, starting from 30 years of age. If treatment of pre-cancer is needed to excise abnormal cells or lesions, cryotherapy (destroying abnormal tissue on the cervix by freezing it) is recommended. If signs of cervical cancer are present, treatment options for invasive cancer include surgery, radiotherapy and chemotherapy.

Particularly in countries where screening programs are not available, diagnosing cervical cancer at an early stage and providing access to effective treatment can significantly improve the likelihood of survival. (Figure 42-1)

HPV Vaccination

There are currently 3 vaccines protecting against both HPV 16 and 18, which are known to cause at least 70% of cervical cancers. The third vaccine protects against three additional oncogenic HPV types, which cause a further 20% of cervical cancers. Given that the vaccines which are only protecting against HPV 16 and 18 also have some cross-protection against other less common HPV types which cause cervical cancer, WHO considers the three vaccines equally protective against cervical cancer. Two of the vaccines also protect against HPV types 6 and 11, which cause anogenital warts.

Clinical trials and post-marketing surveillance have shown that HPV vaccines are very safe and very effective in preventing infections with HPV infections. HPV vaccines work best if administered prior to exposure to HPV. Therefore, WHO recommends vaccinating girls, aged between 9 and 14 years, when most have not started sexual activity. Also, this is the most cost-effective public health measure against cervical cancer.

Some countries have started to vaccinate boys as the vaccination prevents genital cancers in males as well as females, and two available vaccines also prevent genital warts in males and females.

The vaccines cannot treat HPV infection or HPV-associated disease, such as cancer. HPV Vaccination does not replace cervical cancer screening. In countries where HPV vaccine is introduced, screening programs may still need to be developed or strengthened.

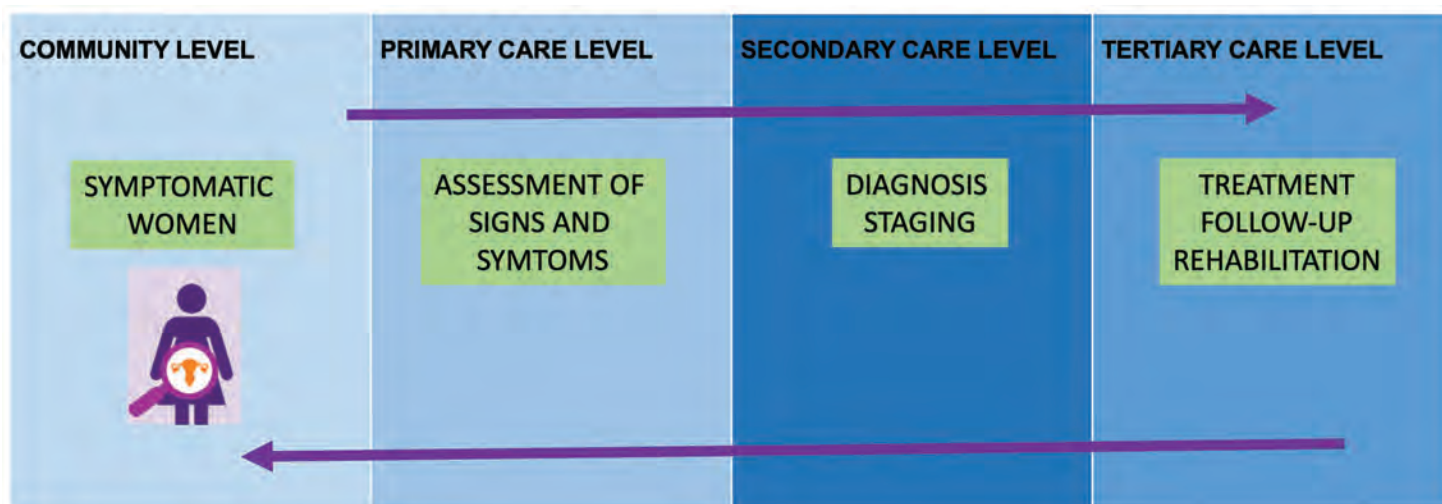


Figure 42-1. Cervical Cancer Early Diagnosis.

Screening and Treatment of Pre-Cancer Lesions

Cervical cancer screening involves testing for pre-cancer and cancer among women who have no symptoms and may feel perfectly healthy. When screening detects pre-cancerous lesions, these can be easily treated, and cancer can be avoided. Screening can also detect cancer at an early stage and treatment has a high potential for cure.

Because pre-cancerous lesions take many years to develop, screening is recommended for every woman from aged 30 and regularly afterwards (frequency depends on the screening test used). For women living with HIV who are sexually active, screening should be done earlier, as soon as they know their HIV status.

Screening must be linked to treatment and management of positive screening tests. Screening without proper management is not ethical.

There are 3 different types of screening tests that are currently recommended by WHO:

- HPV testing for high-risk HPV types.
- Visual inspection with Acetic Acid (VIA)
- Conventional (Pap) test and liquid-based cytology (LBC)

For treatment of pre-cancer lesions, WHO recommends the use of cryotherapy and Loop Electrosurgical Excision Procedure (LEEP). For advanced lesions, women should be referred for further investigations and adequate management.

Comprehensive cervical cancer control includes primary prevention (vaccination against HPV), secondary prevention (screening and treatment of pre-cancerous lesions), tertiary prevention (diagnosis and treatment of invasive cervical cancer) and palliative care. (Figure 42-2)

Symptoms, Diagnosis and Staging

Symptoms of cervical cancer will be determined by the extension and evolution of the disease. The trend may include: irregular, intermenstrual (between periods) or abnormal vaginal bleeding after sexual intercourse; back, leg or pelvic pain; fatigue, weight loss, loss of appetite; vaginal discomfort or odorous discharge; and a single swollen leg. More severe symptoms may arise at advanced stages.

Cervical cancer is a locoregional penetration neoplasm, which means that it remains confined to the pelvis for a long time, this explains why in the early stages the patients are asymptomatic. In its natural evolution the tumor infiltrates the cervical stroma, adjacent tissues and organs. In parallel, it develops distant metastases. During these stages, the most frequent clinical manifestation is postcoital and/or postmenopausal bleeding, or metrorrhagia.

The bladder and/or rectum invasion is manifested by fistulas, as serious and annoying signs and symptoms, as well as difficult handling. The most advanced cases present pelvic pain, pain referred to the sciatic nerve, in addition to one or both legs, low back pain due to infiltration into neighboring tissues such as the sacral plexus. Neoplastic extension can

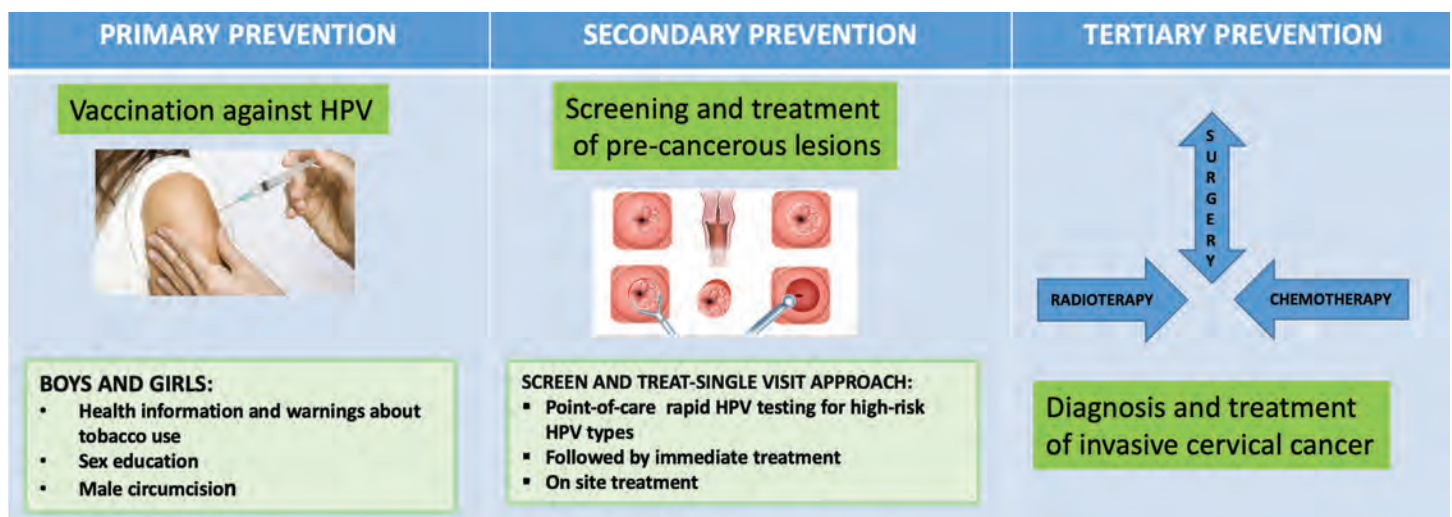


Figure 42-2. Prevention.

cause lymphatic, vascular and urethral block. The symptoms associated with this stage are: nausea, vomiting, anorexia, weight loss, asthenia, anemia, uremia and an attack on the general state.

The dissemination of cervical cancer occurs through the uterine fixation ligaments, parametria, uterosacral ligaments, round ligaments, as well as by continuity to the rectum and bladder. Lymph node dissemination is directly related to the stromal penetration of the tumor, primarily affecting the paracervical lymph nodes, and then the paraurethral, obturator, hypogastric, external pelvic, common iliac, inguinal, para-aortic, mediastinal and supraclavicular chains.

Hematologic dissemination to the lungs and liver can be observed in the terminal phase of the disease. Small cell cervical cancer can affect the central nervous system.

The complete medical history, the extent of the disease and the risk factors continues to be the cornerstone in the diagnosis. The gynecological test with a vaginal mirror can find a normal cervix when pre-invasive or incipient injuries are present. When an ulceration is present, or an induration of an exophytic injury is detected a biopsy should be taken with a puncher. Once the diagnostic is confirmed both by cytology (Pap smear) or pathology, the patient must be staged to get an appropriate treatment.

Once the diagnosis has been made by cytology and there is a high suspicion, the patient should go to the colposcopy service for a representative and directed sampling (early lesions may be imperceptible from a macroscopic point of view). The colposcope interposes increasing glasses that allow both, locating and defining lesions.

Histopathological and cytological diagnosis of early lesions are essential. Cytology has a sensitivity of 78% and a diagnostic specificity of 96 to 99%. The most frequent causes of a false positive reports are:

- a) the inadequate interpretation of chronic inflammatory lesions;
- b) metaplastic lesions.

The etiological function of HPV is very important. It is estimated that more than 50% of women with active sex life have ever been infected with this virus. Even if there are no clinical manifestations, cytology, biopsy or both will be positive. ⁽³⁾

The molecular hybridization is the principal detection method, this is capable to identify the several genotypes of HPV.

E6 and E7 proteins participate in the promotion of premalignant lesions that precede cervical carcinoma.

The diagnosis of cervical carcinoma includes different histological types and varieties.

Requirements to establish a colposcopic diagnosis are:

- The edges of the lesion: defined or irregular.
- The location of the lesion: (in relation to the external cervical opening).
- Coloration (supported by stains with 5% acetic acid or lugol).
- Surface of the lesion (flat, raised or rough).
- Presence or absence of vessels (known as punctuation or mosaicism, according by appearance of atypical vessels).

Once the diagnosis and stage have been established, the treatment can be:

- a. Ablative or destructive, or
- b. Resective.

Destructive methods include nitrous oxide, or liquid nitrogen, both are used for destruction by freezing (cryotherapy). The use of the laser is known as evaporation technique, and the electrofulguration technique uses electrical energy. Conization has a special indication in the treatment of adenocarcinoma *in situ* of the cervix, for this case the scalpel is used (cold technique). Other techniques include the laser beam such as cutting and radiofrequency.

Staging of Cancer of the Cervix Uteri

The hallmark of a good staging system is the ability to define anatomical extent of disease and differentiate survival outcomes. The staging system also allows comparison of patients and their outcomes between centers. Cancer staging is an evolving process that responds to developments in technology that improve diagnosis and treatment, new information about prognostic factors, and outcomes data.

Since publication of the last FIGO (International Federation of Gynecology and Obstetrics) cervical cancer staging in 2009, considerable progress has been made in the use of imaging modalities to evaluate women with cervical cancer. Although FIGO moved to a surgicopathological system of staging for ovarian and endometrial cancer, this was not

as simple for cervical cancer, a disease mainly of under-resourced regions. Although the availability and quality of imaging has increased substantially, not only in high-resource countries but also in some low-middle income countries, the capability to assess the abdomen, pelvis, and the retroperitoneal areas by some imaging modality varies considerably. Moreover, unlike ovary and endometrium, treatment options for cervical cancer include both surgery and radiation depending on the extent of the disease. Advances in minimally invasive surgery (MIS) have led to an increase in para-aortic sampling in advanced cases to determine the need for extended field radiation. Interestingly, even in some less resourced countries such as Sri Lanka, retrieval of para-aortic nodes by laparotomy or laparoscopy is the standard of care in such cases. Thus, although staging continued to be clinical, clinicians in all parts of the world began using new technologies to guide treatment. ⁽⁴⁾

Despite concern that surgicopathological documentation of disease extent may not be feasible where there is poor access to MIS techniques and adequate pathological facilities, the FIGO Gynecologic Oncology Committee determined that the staging classification needed revision to maintain unanimity worldwide, incorporate new technology where feasible, and thereby improve its utility and applicability. Imaging and pathological assessment of the pelvis and evaluation of pelvic and para-aortic lymph nodes should be formally incorporated into the staging of cervical cancer while giving the clinician the flexibility to use it according to available resources.

The following amendments to the staging classification of carcinoma of the cervix uteri were made by the FIGO Committee for Gynecologic Oncology in 2018:

1. Allowing the use of any imaging modality and/or pathological findings for allocating the stage.
2. In stage I, amendments to microscopic pathological findings and to size designations, allowing the use of imaging and/or pathological assessment of the size of the cervical tumor.
3. In stage II, allowing the use of imaging and/or pathological assessment of size and extent of the cervical tumor.
4. In stages I through III, allowing assessment of retroperitoneal lymph nodes by imaging and/or pathological findings and, if deemed metastatic, the case is designated as stage IIIC (with notation of method used for stage allocation). No recommendations for routine investigations, which are to be decided based on clinical findings and standard of care. ⁽⁴⁾ (Table 42-1)

General Recommendations

1. The revised staging system does not mandate the use of a specific imaging technique, lymph node biopsy, or surgical assessment of the extent of tumor. In low-resourced conditions, clinicians can continue to assess the patient clinically as before.
 - a. The size of the primary tumor can be assessed by clinical evaluation (pre- or intraoperative), imaging, and/or pathological measurement.
 - b. Identification of lymph node metastasis should be accomplished using any imaging technique(s) and/or pathological assessment methods available to the provider, and the choice of technique is theirs.
2. It is recommended that the method used for imaging (e.g., ultrasound, computed tomography [CT], magnetic resonance imaging [MRI], positron emission tomography [PET], PET-CT, MRI-PET, etc.) and/or the pathological technique used (e.g., evaluation of the operative specimen, lymph node biopsy, or fine needle aspiration cytology), and the results thereof, should be recorded, so that subsequent data analysis can be performed. The imaging method can be used:
 - a. For measurement of the primary tumor size;
 - b. For assessment of extension into the surrounding tissues and adjacent organs;
 - c. For assessment of location and characteristics of the retroperitoneal lymph nodes;
3. It is recognized that there will be limitations for imaging findings in low-middle income countries as a result of paucity, non-availability, or inadequate access to extensive imaging services.
4. As in the previous staging, when in doubt, the lower staging should be assigned. ⁽⁴⁾

Table 42-1. FIGO Staging of Carcinoma of the Cervix Uteri (2018)

Stage I: The carcinoma is strictly confined to the cervix uteri (extension to the corpus should be disregarded).	
IA	Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion <5 mm.
IA1	Measured stromal invasion <3 mm in depth.
IA2	Measured stromal invasion ≥3 mm and <5 mm in depth.
IB	Invasive carcinoma with measured deepest invasion ≥5 mm (greater than stage IA), lesion limited to the cervix uteri.
IB1	Invasive carcinoma ≥5 mm depth of stromal invasion and <2 cm in greatest dimension. Invasive carcinoma ≥2 cm and <4 cm in greatest dimension.
IB2	
IB3	Invasive carcinoma ≥4 cm in greatest dimension.
Stage II: The carcinoma invades beyond the uterus but has not extended onto the lower third of the vagina or to the pelvic wall.	
IIA	Involvement limited to the upper two-thirds of the vagina without parametrial involvement.
IIA1	Invasive carcinoma <4 cm in greatest dimension.
IIA2	Invasive carcinoma ≥4 cm in greatest dimension.
IIB	With parametrial involvement but not up to the pelvic wall.
Stage III: The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or non-functioning kidney and/or involves pelvic and/or paraaortic lymph nodes.	
IIIA	Carcinoma involves the lower third of the vagina, with no extension to the pelvic wall.
IIIB	Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney (unless known to be due to another cause).
IIIC	Involvement of pelvic and/or paraaortic lymph nodes, irrespective of tumor size and extent (with r and p notations).
IIIC1	Pelvic lymph node metastasis only.
IIIC2	Paraaortic lymph node metastasis.
Stage IV: The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to stage IV.	
IVA	Spread of the growth to adjacent organs.
IVB	Spread to distant organs.
<i>a. Imaging and pathology can be used, when available, to supplement clinical findings with respect to tumor size and extent, in all stages.</i> <i>b. The involvement of vascular/lymphatic spaces does not change the staging. The lateral extent of the lesion is no longer considered.</i> <i>c. Adding notation of r (imaging) and p (pathology) to indicate the findings that are used to allocate the case to stage IIIC. For example, if imaging indicates pelvic lymph node metastasis, the stage allocation would be stage IIIC1r and, if confirmed by pathological findings, it would be Stage IIIC1p. The type of imaging modality or pathology technique used should always be documented. When in doubt, the lower staging should be assigned.</i>	

Prognosis

Indicators for the prognosis in cervical cancer include:

- The clinical stage.
- Presence or absence of lymph node disease.
- Tumor volume.
- Type and degree of histopathological differentiation.
- Depth of stromal invasion.
- Vascular and lymphatic permeability.
- Fitness and medical history.

For patients in clinical stage Ib, the main prognostic factors are considered to be lymph node involvement, invasion of the vascular and lymphatic spaces, tumor volume and degree of extension to the cervical stroma. ^(4,5)

In clinical stages II, III, IV the most significant indicators are metastases to pelvic and paraaortic lymph nodes. Other prognostic factors are age, ureteral obstructions or hydronephrosis, renal function, anemia at diagnosis and functional status. At any stage, especially in the early stages, the most important prognostic factor is lymphatic dissemination. ⁽⁶⁾

Treatment

The main goals of cancer diagnosis and treatment programs are to cure or considerably prolong the life of patients and to ensure the best possible quality of life for cancer survivors. The most effective treatment programs are those that:

1. Are provided in an equitable and sustainable way.
2. Are linked to early detection and accurate diagnosis and staging.
3. Adhere to evidence-based standards of care.

It must be planned jointly by a multidisciplinary team, it must consider the clinical stage (fundamentally), tumor assessment, patient's characteristics and preferences, and the resources availability.

The standard therapy today is surgery only in initial stage, for locally advanced disease is chemotherapy with radiotherapy in concomitant sequence plus brachytherapy with responses in 66%. ⁽⁷⁾

The stage of a cervical cancer is the most important factor in choosing treatment. But other factors can also affect treatment options, including the exact location of the cancer within the cervix, the type of cancer (squamous cell or adenocarcinoma), age and overall health, and whether the patient wants to have children.

Preinvasive Disease

Cervical cancer is preceded by an interval of epithelial dysplastic changes, typically in the transformation zone, known as cervical intraepithelial neoplasia (CIN), which may progress to invasive cancer. Low-grade dysplasia (CIN 1), is confined to the basal one third of the epithelium, and most low-grade lesions regress to normal in about 24 months. Full thickness involvement is known as CIN 3 or carcinoma

in situ (CIS), and the rate of progression to invasive cancer is 12% to 22%.

Treatment Options for Squamous Cell Carcinoma *In Situ* Include:

- Cryosurgery
- Laser surgery
- Loop electrosurgical excision procedure (LEEP/LEETZ)
- Cold knife conization
- Simple hysterectomy (as the first treatment or if the cancer returns after other treatments)

Treatment Options for Adenocarcinoma *In Situ* Include:

- Hysterectomy
- Cone biopsy (a possible option for women who wish to have children). The cone specimen must have no cancer cells at the edges, and the woman must be closely watched after treatment. Once the woman has finished having children, a hysterectomy is recommended.

STAGE IA1

Treatment for this stage depends on whether or not want to maintain fertility and whether or not the cancer has lymphovascular invasion.

Treatment Options for Women Who Want to Maintain Fertility

A cone biopsy is the preferred procedure for women who want to have children after the cancer is treated. (Table 42-2)

- If the edges of the cone do not contain cancer cells (called negative margins), the woman can be watched closely without further treatment as long as the cancer does not come back.
- If the edges of the cone biopsy have cancer cells (called positive margins), then cancer may have been left behind. This can be treated with a repeat cone biopsy or a

Table 42-2. Ideal Requirements for Fertility-preserving Surgery in Cervical Cancer

• Confirmed cervical cancer: squamous, adenocarcinoma, or adenosquamous
• FIGO stage IA1 with PLV, IA2, or IB1
• Desire to preserve fertility
• Tumor size < 2 cm
• No history of infertility
• Limited endocervical affection
• Possibility for resection with margins > 5 mm
• Cervical length > 1 cm
• Negative pelvic ganglia

radical trachelectomy (removal of the cervix and upper vagina). A radical trachelectomy is preferred if the cancer has grown into blood or lymph vessels.

Treatment Options for Women Who Do Not Want to Maintain Fertility

- A simple (total) hysterectomy may be an option if the cancer shows no lymphovascular invasion.
- If the cancer has lymphovascular invasion, you might need a radical hysterectomy along with removal of the pelvic lymph nodes.

STAGE IA2

Treatment Options for Women Who Want to Maintain Fertility

- Cone biopsy with removal of pelvic lymph nodes (pelvic lymph node dissection).
- Radical trachelectomy with pelvic lymph node dissection.

Treatment Options for Women Who Do Not Want to Maintain Fertility

- External beam radiation therapy (EBRT) to the pelvis plus brachytherapy.
- Radical hysterectomy with removal of pelvic lymph nodes and sampling of the para-aortic lymph nodes.

- If none of the lymph nodes are found to have cancer, radiation may still be discussed as an option if the tumor is large, if the tumor has lymphovascular invasion, or if the tumor is invading the surrounding connective tissue that supports organs such as the uterus, bladder, vagina (the stroma).
- If the cancer has spread to the tissues next to the uterus (called the parametria) or to any lymph nodes, or if the tissue removed has positive margins, radiation (EBRT) with chemotherapy is usually recommended. The doctor may also advise brachytherapy after the combined chemo and radiation are done.

STAGES IB and IIA

The main treatment options are surgery, radiation, or radiation given with chemo (concurrent chemoradiation).

STAGES IB1 and IIA1

Treatment Options for Women Who Want to Maintain Fertility

- Radical trachelectomy with pelvic lymph node dissection

Treatment Options for Women Who Do Not Want to Maintain Fertility

- Radical hysterectomy with removal of lymph nodes in the pelvis and some lymph nodes from the para-aortic area.
- If none of the lymph nodes are found to have cancer, radiation may still be discussed as an option if the tumor is large, if the tumor has grown into blood or lymph vessels, or if the tumor is invading the surrounding connective tissue that supports organs such as the uterus, bladder, vagina (the stroma).
- If the cancer has spread to the tissues next to the uterus (called the parametria) or to any lymph nodes, or if the tissue removed has positive margins, radiation (EBRT) with chemotherapy is usually recommended. The doctor may also advise brachytherapy after the combined chemo and radiation are done.
- Radiation using both brachytherapy and external beam radiation therapy may be an option if a woman is not

healthy enough for surgery or if she decides they do not want surgery

- Chemotherapy (chemo) may be given with the radiation (concurrent chemoradiation).

STAGES IB2 and IIA2

Treatment Options

- Chemoradiation: This is usually the standard treatment. The chemo may be cisplatin or cisplatin plus fluorouracil. The radiation therapy includes both external beam radiation and brachytherapy.
- Radical hysterectomy with pelvic lymph node dissection and para-aortic lymph node sampling: If cancer cells are found in the removed lymph nodes, or in the edges of the tissue removed (positive margins), surgery may be followed by radiation therapy, which is often given with chemo (concurrent chemoradiation).
- Some doctors recommend radiation given with chemotherapy first followed by a hysterectomy.

STAGES IIB, III, and IVA

Treatment Options

Chemoradiation: The chemo may be cisplatin or cisplatin plus fluorouracil. The radiation therapy includes both external beam radiation and brachytherapy.

STAGE IVB

At this stage, the cancer has spread out of the pelvis to other areas of the body. Stage IVB cervical cancer is not usually considered curable. Treatment options include radiation therapy and/or chemo to try to slow the growth of the cancer or help relieve symptoms. Most standard chemo regimens include a platinum drug (cisplatin or carboplatin) along with another drug such as paclitaxel, gemcitabine, or topotecan. The targeted drug bevacizumab may be added to chemo or immunotherapy alone with pembrolizumab, may also be an option.

Clinical trials are testing other combinations of chemo drugs, as well as some other experimental treatments.

Recurrent Cervical Cancer

Cancer that comes back after treatment is called recurrent cancer. Cancer can come back locally (in or near where it first started, such as the cervix, uterus or nearby the pelvic organs), or it can come back in distant areas (such as the lungs or bone).

If the cancer has recurred in the pelvis only, extensive surgery (such as pelvic exenteration) may be an option for some patients and offers the best chance for possibly curing the cancer (although it can have major side effects). Radiation therapy (sometimes along with chemo) might be another option. If not, chemo, immunotherapy, or targeted therapy may be used to slow the growth of the cancer or help relieve symptoms, but they are not expected to cure the cancer.

No matter which type of treatment the Doctor recommends, it is important to understand the goal of treatment (try to cure the cancer, control its growth, or relieve symptoms), as well as its possible side effects and limitations. For example, sometimes chemo can improve quality of life, and other times it might diminish it. Patient need to discuss this with the Doctor.

Cervical Cancer in Pregnancy

A small number of cervical cancers are found in pregnant women. Most of these (70%) are stage I cancers. The treatment plan during pregnancy is determined by:

- Tumor size
- If nearby lymph nodes have cancer
- How far along the pregnancy is
- The specific type of cervical cancer

If the cancer is at a very early stage, such as carcinoma *in situ* (stage 0) or stage IA, most Doctors believe it is safe to continue the pregnancy to term and have treatment several weeks after birth. Surgery options after birth for early-stage cancers include a hysterectomy, radical trachelectomy, or a cone biopsy.

If the cancer is stage IB or higher, then the patient, family and health team must decide whether to continue the pregnancy. If not, treatment would be radical hysterectomy and/or radiation. Sometimes chemotherapy can be given during the pregnancy (in the second or third trimester) to shrink the tumor.

In case to continue the pregnancy, the baby should be delivered by cesarean section as soon as the baby is able to survive outside the womb. More advanced cancers typically need be treated immediately.

Radiotherapy

Radiotherapy has been the conventional treatment for all clinical stages for many years. Treatments for early-stage cervical cancer are mainly surgical because the control rate is high and the expected toxicity in surgery is low. When surgery is compared to radical radiotherapy, the data show that toxicity is lower after surgery than what is expected following radiation therapy. The main advantage of surgery over radiotherapy lies in the fact that it preserves the ovaries and sexual functions of young patients, which improves patient quality of life and avoids early menopause. ⁽⁷⁾

The treatment of choice for patients with early-stage cervical cancer is surgery, especially when the possibility of needing adjuvant radiation is low. In the opposite scenario, when adjuvant radiotherapy is thought to be required after surgery (e.g., because of large tumors, the risk of leaving residual tumors after surgery, of lymph node involvement) radical radiotherapy should be consider as first option.

Adjuvant Radiotherapy for Cervical Cancer

To reduce this risk, postoperative radiotherapy treatments are recommended in the following two clinical situations:

1) When there is an intermediate risk of recurrence, in which case, radiation therapy treatment alone is recommended (i.e., when lympho-vascular invasion is observed or the tumor size larger than 4 cm and involves more than one-third of stromal invasion); and **2)** When there is high risk of recurrence, in which case, adjuvant treatment with chemo-radiotherapy is suggested (i.e., in the presence of positive pelvic lymph nodes, positive margins and positive parametrial invasion).

In absence of macroscopic disease, a 45 to 50 Gy dose applied to the pelvis is typically prescribed as an adjuvant treatment. After external radiotherapy, the brachytherapy boost must be individualized. Once these factors were determined, several randomized trials that used adjuvant radiation to reduce local recurrence after surgery were performed.

Irradiation Techniques

If a patient has early-stage cervical cancer (i.e., pre-invasive stages and up to 1A2) and refuses or cannot be taken into surgery because of comorbidity, treatment with radiation therapy is feasible. However, in these cases, brachytherapy as a sole modality is preferred because the risk of lymph node involvement is low. The installation of brachytherapy devices is performed in the operation room, often while the patient is under sedation. The choice of device depends on the anatomy of the vagina (i.e., its size, length and compliance) and especially the target volume that needs to be covered.

There are several treatment schemes for brachytherapy. The choice should be based upon whether the treatment is going, involve low dose rate (LDR) or high dose rate (HDR) brachytherapy. For LDR, the prescribed dose is approximately 65-75 Gy to the vaginal vault, and with HDR, the dose is 35-45 Gy and is given in fractions of 6-7 Gy. Using Manchester and GEC-ESTRO Systems, the treatment is administered at 5 mm depth from the vaginal mucosa.

For patients with stages IB to IIA, the treatment consists of pelvic external radiotherapy and intracavitary brachytherapy with a prescription to point A. Two-dimensional treatment (2D) is based on predefined bone limits, which are localized using fluoroscopy. The tumor, uterus and pelvic lymph node tissue should be covered. The field's arrangement more commonly used an anterior, posterior and two lateral (pelvic box) approaches. The superior border, which is determined based on bone anatomy, is delimited by L4-L5. This is the level at which the bifurcation of the aorta most commonly takes place. The lower border is marked by the inferior limit of the Obturator Foramen. The lateral border of the posterior and anterior fields is indicated by a line that is marked as an imaginary line 2 cm beyond the true pelvic ring. For the lateral fields, the anterior border is 1cm beyond the pubic symphysis, and the posterior border is along an imaginary vertical line that is traced at the level of S2. The superior and lower borders of the lateral fields are the same as the ones for the anterior and posterior fields.

Three-dimensional radiotherapy treatment is based on anatomical limits according to the lymph node region and the extension of the tumor, which are observed on tomography. The region should cover the common, internal and external iliac lymph nodes and the pre-sacral lymph nodes, and the dose should be localized in the Obturator foramen. It also should cover the whole cervix, the uterus, the parametrial tissue that lies on the way from the cervix to the pelvic wall, the uterus-sacral ligaments and the upper half of the vagina.

The peri-rectal lymph nodes should be covered if the pelvic lymph nodes are affected. Prophylactic radiation to the para-aortic lymph nodes is not routinely indicated unless these nodes appear to be affected. If that is the case, these nodes should be covered above the renal vessels, at approximately the T12-L1 level 8.

Brachytherapy should be administered during or after treatment with external radiotherapy. The protocol will depend on the preferences of the oncologic center, the patient's vaginal capacity, grade of tumor regression and the concomitant use of chemotherapy. If the patient was not previously treated with surgery, treatment with brachytherapy should be performed using uterine probe and ovoids (Tandem) to cover the entire cervix. If the patient no longer has uterus, the treatment should be performed using a cylinder or ovoids, depending on anatomy and the volume that needs to be treated.

According to the Manchester System, which is evaluated by the ICRU 38, the dose should be administered to the A point. When using the GEC-ESTRO System, the dose should be targeted to the affected region regardless of pre-determined points of administration. This indicates that the residual tumor and the area presenting a high risk of recurrence should be covered. The final dose of radiotherapy to the A point or PTV (according to the type of brachytherapy) will depend on the clinical stage, which can vary from 65 to 75 Gy in stage IA1 and up to 85 Gy in stage IB and IIA.

Locally Advanced Cervical Cancer

Cervical Cancer in almost half of all cases is stage 1B2. The treatment should preferably involve concomitant chemo-radiotherapy followed by brachytherapy. This protocol has already been described in several works, which have shown that there is an inverse relationship between size of the tumor and the probability of controlling the cancer. That is, the larger the tumor size, the less likely the treatment will be successful. This is because the effect of radiation depends on the amount of oxygen in the tissue. A large tumor generally has extended areas of necrosis and decreased blood flow. This results in a compromised oxygen supply, which means that less oxidation damage is applied to malignant tissues. At the end of the 1990s, a series of publications changed the standard treatment for locally advanced cervical cancer patients, making concomitant chemo-radiotherapy the primary treatment option because it proved that it provided better results than when radiotherapy was used as the sole modality.

The fundamental idea behind the use of combined treatment is based on the synergistic effect between both modalities: chemotherapy acts as a radio-sensitizing agent that increases the tumor's susceptibility to the effects of radiation. This complicity between both treatments has several mechanisms of action, but it mainly inhibits the repair of sub-lethal damage and synchronizes cells in a particular radio-sensitive phase. Also, the combined use of these treatments makes the effects of radiation less oxygen dependent. The first concomitance studies were performed using hydroxyurea. However, hematological toxicity was considerably high, and a randomized study was therefore carried out that compared the results of treatment with pelvic radiotherapy (at a dose of 50 Gy in conventional fractioning, i.e., 2 Gy) combined with the following three chemotherapy agents: cisplatin, fluorouracil and hydroxyurea or with hydroxyurea alone. In all, 526 patients with stages IIB-IVA were included, and the results demonstrated that in both of the groups in which Cisplatin was administered, there was an improvement in OS and PFS, whereas more toxicity was observed in the group that received all three drugs than in the group that received cisplatin as the only drug. This is the reason why the standard treatment for locally advanced cervical cancer is currently radiotherapy plus cisplatin, with both treatments used concomitantly. ^(8,9)

Surgery

Surgery is still the standard treatment for early stage cervix cancer. ⁽¹⁰⁾ This form of cancer generally implies the need for a radical hysterectomy with a bilateral pelvic lymphadenectomy (BPL). ⁽¹¹⁾ Patients who benefit from this procedure include those bearing tumors smaller than 4 mm that are confined to the cervix. The goal of these procedures is to remove the entire tumor and to establish, based on pathological analysis, whether the patient possesses pathological risk factors that support adjuvant radiotherapy and chemotherapy.

However, surgical treatment is not exempt from complications, which have been reported during the intraoperative period in approximately 2% of cases and during the late postsurgical phase in up to 20% of cases. Over the decades, new minimally invasive methods have been implemented to decrease the appearance of these complications while yielding the same oncological results.

The appropriateness of a surgical procedure to resolve cervical cancer depends on the clinical stage of the disease, the desire to preserve fertility, the clinical condition of the

patient, and resource availability. It is necessary to individualize the extent of the surgical treatment to maximize effectiveness and to minimize the morbidity and, consequently, the patient's quality of life.

In 2009, the International Federation of Gynecology and Obstetrics (FIGO) established a clinical staging system for cancer of the cervix, classifying cervical cancer into early and advanced disease. According to the consensus from the international literature, the term early clinical stage (ECS), denotes invasive carcinoma strictly confined to the cervix with a diameter of less than 4 cm without parametrial affection. The stages IA1, IA2, IB1, and IIA1 (smaller than 4 cm in diameter) are considered ECS.

The treatment of choice for ECS cervical cancer is radical hysterectomy, although the clinical indications are not uniform. This procedure is suitable for up to stage IB1 disease, beyond which radical hysterectomy has not been associated with excellent oncological results.

Currently, optimal surgical management of early stage cervical cancer patients consists of decreasing morbidity without compromising the oncological result. Between 25 and 40% of the patients diagnosed with early stage cervix cancer are of reproductive age or have future pregnancy plans; hence, alternative, less radical treatment options must be considered for these patients.

The treatment should be addressed in a systematic manner according to the size of the tumor and the desire to preserve fertility.

Fertility-Preserving Surgery

Fertility-preserving surgery must be considered only for a highly restricted group of patients who satisfy not only oncological criteria but also a set of prenatal and perinatal criteria.

Microinvasive disease, or stage IA1 disease without lymphovascular permeation (LVP), has an incidence of lymphatic metastasis below 1%; thus, cervical conization is the standard treatment in stage IA1 cervical cancer patients with reproductive wishes. Management of stage IA1 disease with LVP is controversial; the recommendation in most publications is cervical conization with BPL and assessment of the sentinel ganglion.

Patients with stage IA2 or IB1 cervical cancer with a tumor size of less than 2 cm and a favorable histological lineage (epidermoid, adenocarcinoma, or adenosquamous) can be

candidates to conservative surgery. Radical trachelectomy with BCL via laparoscopy or via open surgery with or without sentinel pelvic lymph node in cervical cancer is a treatment option. Wethington *et al.* reported in a systematic review that the pregnancy rate of patients treated with radical trachelectomy through the abdomen was 52%.

Non-Fertility-Preserving Surgery

In women without surgical, technical or medical contraindications and without a desire to preserve fertility, extrafascial, or type A, hysterectomy is the standard treatment for stage IA1 cervical cancer without LVP. In patients with stage IA1 with LPV or stage IA2 disease, radical hysterectomy with BPL, or type B hysterectomy, is the standard treatment option; para-aortic lymphadenectomy (PAL) should also be considered in patients who are suspected to have ganglionic disease in the para-aortic lymph nodes.

In patients with stage IB1 disease or with stage IIA1 disease without contraindications, radical hysterectomy with BPL with or without PAL, or type C hysterectomy, is the first treatment option.

In young women, it is convenient to preserve the ovaries whenever possible. Radiotherapy shows similar outcome rates to surgery; however, surgical treatment is preferred for young women, given its associated benefits for quality of life, such as the preservation of ovary function, vaginal integrity, and increased lubrication and vaginal elasticity compared to radiotherapy.

Principles of the Surgical Technique

In 1912, Wertheim was the first to popularize the radical hysterectomy technique; after the description of more than 500 cases, associated with a 10% mortality rate, this technique has evolved.

Subsequently, at Harvard Medical School, Meigs modified the radical hysterectomy technique by including complete parametrial excision via BPL. Then, in 1974, Piver, Rutledge and Smith produced the first hysterectomy classification system. (**Table 42-3**) In 2008, Querleu and Morrow proposed a new classification system that includes a description of the specific anatomic limits and margins of surgical resection. (**Table 42-4**) The resection limits are factors that influence the patient's quality of life.

Table 42-3. Piver-Rutledge-Smith Classification of Radical Hysterectomy

Subtotal / Supracervical The uterus is removed. The superior portion of the cervix is amputated, and the remnant of the cervix is conserved. The uterosacral ligaments are conserved.
Class I Extrafascial hysterectomy. The fascia of the cervix and the inferior segment of the uterus are removed.
Class II Modified radical hysterectomy. The uterine artery is ligated where it bridges over the ureter, and the cardinal and uterosacral ligaments are cut in half at their insertion to the pelvic wall and the sacrum, respectively. One third of the vagina is cut.
Class III Radical hysterectomy. The uterine artery is ligated at its origin to the superior vesical artery or to the iliac artery. The cardinal and uterosacral ligaments are cut at the pelvic and sacral walls. The superior third of the vagina is resected.
Class IV Radical hysterectomy. The ureter is completely dissected from the vesicouterine ligament, the superior vesical artery is sacrificed, and three fourths of the vagina is resected.
Class V Radical hysterectomy. In addition to the above, a portion of the bladder or the distal ureter is resected, followed by the reimplantation of the ureter to the bladder.

Table 42-4. Radical Hysterectomy Classification System of Querleu and Morrow (2008)

TYPE A: Extrafascial hysterectomy or minimal paracervix resection. The extent of paracervix resection is medial to the ureter but lateral to the cervix, and the uterosacral and vesicouterine ligaments are not resected. The vaginal resection is minimal, and trachelectomy is not performed. This technique includes palpation and observation, but not mobilization, of the uterus.
TYPE B: Radical modified hysterectomy or paracervix resection at the level of the ureter. B1: The paracervix is resected at the level of the ureteral tunnel, the uterosacral and vesicouterine ligaments are partially resected, and the neurological component of the paracervix (caudal to the deep uterine vein) is not resected. At least 10 mm of vagina from the cervix to the tumor is removed. A dissection is performed, and the ureter is lateralized without being mobilized. B2: The lateral paracervical ganglia are dissected in addition to the procedures described for B1. The edge between the paracervical and parietal ganglia (iliac and obturator lymph nodes) is defined by the obturator nerve. *Using this technique, the uterine artery is preserved.
TYPE C: Radical hysterectomy or paracervical resection at the junction with the vascular iliac system. The cardinal ligaments are resected from the pelvic wall and the uterosacral ligament is resected at the level of the rectum, including a section of the vesicouterine ureter is completely mobilized. C1: With preservation of the autonomous nerves. C2: Without preservation of the autonomous nerves.
TYPE D: Laterally extending resection D1: The parametrium is resected from the pelvic wall with mobilization of the iliac vessels and with exposition of the sciatic nerve roots. D2: The parametrium is resected from the pelvic wall together with hypogastric vessels, muscular structures, and adjacent fascia. The ureter is completely mobilized.

The first and most important surgical principle to be considered before radical pelvic surgery is an exhaustive understanding of pelvic anatomy. This understanding will decrease the incidence of lesions during the procedure, for example, perioperative lesions of the hypogastric nerves during the resection of the dorsal portion of the paracervix, or damage to vessels important for the anatomical variants.

Radical hysterectomy includes removal of the uterus as a block together with the parametrium (cardinal and uterosacral ligaments) and one third or one half of the vagina.

Since 1974, according to the Piver-Rutledge-Smith description, through 2007, according to the new criteria presented by Hidekazu Okabayashi, up to the 2008 Querleu-Morrow classification, strict anatomical definitions concerning the preservation of autonomous nerves, fertility preservation, and lateral extension are applied to the performance of open, laparoscopic and robotic techniques. The new classification approaches aim to unify traditional concepts and maintain a 3D view of the uterus, the anatomical retroperitoneum, sympathetic innervation and the parasympathetic female pelvis.

The second surgical principle is radical resection of the parametrium: a decisive parameter for the evaluation of the type of radical hysterectomy. The extent of resection must be defined according to three areas of the parametrium (ventral, dorsal, and lateral) and in 3 axes (sagittal, frontal, and transverse). These points are described in the Querleu and Morrow classification system, which system described by Piver does not distinguish between type II and type III hysterectomy. The main difference lies in the reduction in resection of the vesicouterine ligament, below the ureter, and the dissection in the lateral area of the parametrium. Another difference between these forms of hysterectomy is the performance of uterine artery ligation and pelvic lymphadenectomy.

Each step of the procedure must be carefully specified and must have a preoperative and trans-surgical plan for the surgery to succeed. The following must be described:

- The anatomical limits of pelvic ganglionar dissection and the number of lymphatic ganglia dissected. Any suspicious ganglion must be sent for trans-surgical pathological analysis. ⁽¹¹⁾
- Additional procedures to be performed (bilateral salpingo-oophorectomy or ovarian transposition).
- Type of parametrectomy (B, C1, C2).
- Length of vaginal resection.

Surgical Complications

Given the anatomic location, the main complications presenting after radical surgery for cervix cancer are those related to nearby structures, such as the bladder, rectum, ureter, and important pelvic vessels.

The main and most documented morbidity involves the urinary tract. Urodynamic changes have been reported after radical hysterectomy; these changes include detrusor muscle hypoactivity, decreased bladder sensation and reduced filling capacity. This morbidity has been reported in 75%-85% of patients receiving a type III or C2 hysterectomy. Spontaneous recovery of bladder function is expected within 6 to 12 months after the surgery. Discomfort, frequently including urgency, urinary incontinence, and bladder emptying difficulties, is reported 6 to 12 months after the procedure in 30% of patients. Severe bladder dysfunction has been reported in more than 16% of patients. Urinary incontinence is one major complication after radical surgery for cervix cancer. This complication has been observed in 48% to 53% of women at 6 weeks after the surgical intervention, gradually declining to 30% of patients at 3 months after the surgery. Chuang *et al.* described detrusor hypoactivity in 85.7% of patients, detrusor hyperactivity in 10.2% and normal function in 4.1% based on follow-up over a period of 6 months to 30 years after the initial treatment.

The presence of a vesicovaginal or ureterovaginal fistula after a radical hysterectomy has been reported in 0.9% to 2.7% of patients. In these cases, the fistula is primarily located in the anterior wall of the vagina. Risk factors of vesical damage, such as hemorrhage, obesity, diabetes, and post-surgical infection, must be considered.

A series of 361 women surgically treated with radical surgery (285 radical hysterectomy, 42 vaginal radical hysterectomy, 30 laparoscopy-assisted radical vaginal hysterectomy, and 4 abdominal radical trachelectomy) revealed intra-operative complications in 6% of the women, transfusion-related complications in 9%, and post-surgical infections in 4%.

The extent of anatomic nerve lesions during a radical hysterectomy or trachelectomy plays a crucial role in long-term anorectal dysfunction, such as diarrhea, constipation, fecal incontinence, and flatulence; these complications occur after an extensive dorsal parametrial resection or an extensive colpectomy and are less common, although they can impact a patient's quality of life.

Table 42-5. Post-surgical complications Grade III

Reference	N	Urinals ¹ N (%)	Lymphovascular ² N (%)	Gastrointestinal ³ N (%)	Others ⁴ N (%)
F. Fanfani et al. / EJSO 42 (2016) 1519e1525	73	7 (9.58)	1 (1.42)	1 (1.42)	7 (9.58)
Ferrandina. Ann Surg Oncol (2014) 21:1692–1699	362	10 (2.8)	9 (2.5)	4 (1.1)	1 (0.27)
Cetina. World J SurgOncol. 2009 Feb 16;7:19	40	4 (10)	3 (7.5)	1 (2.5)	1 (2.5)
Cetina. Ann Oncol. 2013 Aug;24(8):2043-7.	86	2 (2.3)	3 (3.4)	Not shown	1 (1.5)
1. Bladder dysfunction, urinary infections, fistulas, stenosis or urinary tract injury 2. Limphocele, vascular lesions, pelvic hemorrhage 3. Intestinal perforation, fistulas, 4. Lesions of the obturator or genito-femoral nerves, Deep vein thrombosis and pulmonary thromboembolism.					

Cibula *et al.* reported significant differences between autonomous nerve-preserving and non-preserving procedures with respect to defecation changes at 6 months after the procedure.

Sexual dysfunction often has psychological and functional causes, and anatomic changes play a role in this complication. The current literature is controversial; in women with greater sexual activity, receptivity owing to good vaginal lubrication is achieved when the autonomous nerves are preserved. In addition to bleeding, potential peri- and post-surgical morbidities include the formation of ganglionar dissection-related lymphoceles and lymphedema. Lymphoceles are typically incidentally found; they only rarely cause ureteral hydronephrosis or pelvic pain. The incidence of lymphedema has not been specifically studied because of its low incidence after pelvic lymphadenectomy. (**Table 42-5**)

Minimally Invasive Approaches

Minimally invasive approaches, such as laparoscopy and robot-assisted surgery, have become more popular over recent decades. These approaches are considered to provide benefits to patients receiving bilateral pelvic lymphadenectomy and bilateral pelvic lymphadenectomy to treat cervical cancer without affecting oncological results. No differences

in pathological results have been reported between minimally invasive and open surgical approaches.

When comparing laparoscopy with open surgery, no difference was found in the size of parametrial resection (1.9 cm versus 1.7 cm, $p=0.55$), the percentage of patients with negative borders (96% versus 91%, $p=0.33$), the percentage of patients with ganglionar metastasis (26% versus 14%, $p=0.191$), the 5-year survival rate (92.4% versus 93.6%, $p=0.29$), or the recurrence rate.

The main differences observed for laparoscopy compared to open surgery are a smaller amount of bleeding (55 ml versus 145 ml; $p<0.01$) and reduced hospitalization time (4 days versus 7 days, $p<0.01$), although at the expense of longer surgeries (196 minutes versus 152 minutes, $p<0.01$). Furthermore, the complication rates of these two procedure types are similar.

Notably, certain patient groups exhibit better results when treated with a minimally invasive approach. According to Park, the laparoscopic approach has a lower complication rate in obese, elderly women, without sacrificing the oncologic results. Finally, the laparoscopic approach requires formal training and a learning curve of at least 40 procedures to attain a reduction in surgical time (from 307.7 minutes to 266.3 minutes, $p=0.022$) or in the complication rate (from 25.7% to 2.9%, $p=0.013$).

Systemic Treatment of Cervical Cancer

The systemic management of patients with cervical cancer poses considerable challenges in patients with **A)** advanced disease in concomitant use with radiotherapy, and **B)** with metastatic disease.

1. For well-functioning patients with locally advanced cervical cancer, platinum-based schemes with single-agent radiosensitizers are proposed. The use of doublet therapies, including chemotherapy and molecular targeted therapy, must be further explored.
2. Hysterectomy is an alternative to brachytherapy after chemoradiotherapy in health centers where brachytherapy is unavailable. The two most important factors to consider are the skills of the oncology surgeon and the time between the end of combination therapy and surgery, which must not exceed 6 weeks. ⁽¹²⁾
3. The implementation of concurrent chemoradiotherapy as the standard treatment for locally advanced cancer has decreased the risk of recurrence. ⁽¹³⁾
4. Neoadjuvant or adjuvant chemotherapy has not been proven superior to radiotherapy alone.
5. In metastatic or recurrent disease, combinations of chemotherapy and molecular targeted therapy have the most potential; the combination of bevacizumab an anti-angiogenic agent, plus chemotherapy offers the greatest increase in overall survival to date. However, there are numerous opportunities for drug discovery in cervical cancer therapeutics, i.e., Immunotherapy (pembrolizumab).
6. In general, the rarer histological types are treated in the same way as the predominant lineages (epidermoid and adenocarcinoma) because cases of the other histological types are infrequent. Although some lineages have been proposed to exhibit more aggressive biological behavior, there are not enough clinical studies to support changes in their management recommendations. As general rule, the rarer histological types require a multimodal approach, and it is acceptable for clinicians to adjust the systemic management of these cervical cancer subtypes depending on the patient's situation. Nonetheless, currently, there are no strict guidelines for each variant.
7. In patients that are candidates to receive systemic therapy, it must be known: the clinical stage, proper function renal, hepatic, medullar and pulmonary. Possible risks and benefits, morbidity and mortality.

In advanced disease (metastatic or recurrent) chemotherapy is used in those patients previously treated with surgery, radiotherapy or chemotherapy with pelvic recurrence and not susceptible to resection or radiotherapy, with distant metastases or both. Cis-platinum and its derivatives are considered as the most active drugs. As a single agent and alone it can reach up to 23% of objective response. For ifofosfamide, doxorubicine, 5-FU, taxanes, topotecan or gemcitabine, has an objective response from 11% to 19%.

Adjuvant chemotherapy is not a conventional practice, it improves the expectations of control over the possibility of developing distant metastases, but there are reports that with adjuvant chemotherapy alone in patients with nodal metastases, with or without involvement of the parametria, survival and the five-year recurrence free-period can be 76.1% and 73.6%, respectively.

With concurrent chemoradiotherapy, the results have shown the benefit on overall survival and progression free survival. With this treatment modality, global survival and progression free survival, currently it is the standard treatment. ⁽¹³⁾

Comprehensive Management and Palliative Care

In advanced cervical cancer, multidisciplinary treatment is essential. Is necessary to work to ensure that women with cervical cancer regardless of their economic situation receive the relevant antineoplastic treatment according to the stage of their disease. This strategy has made possible a better survival in patients with advanced disease, however, complications from the disease and treatments significantly deteriorate the quality of life of patients, so it is important to provide supportive and palliative care throughout the disease. ⁽¹⁴⁾

Palliative care offers a comprehensive and multidisciplinary approach to provide prevention and relief of pain, suffering and other physical, psychosocial and spiritual problems associated with chronic, incurable, diseases. Improving the quality of life of the patients and their families.

In palliative care, a philosophy that affirms life and considers death as a natural process, without pretending to influence the moment of its presentation, support systems are offered for patients so they can live as actively as possible until the time of death, and for families to cope with the patient's illness and also their own grieving. This definition assumes that palliative care can be provided throughout the disease and not only at the end of life, the modern perspective in the practice of oncology is to integrate the palliative care philosophy.

Table Recommendations of the SGO for Delivering Palliative Care

1. Express sensitivity to cultural differences and deliver palliative care with compassion, empathy, and respect for a woman as an individual.
2. Establish open communication with women and their families providing the information necessary to understand their condition, prognosis, and treatment options.
3. Alleviate pain and distressing symptoms, whether physical or emotional, maintaining hope and leading to an improvement in the woman's quality of life
4. Recognize that a multidisciplinary approach using the services of professional trained in psychological, social, and spiritual issues optimizes care and wellbeing.
5. Respect a woman's decision regarding acceptance or refusal of further treatment.
6. Recognize the practitioner's responsibility to fully inform women of treatments unlikely to achieve benefit or do harm.
7. Encourage women and families to consider hospice care as an option when appropriate.
8. Understand and support the woman's preferences regarding end of life care.
9. Maintain continuity of care for terminally ill women, avoiding feelings of isolation and abandonment for the woman and her family.
10. Acknowledge the effect that end-of-life care has on the family and provide emotional support including access to social and bereavement services.
11. Recognize that although providing palliative care is emotionally rewarding it is crucial to acknowledge the potential for compassion fatigue and the need to support each other including members of the multidisciplinary team to remain fully engaged.

According to the Worldwide Palliative Care Alliance (WPCA), in the world more than six million people with cancer require palliative care, mostly adults over 60 years old living in low-middle income countries. This number is expected to continue increasing.

Currently there are different models of care, starting these in the last 6 months of life; providing care in the last days of life; incorporate palliative care and support throughout the disease according to the needs of the patient. Experience invites us to recommend comprehensive management and palliative care from the moment of diagnosis until the end of life. ⁽¹⁵⁾

Women with cervical cancer often have lifelong history of economic, social and psychological distress, that with the physical suffering that the disease represents, have important impact in their quality of life. ^(16,17)

For this group, the implementation of a patient and family centered care that anticipate, prevents and treat suffering may have an important impact in their quality of life, and these are the goals of the palliative care (PC) approach. ⁽¹⁸⁾

The American Society of Clinical Oncology (ASCO) has released evidence-based recommendations regarding the incorporation of palliative care into standard gynecologic oncology care. ⁽¹⁹⁾

The Society of Gynecologic Oncology (SGO) echoes these recommendations and states that the delivery of palliative care is essential in delivering quality care to women with gynecologic cancer and has established 11 Principles of Palliative Care. ⁽²⁰⁾ **(Table 42-6)**

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SECTION X
Colorectal and Anus
Cancer

Chapter 43

Adenocarcinoma of the Colon

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Background and Molecular Basis of Colon Cancer

Colorectal cancer is the second leading cause of cancer deaths in the United States. It is the third most common cancer diagnosed in both men and women in the United States. The American Cancer Society estimates that approximately 101,000 new cases of colon cancer will be diagnosed in 2019. ⁽¹⁾

Traditionally, colon cancer was believed to arise through the adenoma to carcinoma sequence. This sequence describes a pathway from polyp to invasive cancer, along which various genetic mutations are acquired leading to malignant transformation with metastatic potential. Some of the key genes involved in this pathway include APC, KRAS, and TP53. ⁽²⁾ The adenomatous polyposis coli (APC) gene is a tumor suppressor gene and is believed to be a key gene in the initial polyp development. Loss of APC function leads to aberrant cell signaling, proliferation and cell adhesion. KRAS is an oncogene, with mutations leading to uncontrolled cell growth. Lastly, TP53 is a gene which encodes p53, which is a tumor suppressor involved in the cell cycle and genomic stability.

Further research into the genetic and molecular basis of colorectal cancer has led to the recognition of two more pathways leading to colon cancer. The traditional adenoma to carcinoma sequence arising from chromosomal instability is believed to represent approximately 75% of all colorectal cancers, mostly arising in the left colon and developing later in life. ⁽³⁾ These two other pathways include microsatellite instability and hyper-methylation.

Microsatellite instability arises from faulty mismatch repair genes. Microsatellite instability specifically refers to areas of repetitive DNA sequences which are more prone to copy

errors. When a patient has a mutation in one of the mismatch repair genes, these microsatellite regions become unstable in length making these mutations identifiable by PCR. Some of the genes credited with mismatch repair include MLH1, MSH2, MSH6 and PMS2. If a cell develops mutations in both alleles of one of these genes, mismatch repair function will be altered, and various tumor suppressor genes known to have repetitive sequences become prone to mismatch errors leading to a rapid accumulation of mutations and progression to malignancy. Microsatellite instability is believed to account for about 10-15% of all colorectal cancers. ⁽³⁾

The third pathway recognized for development of colorectal cancer is due to hypermethylation of DNA promoter regions. Hypermethylation of these promoter regions can block transcription of several tumor suppressor genes, leading to a serrated polyp which can acquire further mutations until a malignant tumor develops. ⁽⁴⁾ Given the rise of serrated polyps in this pathway, it is also referred to as the serrated polyposis pathway. This pathway is believed to account for 5-10% of all colorectal cancers.

Hereditary Cancer Syndromes

Lastly, germline mutations in many of the already mentioned genes can lead to recognized hereditary colorectal cancer syndromes. Hereditary colorectal cancer accounts for only 5-10% of all colorectal cancers but recognizing a significant family history of cancer and having a high suspicion for these hereditary syndromes can have an impact on future generations for screening and overall survival. The hereditary syndromes can be divided into two basic types, polyposis and nonpolyposis syndromes. Within the polyposis syndromes,

various polyps can arise, including adenomatous polyps, hamartomatous polyps and the previously noted serrated polyps.

Mutations in the APC gene lead to one of the better-known adenomatous polyposis syndromes, Familial Adenomatous Polyposis syndrome (FAP). This syndrome has variable penetrance depending on location of the mutation in the APC gene. Patients can have fewer than 100 adenomas which is considered an attenuated phenotype, compared to a severe phenotype which presents with thousands of adenomas. Nearly 100% of patients with FAP will develop colorectal cancer in their lifetime if left untreated. ⁽⁵⁾ Furthermore, because the mutation in the APC gene is a germline mutation, patients are prone to multiple other extracolonic tumors including desmoid tumors, gastroduodenal adenomas and carcinomas, osteomas and papillary thyroid carcinoma.

Juvenile polyposis syndrome, Puetz-Jegher syndrome and Cowden syndrome are all examples of hamartomatous polyposis syndromes. These result from mutations in SMAD4, STK11, and PTEN respectively. ⁽⁶⁾ Lastly, the serrated polyposis syndrome is a recognized entity, but the underlying genetic factors have not yet been clearly identified.

The Hereditary Non-Polyposis Colorectal Cancer (HNPCC) syndrome was previously frequently referred to as Lynch syndrome. Patients will often have a strong family history of colorectal cancer but can also have a familial history of other cancers such as ovarian, endometrial, gastric and pancreatic cancer, frequently presenting at a relatively young age. Tumors will show a pattern of microsatellite instability, consistent with germline mutations in one of the 4 mismatch repair genes discussed previously, MLH1, MSH2, MSH6 and PMS2. ⁽⁷⁾ Immunohistochemistry performed on tumor cells will show under-expression of the proteins associated with these genes depending on which gene is mutated, and germline testing should be performed to exclude a sporadic mutation. If MLH1 is found to be underexpressed, hypermethylation should be assessed, and if present, a mutation in BRAF should be excluded before proceeding to germline testing, as hypermethylation is a frequent cause of MLH1 loss in sporadic cancers. ⁽⁸⁾

Diagnosis and Staging

A diagnosis of colon cancer is confirmed based on endoscopic findings and pathologic confirmation of invasive adenocarcinoma on pathology. Suspicion of colon cancer can be raised by various signs and symptoms such as

anemia, lower GI bleed, obstructive symptoms, or colonic thickening on a Computed Tomography (CT) scan, but at least 30% of patients will be asymptomatic at the time of diagnosis. ⁽⁹⁾

After diagnosis patients should undergo thorough preoperative staging beginning with a history and physical examination. The history should focus on any symptoms including bleeding, decreased appetite or obstructive symptoms, as well as a thorough family history to identify any patients with a strong history of cancer that may be at risk for inherited colon cancer syndromes. Lastly the history should include any significant medical problems that may affect a patient's ability to tolerate surgery in case of a resectable colon cancer. The physical exam, specifically focusing on the abdomen should assess any pain, distention, or hepatomegaly, lymphadenopathy, and if the tumor itself can be palpated if it is particularly large. The pathology should be reviewed to confirm invasive cancer and if any mismatch repair testing was performed. ⁽¹⁰⁾

Lastly, the colonoscopy report should be reviewed to confirm that the colonoscopy was complete to the cecum. There is approximately a 5% chance of synchronous cancers, so a complete colonoscopy is important for surgical planning. ⁽¹¹⁾ Any polyps that were not resected at the time of diagnosis can be endoscopically treated prior to surgery if they will not be included in the planned resection. Anatomic landmarks and the length of the scope can be unreliable when determining the exact location of a primary tumor, so it is important to know if the tumor was tattooed at the time of colonoscopy to ease intraoperative identification. This step is particularly important in the case of small tumors that may be difficult to palpate or cancers that were found in a polypectomy specimen. ⁽¹²⁾ If the colonoscopy could not be completed due to a distal obstructing tumor, the proximal colon can potentially be cleared using a contrast enema or CT colonography. If the tumor is completely obstructing it may be possible to intraoperatively evaluate the colon using on-table colonic lavage and colonoscopy or alternatively completing a colonoscopy after the patient has recovered from surgery.

Routine labs should be sent as well as a serum carcinoembryonic antigen (CEA) level. Elevated CEA levels greater than 5 ng/ml confer a worse prognosis stage for stage, although the CEA may be elevated without any distant disease at time of diagnosis. ⁽¹³⁾ Furthermore, it should return to normal after surgical resection and a persistently elevated CEA may indicate the presence of persistent disease. If the CEA does return to normal after surgery, yearly testing of CEA levels can then be used

during surveillance to prompt further workup for detection of metastatic disease.

To complete the staging, the patient should undergo a CT scan of the chest, abdomen and pelvis with oral and intravenous contrast if there is no history of contrast allergy.⁽¹⁴⁾ The CT will assess for metastases, as well as identify any local findings that may complicate resection of the tumor such as hydronephrosis due to ureteral involvement, direct extension of tumor to the abdominal wall or psoas muscle, or involvement of adjacent loops of bowel requiring *en bloc* resection. **Figure 43-1** demonstrates a tumor at the hepatic flexure that is possibly invading the duodenum and the head of the pancreas. Given these findings, the patient was counseled on the potential need for *en bloc* resection, possibly requiring a pancreaticoduodenectomy and a hepatobiliary surgeon was available at the time of the surgery. The tumor was in fact invading the pancreas and an *en bloc* resection revealed a T4 N0 tumor with negative margins on pathology. This case demonstrates how critical the imaging is in planning a successful operation.

Positron emission tomography-computed tomography (PET-CT) has almost no role in the initial staging process for colon cancer. It can be useful as an adjunct to initial CT imaging if metastatic disease is found to assess extent of metastases and resectability.⁽¹⁵⁾ Magnetic Resonance Imaging (MRI) also should not be used in the initial staging of colon cancer but has been shown to be useful in assessing small liver lesions that may be suspicious on CT scan as well as identifying additional liver metastases that may be missed by CT but are more easily identified with MRI.



Figure 43-1. Axial image from a staging CT scan of the abdomen and pelvis demonstrating concern for direct involvement of the duodenum and pancreas by hepatic flexure tumor.

Surgical Anatomy of the Colon

Before discussing the surgical approach to colon cancer, it is important to understand the anatomy of the colon. The colon is attached to the lateral borders of the abdomen on the left and right by peritoneal attachments. These attachments are often referred to as the white line of Toldt. Posteriorly, the ascending colon, descending colon and the colonic mesentery are attached to the retroperitoneum and can be separated from the retroperitoneum with careful dissection in this avascular plane. The transverse colon hangs from the two flexures in the middle of the abdomen, with the greater omentum of the stomach fused to its surface. Dissecting the omentum free of the transverse colon allows entrance into a space commonly referred to as the lesser sac. After the descending colon is the sigmoid colon which is highly variable in length and position. It's attachment to the pelvic sidewall is quite variable, sometimes closely adherent, and other times relatively detached hanging from the sigmoid mesentery prior to its transition to the rectum in the pelvis. The end of the colon and its transition to the rectum in the pelvis can be recognized as the epiploic appendages do not exist on the rectum and the tenia coli splay out so they are no longer separately identifiable bands.

The blood supply to the colon comes from two main sources. The first source are branches from the superior mesenteric artery, while the second is the inferior mesenteric artery and its subsequent branches. These two blood supplies separate the colon into its embryologic origins with the proximal colon originating from the midgut and therefore supplied by the SMA, while the colon distal to the splenic flexure comes from the hindgut and is therefore supplied by the inferior mesenteric artery. The branches of the Superior Mesenteric Artery (SMA) to the colon most commonly recognized include the ileocolic artery which supplies the terminal ileum, cecum and ascending colon and the middle colic artery which supplies the transverse colon. The blood supply can be highly variable with a right colic artery sometimes arising from the ileocolic artery, while at other times it can come directly from the SMA or not exist at all. The middle colic artery most commonly branches into a right and left branch which lead toward the hepatic and splenic flexure respectively. The Inferior Mesenteric Artery (IMA) takes off lower from the aorta than its superior counterpart and supplies the descending and sigmoid colon with the left colic artery supplying the descending while several smaller sigmoid branches supply the sigmoid colon. The distal most aspect of the IMA continues toward the rectum and is commonly referred to as the superior rectal artery. An important collateral between these arteries is

commonly referred to as the marginal artery which runs in close proximity to the mesenteric border of the colon. The anatomy of the marginal artery is highly variable and is frequently absent at the transition of the splenic flexure making this a recognized watershed area at risk for ischemia.

The venous drainage of the colon consists of the superior mesenteric vein and inferior mesenteric vein and generally follows back along the route of the arteries. The Superior Mesenteric Vein (SMV) is usually in close proximity to the SMA while the Inferior Mesenteric Vein (IMV) travels somewhat separate from the IMA as it has to ascend higher into the abdomen. The IMV joins the splenic vein after passing posterior to the pancreas prior to meeting the SMV to create the confluence of the portal vein.

Lastly, the colon has a vast network of lymphatic drainage with tiers of lymph nodes which also travel along the route of the arteries. The lymph nodes can be split into anatomic levels as they travel back along the arteries. The epiploic and paracolic nodes are in closest proximity to the colon wall, while intermediate nodes exist at the level of the various arterial branches. Lastly the main nodes lie in proximity to the SMA and proximal IMA. The lymph nodes are an important consideration when discussing the surgical management of colon cancer as well as colon cancer staging.

Surgical Management of Colon Cancer

There are many surgical approaches to the management of colon cancer. This chapter will give a brief overview of the approaches while highlighting key concepts in surgical technique. When considering the resection of a colon cancer, it is important to discuss the extent of resection and the management of the mesocolon and associated feeding vessels. Colonic tumors mostly grow in a circumferential manner around the colon wall but can have some longitudinal extension along the colon, therefore it is important to have a minimum of 5cm margin free of tumor to decrease the risk for recurrence at the subsequent anastomosis. A greater than 5 cm margin will also ensure that paracolic lymph nodes that may harbor lymph node metastases will be included in the resected specimen. ⁽¹⁶⁾ In Japan, the minimum resection margin is considered to be 10 cm to further ensure the inclusion of these lymph nodes. The surgical concept of total mesorectal excision originally reported by Professor Richard (Bill) Heald can also be applied to the resection of colon cancers. Similar to the dissection of the rectum along embryologic planes to ensure complete removal of tumor and lymph nodes, the colon and its associated mesentery

can be dissected from the retroperitoneum in an avascular plane. This allows for the intact removal of the primary tumor and lymph nodes traveling along the vasculature. The colonic mesentery should be intact after dissection so that no lymph node deposits are left in the abdomen risking future local recurrence. Lastly, the feeding vessels to the tumor should be ligated centrally at the start of the feeding vessel. For example, during a right colectomy, the ileocolic vessel should be ligated at the takeoff from the SMA, while in a sigmoid colectomy the IMA should be ligated at the level of the aorta. This high ligation, similar to maintaining an intact mesocolon, increases the chances of resecting any metastatic lymph nodes that may exist along the vessel. Hohenberger *et al.* initially described these concepts as the complete mesocolic excision and reported their outcomes for 1329 patients. They showed improvement in 5-year local recurrence rates from 6.5 to 3.6% and improved 5-year survival from 82.1% to 89.1% when comparing patients operated using the technique of Complete Mesocolic Excision (CME) to those who underwent standard excision prior to the adoption of these techniques. ⁽¹⁷⁾ There still remains controversy regarding the exact extent of resection and the extent of lymphadenectomy that should be performed, weighing the oncologic benefits against the potential risks of more technically challenging resections. Multiple ongoing trials are attempting to address some of these questions, but these key concepts should still be considered and generally adhered to during surgery until further data clarify these matters.

When considering what surgery should be performed to treat a newly diagnosed colon cancer, it is dependent on the location of the tumor in the colon. The specific types of resection that can be performed include a right hemicolectomy, extended right hemicolectomy, left hemicolectomy, extended left hemicolectomy, and in certain situations a subtotal colectomy or total abdominal colectomy with an ileorectal anastomosis. A right hemicolectomy is an appropriate resection for any tumor from the cecum to proximal transverse colon and will include the ileocolic artery and right branch of the middle colic vessels. An extended right hemicolectomy will treat tumors from the cecum to approximately distal 2/3 of the transverse colon and would again include the ileocolic vessels as well as high ligation of the common branch of the middle colic artery. **Figure 43-2** provides examples of the extent of resection for a right hemicolectomy and extended right hemicolectomy. **Figure 43-3** demonstrates a right hemicolectomy for an ascending colon mass after ligation of the vessels and division of the mesentery, as well as the subsequent side to side ileocolic anastomosis. A left hemicolectomy is

appropriate for tumors from the distal transverse colon to the sigmoid colon and will include the IMA as well as the left branch of the middle colic artery. An extended left will cover the same tumors as a left hemicolectomy except it will include tumors more proximal in the transverse colon and instead of taking the left branch of the middle colic, the middle colic will be ligated at the main branch.

The two main approaches to surgery can be divided into open and minimally invasive techniques. When choosing the ideal approach to colon cancer it is important to consider the patient's surgical history, the size of tumor including

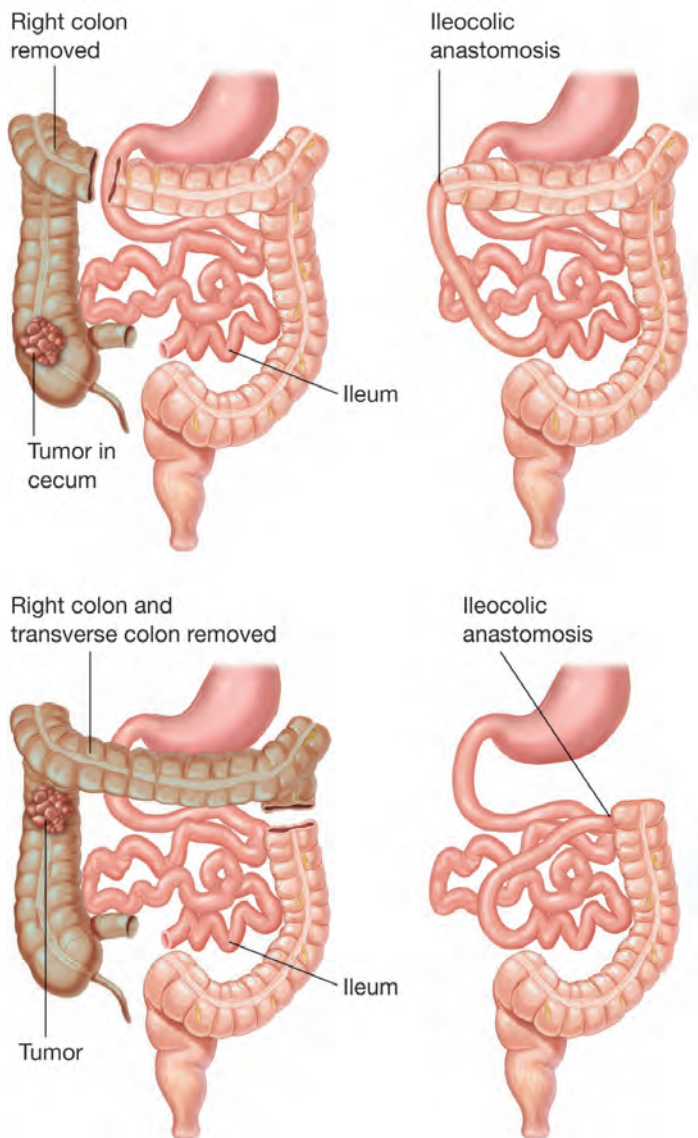


Figure 43-2. Examples of the extent of resection for a right hemicolectomy and extended right hemicolectomy. Figure reused with permission © Wolters Kluwer. ⁽²²⁾

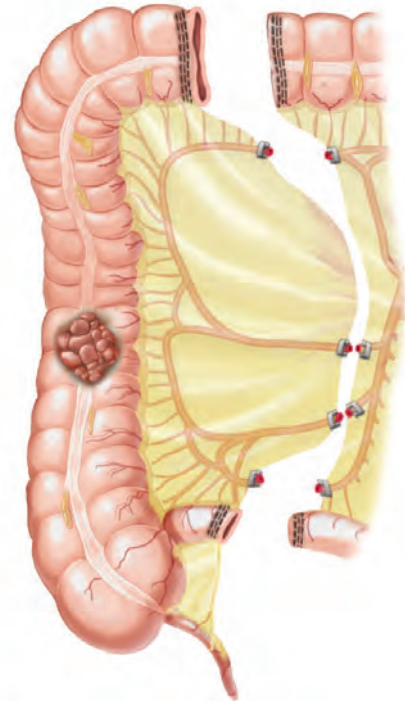


Figure 43-3. A right hemicolectomy for an ascending colon mass after ligation of the vessels and division of the mesentery, as well as the subsequent side to side ileocolic anastomosis. A left hemicolectomy is appropriate for tumors from the distal transverse colon to the sigmoid colon and will include the IMA as well as the left branch of the middle colic artery. An extended left will cover the same tumors as a left hemicolectomy except it will include tumors more proximal in the transverse colon and instead of taking the left branch of the middle colic, the middle colic will be ligated at the main branch.

Figure with permission © Wolters Kluwer. ⁽²²⁾

any local invasion which will dictate the extent of resection, and lastly the surgeon's own expertise and comfort with each approach. If the patient has an extensive history of prior abdominal surgeries, a laparoscopic approach may not be feasible due to intra-abdominal adhesions. Similarly, if the tumor is particularly large, or appears to be adherent to adjacent structures requiring an extended *en bloc* resection, a minimally invasive approach may not be feasible or oncologically sound, risking tumor perforation when manipulating the tumor or inadvertently separating the tumor from structures directly invaded by the primary tumor that should be resected *en bloc*. Assuming the tumor is relatively small, and any approach is feasible, then it is

important to consider the surgeon's own experience and comfort and they should choose the operative technique which allows them to complete the surgery safely with good technique following accepted principles.

When laparoscopy was initially introduced for colectomy for colon cancer, there were reports of port site recurrences. Ultimately, multiple trials have shown no differences in oncologic outcomes when comparing minimally invasive to open approaches. Subsequently there have been reports and video presentations of various approaches to minimally invasive surgery for colon cancer. These modalities include hand-assisted surgery, laparoscopy, single port laparoscopy and robotic surgery, as well as various methods of making an anastomosis and extracting the specimen. These approaches are too numerous to discuss all of them in one chapter, but a brief overview of the concepts will be discussed here.

Open surgery can be performed through a midline, paramedian or oblique incision. Some surgeons prefer to avoid the midline incision to decrease future risk of incisional hernia while a midline incision is a somewhat more versatile incision allowing the surgeon to operate easily in any quadrant of the abdomen. Once the abdomen is entered, the entire abdominal cavity should be inspected to exclude metastatic disease. A wound protector should be placed in the incision to protect against tumor seeding the incision, as well as decrease the risk of surgical site infections. Most often the colon is then mobilized from the lateral wall of the abdomen by incising the white line of Toldt, and subsequently dissecting the colon and its mesentery away from the retroperitoneum. The ureter should be identified during this process to make sure it is left down with the retroperitoneum.

If a right hemicolectomy is being performed, the right colon will be mobilized toward the midline revealing the duodenum which should also be dissected free of the mesocolon and left in the retroperitoneum. The hepatic flexure is incised, the omentum is divided, and the lesser sac is entered to complete the mobilization of the colon. The vessels can be ligated centrally; for a right hemicolectomy the ileocolic vessel is ligated just distal to the takeoff from the SMA. The mesentery can be divided with modern energy devices or can be divided between clamps and ligated with surgical ties. The right branch of the middle colic will similarly be isolated just distal to its branch from the main middle colic vessel and ligated in a similar fashion. The transverse colon and terminal ileum can then be divided with gastrointestinal anastomosis (GIA) staplers to remove the specimen from the field and a side to side anastomosis can be performed again using the GIA stapler.

When performing a colectomy using minimally invasive techniques there are various approaches to initiating the dissection. One popular approach is to start lateral to medial, similar to the open approach, bringing the colon to the midline and separating it from the retroperitoneum. The lesser sac is then entered to takedown a flexure and subsequently taking vessels in an intracorporeal fashion prior to exteriorizing the specimen and creating the anastomosis. Alternatively, the incision can be widened, the colon can be exteriorized and the vessels can then be ligated, the specimen removed and an anastomosis created. An alternative approach to the lateral to medial dissection that is also popular is the medial to lateral approach. This approach starts on the medial aspect of the colon and its mesentery, incising the peritoneum and isolating either the ileocolic or IMA depending on which side of the colon the tumor is located. Once dissected from the retroperitoneum and the ureter has been identified, a high ligation of the vessel can be laparoscopically performed, and the dissection can be further carried out laterally until reaching the sidewall of the abdomen. If performing a left hemicolectomy, the inferior mesenteric vein is also isolated during this medial to lateral dissection and ligated near the pancreas. Once the mesentery is adequately mobilized, then the surgeon starts laterally, incising the white line of Toldt, mobilizing the flexure. The lesser sac is entered by dissecting through the omentum and the medial aspect of the flexure is further mobilized for length. Again, once the colon is fully mobilized, it can be exteriorized by lengthening one of the port incisions, and the specimen can be removed, and an anastomosis created. Either of these approaches is acceptable and many surgeons are comfortable doing both. Furthermore, this dissection should be amenable to any minimally invasive approach chosen by the surgeon. If familiar with both approaches, it can be beneficial during difficult cases as the surgeon can switch from medial to lateral and vice versa to continue progressing the case without converting to open. Regardless of approach, it is important to remember that performing an oncologically sound surgery and maintaining patient safety is paramount over avoiding conversion to open. Converting from a minimally invasive approach to open should not be considered a failure if it is done with the patient's best interests and safety in mind.

Creation of the Anastomosis and Leak Testing

There is no evidence to conclude superiority between a stapled anastomosis and a hand-sewn anastomosis. Anastomotic leak rates have shown to be equivalent no matter the anatomic location. The only significant difference

is that the hand-sewn anastomosis will take longer, while the stapled anastomosis requires more expensive equipment, specifically the staplers. Furthermore, there is no significant evidence to support over-sewing the staple line to try and prevent leaks. When considering a left hemicolectomy versus an extended right hemicolectomy for a mid to distal transverse colon cancer, some surgeons will choose the extended right because they prefer the ileocolic anastomosis over a colo-colonic anastomosis, but this is surgeon preference.

When performing a left hemicolectomy or sigmoidectomy and creating a colorectal anastomosis, it is important to perform some form of test for anastomotic leak. There are multiple approaches to performing this leak test, but generally the proximal bowel is clamped, the pelvis is filled with saline and the rectum and anastomosis are insufflated with air to check for bubbles leaking from any defects in the anastomosis. It is the authors' preference to perform flexible sigmoidoscopy as it allows good insufflation of the rectum as well as direct visualization of the anastomosis checking for any anastomotic bleeding or any apparent defects in the staple line. If a leak is identified, it is generally recommended that the anastomosis should be resected, and redone if technically feasible with adequate bowel length. Some surgeons alternatively will place a suture to seal the leak and are satisfied if there is no leak on a repeat leak test. Multiple studies have shown decreased leak rates in patients who underwent anastomotic testing compared to groups who did not have any assessment of the anastomosis. Moreover, the threshold for proximal fecal diversion may be higher when any leak was suture reinforced.⁽¹⁸⁾

In addition to air leak testing and endoscopic visualization, fluorescence angiography has become a routine part of the authors' practice to utilize indocyanine green (ICG) for perfusion assessment, particularly in left sided resections. ICG evaluation is undertaken prior to determining the proximal anastomotic margin, after closing but prior to firing the circular stapler, and again endoscopically after anastomotic creation. The first evaluation is extracorporeal, the second laparoscopic intracorporeal and the third is transanal.

Special Considerations

There are a few scenarios that surgeons will encounter that are important to discuss as the clinical decision making can be challenging. The first situation to consider is synchronous tumors that are far apart, such as a cecal tumor and a

sigmoid tumor. It may be tempting to consider two separate resections with two anastomoses, but this method increases the complexity of the case, doubles the risk of anastomotic leak with two anastomoses and is potentially not sound from an oncologic viewpoint. A simpler approach is to perform a subtotal or total abdominal colectomy depending on tumor location and an ileocolic/rectal anastomosis. Both tumors are removed in a single specimen, there is only one anastomosis and all vascular pedicles have been removed with their associated lymph nodes to improve pathologic staging of the tumors.

Another clinical scenario that may be encountered is the patient with an obstructing colon cancer. The management of these patients can be complex and is dependent on the acuity of their presentation. Tumors located on the right side of the colon are frequently larger at presentation but may be less likely to completely obstruct due to the liquid nature of enteric content in the right side of the colon. However, a tumor in the sigmoid colon can more rapidly obstruct as the sigmoid is the narrowest part of the colon and the stool has started to thicken. If a tumor is diagnosed on colonoscopy and appears to be nearly obstructing but the patient was asymptomatic, it is likely they can still undergo all the necessary staging and undergo a timely elective surgery. If the patient presents to the emergency department completely obstructed and an acute abdomen, emergency surgery is likely the only option. Some patients will present with distention and altered bowel movements and abdominal CT will demonstrate a large bowel obstruction, but they are not acutely ill. Approaches to these patients include proximal diversion which will relieve the obstruction but does not treat the tumor, urgent surgery which will treat the tumor but has significant risk of morbidity as well as stoma creation, and lastly self-expanding metal stent (SEMS) placement to relieve the obstruction, followed by surgery during the hospitalization.⁽¹⁹⁾ SEMS provides the benefit of transitioning to a semi-elective surgery but there are several potential complications including tumor perforation, stent migration and stent obstruction. Several studies have compared SEMS to emergent surgery and a recent review shows the risk of perforation is approximately 10 percent, stent migration is 10%, and stent obstruction is approximately 11%. Long term oncologic data is still lacking although there are reports of increased recurrence after stenting most likely due to tumor fracture and perforation.⁽²⁰⁾ Unless the patient is unable to tolerate surgery or is found to have extensive metastatic disease, it remains our preference to proceed with surgery. Stenting does seem to be a viable option for patients with unresectable disease as a means of palliation while avoiding the morbidity and potential mortality of surgery.

The last scenario to discuss is the management of the primary colon cancer in the setting of distant metastases. Historically, patients frequently underwent resection prior to starting chemotherapy given concern that the primary tumor would progress to obstruction or perforation and the patient would require emergency surgery. With the advent of FOLFOX based chemotherapy, tumor response has increased significantly, yet patients are still most likely to succumb to their disease due to the distant metastases, not the primary tumor. Patients who are asymptomatic at the time of diagnosis or with minimal symptoms such as blood in their stool are unlikely to progress to obstruction. Starting with chemotherapy increases their chances of downstaging metastases to a resectable stage increasing the chances for improved long-term survival.⁽²¹⁾ Lastly, many of the mild symptoms such as hematochezia are likely to decrease after starting chemotherapy as the primary tumor may respond to the treatment.

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Chapter 44

Rectal Cancer

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The molecular pathogenesis of rectal cancer is much like that of colon cancer with the adenoma carcinoma sequence being the most common pathway to developing sporadic rectal cancers. However, the management of rectal cancer is quite different from colon cancer since all of these differences include initial evaluation with MRI, the use of preoperative neoadjuvant therapy, the “wait and watch” option, and the possibility of local excision.

Screening for Rectal Cancer

Based upon recent data showing a rise in the overall incidence of colorectal cancer as well as the incidence of colorectal cancer in younger patients, the recommendations from the American Cancer Society for age of first screening colonoscopy in the average risk patient is now 45 years of age as compared to the previously recommended 50 years of age. Colonoscopy is offered every 10 years if the initial colonoscopy results are normal.

There are multiple acceptable screening methods for colorectal cancer for people at average risk encompassing stool-based as well as structural exams. Stool-based tests include annual fecal immunohistochemical test (FIT), annual guaiac-based fecal occult blood test (gFOBT) in conjunction with flexible sigmoidoscopy every three years, and multi-targeted stool DNA test (MT-sDNA) every 5 years. Any abnormal screening test results from stool-based tests should be followed up with a colonoscopy. In addition to colonoscopy, other structural screening modalities include CT colonography or virtual colonoscopy every 5 years and flexible sigmoidoscopy every 3 years. Again, any abnormal results will require a colonoscopy.

Patients with a family history of colorectal cancer or adenomatous polyps are at a higher risk for developing colorectal cancer. Therefore, it is recommended that people with a first-degree relative with colorectal cancer or adenomatous polyps diagnosed at age <60 years or two first degree relatives diagnosed at any age should have a screening colonoscopy starting at age 40 years, or ten years younger than the earliest diagnosis in their family. These patients should get follow up colonoscopy every 5 years. If the diagnosis of the first degree relative was at age equal to or greater than 60 years of age, then screening with colonoscopy would start at 40 years of age; however, follow up would be that for average risk patients at every 10 years.

Preoperative Evaluation and Staging

Once a diagnosis of rectal cancer is made, accurate preoperative staging is important for prognosis and treatment. Thorough evaluation and treatment of patients with rectal cancer begins with a complete history and physical exam and a focus on duration and quality of symptoms such as abdominal or rectal pain, changes in bowel habits, blood per rectum, ability to control the bowels, and unintended weight loss. The physical exam should be complete and focus on the abdominal exam including any tenderness or distension, hepatomegaly, or inguinal lymphadenopathy. A digital rectal exam should be performed to assess the location and size of the tumor, whether it is obstructing and whether it is fixed to surrounding structures including the sacrum, pelvic side wall, levators, prostate, vagina, or anal sphincters. An important adjunct to the digital rectal exam is flexible sigmoidoscopy that can usually be completed in the initial office visit to determine the location and characteristics of the tumor as well as to obtain any biopsies.

The preoperative evaluation should also include a complete colonoscopy to ensure identification and removal of any synchronous lesions in the colon. In the case of an obstructing rectal tumor, colonoscopy may not be feasible, and the patient will need to defer a complete colonoscopy until after initial treatment.

Staging is critical in the pre-treatment assessment of rectal cancer as it directs the treatment strategy and can directly affect operative planning. Local staging with a magnetic resonance imaging (MRI) of the pelvis as well as evaluation for distant disease with CT of the chest, abdomen and pelvis needs to be preoperatively completed; rectal cancer is clinically staged using the TNM classification.⁽¹⁾ MRI is the preferred method of locoregional staging as compared to endorectal ultrasound, however there may be a role for endorectal ultrasound in accurate local staging in early rectal cancers.

Local Staging

Magnetic resonance imaging (MRI)

High resolution pelvic MRI is a very powerful tool in the management of rectal cancer. It plays a crucial role in the staging rectal cancers. By virtue of providing axial images, pelvic MRI can evaluate the tumor and its relation to surrounding structures, aiding pre-operative planning. It can determine basic information such as tumor size, morphology, height from the anal verge, as well involvement of the sphincter complex. A recent consensus panel agreed that MRI is the most accurate method of rectal measurement.⁽²⁾ Pelvic MRI provides T staging as it provides high resolution T2 weighted imaging of the tumor itself in order to assess tumor depth into the submucosa, muscularis propria and extramural invasion. Pelvic MRI also evaluates the mesorectum for involved lymph nodes, thereby providing nodal staging information which affects management. Furthermore, the mesorectal fascia can be evaluated preoperatively for tumor involvement; pelvic MRI circumferential resection margin involvement has good correlation with postoperative pathologic circumferential margin status, especially if the tumor is within 1 mm or less of the mesorectal fascia.^(3,4) Pelvic MRI can determine tumor regression grade post neoadjuvant treatment as fibrosis and tumor can be delineated on T2 weighted pelvic MRI. This type of information allows for predicting clear circumferential resection margins and helps identify patients who have had a complete radiologic response to chemoradiation therapy and thus may be candidates for non-surgical ("watch-and-wait") management.

Endorectal ultrasound (ERUS)

ERUS is safe and, in certain situations, more easily accessible than pelvic MRI. Although ERUS can provide T and N staging, its accuracy is variable as compared to pelvic MRI and has ultrasonographer-dependency. It is most accurate for early tumors, especially T0 and T1. However, ERUS, is limited by the field of the transducer, and thereby poor at predicting circumferential resection margin status. ERUS has no role in assessing tumor response to chemoradiation as it is limited by inflammation, necrosis, fibrosis and edema. ERUS has a minimal role in bulky tumors and stenosis, due to technical aspects and its limited ability to evaluate locally advanced tumors. In the vast majority of settings, pelvic MRI has replaced ERUS.

Evaluation for Metastatic Disease

Computed tomography (CT)

Rectal adenocarcinoma primarily spreads through the lymphatics, to the liver and lungs, thus rectal cancer staging includes an initial evaluation for metastatic disease. The American College of Surgeons (ACS) Commission on Cancer (CoC) National Accreditation Program for Rectal Cancer (NAPRC) standards for evaluation of metastatic disease in rectal cancer is a contrast-enhanced CT scan of the chest, abdomen and pelvis (The National Accreditation Program for Rectal Cancer Standards Manual 2017 Edition)⁽⁵⁾ Positron emission tomography is not routinely used at initial evaluation, and is generally reserved for equivocal findings on contrast-enhanced CT. Any suspicious areas of metastatic disease seen on axial imaging should be confirmed with a biopsy, if feasible.

Carcinoembryonic antigen level (CEA)

Serum CEA is the primary tumor marker used in prognosis and monitoring of rectal cancer. Initial serum CEA levels of ≥ 5.0 ng/mL are associated with increased overall mortality and worse prognosis.⁽⁶⁾ This information is also useful for post-operative surveillance for recurrence.⁽⁷⁾ Currently, no other serum tumor markers are clinically used in the evaluation and surveillance of rectal cancer.

Surgical Management of Rectal Cancer

The goal of rectal cancer surgery is for oncologic cure and preservation of defecatory and urinary and sexual function. Surgical management of rectal cancer ranges from local excision to proctectomy with or without restoration of

evacuatory function. Understanding the anatomy of the tumor within the rectum and mesorectal involvement is intrinsic to preoperative planning.

Anatomy of the Rectum

The rectum is the distal most segment of the large intestine, approximately 12-15cm in length based upon patient body habitus. The rectum occupies the pelvis from the sacral promontory to the anorectal junction. Unlike the colon, the rectum lacks haustra and tinea due to the fact that it has a complete layer of longitudinal muscle in its wall. The rectum is also wider and more distensible than colon and does not have epiploica. There are three rectal valves termed valves of Houston with the lowest or first rectal valve located about 3 to 5 cm from the anorectal junction, although variation does exist. In an average sized person, the peritoneal reflection corresponds to the middle or second rectal valve, approximately 6-10cm from the anorectal junction.⁽⁸⁾

The mesorectum is an envelope of tissue that surrounds the rectum, containing adipose tissue as well as blood vessels, autonomic nerves, lymphatics and lymph nodes. The mesorectum is surrounded by the mesorectal fascia forming a distinct anatomic package which is ideally kept intact during total mesorectal excision for rectal cancer.

The rectum is well vascularized with blood supply from the superior, middle and inferior rectal arteries. The superior rectal artery is a continuation of the inferior mesenteric artery and gives rise to rectosigmoid and upper rectal branches. The middle rectal artery is a branch of the internal iliac artery. The inferior rectal artery is a branch off of the internal pudendal artery arising in Alcock's canal supply the distal rectum and the anus.

During resection, the anatomical relation of the rectum and mesorectum to local structures needs to be considered. Posteriorly, the rectum and mesorectum are bordered by the sacrum, coccyx, sacral nerve roots, as well as the piriformis and levators caudally. Anteriorly, in men, the rectum and mesorectum neighbors the seminal vesicles, neurovascular bundles (nervi erigentes), prostate and urethra. Anteriorly, in women, structures near the rectum include the vagina, uterus and bladder. Lateral anatomic structures that need to be considered in either gender include the ureters, hypogastric nerves and internal iliac vessels.

Local Excision

There is appreciable morbidity and mortality associated with proctectomy for early rectal cancers, including anastomotic leak, infections, wound complications, and urologic and evacuatory dysfunction. These problems do not take into account the impact of stoma creation on patient lifestyle. In very early rectal cancers, these risks may not be inherent to appropriate surgical treatment, as there is a role for endoscopic resection as well as transanal excision with careful patient selection.

For very early rectal cancers such as intramucosal adenocarcinoma or T1 sm1 cancers there has been increasing use of endoscopic resection as long as the tumor is well to moderately differentiated, with no perineural or lymphovascular invasion, less than 4 cm and involving less than 30% circumference, with good short and long-term oncologic outcomes.^(9,10)

With regard to transanal resection, such as transanal endoscopic microsurgery (TEMs) or following transanal endoscopic surgery (TES), local recurrence can be as high as 26% across all T1 tumors treated by local excision.⁽¹¹⁾ Further studies into selection of T1 tumor for local excision revealed that level of invasion into the submucosa affects tumor behavior. T1 lesions are further classified depending upon level of invasion into the submucosa: sm1, sm2 and sm3⁽¹²⁾ with invasion into the upper third, middle third and lower third of the submucosa, respectively. There is evidence that T1 sm2 and sm3 lesions may behave more like T2 tumors with regard to recurrence after local excision. Depth of submucosal invasion is predictive of local recurrence with depth greater than sm1 being highly predictive of local recurrence.⁽¹³⁾ Furthermore, T1 tumors have a 0-3% chance of lymph node positivity whereas sm2, sm3 and T2 lesions have a 15-25% chance of lymph node positivity.⁽¹⁴⁾ Current NCCN guidelines recommend local excision as an alternative to resection with T1 tumors only when there is no radiographic evidence of lymph node involvement based upon ERUS or pelvic MRI, less than 30% circumference, < 3cm, well to moderately differentiated, mobile /non-fixed, margins clear (> 3mm), no lymphovascular invasion or perineural invasion, within 8 cm of the anal verge and full thickness excision must be feasible.⁽¹⁾ Other factors that will influence the decision for a transanal excision include histopathologic risk factors for recurrent disease such as tumor size, grade, lymphovascular invasion and tumor budding.⁽¹⁵⁻¹⁷⁾

Proctectomy

Proctectomy is generally indicated in the setting of T1 sm2 or sm3 or more advanced tumors due to the increased risk of lymph node positivity. The operation performed (low anterior resection (LAR) or abdominoperineal resection (APR)) is determined by the ability to obtain an R0 resection with a complete mesorectal envelope or total mesorectal excision (TME). Indications for an APR include bulky tumors that preclude a negative distal margin, or involvement of anal sphincters.

Regardless of which approach (laparoscopic, robotic, open, transanal TME (taTME)) is employed to complete the proctectomy for rectal cancer, it is paramount that the proctectomy is completed with a TME. TME or en-block resection of the rectum and mesorectum along the mesorectal fascia, keeping the mesentery of the rectum intact and within its envelope, was initially described by Heald *et al.* in 1982. TME is the gold standard in rectal cancer resection as it has been shown to significantly reduce local recurrence rates, improving oncologic outcomes⁽¹⁸⁻²⁰⁾ with no significant increase in morbidity. TME quality is one of the main prognostic factors associated with local recurrences of rectal cancer.

Low Anterior Resection

If a clear distal margin is attainable and there is no involvement of the anal sphincters, LAR is completed using either minimally invasive approaches, or an open operation. After mobilization of the sigmoid and descending colon, including the splenic flexure to help create a tension-free anastomosis, a high ligation of the inferior mesenteric artery is completed, following oncologic principles. The authors also perform routine high ligation of the inferior mesenteric artery even if there is no clear tumor proximal to the superior rectal artery. Inferior mesenteric vein ligation is often needed to gain length for a tension-free anastomosis, for example, in the setting of coloanal anastomosis. The rectal dissection is then completed in the avascular mesorectal plane starting posteriorly, proceeding laterally, and then terminating anteriorly. If the tumor is anterior, the dissection plane is anterior to Denonvillier's fascia. If the tumor is not anterior, keeping Denonvillier's fascia intact will help minimize injury to the nervi erigentes.

Options for anastomotic technique include stapled or hand sewn. A straight colorectal anastomosis can be performed. Other options include a colonic J-pouch or a side to end anastomosis, both of which have been shown to have better

short-term function than a straight coloanal anastomosis.^(21,22) The authors' preference is construction of a colonic J-pouch whenever the patient has adequate colonic length and pelvic width.

Large landmark randomized controlled studies such as the COLORII trial have shown that the short-term morbidity and mortality of laparoscopy in rectal cancer has equivalent to improved outcomes as compared to open resection, including decreased wound infection, length of stay and narcotic use.⁽²³⁾ Studies also have also consistently demonstrated similar oncologic outcomes based upon surrogate measures such as TME rates and CRM positivity with regard to laparoscopic versus open surgery.⁽²⁴⁻³⁰⁾ Long term outcomes are under investigation, however, 3-5 year oncologic outcomes data show no difference in disease-free or overall survival or distant or local recurrence.^(25,27,28,31-33)

Conversion from laparoscopic to open resection, however, has been shown to be associated with decreased overall survival and increased local recurrence rates.^(25,33,34) The safety and efficacy of robotic surgery for rectal cancer resection has been studied in observational studies as well as small randomized controlled trials. Small studies also show no difference in complications, length of stay CRM or lymph node yield between robotic and laparoscopic surgery.⁽³⁵⁻³⁷⁾ The ROLARR trial showed that robotic resection did not confer a benefit for curative resection compared to laparoscopic resection.⁽³⁸⁾

Conversion rates of minimally invasive compared to open TME cases are higher in a subset of cases, specifically patients with a narrow (male) pelvis, bulky tumors, obesity and previous neoadjuvant chemotherapy.⁽³⁹⁾ Bulky, low rectal tumors in a narrow pelvis can provide a significant challenge to minimally invasive approaches from the abdomen only to get adequate circumferential margins, an intact mesorectal envelope, as well as to get distal to the tumor to obtain adequate distal margins. With taTME, the distal margin can be determined and defined in a transanal fashion, with the tumor under direct vision. TaTME is a "bottom up" approach (in conjunction with a simultaneous top down approach in a minimally invasive fashion), facilitating the most difficult portion of the operation in the distal half of the pelvis. TaTME has been recently developed to help diminish the possibility of conversion, as well as theoretically helping to clearly identify and determine the distal margin of resection. TaTME may have the potential advantage of better visualization of hard-to-access anatomical areas and may also lead to better nerve preservation and identification of the resection plane, especially in patients with locally advanced rectal cancer.⁽⁴⁰⁻⁴²⁾

Lateral Lymph Node Dissection (LLND)

With the evolution of high-resolution pelvic MRI, the ability to assess lateral lymph nodes for tumor involvement in rectal cancer is improved and potentially more reliable. Preoperative staging pelvic MRI may play a role in predicting LLN metastasis and may help determine indications for LLND.⁽⁴³⁾ Currently, there is no clear consensus with regard to treating LLNs.⁽⁴⁴⁾ It is unclear who should undergo a LLND at the time of proctectomy with TME.

The Japanese Society for Cancer of the Colon and Rectum recommends routine bilateral LLND for patients with rectal T3 or T4 cancers that are below the peritoneal reflection.⁽⁴⁵⁾ This recommendation is in contrast with current NCCN guidelines stating that clinically suspicious nodes beyond the field of resection should be biopsied and/or removed, if possible. Extensive resection of M1 lymph node is not indicated. Extended lymph node resection is not indicated in the absence of clinically suspected nodes. (NCCN Guidelines Version 3.2019 Rectal Cancer).⁽¹⁾ In the United States and Western regions, the approach to locally advanced rectal cancer is multimodal treatment with neoadjuvant chemoradiation therapy along with TME. However, in Japan the standard is routine use of TME with prophylactic bilateral LLND without radiation therapy for low rectal cancers. A critical difference between Japanese and Western populations is BMI.

As with any procedure, there are risks and benefits to prophylactic LLND. Although, LLND may affect control of microscopic disease, there is significantly higher blood loss and longer operative times with patients who undergo TME with LLND as compared to those who undergo TME alone.⁽⁴⁶⁾ There is some evidence that laparoscopic LLND may be helpful in reducing blood loss and allow for the retrieval of more lymph nodes when conducting LLND.⁽⁴⁷⁾ There is also considerable concern for functional compromise due to the risk of post-operative urinary and sexual dysfunction as a result of injury to vessels and nerves in the pelvic sidewall expected with LLND.⁽⁴⁸⁾ However, some data suggest functional compromise is more dependent upon tumor location and intraoperative blood loss as opposed to LLND.⁽⁴⁹⁾ As neoadjuvant CRT may not be enough to treat lateral pelvic node disease or prevent recurrence, the optimal role for LLND is likely in the treatment of select patients.

Studies have shown that the size of the lateral lymph node and response of the lateral lymph node to CRT are key factors in predicting lateral pelvic recurrence. The rate of LLN recurrence increases with the size of the LLN.⁽⁵⁰⁾

Multiple studies have shown that persistent LLN greater than 5mm in size after CRT was associated with residual tumor.⁽⁵⁰⁻⁵²⁾

A retrospective, single center study showed that post-neoadjuvant chemoradiation (CRT) lateral pelvic node size of ≥ 5 mm is strongly associated with pathologic positivity of the node. In this study, post-neoadjuvant CRT lateral pelvic node size < 5 mm did not render node positivity on final pathology. It was concluded that LLND along with TME should be considered in patients with clinical evidence of lateral pelvic node metastasis status post-neoadjuvant CRT lateral pelvic node size of ≥ 5 mm.⁽⁵²⁾ Further studies are necessary to determine clear and consistent guidelines for the treatment of lateral lymph nodes in rectal cancer.

Abdominoperineal Resection

Similar to LAR resection, the abdominal portion of the APR can be performed in either a minimally invasive or an open manner.

There are three varying approaches to the perineal portion of the procedure; intersphincteric, ischioanal, and extralevator. The perineal portion of the procedure can be performed either in the lithotomy or the prone jackknife position.

There is little role for intersphincteric APR in the treatment of rectal cancer as indications for APR include very low bulky tumors precluding a negative margin and tumors with sphincter involvement. Furthermore, data showing that microscopically negative margins even < 1 cm are associated with low local recurrence rates.⁽⁵³⁻⁵⁵⁾ Either ischiorectal or extra-levator APRs are employed in the setting of rectal cancer. Exceptions might be in patients with baseline severe incontinence with upper rectal tumors.

Extra-levator abdominoperineal excision (ELAPE) allows for a wide local excision of the levators with a cylindrical shape so as not to create a “waist” in the mesorectum at the level of the levators. The levators are divided near their insertion on the pelvis. With ischiorectal APR, both sphincters are resected, however the levators are not widely excised, thereby producing a “waist” at the mesorectum at the level of the levators. ELAPE is associated with improved circumferential resection margin, however this result is at the expense of increased wound complications due the wider excision of the levator ani muscles. Most perineal wounds after APR are amenable to primary closure, however complications can double in the setting of neoadjuvant radiation therapy. Methods of perineal reconstruction include cutaneous and myocutaneous flaps

such as V-Y advancement flap, vertical rectus abdominous flap (VRAM), and gluteal and gracilis flaps.

When choosing a site for the end colostomy and when maturing the colostomy associated with an APR, careful consideration should be made regarding the location of the stoma on the patient's abdominal wall and preoperative marking should be undertaken by an enterostomal therapist as this stoma is permanent. It should be away from any abdominal scars, above or below the belt line and abdominal creases, and within the rectus muscle. Patient preferences should be taken into account to ensure that the patient can see and reach the stoma for management.

Radiation Therapy

Radiation therapy is a mainstay of rectal cancer treatment as it improves local control and increases the rate of sphincter preservation. The German CAO/ARO/AIO-94 trial in the early 2000s was a landmark study that defined the role of preoperative chemoradiation therapy in the treatment of rectal cancer in reducing the rate of local recurrence.^(56,57) Radiation is generally given with a 5-fluorouracil and leucovorin. In addition to increased efficacy, preoperative chemoradiation has also been shown to have decreased acute and chronic toxicity as compared to adjuvant chemoradiation. Neoadjuvant treatment also has the benefit of an increased sphincter preservation rate due to tumor downgrading. One downside of neoadjuvant chemoradiation is the possibility of overtreatment in patients with stage I disease.⁽⁵⁷⁾

Short course radiation therapy of 5 treatments of 5 Gy administered in one week is another option for radiation in the neoadjuvant setting as compared to 28 treatments of 1.8 Gy given in 28 doses over the course of 6 weeks.⁽⁵⁸⁾ This regimen has been shown to have significant improvement on overall survival and local recurrence as compared to surgery alone.⁽⁵⁹⁾ Currently, both short course radiation therapy followed by surgery in one week and long course radiation therapy followed by surgery in approximately 6 weeks are considered standard of care. Randomized trials comparing the two approaches show no difference between the rate of sphincter preservation, disease-free survival or overall survival, nor is there any difference in toxicity. Long course radiation has been shown to have higher rates of complete pathologic response; however, this may be due to the interval between the radiation therapy and the date of surgery.^(60,61) Further trials are ongoing to optimize radiation therapy in rectal cancer patients with respect to long or short course radiotherapy.

Although the role of radiation therapy in the treatment of rectal cancer is now mostly in the neoadjuvant setting, adjuvant radiation therapy is still used in patients who were thought to have stage I disease upon preoperative staging but upstaged on post-operative review of the pathology.

Chemotherapy

Concurrent delivery of fluoropyrimidine-based chemotherapy with radiation therapy is used in the treatment of locally advanced rectal cancer. The use of combined chemoradiation was clearly shown to enhance the tumoricidal effect of radiation, resulting in higher rates of complete pathologic response, reduction in stage and tumor size, and decreased rates of lymphovascular or perineural invasion⁽⁶²⁾ compared to radiation alone. The current standard of care for locally advanced rectal cancer is neoadjuvant chemoradiation, followed by surgical excision and adjuvant systemic chemotherapy depending upon surgical pathology results and the presence of node positive disease. Although, neoadjuvant chemoradiation reduces local recurrence, it does not impact overall survival or the risk of distant metastasis.^(63,64)

The role of neoadjuvant chemotherapy in rectal cancer is actively under investigation. It is thought that earlier introduction of systemic chemotherapy maybe the optimal approach to reduce distant recurrence and increased long term cure rate. Some authors believe that the neoadjuvant approach may allow for less toxicity with better patient adherence. Thus, total neoadjuvant therapy is being more widely used.^(65,66)

Decision Making and Multidisciplinary Teams

Rectal cancer care is complex with a need for standardization of management strategies, improved coordination amongst the care team as well as improved communication between the team and the patient.⁽⁶⁷⁾ There can be high variability in the treatment and outcomes of rectal cancer by hospital volume and geographical location.⁽⁶⁸⁾ With a multidisciplinary team (MDT) approach bringing experts and specialists together, the decision can be made on a case by case basis in the context of a multidisciplinary meeting, with the goal of reduced variation in treatment and outcomes and arriving at the optimal consensus management strategy. Multidisciplinary teams have promoted improvements in survival, clinician and patient satisfaction as well as communication, evidence-based decision making, and the coordination of care and treatment planning in the management of rectal cancer.⁽⁶⁹⁾ MDT meetings can directly impact patient management including

operative planning, especially in locally advanced cases. The ACS Coc NAPRC should help optimize outcomes in the USA. ^(70,71)

Watch and Wait

Non-operative management of rectal cancer in order to improve quality of life via organ preservation, has been pioneered by Dr. Angelita Habr-Gama's group in Sao Paulo, Brazil. In their initial protocol, patients with early rectal cancers were treated with chemoradiation therapy and then assessed at 8 weeks, clinically, endoscopically and with imaging. ⁽⁷²⁾ Patients with persistent disease proceeded to surgery whereas those patients who appeared to have a complete clinical response underwent close surveillance according to a strict protocol. Patients who relapse underwent salvage surgery. Studies have suggested that there is no oncologic harm to this approach in carefully selected patients. More recently, this approach has been studied in T3 and T4 node-negative disease, noting a longer time to complete response of up to 16 weeks. ⁽⁷³⁾

Ongoing studies are being conducted to study the safety and efficacy as well as to identify the population of patients who will benefit from non-operative management and determine how long to wait for optimal response in addition to best surveillance methodologies and regimens.

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Chapter 45

Anal Cancer

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Background

Anal cancer is an infrequent malignancy representing less than 1% of all new cancers diagnosed annually, which comprises only 2.7 percent of all digestive system malignancies in the United States; only 8300 new cases are diagnosed annually. ⁽¹⁾ The risk for women is approximately two-fold higher than for men, and there has been a persistent rise in disease incidence in the past decade. Several important risk factors have been identified, including human papillomavirus (HPV) infection, smoking, sexually transmitted diseases (STDs) with human immunodeficiency virus (HIV) in specific anoreceptive intercourse, and immunosuppression. The mainstay of treatment of anal cancer is chemoradiotherapy. The role of surgery is reserved for salvage procedures for recurrent, non-responsive disease and as palliative treatment. Familiarity with disease presentation, diagnosis, and medical and surgical treatment is important for primary caregivers and for general and colorectal surgeons.

Anatomy

The anal canal extends from the anorectal ring to the anal verge, (Figure 45-1) where squamous epithelium of the anal canal distal to the dentate line meets the hair-bearing perianal skin. A transition zone containing columnar, transitional, and stratified squamous epithelium lies just above the dentate line. The functional anal canal is defined by the sphincter complex, measures 3-5 cm in length, and its superior border is the puborectalis sling with the upper end of the anal sphincter. The anal margin is composed of skin that extends distally to the anal verge, which can be seen completely on physical exam and is within 5 cm from the anus.

Distally to the dentate line, primary lymphatic drainage is to the inguinal lymph nodes, whereas proximally drainage is to the inferior mesenteric and internal iliac lymph nodes.

HPV Infection, Condyloma Acuminatum, and Anal Intraepithelial Neoplasia (AIN)

HPV Infection

The association of anal squamous cancer with the HPV virus is well established. ⁽²⁾ HPV is the most common STD in the United States, with over 15% of the population infected. Only part of the many identified viral serotypes are found to be associated with anal lesions, with an even smaller fraction established as premalignant. This fact also explains the simultaneous occurrence of other HPV-related cancers, especially vulvar and cervical cancers with both anal benign lesions and neoplasia. The important recommendation of vaccination against HPV is a result of the understanding of the correlation between this STD infection and a later malignant transformation, with an effort at prevention by timely vaccine administration. ⁽³⁾

Condyloma Acuminata

Condyloma acuminata (anal warts) are premalignant lesions with an increased risk for developing anogenital cancers. The risk is up to 20 times higher compared to unaffected populations after a 10-year period. Its key histologic feature is the presence of koilocytes representing epithelial cells with vacuolated cytoplasm, which is evidence of HPV

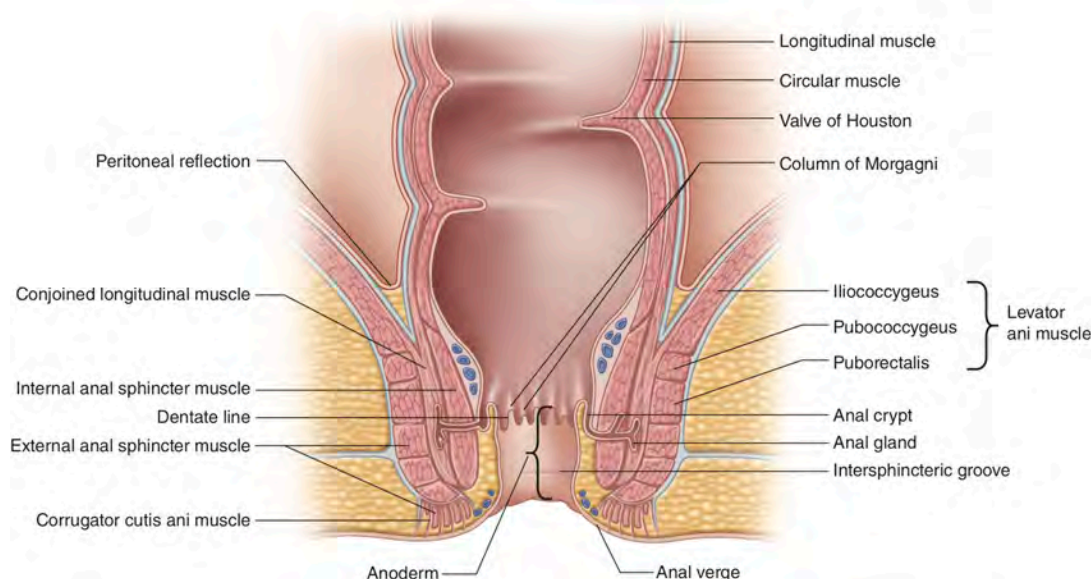


Figure 45-1. Anatomy of the anal canal. (With permission from Carmichael C, Mills S. *Anatomy and Embryology of the Colon, Rectum, and Anus*. In: Scott R. Steele SR, Hull TL, Read TE, Saclarides TJ, Senagore AJ, Whitlow CB, eds. *ASCRS Textbook of Colon and Rectal Surgery*, 3rd ed. Springer, New York 2016;pp:3-26. © Springer 2016).

infection. Female patients diagnosed with condylomas must undergo a genital examination and Pap smear. It is important to involve an experienced surgeon early in the course of treatment because of the probability that surgical intervention will likely be required at some point.

There are various medical and surgical treatments available that vary based on size, number, and location of lesions. An appropriate biopsy follow-up for signs of dysplasia and malignancy development is essential for every patient, regardless of the therapeutic pathway undertaken.

Imiquimod cream and Interferon alpha are agents with antiviral activity. The latter option is available in both systemic and topical forms but is limited in use to its toxicity. Other topical therapies include antimetabolite 5-Fluorouracil (5-FU), trichloroacetic acid, and the antimitotic agent podophyllotoxin. All of these agents have a response rate varying between 20 and 50%, with a recurrence rate of approximately 50%. They all carry significant side effects, mainly local irritation and ulceration with a potential risk of oncogenicity. Lesions larger than 1-2 cm, those located in the anal canal, or after failure of medical therapy usually warrant ablative therapy or surgical excision. Office cryotherapy treatment with liquid nitrogen also may be effective, but often requires multiple sessions. Although laser therapy was described as effective, it requires

anesthesia and is cost prohibitive. Another option is argon plasma beam application.

Surgical excision is a viable option, especially for larger and recurrent lesions. However, care should be taken to leave sufficient skin bridges to avoid anal stenosis and to maintain the dissection within the subcutaneous layer, preserving the sphincter muscle complex. Flap reconstruction, primarily gluteal, is needed in cases where there is a large excision with a significant defect, not allowing for primary closure.

One special type of lesion is the Buschke-Lowenstein tumor, or giant wart, considered to be an intermediate neoplasm on the path to squamous cell carcinoma. It has some local invasive properties and, as such, a wide local excision is essential with a minority of patients requiring abdominoperineal resection.

Anal Intraepithelial Neoplasia (AIN)

AIN lesions are precursors to the development of squamous cell carcinoma and are divided into 1, 2 and 3, representing low, moderate, and high grades of dysplasia, respectively. There is a known etiologic correlation with vulvar and cervical intraepithelial neoplasia with a strong association with HPV infection. AIN and HPV also share the same risk factors. The histologic appearance of higher

mitotic activity and evidence of expansion throughout the epithelial layer differentiates the different types. However, the basement membrane stays intact and is not invaded by the dysplastic process. There are some reports of successful prevention of AIN with HPV vaccines, but the treatment strategies are controversial after its diagnosis. The primary goal is either prevention of squamous cell carcinoma (SCC) or its detection in the earliest possible stage, due to its direct impact on patient survival. ⁽⁴⁾ The use of high resolution anoscopy (HRA) is important in the initial diagnosis and follow up with multiple biopsies taken from all suspicious areas. Ablative therapies such as laser, fulguration, and cryotherapy are all flawed by high recurrence rates and potential local complications, mainly anal stenosis. The addition of Lugol solution might help to identify indeterminate lesions when suspicious areas do not stain with its application. Acetowhitening is also helpful in identifying the areas of concern for dysplasia.

AIN III, which is also in-situ SCC, is called Bowen's disease when presenting with an erythematous, scaly, or moist nodular surface. It presents with pruritus or burning and sometimes bleeding. It is often mistaken as eczema or skin rash and treated locally by a dermatologist. The treatment of choice is wide local excision with negative surgical margins. Substantial recurrence rates have been reported after resection.

Squamous Cell Carcinoma

SCC is the most common malignancy of the anal canal. It is believed to arise from the precursor lesion, AIN. HPV infection carries an important impact on the development of SCC, with several serotypes such as 16 and 18 having a higher oncogenic potential. The prevalence of transformation to SCC is much higher in patients with concomitant HIV infection. Clinical presentation of SCC includes bleeding, pain, pruritus, discharge, and incontinence. Unfortunately, many patients are initially misdiagnosed resulting in a substantial delay in treatment, therefore a high degree of suspicion is required by the primary physician.

Staging

After performing a thorough physical examination with lymph node palpation, rectal examination, and biopsy to establish the diagnosis, further staging is performed according to tumor size, nodal involvement, and metastatic spread (TNM). Abdominal and chest computed tomography

(CT) are indicated with optional pelvic magnetic resonance imaging (MRI) for more advanced lesions. Positron emission tomography (PET) CT from skull to mid-thigh should also be considered according to National Comprehensive Cancer Network (NCCN) guidelines but should not replace CT with oral and IV contrast. A biopsy or fine needle aspiration (FNA) of suspicious lymph nodes should also be considered. ^(5,6)

Treatment

Historically, treatment of anal margin SCC has consisted of surgical resection with wide local excision for small sized tumors and abdominoperineal resection (APR) for larger and locally invasive cancer. A high percentage of local recurrence was reported for local excision with disease cure rates as low as 40% in some series. The introduction of chemoradiation by Dr. Norman Nigro in 1974 revolutionized the treatment of SCC. It has improved local recurrence as well as survival rates to above 80%, with a dramatic reduction in permanent colostomy rates. Chemotherapy agents, which are currently recommended with radiotherapy, include 5-FU or its oral fluoropyrimidine prodrug Capecitabine with Mitomycin C. Substantial toxicities were reported with the addition of other agents such as Cisplatin or the EGFR inhibitor Cetuximab.

Radiation therapy should deliver 45Gy in 25 fractions over 5 weeks. There are some reports of better results with intensity modulated radiation therapy (IMRT) and should be encouraged in centers with appropriate expertise, instead of the standard 3-D conformal radiation.

Indications for Surgery

Primary surgical treatment is not often indicated, although local excision might be considered in anal margin tumors that are smaller than 2 cm (T1) and are not poorly differentiated. Adequate surgical margins of more than 1 cm are required. ⁽⁷⁾ Local excision might also be considered for superficially invasive lesions off the anal canal with less than 3 mm basement membrane invasion. This last group of patients has become more common over the last years due to screening in high-risk populations. Patients who have undergone chemoradiotherapy are evaluated initially 2-3 months after completion of treatment. Individuals with persistent, progressing, and recurrent disease after treatment with the Nigro protocol are the primary candidates for surgery. Of note, persistent disease without progression may still regress several months after completion of chemoradiation.

Patients with disease persisting after six months, progressing disease, or recurrence should be biopsied and restaged with repeat CT of the abdomen, pelvis and chest and possible PET. Subsequently, surgery may be indicated for patients without metastatic disease.

Surgical Approach

The operation of choice for patients undergoing surgery for anal SCC is APR. It has varying results in regards to loco-regional control after five years, with local failure rates reported in up to 50% of cases and a 5-year survival rate of 50-70%.⁽⁸⁾ The surgical principles are basically the same as with rectal cancer implying the total mesorectal excision (TME) planes with excision of the anal canal. A wider extra-sphincteric perineal resection is sometimes required because of potentially high wound complication rates due to the previously irradiated skin. In these patients, a strong consideration for flap reconstruction is prudent, possibly with vertical rectus or local myocutaneous flaps. A salvage surgical resection should be considered for patients with progressing, residual, or recurrent disease after primary chemoradiotherapy. It can achieve local control in 60% of cases, and a 5-year survival rate of 30-60%. HIV-positive individuals have comparable results with salvage procedures but with a somewhat higher complication rate. APR is indicated in the majority of patients since achievement of a negative surgical margin is crucial. Radical groin dissection is to be considered for patients with recurrent or persistent groin disease but not for patients with positive response to chemoradiotherapy. This carries serious side effects with approximately 25% of patients having wound infection and up to 40% experiencing extremity edema. The groin dissection could be performed with or without the APR, depending on disease location and involvement of the primary site. An individualized approach to therapy based on sentinel lymph node biopsy may be useful in selecting patients who are candidates for inguinal irradiation, although for some patients more extensive surgery may be required. A posterior or sometimes total pelvic exenteration may be considered for selected patients with locally aggressive disease. These extensive procedures should only be undertaken in an experienced referral center.

Distant metastases are unusual, noted in only approximately 10-20% of patients. Metastases generally portend a grave prognosis and are treated with systemic chemotherapy. The most common regimen is (5-FU) and cisplatin with potentially similar results with FOLFOX.

Surgery in this setting is limited for palliation of symptoms, such as pain and bleeding. Isolated liver and lung metastases, when primary disease is under control, may also be considered for resection in highly selected patients with potential long-term survival.

Other Tumors

Other anal canal tumors comprise less than 10% of cancers in this region and are heterogeneous in origin.

Adenocarcinoma of the anal canal is rare. There is some debate regarding its origin, which could potentially be from the anal glands, glandular cells in the anal transition zone, columnar cells in the upper anal canal, or even within prior fistula tracts. The treatment algorithm, however, is similar stage by stage to low rectal cancer with the difference being APR as opposed to sphincter-preserving surgeries.

Anal melanoma is a very rare aggressive form of melanoma with a poor prognosis mostly due to distant metastatic spread. The treatment of choice is radical surgical resection (APR).

Anal canal lymphomas, both Hodgkin's and non-Hodgkin's, are more common in immunocompromised patients with the treatment being chemoradiotherapy. There are scattered reports of anal canal neuroendocrine tumors as well as gastrointestinal stromal tumors (GISTs) and sarcomas. Each case needs to be discussed on an individualized basis with the decision for local or radical surgical resection or administration of adjuvant/neoadjuvant chemotherapy with or without radiation depending, on the tumor size and characteristics.

Paget's Disease

This rare clinical entity mimics eczema or dermatitis. Unfortunately, due to its usually mild presenting symptoms, diagnosis is often delayed. This lesion arises from skin apocrine glands.

Except for its local presentation there is a high association with synchronous visceral malignancies, especially colorectal cancer with a reported incidence of above 80% of concurrent tumors. Thus, colonoscopy is required prior to local management of the disease. Local therapy varies from MOHS procedures and obtaining clear resection margins to wide local excision, often with flap reconstruction. The local recurrence rates are substantial and close follow up is mandatory.

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Chapter 46

Other Benign and Malignant Tumors of the Bowel

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Lipomas

Lipomas are the most common non-epithelial benign tumors of the colon and gastrointestinal system, of unknown origin, a prevalence in autopsies and surgical series of 0.035 to 4% is reported. ⁽¹⁾ They do not develop malignant degeneration, but there are reports of liposarcomas in the small intestine. Multiple familial lipomatosis and Weber-Christian disease are associated with two rare syndromes. In most cases they are unique, but they can be multiple in 10 to 24%. They are more frequent in women with a 1.5 to 2.0 ratio. ⁽²⁾

Diagnosis

In general, they are asymptomatic lesions or incidentally found. The size of the lesion correlates with the symptoms. The lesions of more than 2 cm are symptomatic; 75% of lipomas are greater than 4 cm. They produce symptoms, which include abdominal pain, bleeding, alteration of the intestinal habit. The pain may be secondary to intermittent intussusception due to prolapse of the mass or obstruction. There may also be anemia or palpable mass. Infrequent presentations include massive bleeding, perforation, anal prolapse and spontaneous amputation. ⁽³⁾

Radiologically, the characteristic lesion in the barium enema is extremely well demarcated, smooth, oval and radiolucent. Topographically, it is defined as a soft tissue lesion. Endoscopically, the typical lesion of a subepithelial lipoma is a sessile, yellowish, smooth, hemispherical polyp, rarely pedicled. There are several endoscopic signs. The first is that manipulating it with the biopsy forceps feels like a soft and pliable lesion, easily indentable and that when you stop pushing it takes its original shape as a “pillow sign” pillow.

Another characteristic sign is the sign of “squeeze” where the shape of the mass changes with external compression or peristalsis. Another sign is that when pulling the mucous membrane and it is separated from the submucosa as in a tent or sign of the “tent”.

The mucosal biopsy is usually normal and may eventually expose the underlying fat or “naked fat” sign. In endoscopic ultrasound, a hyperechoic lesion that originates in the third layer (submucosa) of the colon is typically demonstrated. ⁽⁴⁾ The diagnosis of lipomas can sometimes be difficult especially when it is ulcerated, necrotic or firm and can mistakenly mimic a malignant polyp. Another infrequent presentation that can be confused with a lipoma is a lipomatous ileocecal valve.

Histologically, the typical lesion of the lipoma reveals mature adipose tissue surrounded by a fibrous capsule, where several fibrous septa can penetrate fatty tissue. 90% are submucosal and 10% subserous, rarely originate from the muscularis propria. Necrosis, cystic degeneration, ulceration and calcification can be found in the specimen, especially in lesions of long evolution. Some pseudomalign findings include nuclear atypia but they are actually reactive inflammatory changes. No malignant sarcomatous transformation of a lipoma has been reported in the colon. ⁽¹⁾

Treatment

In view of the fact that colonic lipomas are benign lesions and some are large and asymptomatic, resection is indicated when there are clinical complications. Asymptomatic lipomas smaller than 2 cm do not require treatment because their growth is slow and the risk of complications such

as bleeding or obstruction is relatively low. Endoscopic resection of lipomas can be carried out but has significant risks; some reports indicate a perforation rate during the procedure up to 43%. The risk of perforation during an endoscopic resection of the lipoma is greater when the lesion is greater than 2.5 cm. The criteria for endoscopic resection include: sessile or pedunculated lesions with a base of less than 2 cm, as long as the mobility of the latter is determined. ⁽⁵⁾ Immobile lesions involving deep layers such as the muscularis propria are preferably treated by intestinal resection. Large pedunculated lipomas have a stem, but in reality, they are pseudopediculus of invaginated serosa. ⁽⁶⁾

Any lipoma that can not be safely resected during an endoscopy for indication of the presence of symptoms or their complications should be managed surgically. Surgery is also the modality of first choice when there is intussusception or intestinal obstruction. ⁽⁷⁾ The surgical options include segmental colectomy, colotomy with enucleation or local excision; both with an open or laparoscopic approach, a laparoscopic segmental resection is preferable. Lipomas located on the subserosa surface can be resected by simple excision without opening of the intestine. Finally, another option that can be used with better safety is endoscopic polypectomy guided by laparoscopy. ⁽⁸⁾ The prognosis of these lesions is excellent since they do not recur if they are completely resected. ⁽¹⁾

Leiomyomas and Leiomyosarcomas

Leiomyomas and leiomyosarcomas are tumors that originate from smooth muscle. Recent advances in immunohistochemistry and molecular genetics have discovered that the true smooth muscle tumors (leiomyomas and leiomyosarcomas) must be differentiated from gastrointestinal stromal tumors (GIST) because these have a different origin. The most important finding is that most GISTs are accompanied by a somatic mutation CD 117 (C-kit) a tyrosine kinase receptor normally expressed by the interstitial cells of Cajal, mast cells and germ cells and therefore the cytogenetics of tumors GIST is related to muscular, neural, Cajal, Schwannian and fibrous lines. ⁽⁹⁾

Leiomyomas are rare lesions of the colon and occur more frequently in the transverse, descending or sigmoid colon. They are associated with tuberous sclerosis. The growth pattern of leiomyomas may be endocholic, exozoid, combined or concentric lesions. The endocholic is confined to the intestinal wall and lumen and occurs in 47% of cases and the exocolic is extra-luminal and occurs in 32% of cases.

The concentric lesions are the result of circumferential infiltration. Regarding leiomyomas, they usually originate from the muscularis mucosae, 29% are located in the rectum and 49% in the sigmoid. ⁽⁷⁵⁾ The colon is the second most common site of origin of intestinal leiomyomas followed by the esophagus. Most leiomyomas are less than 2.2 cm. Recurrences have not been found in follow-ups of up to 46 months. ⁽¹⁰⁾

Clinical and Radiological Manifestations

Leiomyomas are usually asymptomatic and are discovered incidentally. Clinical manifestations include pain, palpable mass, hemorrhage, rarely nausea, vomiting, weight loss, constipation, fever, anemia, diarrhea and alteration of bowel habit secondary to obstruction, intussusception or perforation. Radiologically it is a well-defined circumscribed mass that can ulcerate or perforate the mucosa. The tomography typically demonstrates a well-defined lesion with homogeneous increase in intravenous contrast. The radiological findings of lymphadenopathy, metastatic lesions, degenerative changes and tumors larger than 5 cm suggest leiomyosarcoma (malignant). The growth pattern is not useful in distinguishing the type of tumor, but roughly, it is considered that the exozoid lesions usually correspond to leiomyosarcomas. ⁽¹¹⁾

Endoscopy and Endoscopic Ultrasound

In colonoscopy, colonic leiomyomas appear as solitary, smooth, red lesions with normal mucosa over them, they can also occur as pedunculated polyps. It is important to distinguish them from leiomyosarcomas because the prognosis differs. Endoscopic ultrasound is useful to evaluate the size, location within the wall and its extension. The benign are homogeneous hypoechoic masses within the fourth layer of the intestine. Finding tumor invasion in the wall, lymph nodes, lesions larger than 4 cm, irregular edges, echogenic foci and anechoic cysts suggests leiomyosarcoma. ⁽¹²⁾

Pathology

It is important to differentiate smooth muscle tumors such as leiomyomas, leiomyosarcomas and leiomyoblastomas (smooth muscle tumors with epithelioid appearance) of gastrointestinal stromal tumors. Actually, GIST are mesenchymal tumors and not smooth muscle tumors. The

leiomyomas are stained in special immunohistochemical stains for desmin or smooth muscle actin and are negative for CD117 C-Kit or CD 34, have low cellularity and eosinophilic cytoplasm. The most specific marker of GIST tumors is the expression of CD 117 that separates them from true smooth muscle tumors.

Leiomyomas are lesions well circumscribed to microscopy, with branches of smooth muscle that originates from the muscularis mucosae and without mitotic figures but may originate from the muscularis propria or from the vessels of the mucosa. Usually Leiomyomas lesions are smaller than 5 cm. To differentiate and determine malignancy there are some histological criteria such as the number of mitotic figures and nuclear abnormalities. The presence of mitosis is the characteristic finding of malignancy, especially when there are 5 or more mitoses in a high grade field. Other microscopic criteria for malignancy include necrosis, increased cell size, irregularity of shape, decrease and disorganization of myofilaments, reduction of the collagen stroma and presence of cells with oval nuclei and nuclear pleomorphism. ⁽¹³⁾

Treatment and Prognosis

Some authorities have argued that colorectal leiomyomas are precursors of malignant leiomyosarcomas, therefore they recommend treating them immediately because of their malignant potential. Endoscopic resection of leiomyomas is controversial and large submucosal leiomyomas should be resected surgically to ensure adequate margins, but endoscopic resections of pediculated leiomyomas of up to 1.5 cm have been reported. ⁽¹⁴⁾ In general, surgical resection is the ideal surgical option. Lesions less than 3 cm away from the dentate line require transanal excision and is enough when the lesion has been resected with normal tissue margins. For transanally inaccessible lesions, excision by the posterior transesphytonic York Mason approach is feasible as an alternative to a low anterior resection. If the lesion is histologically malignant, radical surgical excision should be performed. ^(15,16)

Leiomyosarcomas are smooth muscle tumors of the bowel wall that are characterized by insidious evolution and may remain asymptomatic for quite some time. Tumors of low malignancy, which are treated by resection, can live for many years even with residual tumors or metastases. Most are seen in the lower third of the rectum and are more common in men. Large tumors that spread extensively to perirectal tissue are surgically difficult to resect and often have local

recurrences. They usually do not metastasize to the lymph nodes since their spread is hematogenously; unless they are poorly differentiated or of the leiomyoblastoma variety. ⁽¹⁷⁾ This type of tumor is not radiosensitive and chemotherapy with vincristine, cyclophosphamide, actinomycin and adriamycin has been used. ⁽¹⁸⁾ Leiomyosarcomas require surgical resection, evaluation of the peritoneal cavity and the presence of metastases. Typically, the dissemination is hematogenous and not lymphatic, the liver followed by the lung and peritoneum are the sites of metastasis in order decrescendo and finally the mesenteric nodes. If the primary lesion is symptomatic and there is no distant metastasis, surgical resection of the primary lesion may result in a better long-term prognosis due to its slow growth. After any resection, periodic endoscopic follow-up and CT scan are recommended. The prognosis of leiomyomas of the colon is good and no cases have been reported after surgical resection. The 5-year prognosis of colorectal leiomyosarcoma is 20 to 50%. ^(19,20)

GIST Colorectal Tumors

General and Physiopathogenic

Gastrointestinal stromal GISTS tumors were initially described by Stout in 1962, ⁽²¹⁾ are mesenchymal tumors that originate from the intestinal wall, omentum or retroperitoneum that have positive staining for CD 117 immunohistochemical markers and of this 70% are also positive for CD 34. When we compare large intestine to stomach GISTS, the radius GISTS / Smooth muscle tumors are greater in colorectal GISTS. Initially, polypoid leiomyosarcomas were reported with a better prognosis than GIST, but 90% of the cases previously described as leiomyosarcomas were GISTS in different series. Miettinen in 2001 described a series of 144 anorectal GISTS tumors that had initially been described as leiomyomas and that were reclassified as positive GISTs for CD 117. ⁽⁹⁾

The most common site of GIST tumors is the stomach in 45 to 55%, followed by 25 to 35% in the small intestine and 10 to 20% in the colon and rectum. Colorectal GISTS constitute 12% of the total, of the colorectal region are located mostly in the rectum and anus in 80% of cases. The age of presentation is around 60 years, ranging from 16 to 94 years in the different studies. The male / female ratio is 1.1 to 2.1 with male predominance. ⁽²¹⁾ A smaller percentage also occur in the omentum, mesentery or retroperitoneum. Up to 30% of GISTS are considered malignant. The average survival is 3 years and at 5 years it is 45%. Patients with

gastric GISTS tumors have a better prognosis. ⁽²¹⁾ In general, there are no associated factors but neurofibromatosis type I is mentioned, and the Carney triad and familial GISTS are described as predisposing factors. ⁽²²⁾

Recent studies indicate that the progenitor cells of GIST are the interstitial cells of Cajal or other pluripotent mesenchymal stem cells. ⁽²³⁾ They seem to originate from the mutation in the C-kit, tyrosine kinase of the interstitial cells of Cajal that results in the permanent activity of the enzyme. Normally the C-kit tyrosine kinase stimulates the stem cell factor resulting in cell proliferation and growth. The kit activates a cascade of intracellular growth and signs of differentiation that are necessary to maintain hematopoiesis, development of mast cells, gametogenesis, melanogenesis and development of interstitial cells of Cajal. ⁽²⁴⁾

A lower percentage of GISTS appears to be C-kit negative in immunohistochemistry and usually have a mutation in a different tyrosine kinase, in the alpha receptor of the platelet-derived growth factor (PDGFRA).

Some positive immunohistochemical stains have also been reported in GISTS tumors, such as smooth muscle actin in 25% and desmin in 5%. ⁽²⁵⁾ Several studies have shown that the expression of CD 34 is variable from 38% to 94%. Initial work on the expression of CD 117 showed that 85% were positive, but subsequent studies have revealed positivity of 90% to 100%. ⁽²⁴⁾ Other tumors that present CD 117 + include metastatic melanoma, Ewing's sarcoma, endometrial cancer, follicular and papillary carcinoma of the thyroid and seminoma among others. Other markers such as desmin, S-100, beta-catenin can also be used to differentiate GISTS respectively from others such as solitary fibrous tumors, schwannomas, desmoid fibromatosis. A common benign lesion CD34 positive but C-kit negative is the inflammatory fibroid polyp of the anus.

Clinical Presentation and Diagnosis

The most common clinical presentation is hematochezia, abdominal or rectal pain and a mass at endoscopic examination. The majority produces bleeding, obstruction or pelvic-rectal pain. Anorectal GISTS present with nonspecific symptoms of bleeding, pain, mass sensation, constipation and anemia. Most rectal GISTS are located less than 10 cm from the margin of the anus. Because of its submucosal location, mucosal biopsies are usually normal and nonspecific.

Computed tomography (CT), magnetic resonance imaging (MRI), endoscopy, and endoscopic ultrasound are important tests. They are used to determine the size, limits, and presence of metastatic disease. CT scan of the thorax, abdominal and pelvis should also be performed. The radiological appearance of anorectal GISTS is described as well-circumscribed masses that may be large but without adenopathy. Evidence of central hemorrhage is a characteristic finding of GISTS compared to carcinoma, resembling cysts or areas of low attenuation in CT scan. ⁽²⁶⁾

Histologically, the GISTS demonstrate three morphological patterns: fusiform, epithelioid or mixed. The fusiform or elongated cell variant constitutes 70% of the tumors of the entire gastrointestinal tract and the epithelioid variant is 20% of all. Tworek studied 22 anorectal GISTS and found that the majority were of the fusiform variant and when they colonic GISTS the most frequent variant was the epithelioid. ⁽²⁷⁾ These tumors although they do not have lymphatic dissemination, have a high potential for long-term recurrence, even after 4 years of surgical resection.

Chak described that endoscopic ultrasound suggests malignancy when there are lesions larger than 4 cm, irregular extraluminal borders, echogenic foci and cystic spaces within the tumor. ^(28, 29)

Surgical Treatment

The primary treatment of GISTS tumors consists in the excision of the tumor with good margins (complete surgical resection). Depending on the site and size of the tumor, it may involve partial resections in bulky tumors. Enucleation of the tumor is not recommended. Resection of the lymph nodes is also not recommended. The type and extent of operation are dependent on the tumor size and location, rather than the subtype of the differentiation line. Surgery is the mainstay of the curative treatment of GISTS, independent of location and extension, but even with good surgical and early treatment, there is a high risk of local and hepatic recurrence. Some authors mention recurrences of 40% 2 years after surgery. Thus, the enucleation of the tumor leaving the pseudocapsule is outlawed.

Surgical resection is indicated as long as there is no metastasis or when after treatment of metastatic, unresectable or recurrent disease with biological treatment a stable response of the disease is achieved. Full-thickness transanal excision is indicated for small lesions in the lower rectum and low anterior resection or perineal abdominal resection when radical resection is required. Local or transanal excision

of full thickness is safe in low-risk tumors, less than 3 cm and with less than 6 mitoses per 50X of the microscopic field. Large tumors or tumors with 5 or more mitoses per high power field should have a low anterior resection with coloanal anastomosis or perineal abdominal resection and should be considered for adjuvant therapy with biological treatment. ⁽²⁵⁾

Biological Treatment

Surgery alone is not curative for most GISTS. It has been found that neither single radiation therapy nor surgery has a benefit. With the advent of biological treatment, an inhibitor of tyrosine kinase (Imatinib mesylate) ST1571, “Gleevec or Glivec”, was discovered, dependent on the presence and mutation of CD 117. This drug has shown spectacular results in the treatment of solid tumors, with total regression but high recurrence when suspending it. It works by blocking the abnormal activation of the KIT oncoprotein. Imatinib was initially used for patients with chronic myeloid leukemia and for GISTS at a dose of 400 mg BID or every day for a year to maintain a stable or partial response disease, initiated 84 days after surgery resulting in overall survival of 97% to 3 years and as a neoadjuvant cytoreductive treatment to respect adjacent organs or vital structures for 8 to 12 weeks at a dose of 600 mg per day until the day of the surgical procedure. Demetri used Imatinib in 147 patients with metastases or unresectable tumors and found that 54% had a partial response and 41% response with stable disease. The autor demonstrated a 70% response in patients with metastasis. ⁽³⁰⁾

The use of Imatinib as a postoperative adjuvant after surgery is currently being investigated, also for tumors that are unresectable or marginally resectable since the pre-operative period (neoadjuvant), since they dramatically decrease tumor size and facilitate surgical resection. In February 2001, the FDA approved Imatinib mesylate for metastatic or unresectable disease and has shown an 86% response including 53.7% partial response and 27.9% stable disease. Mild adverse events include periorbital and peripheral edema, diarrhea, nausea, and fatigue in 98% of cases, but there are also severe adverse events in up to 21% of cases including gastrointestinal or tumor hemorrhage. Current estimates that up to 90% of patients are alive at 64 weeks with this medication. ⁽³¹⁾

A complete response to treatment is rare, but some patients with an unresectable disease may become resectable with conservative sphincter surgery. These reports indicate that

the cytoreductive treatment with Imatinib increases the number of patients available for surgical resection with curative intent and reinforces the fact that surgical resection is the essential treatment for this disease. The indications for the biological treatment are summarized below. (**Table 46-1**)

Table 46-1. Indications for Biological Treatment

- Metastatic Disease
- Unresectable Disease
- Recurrent Disease
- After Surgery in Patients with High-Risk Criteria

Modified from Van der Zwan SM, DeMatteo RP.
Gastrointestinal stromal tumor: 5 years later. *Cancer*
2005;104:1781-8 ⁽³¹⁾

Patients with the PDGFRA mutation are resistant to Imatinib and for this indication, another “Sunitinib” biological treatment has been used, which is under study. ⁽²⁵⁾

Prognosis and Follow-up

Many authors have tried to differentiate malignant and benign GISTS. The most common characteristic cited as a factor indicating bad prognosis is the tumor size and the index or mitotic activity described as the number of mitoses per 50X. High-grade tumors are associated with worse prognosis independent of size and invasion. It is mentioned that high-grade tumors are defined as those greater than 10 mitosis by 50X and low grade those with less than 10. Low-grade tumors have a 5-year overall survival of 72% and high-grade tumors of 18%. (**Table 46-2**) Several studies have shown that the overall survival at 5 years is 78% in patients with tumors smaller than 10 cm compared with 38% with tumors larger than 10 cm. Other authors have shown that 6 or more mitosis in 50X is an indicator of malignancy. ⁽²⁷⁾ As mentioned, in general, gastric tumors have a better prognosis than intestinal GISTS of the same size and mitotic activity. The general view that anorectal GISTS have a poor prognosis is based on observing a local recurrence of 75% in tumors greater than 5 cm independent of the mitotic index and 62% in tumors below 5 cm but with 5 or more mitoses. Other prognostic factors include the aforementioned endoscopic ultrasound findings, the location of the tumor in the muscularis propria and those tumors that contain mutations in exon 11, have a higher mitotic index, recurrent disease, and mortality. ⁽²¹⁾

Table 46-2. GISTS Risk Category Depending on the Tumor Size and Mitotic Count

Very low:	Less than 2 cm and mitotic index less than 5 in a 50X field.
Low:	Between 2 and 5 cm and an equal mitotic content of less than 5 times 50X.
Intermediate:	Less than 5 cm and mitotic index 6 to 10 / 50X or 5 to 10 cm and mitotic count less than 5 / 50X.
High:	Tumors larger than 5 cm and counts greater than 5 / 50X or larger than 10 cm, independent of mitotic count or greater than 10 mitotic counts / 50X.
Modified from Fletcher CDM, Berman JJ, Corless C, <i>et al.</i> Diagnosis of gastrointestinal stromal tumors: a consensus approach. Hum Pathol 2000;33:459-65. ⁽³²⁾ Changchien CR, Wu MC, Tasi WS, <i>et al.</i> Evaluation of prognosis for malignant rectal gastrointestinal stromal tumor by clinical parameters and immunohistochemical staining. Dis Colon Rectum 2004;47(11):1922-9. ⁽³³⁾	

Mietinem showed that tumors with very low risk had a recurrence of 5%, increased to 25% when the tumor had a low risk and up to 66% of recurrence had metastasis. Rescue therapy with a second-line tyrosine kinase inhibitor and re-excision can prolong overall survival. ⁽²⁵⁾ Finally, for the follow-up, in addition to the physical examination and CT scan abdominopelvic every 3 to 6 months, for 3 to 5 years, it is necessary to continue later every year.

Lymphomas

Primary colorectal lymphomas are infrequent diseases of unknown origin ⁽³⁴⁾ and represent 0.16% to 2% of the colorectal malignancy. An increase in the 2/1 ratio has recently been observed in favor of men. Up to 40%

of lymphomas are of extranodal origin and the most common place is the gastrointestinal tract. Most extranodal gastrointestinal lymphomas occur in the stomach and small intestine, followed by the colon. ⁽³⁵⁾ Colorectal lymphomas occupy 15% to 20% of gastrointestinal lymphomas ⁽³⁶⁾ and approximately 70% are located in the cecum and ascending colon. ⁽³⁷⁾ Clinically they are characterized by abdominal pain, palpable mass, hematochezia or mane or weight loss. Gastrointestinal lymphomas are divided into primary and secondary lymphomas. The primary ones originate in the colon and rectum, while the secondary ones represent a metastasis to the gastrointestinal tract. Primary lymphomas, if detected early, are potentially curable, while secondary lymphomas by definition occur at a late stage and typically have a poor prognosis. The Dowson criteria are widely used to define a primary colorectal lymphoma. (Table 46-3)

Table 46-3. Dawson's Criteria of Primary Gastrointestinal Lymphoma

• Absence of superficial palpable lymphadenopathy. • No enlargement of mediastinal lymph nodes in radiographic images. • No abnormalities in white blood cell count or its differential. • Prevalence of intestinal lesion in laparotomy with or without involvement of regional nodes. • No liver or spleen condition.
Modified from Dawson IMP, Cornes JS, Morson BC. Primary malignant lymphoid tumors of the intestinal tract. Report of 37 cases with a study of the factors influencing prognosis. Br J Surg 1961;40:80-9. ⁽³⁸⁾

In order to define whether it is a primary or secondary lymphoma, it is important to perform complementary studies such as CT scan, peripheral rub, liver tests, and bone marrow. Most lymphomas of the colon and rectum are non-Hodgkin's lymphocytes, diffuse large cell variety, other types include low-grade mucosa-associated lymphoid tissue (MALT) lymphomas (MALTOMAS), mantle cell lymphomas, and T-cell lymphomas. The World health Organization (WHO) classifies them into:

- Large cell lymphoma B
- Extranodal lymphoma of the marginal zone or MALT lymphoma (MALTOMAS)
- Lymphoma of mantle cells
- Burkitt's lymphoma and
- Follicular lymphoma ⁽³⁹⁾

The most common histological type of the gastrointestinal tract and colon is non-Hodgkin B, diffuse large cell lymphoma. The second most common is low-grade B-cell malformation. Mantle cell lymphomas are diffuse small-cell lymphomas that occur especially in men and are of poor prognosis, but usually correspond to a systemic disease with colorectal involvement. T-cell and Hodgkin lymphomas are rarely described as isolated cases. ⁽³⁶⁾ High-grade B lymphoma in an infected human immunodeficiency virus (HIV) is considered a condition to define acquired immune deficiency syndrome (AIDS). Ninety percent of the cases of non-Hodgkin's intestinal lymphomas consist of discrete single lesions and in 10% there are multiple or diffuse lesions. Eventually, adenocarcinoma of the colon has been reported in synchrony or metachrony. The cecum is the area most frequently involved in 60%, followed by the rectum in 20% and is by the abundant lymphoid tissue of the ileocecal region. ⁽¹⁸⁾

Clinical Manifestations

They occur at an average age of 55 years. It affects men twice as much as women. But in general, they occur between the fifth and seventh decade of life. There are vague or nonspecific symptoms that delay the diagnosis. Abdominal pain and weight loss are the predominant symptoms, followed by gastrointestinal bleeding and changes in bowel habit. Less frequent symptoms include fever, fullness, vomiting, anorexia, and weakness. Rare presentations include intestinal obstruction, intussusception, toxic megacolon, appendicitis, and intestinal perforation. A palpable mass is

the most frequent physical sign. Lymphoma is the second most common cause of acute low-grade bleeding in patients with HIV. Symptoms such as bloody diarrhea, fever, and abdominal pain can be confused with inflammatory bowel disease. ⁽⁴⁰⁾

Diagnosis and Staging

In most cases the diagnosis is made during a laparotomy, however usually the radiological and endoscopic findings suggest malignancy. In the barium enema an intraluminal mass, nodularity of the mucosa or annular stenosis can be observed. In rare cases, aphthous ulcers that can be confused with inflammatory bowel disease or infectious colitis, but in the CT scan can only be found thickening of the colonic wall. Colonoscopy exhibits a large variation of findings ranging from small superficial erosions to large and ulcerative tumors. ⁽⁴¹⁾ The biopsy can be diagnostic up to 85% of cases. There is no correlation between endoscopic and histological morphological findings of lymphoma. It can even be observed numerous polypoid lesions consistent with malignant lymphomatous polyposis and associated with MALTOMA. The endoscopic findings in colorectal lymphomas are generally similar to inflammatory bowel disease, characterized by intermittent lesions, sporadic superficial ulcers or nodularity that may resemble Crohn's disease or erythematous areas of ulcerative colitis. Recently, an endoscopic classification of colorectal lymphomas ⁽⁴²⁾ includes fungantes, ulceratives, infiltratives types and mixtures of them. The ileocecal and rectosigmoid region is frequently affected, usually the lesions are described as polypoid tumors, diffuse proctitis, submucosal nodules or "putative carcinomas". Lymphoma starts in the submucosal lymphoid tissue and usually affects large segments of the colon in a uniform and continuous manner. Submucosal infiltration histologically extends beyond the macroscopically affected area. Intermittent lesions may also be present. ⁽⁴³⁻⁴⁶⁾

Radiologically, a lymphoma is suggested when there is an important bulky extracolonic component, concentric dilatation of the lumen, polypoid filling defects in the terminal ileum and the ileocecal valve. ⁽¹⁸⁾ The radiological findings can be localized or diffuse and are characterized by polypoid masses, circumferential or cavitary lesions, focal nodularity of the mucosa, diffuse ulcerations or nodular lesions. In most cases, they are large fungal lesions, ulcerations of the mucosa are unusual. ⁽⁴⁷⁾ The staging used is a modification of the Ann Arbor System proposed by Musshoff. (Table 46-4)

Table 46-4. Ann Arbor Extranodal Staging for Colorectal Lymphomas

IE:	Single extranodal lesion without nodes.
IIE:	Single extranodal lesion and adjacent positive nodes.
III:	Multiple lesions on both sides of the diaphragm, including sites extranodal or spleen.
IV:	Bone marrow involvement, central nervous system or diffuse visceral infiltration.
Modified from Quayle FJ, Lowney JK. Colorectal Lymphoma. Clin Colon Rectal Surg 2006;19:49-53.	

Pathology

Primary gastrointestinal lymphomas are almost always non-Hodgkin's lymphomas. Actually, they represent less than 4% of primary colorectal lymphomas. As mentioned, the most frequent variant is diffuse large B-cell lymphoma. The WHO classification recognizes 5 histological varieties of lineage B: extranodal marginal MALT type lymphoma, follicular lymphoma, mantle cell lymphoma, diffuse B large cell lymphoma and Burkitt's lymphoma. According to the REAL classification, intestinal T-lymphoma is subdivided into enteropathy associated with T-cell lymphoma and T-cell lymphomas not associated with enteropathy. Diffuse large-cell lymphoma B has a frequency ranging from 47 to 81%, but next to the MALTOMA they occupy 90% of the cases.⁽⁴⁸⁾ At the time of diagnosis, 14 to 24% are in stage IE and the great majority in stage IIE, between 62% and 86%.

At macroscopic examination, the tumor reveals protruding or ulcerated lesions resembling a carcinoma or a diffuse process that extends over a large segment of the colon, sometimes with numerous polypoid intraluminal excrescences,⁽¹⁸⁾ the wall of the intestine is thickened and has a firm consistency. The presence of a non-ulcerated submucosal pattern on the rectal wall should be differentiated from other benign lesions. Primary non-Hodgkin type B colorectal lymphomas can be high grade, intermediate or low, 78% correspond to high grade lesions, 22% intermediate and low grade. Here are some positive immunohistochemical markers of the different types of lymphoma:

- High or low grade lymphomas (CD 20, CD 3, CD 56)
- High or low grade maltomas (CD 20, CD 19)
- Lymphoma B of mantle cells (malignant lymphomatous polyposis) (CD 5, cyclin D1)
- Burkitt's lymphoma (CD20, EBV, C-MYC)

With regard to malignant T-cell lymphomas, most are the product of the long-term complication of a celiac sprue and the malabsorption syndromes. Some are CD56 positive or are associated with Epstein Bar virus. They are referred to as T-cell lymphoma associated with enteropathy. The majority of B-cell lymphomas are solitary lesions of the small intestine and the most affected portion is the ileum followed by the jejunum and duodenum respectively. Diffuse infiltration in the ileum, prominent transverse mucosal folds, or ulcerated circumferential lesions are the most common microscopic features of T lymphomas.

The concept MALT "Lymphoid tissue associated with mucosa" was proposed by Isaacson to define the immune system component of the intestinal wall, this includes the Peyer's plates of the ileum, the lymphocytes and plasma cells in the lamina propria and the intraepithelial lymphocytes. This immune compartment has distinctive functional and morphological findings and is applied not only to low grade small lymphocyte lesions but has extended to lesions of large cells with intermediate or high grade. The positive markers are CD19, CD20 and there is negativity of CD5, CD10 and CD23. The majority of colorectal lymphomas are of low grade and belong to the category of maltomas, characterized by infiltration of the glandular epithelium by neoplastic lymphocytes, a microscopic finding called "lymphoepithelial lesion", another characteristic finding of low-grade lymphomas are the "bodies of Dutcher", true intranuclear eosinophilic inclusions of immunoglobulin and cytological atypia. Low-grade lymphomas are characterized by their slow clinical evolution and tendency to remain localized for a long time, with a propensity to affect mucous membranes.⁽⁴⁹⁾

Intestine lymphomas macroscopically can produce prominent folds of the mucosa, ulcerations in the colon and what has been called lymphomatous polyposis in the

form of countless tiny polyps. This presentation can occur in mantle cell lymphomas, follicular lymphomas, maltomas or large cell s lymphomas.⁽⁵⁰⁾

Pathogenesis and Risk Factors

The basic pathogenesis is the antigenic stimulus that causes lymphocyte proliferation and eventually malignant transformation with clonal expansion. The antigenic stimulus involved in the development can be from an autoimmune disease, chronic infection or chronic inflammation. A different model hypothesizes in immunocompromised patients that the malignant transformation is the result of the Epstein-Barr virus. Associated conditions that are cited include patients with inflammatory bowel disease, organ transplantation, HIV, or using immunosuppressants such as mercaptopurine and azathioprine. It is associated with celiac disease, chronic diverticulitis, *H pylori* and alpha chain disease too. Although the association between inflammatory bowel disease and lymphoma is controversial, some studies have indicated a higher frequency of lymphomas in inflammatory bowel disease, which population studies have not confirmed. (Table 46-5)

Table 46-5. Predisposing Factors or Associated with Gastrointestinal Lymphoma

- HIV infections - AIDS
- Inflammatory bowel disease: Ulcerative colitis and Crohn's disease
- Organ transplants
- Immunocompromise
- Celiac Disease

Modified from Crump M, Gospodarowicz M, Shepherd FA. Lymphoma of the gastrointestinal tract. *Semin Oncol* 1999;26(3):324-377.⁽⁵¹⁾

Treatment

The treatment of anorectal lymphoma differs drastically depending on the status of the HIV and grade of the lymphoma.⁽²⁵⁾ It is important to perform an HIV test on every patient with a primary colorectal lymphoma and properly stratify it. The majority of colorectal lymphomas that require surgical intervention are in stages IE or IIE, that is, disease confined to the colon with or without the regional lymphatic disease. The therapeutic options include surgery, chemotherapy, and radiotherapy. A multidisciplinary team

involving surgeons, gastroenterologists, pathologists, oncologists, and colorectal surgeons is required.⁽⁵²⁾

In fact, the optimal management of primary colorectal lymphoma has not been determined by controlled clinical trials. Traditionally, surgical excision, if technically possible, is the mainstay of treatment. Surgery is usually required in patients with obstruction or intussusception. Patients obstructed with colonic distal lymphomas and poor surgical prognosis can be treated palliatively with colonic stents. Right hemicolectomy is the most common surgery because this neoplasia occurs more frequently in the cecum. The resection should include regional lymph nodes and primary anastomosis. The only reason not to perform the laparoscopic approach is local tumor invasion of adjacent structures or a large volume tumor that requires a large incision to remove the specimen; otherwise, laparoscopic resection is the treatment of choice.⁽⁵³⁾

In the absence of disseminated disease, as mentioned above; surgical resection is the treatment of choice. Corman's book recommends that a lymphoma confined to the resectable rectum, surgical excision must be followed by radiation therapy. If the tumor is unresectable, radiotherapy is extremely beneficial. When there is a systemic disease, chemotherapy is the choice.^(18,54) Adjuvant chemotherapy can be added to prevent recurrence and improve prognosis. Several schemes have been used, but the traditional ones are: CHOP (cyclophosphamide, vincristine, doxorubicin and prednisone), MOPP (Mechlorethamine, vincristine, procarbazine and prednisone) or DBVD (doxorubicin, bleomycin, vinblastine and dacarbazine). The first line of chemotherapy is CHOP for all high-grade or intermediate B-cell lymphomas, others have added R-CHOP with better response, disease-free progression, and overall survival.⁽⁵⁵⁾

The risk of spontaneous perforation of the intestinal lymphoma is high and it is estimated in 30% of the cases, therefore colectomy is beneficial to prevent this complication. Some authors suggest that in early diagnoses, chemotherapy could avoid surgery, which is controversial. Several authors have shown in special cases of primary lymphomas of the rectum the complete clinical response after the combination of radiotherapy and chemotherapy.⁽⁵⁶⁾

Low-grade lymphomas such as malignomas may be resistant to chemotherapy and surgery serves as a definitive treatment.⁽³⁶⁾ Some observations regarding colorectal MALT lymphoma indicate regression after antibiotic regimens used to eradicate *H. pylori*, even in *H. pylori* negative patients, no one knows for sure why.⁽⁵⁷⁻⁵⁹⁾ Maltomas of the colon are usually solitary lesions but may present as multiple

polypoid lesions. ⁽⁶⁰⁾ Most localized rectal malformations have been treated with radical resection and radiotherapy improves survival. It must be observed if the excision has negative margins. The locoregional radiation is used if these margins are positive. However, some cases can be managed with radiotherapy as the only possibility. ^(56,61-63) Of a series of 17 colon malignancies, two cases presented complete regression with chemotherapy or concomitant treatment for *H. pylori* infection. The rest were managed by surgical resection and some of them with chemotherapy as well. ⁽⁶⁴⁾

Lymphomatous polyposis usually corresponds to a mantle cell lymphoma that affects the gastrointestinal tract and is characterized by diarrhea, weight loss, abdominal pain, bleeding, anemia, and multiple polyps from the stomach to the rectum. It can be confused with familial adenomatous polyposis and the treatment is chemotherapy based on cyclophosphamide, doxorubicin vincristine, prednisone and bleomycin. ⁽⁶⁵⁾

In the case of indolent lymphomas such as mantle cell lymphomas, follicular lymphomas and T-cell lymphomas, the treatment of choice is complete surgical resection and radiation since they have little response to chemotherapy.

In a patient with organ transplantation and colorectal lymphoma, it is ideal to suppress or reduce immunosuppressive therapy, followed by surgical resection and adjuvant chemotherapy. B-cell lymphomas, related to AIDS, are classified as having a high degree of aggressiveness but have recently shown that they benefit from combined antiretroviral treatment, chemotherapy and granulocyte colony-stimulating factors. ⁽²⁵⁾

Radiotherapy is used for local recurrence, stages III and IV or systemic recurrences and in follicular lymphomas. ⁽⁶⁶⁾ In stages I and II, local treatments are highly effective and malignomas are highly sensitive to radiotherapy at moderate doses.

In conclusion, although some oncologists believe that colorectal lymphomas can be controlled with chemotherapy, surgery for surgical excision of the tumor continues to be the mainstay of treatment in colorectal lymphoma and chemotherapy is reserved for relapses after localized therapy for high-grade tumors, components of large cells or advanced stages of the disease ^(56,67) others include stage II. ⁽⁶⁸⁾

Monitoring and Prognosis

The recurrence of lymphoma varies from 33 to 75%, therefore a follow-up with annual colonoscopy and

abdominal CT scan is required to evaluate the presence of relapse. Regarding the factors of poor prognosis, several factors are mentioned in the literature, such as advanced age, inoperable tumor, lesion greater than 5 cm, transmural invasion, lymph node involvement, advanced stages, high-grade histology and the presence of symptoms in a B-lymphoma. The histological type also affects survival; for example, malignant lymphomatous polyposis has a poor prognosis, whereas low-grade malignomas have a good prognosis even without surgery or chemotherapy.

In patients treated with surgery and adjuvant therapy, the 5-year survival rate varies from 20% to 55%. Colorectal lymphomas generally have a worse prognosis than lymphomas of the stomach or small intestine and even less than colorectal adenocarcinoma, and on average it is 27% at 5 years for locally advanced disease and 5% to 15% for disseminated disease. The average survival is usually 24 to 36 months, but it is better when chemotherapy is added to surgery, especially in stages IIE. ⁽³⁶⁾ This average prognosis of 50% at 5 years decreases to 12% at 5 years when the regional lymph nodes are affected.

Burkitt Lymphoma

Burkitt's lymphomas are aggressive forms of non-Hodgkin's B-cell lymphomas that are usually diagnosed in children and young adults and less frequently in adults. Three variants are recognized: endemic, sporadic and associated with immunodeficiency. Histologically, they are small non-cleaved cell lymphomas with stellate sky image characteristics due to the great proliferation and spontaneous cell death. ⁽⁶⁹⁾ The cytogenetic translocation of the MYC oncogene on chromosome 8 is characteristic of the disease. However, the clinical presentation differs depending on the variant. The endemics correspond to the head and neck region and have been associated with the Epstein-Barr virus. The sporadic is manifested in the intestines, in the ileocecal region and only 15 to 30% have Epstein-Barr virus positive. Sporadic Burkitt's lymphomas account for 1% to 2% of lymphomas in adults and 40% of lymphomas in children. Other affected areas include, in addition to the ileocecal area, the ovaries, kidneys, omentum and Waldeyer's ring. When there is involvement, most have chronic symptoms such as an ileocecal mass, but they can present as colonic ischemia, acute appendicitis or intussusception. The variant associated with immunosuppression is observed in patients with HIV-AIDS or transplanted patients and usually presents with generalized lymphadenopathy. ⁽⁷⁰⁾

Burkitt lymphomas are high-grade lymphomas and are immunohistochemically positive for CD 45, CD20, CD10, BCL-6 and negative for CD3, DTT, BCL-2. The treatment of choice is a surgery with complete resection followed by chemotherapy by hyper-CVAD + rituximab course according to the Thomas protocol of 8 cycles. ⁽⁷¹⁾ When there is extensive abdominal involvement or disseminated metastatic disease, it is preferred to perform a biopsy followed by chemotherapy before resection and anastomosis. ⁽⁷²⁻⁷⁴⁾

Colonic Complications of Leukemia

They have been divided into those caused by leukemic invasion of the bowel and complications from immunocompromise that will not be detailed here. Leukemic infiltration of the colon is relatively infrequent. The most common symptoms are non-specific, such as abdominal pain, bloating, diarrhea, and hematochezia. The radiological and endoscopic findings range from localized small lesions, diffuse polyposis, appearance of colitis, intestinal thickening with plaques, and in the CT scan diffuse thickening of the intestinal wall. The treatment consists of treating the underlying leukemia and surgery only for complicated cases.

Secondary Lymphoma

This entity is more common than primary colorectal lymphoma and of different distribution since it preferentially affects the left and rectum colon. Most cases of secondary colorectal lymphoma are asymptomatic and by definition are advanced stages with poor prognosis. When they have symptoms, they develop bleeding, obstruction or perforation and usually survive less than 3 months.

Carcinoids and Intestinal Neuroendocrine Tumors

Generalities

Carcinoid tumors originate from enterocromaphine cells, part of the diffuse endocrine system, belong to the group of tumors called neuroendocrine. They can be found throughout the body, lung, skin, urogenital system, digestive system, thyroid, parathyroid and adrenal glands and are subdivided into low grade or carcinoid and high grade tumors. The clinical and histological recognition of carcinoid tumors

was first described by Lubarsch in 1888. The term “Karzinoid” means resembling carcinoma and originated in 1907 by Oberndorfer, in an attempt to emphasize the benign and different nature of the lesion. These tumors are similar histologically to the carcinoma but of a different course. However, their malignant potential is now recognized and they are considered malignant neoplasms. The association between carcinoids and serotonin production was first described by Lembeck in 1953 and the first description of the carcinoid syndrome was made by Waldenström in 1954. ⁽⁷⁵⁾ In 1969, Pearse recognized the APUD qualities of the tumor “Amine precursor uptake and decarboxylation” and were named in that decade Apudomas. In 1978, the first description of undifferentiated small cell tumors of the colon and rectum was made by Gould and Chejfec. ⁽⁷⁶⁾

Neuroendocrine tumors and low-grade carcinomas originate from the same epithelial neuroendocrine cells, after damage to the mother cell and high-grade neuroendocrine carcinomas originate from APUD tissue. Carcinoids originate from the kulchitsky cells or basogranular enterocromaffins located in the crypts of Lieberkühn. The carcinoid term is used only for well-differentiated neuroendocrine tumors with low or non-malignant potential. ⁽⁷⁷⁾ Some authors refer three tumor varieties according to the histological pattern: pure neuroendocrine tumors, predominantly neuroendocrine and tumors with neuroendocrine similarity and exocrine expression. ⁽⁷⁸⁾ Of course, the prognosis is worse for pure neuroendocrine tumors and small cell pattern and is better for those of the intermediate cell type. ⁽⁷⁷⁾ It is not recommended to use the term “Apudomas” but the neuroendocrine tumor. ⁽¹⁸⁾ The truth is that the WHO has proposed that the term best used for these tumors is that of gastroenteropancreatic neuroendocrine tumors since carcinoid does not adequately cover the spectrum of heterogeneity of neoplasms. ⁽⁷⁹⁾

In different studies it has been shown that carcinoid tumors, independent of the tumor site, have a higher prevalence of malignant tumors, especially in the breast, uterus, hematopoietic system and especially gastrointestinal adenocarcinomas. Malignant carcinoids are well differentiated neuroendocrine carcinomas that could correspond to tumors that have invaded the muscularis propria or metastasized to regional lymph nodes or distant sites such as liver or lung. After receiving a biopsy or histopathological examination with carcinoid or neuroendocrine tumor, the next step is the biochemical tests of 5-hydroxytryptamine platelet, urinary 5-HIAA, serum chromogranin A, and tumor staging. ⁽⁸⁰⁾

Pathology

The characteristic histological findings are uniform ovoid cells with a round hyperchromatic nucleus, little mitotic activity and granular cytoplasm. Carcinoid tumors have an affinity for silver salts and two types of argentaphin and argyrophilic reactions have been described. The argentaphinic reactions are secondary to the ability of serotonin to reduce silver but are called argyrophilic, when the tumor is able to take the silver without reducing it. Carcinoids of the colon are usually argyrophilic but not argenaphinic

They are composed of small round cell shells that demonstrate neurosecretory granules in ultrastructural examination, these vesicles contain neurosecretory granules that correspond to synaptic vesicles found in neurons. In addition to these reactions, immunohistochemical stains such as chromogranin, neuron-specific Enolase and Synaptophysin are used to identify the neuroendocrine origin of the tumor. ⁽⁷⁵⁾ Pathological findings such as nuclear pleomorphism, with multiple mitoses, positive ki-67 and synaptophysin help in the diagnosis. Chromogranin A is the best global marker for neuroendocrine tumors and is usually elevated by more than 50-100% of normal. ^(81,82) In general, carcinoids have a benign behavior, but high-grade neuroendocrine tumors are especially aggressive with a high prevalence of metastasis. ⁽⁷⁷⁾ No other criterion than the spread of the tumor predicts the behavior of the carcinoid. In particular, histological criteria and tumor size fail to specify and distinguish the malignant potential of carcinoids. There are 5 histological varieties proposed by Johnson:

1. Insular: It is the most frequent and favorable prognosis.
2. Trabecular: The second most frequent, also of favorable prognosis.
3. Glandular: Not frequent and poor prognosis.
4. Undifferentiated: Bad prognosis.
5. Mixed: Prognosis favorable, includes the island component and other variety. ⁽⁸³⁾

In general, they produce more than 30 bioactive components including amines such as serotonin, histamine, proteins and prostaglandins. Serotonin is derived from tryptophan and requires two steps; the first is a hydroxylation and the second is decarboxylation. Then serotonin is stored and transported in platelets.

The size and depth of the lesion correlates with the incidence of metastatic disease. Rectal carcinoids below 1 cm have a very low risk of metastasis but increase in intermediate lesions between 1 and 2 cm to 34% and above 2 cm have more than 80%. The depth also influences the risk of metastasis, since when it is confined to the mucosa it is 12% and beyond it (muscularis propria) of 88%. Other factors associated with increased risk of metastasis are aneuploidy in DNA, 2 mitosis or more in 10x fields and atypical findings in histology.

The exact etiology of carcinoid tumorigenesis is unknown, but experimental studies indicate that N-Myc and C-jun oncogenes are linked. The first genetic events are considered to occur on chromosome 18q in the genesis of tumors of the middle intestine; followed by a loss of 16 q or 4p gain, such as late genetic mutations, especially detected in tumor metastases. It is of interest that 80% of carcinoid tumors have somatostatin receptors, a situation that is useful in the treatment of advanced cases. In addition, adenocarcinomatous differentiation is of poor prognosis. ⁽⁸¹⁾

The treatment of neuroendocrine tumors depends on the location and tumor size and is mainly surgical. In general, lesions smaller than 1 cm require less aggressive surgery with free margins; lesions larger than 2 cm, segmental bowel resection including generous lymph node resection. For intermediate lesions between 1 and 2 cm, the general condition, the anatomical location of the lesion, histological findings, the consequence of definitive resection (conserve or not sphincters) and the feasibility of follow-up after resection should be evaluated. ⁽⁸⁴⁾

Patients usually require cardiac studies because of the possibility of carcinoid heart disease and for this purpose an echocardiography is performed. The three most common cardiac lesions are pulmonary stenosis, in 90% of cases, tricuspid insufficiency in 47% and tricuspid stenosis in 42%. Hypertrophy of the right heart is less frequent.

The 74% of carcinoids occur in the gastrointestinal tract and of these 28.7% in the small intestine, 19% in the appendix and 13% in the rectum. ⁽⁸⁵⁾ Carcinoid tumors are at high risk of having other non-carcinoid tumors and of being multicentric. Adenocarcinomas of the colon are the most common tumors as the second primary malignancy. Most of them are synchronous to the carcinoid tumor. ⁽⁸⁴⁾

Rectal Carcinoids

Rectal carcinoids are rare tumors and occupy 1% of rectal tumors. The rectum is the third most common location after the small intestine and appendix. They are slightly more frequent in women of middle age from 48 to 59 years. The incidence of rectal carcinoids in examinations of sigmoidoscopy screening is one for every 1,400 proctosigmoidoscopies.⁽⁸⁵⁾ The incidence of multiplicity is 1 to 4%, a second malignancy can occur in 5 to 32% and the 5-year survival varies from 70 to 80%.⁽⁸⁴⁾

Presentation

The majority of rectal carcinoids are asymptomatic and are discovered incidentally, sometimes they may present with rectal bleeding, constipation, alteration of bowel habit and rectal pain or less frequently tenesmus, pain at evacuation, anal itching and weight loss.⁽⁸⁶⁾

Diagnosis

Many of the rectal carcinoids are detected by digital rectal examination or rigid proctosigmoidoscopy and most are found in the middle rectum 5-10 cm from the margin of the anus, consisting of firm, nodular, smooth and hard lesions on digital rectal examination. During endoscopy they appear as submucosal lesions, yellow, firm and sessile. Rarely they can appear whitish or reddish, semipediculate or pediculated or depressed. Endoscopic biopsy is diagnostic up to 88% of cases. Endorectal ultrasound shows homogeneous hypoechoic images, with smooth contours, sometimes with hyperechoic central areas. 5-hydroxyindolacetic urinary tests in rectal carcinoids are not useful. Tumors are classified as T1 (mucosa and submucosa); T2, invasion of the muscularis propria; T3, penetrate the wall to the subserosa and T4 perirectal invasion. The size of the tumor correlates with the invasion of the intestinal wall because usually tumors smaller than 2 cm do not produce lymphatic metastasis.⁽⁸⁶⁾

Treatment

Therapeutic decisions are based on the size of the tumor, usually lesions smaller than 1 cm can be treated by local resection. When they are between 1 and 2 cm, transmural resection and when they are greater than 2 cm an extended

surgical resection. In addition, therapeutic decisions are influenced by the depth of the invasion, positivity of the lymph nodes and the presence of distant metastasis.⁽⁸⁷⁾

Lesions smaller than 1 cm, without lymph nodes and without metastases require complete local excision. Even so, these small lesions have 1-3% of malignant disease. Surgical procedures include local excision with the biopsy forceps and local transanal excision or fulguration. There are also several endoscopic mucosal resection (EMR) techniques, "Strip biopsy" and resection with the polypectomy loop. However, it should be noted that standard polypectomy and endoscopic mucosal resections (EMR) are associated with high chances of having positive margins of 56% and 20% respectively. Prior to local excision, a total colonoscopy is required to rule out a synchronous lesion. Regarding the type of procedure in relation to the location of the lesion, lesions in the lower half of the rectum are managed by transanal resection, whereas high rectal lesions can be resected endoscopically with a polypectomy loop. These types of lesions need follow-up with colonoscopy, chest x-ray, endoscopic ultrasound and abdominal CT scan.

Lesions between 1 and 2 cm have a risk of metastasis of 11%, a local excision is sufficient for the disease control, but if there are unfavorable factors such as invasion of the muscularis a more extensive resection is required. For this, endorectal ultrasonography can be valuable. In the absence of regional lymph nodes or distant metastases, intermediate rectal carcinoids should be resected by transanal excision. This surgical approach provides an adequate specimen for pathology to evaluate wall invasion. The long-term survival after resection of these intermediate tumors when confined to the submucosa is excellent; however, up to 47% have atypical histology or invasion of the muscularis propria and are associated with metastasis or may develop metastases after resection.

The treatment of injuries involving the muscularis propria, larger than 2 cm or with positive lymph nodes usually require extensive surgery such as abdomino-perineal resection or low anterior resection; however, this is controversial, because it has recently been found that even doing radical surgery with complete resection does not improve survival and the risks of recurrence are high. Whenever radical surgery is going to be performed, it is important that there is no distant metastasis. If the case presents with distant metastasis, surgery is only offered for palliative purposes to control local complications such as bleeding or obstruction.^(88,89)

Prognosis

Both the size and the stage of the disease correlate with long-term survival after resection and in small lesions up to 1 cm it is 100%, but it has a mortality of 13% when the tumor is 1-2 cm. Lesions up to 1.9 cm have an excellent disease-free survival of 10 and 27 years after resection. When the submucosa is invaded, the long-term survival is 75%. T3 and T4 tumors have a bad prognosis with an average survival of 7 months. When they have positive nodes, it is 44% at 5 years and 7% when they have distant metastases. The absence of metastases guarantees an excellent 5-years prognosis of 92% ⁽⁸⁴⁾

Carcinoid of the Appendix

Appendix carcinoids typically behave differently than small bowel carcinoids and are found incidentally during an appendectomy. The prevalence of carcinoids is 0.32% in a study of more than 34,000 appendectomies. ⁽⁹⁰⁾ The carcinoid of the appendix occupies 8 to 19% of all carcinoid tumors and 75% of cases is located at the tip of the appendix. It can present as acute appendicitis, rarely produces a carcinoid syndrome (less than 10%), 4% have multicentricity and 13 to 32% have a second malignancy. The 5-year prognosis is greater than 90%. ⁽⁸⁴⁾ It is rare that the appendix carcinoid has lymphatic metastasis, but it becomes 11% when it is between 1 and 2 cm and 30-60% when it is greater than 2 cm.

Appendectomy is the choice in lesions smaller than 1 cm, whereas when it is larger than 2 cm, a right hemicolectomy is preferred. Intermediate lesions between 1 and 2 cm should be individualized, weighing the risks of extensive surgery against the residual tumor. Factors suggesting greater recurrence include lymphovascular invasion, invasion of the base of the mesoappendix by direct extension, lymph nodes or positive surgical margins and adverse histology that will require extensive resection after a positive transoperative study or in a second stage in the short term.

Carcinoid of the Colon and Small Intestine

Colorectal neuroendocrine tumors are rare and tend to be poorly differentiated, with a poor prognosis with a tendency to rapid metastasis. ⁽⁷⁷⁾ They are extremely rare tumors and predominate in women from 64 to 68 years of age. Tumors of the small intestine occupy 20% to 29% of all tumors, are more common in the ileum than in the jejunum, commonly have liver metastases, the prevalence of multiple tumors

is 30% to 40%, and a second malignancy is 29% to 52%. Survival at 5 years is 55%. ⁽⁸⁴⁾ Carcinoids of the small intestine are often associated with lymphatic metastases and structural abnormalities such as intussusception, mesenteric fibrosis, and small bowel angulations. Lesions smaller than 1 cm have lymphatic metastasis in 20 to 30%.

Within the colon, the most common carcinoids occur in the cecum with a frequency of 39% to 50%, followed by 15% in the ascending colon, 15% in the transverse, 15% in descending and 15% sigmoid. They rarely present carcinoid syndrome (less than 5%), from 20 to 35% have a second primary malignancy and their overall survival at 5 years from 33 to 42%. Adenocarcinomas can occur simultaneously in 3 to 10%.

Clinical Presentation

Carcinoid tumors are incidentally found or may occur as a result of the production of local or systemic symptoms. The local symptoms are related to the site of the origin or site of the metastasis, while the systemic symptoms are related to the production of bioactive components. Local symptoms of small bowel carcinoids may produce periodic symptoms of abdominal pain, small bowel obstruction caused by intussusception or mesenteric fibrosis, intestinal ischemia, or hemorrhage. Liver metastases can give hepatomegaly and pain in the right upper quadrant. Small bowel injuries are usually multiple. There are nonspecific local events associated with intestinal neuroendocrine tumors, for example fibrosis that can cause obstruction due to adhesions or narrowing of the intestinal lumen, hydronephrosis and secondary renal failure or even mesenteric ischemia due to constriction of the mesenteric vessels. ⁽⁸¹⁾

The vast majority of patients with neuroendocrine tumors of the colon are symptomatic and within the symptoms include abdominal pain, weakness, malaise, weight loss, anorexia, rarely diarrhea, bleeding, nausea and vomiting, 40% may have a palpable abdominal mass.

Diagnosis

Barium enema, CT scan, colonoscopy, laparoscopy and liver biopsy, urinary levels of 5-hydroxy-indoleacetic (5-HIAA) are performed. Barium enema demonstrates large, ulcerative annular lesions or obstruction. There is a poor correlation between the size and depth of the invasion. It can affect pericolic fat in 85% of cases. Metastatic disease

occurs in 64% of colon carcinoids, compared with 3 to 5% of the appendix and 14-34% of the rectum. Increased levels of substance P, serotonin or urinary 5-HIAA can be observed for 24 hours. Biochemical studies are performed especially on tumors of the small intestine, the 24-hour urine test of 5-HIAA. The normal excretion of this metabolite is between 2-8 mg / 24 hours, as long as the patient restricts fruits such as bananas, pineapple, kiwi, avocados and tomatoes, plums and some medications such as aspirin, acetaminophen or cough syrups, contain guaifenesin previously. ⁽⁹¹⁾

It is a fact that tumors of the midgut produce high levels of serotonin, the others rarely produce them. In different series it has been shown that the 5-HIAA values in the urine are abnormal in 92% of the midgut tumors and 29% of the tumors of the intestine.

CT scan and MRI are the tests required in the management of intestinal and colorectal neuroendocrine tumors. Typical findings include a triad of calcified mass, spiculations and stranding that suggests localized fibrosis. ⁽⁹²⁾ Radiologically, mesenteric angulations and fibrosis are observed, which is more evident than the mass and lesions of soft tissues shattered in the mesentery.

Treatment and Prognosis

Colonic carcinoids have an aggressive behavior and frequently have lymphatic metastasis and a poor prognosis.

The treatment is surgical, the type of operation depends on the location of the tumor, resection is the standard treatment, it must be resected with its lymph node component. The carcinoid of the colon is the one with the worst prognosis of all gastrointestinal carcinoids and the overall survival at 5 years is 20 to 37% and the average survival is 4.5 months, this correlates directly with the stage of the disease and for that the modified Dukes classification has been used. Among the unfavorable prognostic factors of colonic carcinoids are histological parameters of poor differentiation, high grade nuclei, mitotic tumor index greater than 20 mitoses in the 10X field. Both malnutrition and disseminated metastatic disease contribute to high operative mortality, which averages 22%. When a distinction is made between location in the cecum and other sites of the colon; the blind is associated with a prevalence of metastasis of 71% compared with 33% in other places. ⁽¹⁸⁾

It has also been mentioned that the size, the degree of invasion, the tumor stage, the histological pattern, degree of differentiation, nuclear grade and mitotic index are the prognostic factors. Radiation therapy and chemotherapy are not effective at all in the treatment of colorectal carcinoid. The 5-year survival is 70% with local disease, 44% for regional metastases and 20% for distant metastatic disease. Death usually occurs due to liver failure secondary to local tumor progression or heart disease. ⁽⁹⁰⁾

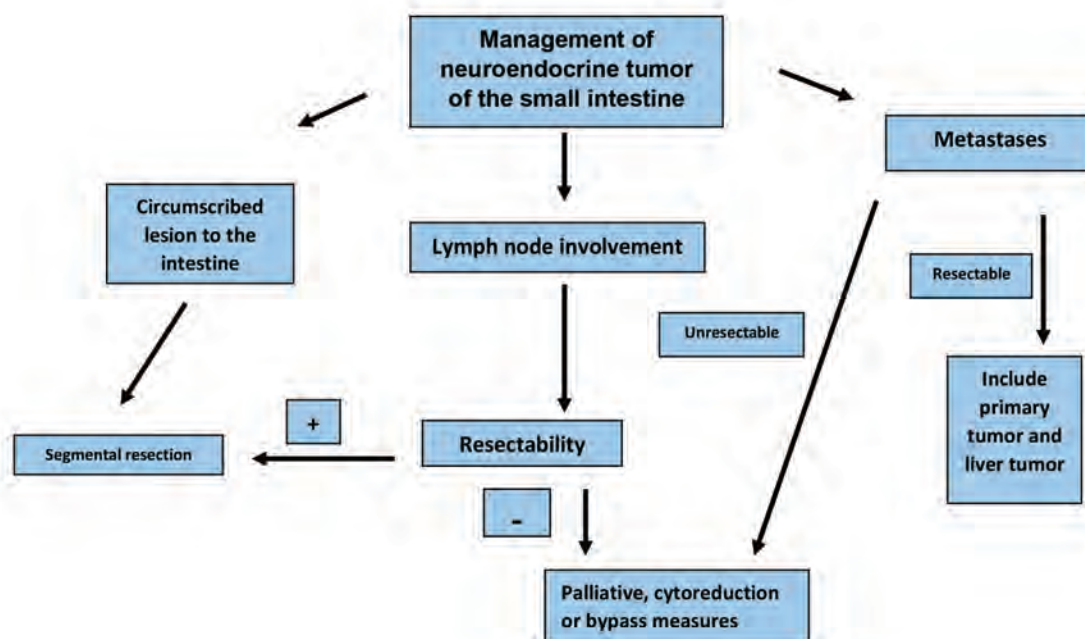


Diagram 46-1. Therapeutic algorithm of intestinal neuroendocrine tumors.

When there is an intestinal lesion with regional macroscopic positive nodes, these lesions require aggressive surgical management and the objective is to resect all the possible macroscopic disease including nodal and peritoneal disease with positive histopathological margins. ⁽⁸⁴⁾

When comparing the prognosis of neuroendocrine tumors of the right colon with the left, those with a prognosis at 5 years of survival for localized, regional and distant disease of 78.5, 78 and 43.6% respectively. In contrast, distal colon tumors 74% have metastasized at the time of diagnosis and overall survival at 5 years is 33 to 42% because they are large tumors or have metastases at diagnosis.

In the small intestine, tumor size is not a predictor of metastatic disease. The presentation of the lesion may be obstruction or intestinal ischemia. Mesenteric occlusion results from tumor factors including desmoplastic reaction, vascular elastosis and secretion of tumor products. Generally small bowel resections require margins of 10 cm on each side. ⁽⁸⁴⁾

Finally, the clinical course of the patient with metastatic carcinoid is variable and some patients remain symptom-free for years. Survival at 2 years even in the presence of liver metastasis is common, if the patient is asymptomatic at the time of presentation, observation seems to be the most appropriate course, the most important goal of the treatment of metastatic disease is the palliation of the symptom.

The following chart differentiates the characteristics of the rectal neuroendocrine tumors from those of the colon. (Table 46-6)

Carcinoid Syndrome

The systemic symptoms produced by carcinoid tumors refer to the carcinoid syndrome. This consists of the combination of vasomotor symptoms such as flushing, changes in blood pressure, diarrhea and bronchospasm. These symptoms are the result of the release of active tumor products to the circulation such as catecholamines, histamine, tachykinins and kalikrein. The liver is able to metabolize and inactivate large amounts of tumor products. However, the carcinoid syndrome occurs only in the presence of liver metastases or when there is a primary carcinoid located outside the portal venous system. These episodes are precipitated by emotional stress, heat, alcohol consumption, defecatory effort and anesthetics.

The heart can be affected by carcinoid tumor products, particularly in those patients with carcinoids of the midgut and liver metastases. Serotonin has an effect on myofibroblasts resulting in fibroplasia, increased vascular tone, bronchoconstriction, platelet aggregation and these effects can cause pulmonary hypertension, pulmonary or tricuspid valve stenosis and right ventricular hypertrophy with fibrosis and with a typically normal left heart. The carcinoid crisis is a medical emergency and can be activated by the effect of anesthetics, embolization, tumor manipulation or chemotherapy. It is characterized by flushing, hypotension, bronchospasm, arrhythmias and hyperthermia, as well as diarrhea, confusion and stupor. The crisis is limited or avoided by treatment with somatostatin and histamine blockers before the procedure.

Table 46-6. Differences Between Rectal and Colonic Carcinoid

Characteristic	Rectal	Colonic
Age	Young	Old
Most Frequent Gender	Male	Female
Frequency	13 - 30%	0.6 - 7%
Type of Presentation	Early	Late
Metastases	Low	High
Symptom	Asymptomatic	Symptomatic
Resolution	Endoscopic	Surgical
Prognosis	Good	Bad

Modified from Hahnloser D, Nelson H. Carcinoid tumors of the large and small bowel. In Fazio VW, Church JM, Delaney CP, eds. Current therapy in colon and rectal surgery. 2nd ed. Philadelphia, Elsevier/Mosby;2005:473-8.

Physiopathology

The overproduction of serotonin is implicated in the pathogenesis of the carcinoid syndrome. Serotonin is metabolized in the liver to 5-HIAA and excreted in the urine. Carcinoids that drain into the portal circulation can secrete large amounts of serotonin without causing carcinoid syndrome, which results from tumor secretion into the systemic circulation that prevents liver degradation. This occurs when there is hepatic metastasis, occasionally with retroperitoneal metastasis, peritoneal or extensive nodal metastasis. The most common cause of the carcinoid syndrome is metastatic liver disease originating from a carcinoid of the small intestine.

Treatment

The medical treatment of patients with carcinoid tumor has two purposes: palliation of systemic symptoms and treatment of metastases. A variety of palliative surgical procedures for carcinoid syndrome and metastatic disease, including partial liver resection or resection of metastatic disease, have been described. If hepatectomy is not possible, embolization of the hepatic artery or its ligation may produce long-term remissions and relief of symptoms. The most effective program in the treatment of carcinoid syndrome is the surgical removal (cytoreduction) of both the primary and secondary tumor to limit the production of polypeptides.⁽¹⁸⁾ In patients with unresectable disease, bypass, cytoreduction, or stoma formation may be necessary. Within the medical treatment of the carcinoid syndrome are mentioned octreotide, interferon and chemotherapy. Octreotide is effective in relieving diarrhea and flushing. It has antiproliferative effects since it temporarily decreases primary and metastatic lesions at an initial dose of 100 ug subcutaneous TID, but patients may require daily maximum doses of 1500 ug. Other authors have indicated average daily doses of 400 ug of octreotide with excellent results in more than 80% of patients.

Interferon improves diarrhea and flushing in 66% of patients, decreases tumor size and slows the growth of the lesion. Other serotonin antagonist drugs may be used for the treatment of diarrhea and flushing, including methysergide, cyproheptadine, ondansetron and ketanserin, and drugs that act by other routes such as histamine receptor antagonists, kallikrein inhibitors, blockers alpha adrenergic, beta-adrenergic blockers and phenothiazine derivatives.

To prevent carcinoid crisis due to tumor manipulation or anesthetic drugs, a pre-operative prophylaxis of 100 to 400 ug subcutaneous octreotide is recommended, avoiding drugs such as morphine, halothane and atracurium and regional blocks.⁽⁸⁴⁾

Chemotherapy is usually ineffective in patients with metastatic tumor.⁽⁹³⁾ However, some protocols have been described with promising results and radiotherapy has little use except for painful bone metastases.⁽⁷⁵⁾

Prognosis

The carcinoid syndrome has a poor prognosis and survival of 36 months has been observed on average after the first episode of flushing and at 6 years only 25% survive. Octreotide and interferon improve survival.

Other Tumors

Here we include metastatic tumors that occur as part of a disseminated process, these tumors form disc lesions in which there is an ulcerated central area, normal mucosa that extends to the ulcer giving indirect evidence that the metastatic focus begins in the submucosa. This phenomenon is quite common in malignant melanoma and primary carcinomas of the breast and lung. It has also been observed in renal carcinomas. Mesotheliomas can present as metastatic lesions with multiple polyps in the colon. On the other hand, prostatic carcinomas can also extend to the rectum and simulate primary rectal neoplasia. The primary epidermoid carcinomas of the colon and the hemangiopericytomas should also be mentioned.

Conclusions

In this chapter, we review in detail the most frequent rare tumors of the colon, such as neuroendocrine tumors, lymphomas, leiomyomas, GISTS tumors. This type of tumors requires special immunohistochemical staining including a panel of smooth muscle actin, desmin, vimentin, chromogranin A, synaptophysin, CD 117, common leukocyte antigen, CD 20, CD45, CD3, EBV, CD5 for an adequate classification and expertise of a pathologist with oncological specialty, in addition to the appropriate complementary studies for staging and treatment.

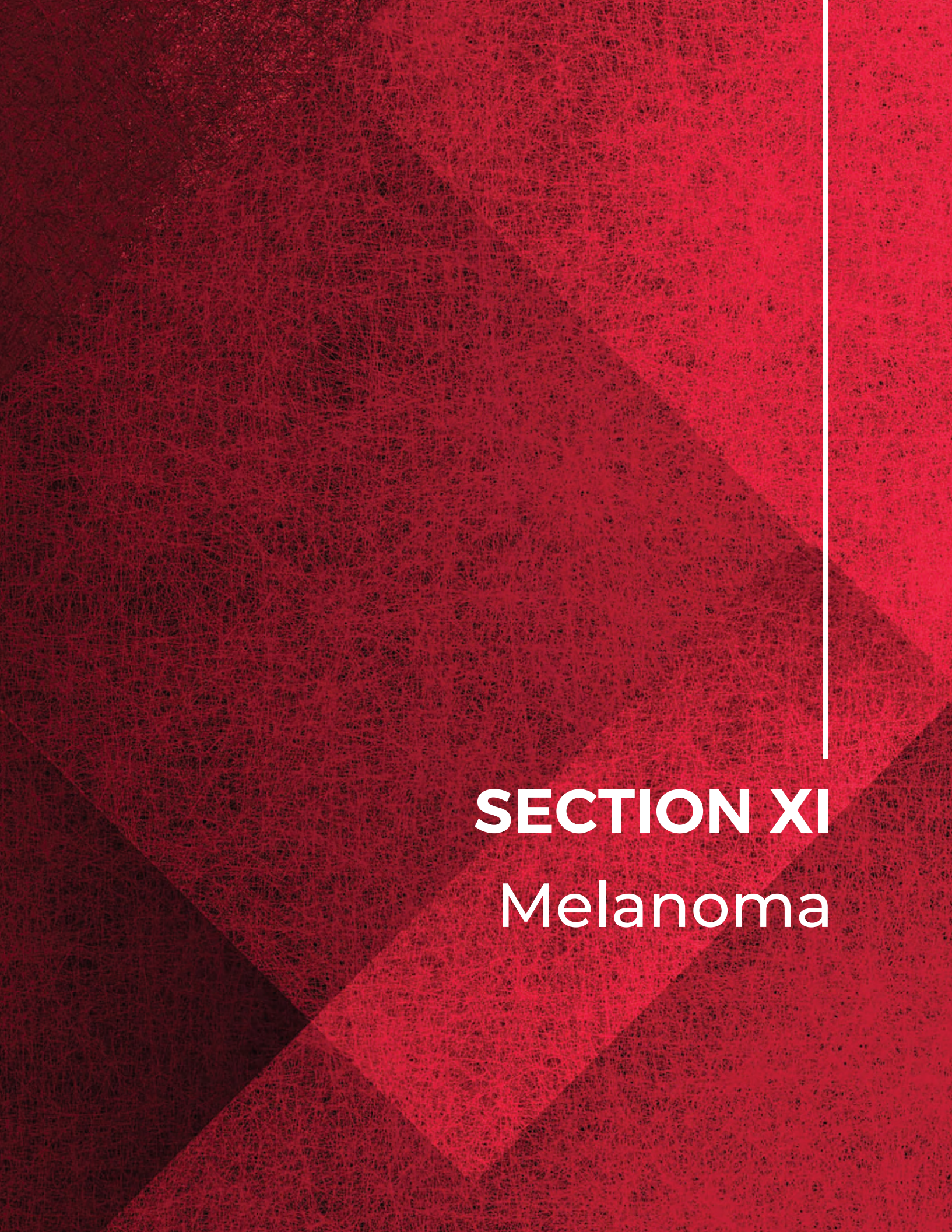
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SECTION XI

Melanoma

Chapter 47

Epidemiology of Melanoma in Latin America

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Cutaneous melanoma (CM) is a complex disease in which a combination of environmental factors, ethnic traits and genetic anomalies interact extensively. The better understanding of the many pathways in which this disease presents and evolves in different ethnic groups is critical to design better early diagnosis strategies and more efficient treatment protocols. Although well studied and documented in first world/high incidence countries, epidemiological profiles for Latin American countries fall short in large studies and more standardized methods of data acquisition. Few studies address this issue, but important information is provided that could serve as a primer while more data and further epidemiological studies become available. In general, melanoma incidence in Latin America is low, varying between 1-5 per 100,000. ⁽¹⁾ Unfortunately, the mortality rates are higher compared to western countries with high incidence of CM. Economic factors, low awareness levels for the disease among patients and suboptimal screening strategies seems to be, at least, some of the plausible causes. Other important consideration is that the incidence of acral lentiginous melanoma (ALM) is higher in Latin America, which often carries not only a delayed clinical diagnosis but also a more aggressive behavior.

Even though native populations display a more pigmented skin trait (which in turn provide better UV protection), it is important to consider the heterogeneous composition of the ancestral origins in Latin America, in which European, Asian and African origins are prevalent in different proportions throughout the continent. For example, genetic counseling studies have demonstrated that more than 70% of multiple primary melanoma patients (both sporadic and familiar) had the four grandparents of European origin. ⁽²⁾ Furthermore, the presence of mutations in the well-known

CDKN2A high-risk gene in this group demonstrated a prevalence rates higher to the ones reported in Spain (8,2-9%), meanwhile some moderate-risk polymorphisms in gene MC1R (which plays a key role in skin pigmentation and its capacity to respond UV radiation) exhibit more variants (with different profiles between populations). ^(2,3)

In terms of incidence by anatomical site, several studies suggest that men tend to have a higher proportion of CM on the trunk than woman, and woman with higher proportion in limbs (upper and lower). However, some differences are noted in particular geographical regions: more Southern countries (Uruguay, Argentina, Brazil) have a predominantly “Western world” pattern of anatomical site distribution, while in the Northern part (Central America, Colombia, Guyana) the anatomical site distribution shows an increased incidence in lower limbs. ⁽¹⁾

Pathways in Development of Melanoma

It is now widely accepted that cutaneous melanoma epidemiology is the result of two mayor pathways: Environmental (mainly UVR exposure) and genetic susceptibility (specific mutations, polymorphisms in pigmentation genes). Exposure to UV radiation possess the major environmental risk factor for melanoma. More than 70% of all cases (sporadic melanoma) are directly related to cumulative exposure to UV radiation. ⁽⁴⁾ This group is characterized by somatic mutations in BRAF, NRAS and TERT genes. BRAF mutations are usually associated in younger-age, trunk-located with absence of chronic sun damage patients, while the NRAS mutations are more often related with older patients, with chronic solar damage. ⁽⁵⁾

Less than 10% of all patients have positive familiar history of melanoma (first or second degree). The presence of heritable genetic alterations represents a key component in this subgroup of patients. Up to this time, more than 26 genes related to melanoma susceptibility have been identified and grouped in low, intermediate and high penetrance genes, and although great advances have been made in this field, there is a considerable number of familiar melanoma cases in which the exact genetic basis is still unclear. ⁽⁶⁾ It has been theorized that there are still more susceptibility genes to be discovered or a polygenic susceptibility model should be proposed.

Up to date, the most extensively studied and maybe most important genes are CDKN2A and CDK4, both in the group of high penetrance genes. Carriers of CDKN2A mutation have a substantial lifetime risk of developing CM. ⁽⁷⁾ Other high-penetrance rare mutations in BAP1, Rb1 and POT1 genes have been found and now under extensive investigation.

In the low/intermediate group, the MC1R and MITF mutations/polymorphisms are also associated in the development of melanoma. MC1R is one of the major determinants of skin pigmentation/hair color, in which several polymorphisms (those related with fair skin, freckling and red hair) are linked to an increased risk for melanoma. ^(7,8)

Diagnosis, Clinical and Histological

General Considerations

Even though diagnosis of cutaneous melanoma is often a “straight-forward” exercise for the experienced clinician, two important considerations should be taken into account:

1. An early diagnosis has a profound impact in survival rates and morbidity associated to this disease, and
2. The traditional clinical algorithm of ABCDE (Asymmetry, Borders, Color, Diameter, Evolution) has proven to be ineffective in up to 1/3 of early melanomas. ⁽⁹⁾

We are then facing a new paradigm in melanoma diagnosis, giving that the “state-of-the-art” relies not only in the traditional clinical criteria but also in a more comprehensive approach, including the individual susceptibility for melanoma, a structured algorithm for evaluation of pigmented lesions and the adequate use of diagnostic resources (digital dermoscopy, total body mapping, reflectance confocal microscopy, histological analysis).

Last decades have been decisive for a more detailed understanding of the risk factors and high susceptibility conditions, along with major technological advances in image acquisition and processing, setting new diagnostic standards for cutaneous melanoma.

Diagnostic Approach

For most cases, an adequate clinical evaluation and the correct use of the well-known clinical ABCD algorithm represent the most valuable tool to accurately diagnose a cutaneous melanoma, followed by the dermoscopic evaluation using one of the several pattern-analysis protocols available. ⁽¹⁰⁾ It is beyond of the scope of this book a detailed review of each dermoscopic protocol, but noteworthy is the 2-step diagnostic algorithm for pigmented lesions from Malvehy *et al.*, ⁽¹¹⁾ for which further reading is highly recommended.

The contemporary diagnostic approach is then based in a precise balance between early diagnosis and optimization of costs (preventing unnecessary biopsy procedures). Keeping this in mind, current best practice includes:

1. Recognition of high risk/susceptibility patients: A high nevi count/atypical nevi syndrome, host phenotype (fair skin, light-colored eyes, red hair, photosensitivity) and familial history of melanoma are important risk factors to be considered not only as clinical background, but also to define the most appropriate follow-up strategy.

2. Perform complete visual examination (whole body): Although the greater number of times the patient seeks medical advice for a lesion that has changed or recently appeared, not uncommonly melanoma is diagnosed through a routinely medical skin check-up (that was unnoticed by the patient). This is particularly true in high risk/high susceptibility individuals.

3. Dermoscopic evaluation in each suspicious lesion: The routinely use of dermoscopy increases diagnostic accuracy in up to 30% over the classic visual examination ⁽¹²⁾ as well as preventing unnecessary biopsies. ⁽¹³⁾

4. Total Body Imaging / Sequential Digital Dermoscopic Imaging/ Reflectance Confocal Microscopy: Patients with a high nevi count or atypical nevi syndrome may benefit with this non-invasive technology to monitor new or changing lesions over time. The identification of such lesions then demands dermoscopic evaluation to define the clinical conduct: If it fulfills dermoscopic criteria suspicious for melanoma, then biopsy excision is granted. Doubtful/equivocal lesions could be managed by Sequential Digital

Dermoscopic Imaging (SDDI) or Reflectance Confocal Microscopy (RCM).⁽¹³⁾ This relatively new diagnostic tool is a non-invasive/real-time optical device that uses a low-power laser beam at 830nm with cellular resolution that enables visualization of the epidermis, dermal-epidermal junction and papillary dermis (in most cases). RCM is a second-level screening test that improve the diagnostic accuracy of melanoma, and in the context of patients under SDDI it prevents unnecessary biopsy procedures in up to 70%.⁽¹⁴⁾

5. Biopsy procedure: Histological evaluation remains as the gold-standard for melanoma diagnosis. It also provides critical information to estimate biologic behavior, prognosis and of course to design the better treatment protocols. Whenever possible, a narrow-margin excisional biopsy is preferred. Incomplete biopsies (punches, curettages, incisions) should be avoided (except for qualified circumstances), due to a clear risk for pathological misdiagnosis or inadequate assessment of important histological information regarding the tumor (Breslow thickness, regression, satellites, etc.).⁽¹⁵⁾

Tumor Subtypes

Superficial Spreading Melanoma

Clinical features

The Superficial Spreading Melanoma (SSM) represent the most common type of all melanomas, presenting generally as a pigmented macule with a slow growing behavior. With time, this macule evolves to a plaque and eventually develops a vertical growth phase (where a nodular component may appear). The SSM best correlate with the classical ABCD clinical criteria (with an asymmetrical appearance, irregular borders, more than 2 colors and a diameter greater than 6 millimeter). The prototypical patient presenting with SSM is a fair skin, mid-age (fourth-fifth decades) with a history of intermittent sun/UV exposure. In males, the most affected sites are trunk and upper back, while in females, the lower extremities.

Dermoscopically, the presence of suspicious structures like atypical pigment network, multiple colors, brown or blue/gray dots, radial streaming, pseudopods, blue-white veil, scar-like zones and atypical blood vessels are frequently found (individual or a combination of them).^(16,17) It is of cardinal importance to remember that not infrequently the lesion starts as a small lesion almost indistinguishable from other benign lesions from the patient. Moreover, it is well documented that up to one-third of all melanomas (in early

stages) are missed when the conventional ABCD clinical criteria is used alone.⁽⁹⁾

Histopathology

The hallmark of the SSM is the presence of a radial growth phase. It is characterized by an asymmetrical radial atypical melanocytic proliferation, with scattered single-cells or clusters in the epidermis (in-situ component). It also may include microinvasion to the papillary dermis and regression phenomena. In an invasive SSM with vertical growth phase, cohesive atypical melanocytes are present in the dermal component (or beyond), with mitotic activity, apoptotic bodies and sometimes regression phenomenon.

Nodular Melanoma

Clinical features

The second most common type of cutaneous melanoma is the Nodular Melanoma (NM). Unlike the SSM, in which the evolution starts with a slow-growing pigmented lesion, the NM often behaves in a much more aggressive manner; arising over periods of several weeks or months. The classic clinical presentation is of a dark (blue-black o blueish) nodule, sometimes eroded o even with focal hemorrhage. The prototypical patient is also fair skin, somewhat older (fifth-sixth decades) with a fast growing lesion in the trunk or limbs. The clinical ABCDE sometimes lack asymmetry and the color is usually uniform (in early stages), making the early diagnosis extremely difficult.⁽¹⁸⁾ Dermoscopy has also several limitations, not only for the lack of a radial growth phase, but also by the fact that NM tend to be less pigmented (or even amelanotic) that their counterparts. A careful evaluation (and a high clinical suspicion index) is mandatory. The presence of atypical vessels (lineal-irregular, hairpin vessels) and/or milky-red or pink areas are highly suspicious for an hypopigmented/amelanotic NM, while the presence of blue or black dots/globules in at least 10% of the lesion for the pigmented NM.⁽¹⁹⁾

Histopathology

By definition, the NM has no radial growth phase more than three (3) rete-ridges beyond the tumoral component. Cohesive nests of atypical melanocytes (epitelioid, spidled or mixed), with pushing borders and mitotic activity. The overlying epidermis can display thinning or even ulceration.

Lentigo Maligna / Lentigo Maligna Melanoma

Clinical features

Lentigo Maligna (LM) represents a subtype of melanoma in-situ that presents in individuals with chronic photodamage. LM is observed in older patients (seventh to eight decades), with a long standing pigmented lesion that evolves slowly. Anatomical sites are predominantly those traditionally more exposed to sunlight (especially face and neck). The clinical classic presentation is a tan/tan-brown macule with irregular borders with a very slow growing behavior. Lentigo Maligna Melanoma (LMM) represent the invasive phase of a LM, usually after a very long period of time (generally years). Although this “slow behavior” represent some advantages for clinical diagnosis, there is a high subclinical radial compromise, leaving an elevated rate of local recurrences, so an early/prompt diagnosis is always desirable. Dermoscopic evaluation (in facial skin) usually displays asymmetric pigmented follicular openings (with obliteration), annular granular pattern of gray dots and rhomboidal pigmented structures. ^(20,21)

Histopathology

Being an in-situ melanoma, LM is confined to the epidermal compartment. It is characterized by an atypical melanocytic proliferation along the basal layer, with compromise of follicular structures (at least partially), in the context of a skin with chronic solar damage (actinic keratosis, solar elastosis). When dermal invasion is documented, LMM diagnosis is then established. Generally, the invasive component is multifocal, with a spindle cell morphology, and usually with accompanying desmoplastic response with, not infrequently, perineural invasion.

Acral Lentiginous Melanoma

Clinical features

Although rare in Caucasians (less than 8% in the majority of countries), Latin America’s ethnic composition calls for a higher index of suspicion and a more careful evaluation of dubious lesions. The proportion of ALM in Central and South America appears to be substantially higher. ⁽¹⁾ Furthermore, it represents an issue due to its more aggressive biologic behavior and consequently a higher mortality.

ALM usually presents in older populations (sixth to seventh decades), with a predilection for the soles, followed by

palms and ungual apparatus (especially in the great toes and the thumbs). The clinical appearance is variegated, usually starting as a pigmented macule with irregular borders (black-brown or a combination of colors). Progression in size and elevation, as well as ulceration or even bleeding is possible. The subungual variant of ALM presents with a brown pigmentation of the nail bed, with the presence of irregular longitudinal streaks and sometimes with pigmentation of the nailfolds (Hutchinson’s sign). It is important to bear in mind that the application of the clinical ABCDE criteria could be troublesome due to the specific characteristic of volar skin and ungual regions, giving an irregular appearance to almost all lesions (including benign nevus). Dermoscopic evaluation greatly improves the sensitivity and specificity in diagnosis of ALM. The presence of a parallel ridge pattern is possibly the single most important dermoscopic feature found in ALM, and in subungual ALM the presence of brown background along longitudinal irregular lines. ^(22,23)

Histopathology

A subtle atypical melanocytic proliferation along the basal layer represents the early histological changes (radial growth phase). With the progression of the disease, a more conspicuous melanocytic proliferation is observed, with migration to upper epidermal stratum, irregular acanthosis, elongation of rete-ridges and a dermal chronic inflammatory infiltrate (lichenoid, band-like). The invasive component usually has a spindled cell morphology, with prominent desmoplastic reaction, and noteworthy, perineural invasion in up to 15% of the cases.

It is important to stress that the early stages of subungual ALM are not only difficult to diagnose clinically, but also challenging for dermatopathologists. Not infrequently the melanocytic proliferation is subtle, and the atypia barely identifiable. ⁽²⁴⁾ Adequate feedback and good communication with the pathologist is of cardinal importance when evaluating doubtful lesions.

Other Types

Several rare types of cutaneous melanoma account for less than 5-7 % of all cases. Some of the most important are:

1. Desmoplastic melanoma, with a local aggressive behavior is usually present in head and neck areas of older persons, often in association with lentigo maligna. ⁽²⁵⁾

2. Nevroid Melanoma is actually an invasive melanoma with local recurrence and metastatic capabilities. It represents one of the most complex to diagnose (both clinical and histological). A black or brown nodule located in trunk or limbs of adult patients is the most common presentation, but amelanotic variants are also documented.⁽²⁶⁾
3. Amelanotic melanoma portrays a major clinical challenge that requires not only a high index of suspicious but also the aid of several dermoscopic clues for diagnosis. It often presents in photo-exposed skin of elderly persons, as an erythematous macule or plaque, often scaly with irregular borders.⁽²⁷⁾ As we can see, a broad differential diagnosis must be considered: Irritated seborrheic keratoses, squamous cell carcinomas, basal cell carcinomas, irritated verrucae, dermatofibromas, etc.
4. Not to be confused with a polypoid configuration of other melanoma subtypes, the Polypoid Melanoma is actually considered a rare clinical variant of a nodular melanoma mainly seen in young patients, in which at least 50% of the tumoral mass is located above the adjacent skin surface (in a sessile/polypoid arrangement). It is characterized for a fast growing/highly vascularized neoplasia with an aggressive behavior.^(28,29)
5. Mucosal Melanoma is an extremely rare variant occurring mainly on head and neck mucosal surfaces. Due to its particular anatomical localization, biologic behavior and therapeutic considerations, it is discussed in more detail ahead in this chapter.

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Chapter 48

Epidemiology of Cutaneous Melanoma in South America

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In Argentina the most reliable epidemiological data are those of the Argentine Cutaneous Melanoma Registry (RAMC - *Registro Argentino de Melanoma Cutáneo*) since the different provinces lack specific records of this pathology.

The RAMC began its activities in October 2003, recording the cases of Melanoma with a diagnosis date as of January 1, 2002. Most of the information is spontaneously received from different professionals and Institutions. The cases come from varied specialties (dermatologists, oncologists, surgeons and pathologists, etc.), from different types of public and private Institutions and from cancer records of different Provinces. The variables required for each Cutaneous Melanoma (CM) include: personal data, family and personal history of CM and the topographic and histological data of the present tumor.

There were 3,832 tumors registered until the month of April 2009. 49.4% occurred in women and 50.6% in men. The age of presentation of tumors in women was 55.1 years with a range of 2-99 years (SD = 17.8) and 58.5 years in men with a range of 3-100 years (SD = 16.7) ($p < 0.001$).

The location of the tumors differs according to gender: the presentation in the lower limbs is more frequent in women and in the trunk in men. This difference was statistically significant ($p < 0.001$) and is consistent with what happens in countries with a majority of Caucasian population.

The most frequent type was superficial extensive melanoma (54%) followed by nodular melanoma (27%), lentigo malignant melanoma (8%) and acrolentiginous melanoma (6%). This distribution does not vary in genders.

A total of 596 (15.6%) lesions corresponded to melanoma *in situ*, constituting a low percentage in relation to the

statistics of the United States and Europe, which logically is the index of a majority of late diagnoses.

Among invasive melanomas, 46% had a Breslow thickness less than 1.01 mm. Among women, the thickness of Breslow differs with age at diagnosis. In those, under 40 years of age, 61.8% of the lesions had a Breslow < 1 mm and 7.1% a Breslow > 4.0 mm. In contrast, in those older than 70 years, 40.5% had a Breslow < 1 mm and in 18.4% of cases the thickness exceeded 4 mm. In males, no significant association was found between Breslow and age.

The data on the presence or absence of ulceration was obtained in 2,752 cases (71.8%). Of these, only 688 presented ulceration (18%) and did not present it with 2,064 tumors (53.9%).

RAMC does not collect information on the ethnic origins of the patients, however, it is likely that there are regional variations in the frequency of the different ethnic groups since it is known, for example, that the frequency of the general population with Amerindian origins is greater in the northwest than in the center of our country.

The socio-economic reality of the different regions of the country, as well as the educational level of the population, could also have an influence.

Chile

In general, there is scarce information on the epidemiology of melanoma in Chile. The estimated standardized incidence rate for 2008 was 2.2, that same year the standardized mortality rate was 0.65. Between 1983 and 2008 the average mortality rate was 0.77, showing a 25% increase,

statistically significant. Regarding survival, there are only local jobs where it is observed that it ranges between 100% and 33% at 5 years according to Clark level and TNM stage. More studies are required, and strategies focused on prevention.

Uruguay

In Uruguay, the incidence rate adjusted for age is 3.1 per 100,000 in men and 2.8 in women. The mortality rate, also expressed in terms of rates adjusted for age, is 1.3 cases per 100,000 men and 0.8 in women. The analysis of trends in mortality rates in the last decade has shown that in men the figures have remained relatively stable, while in women there has been an increase of approximately 2% per year, which nevertheless does not reach still be statistically significant.

Perú

In the National Institute of Neoplastic Diseases (INEN – *Instituto Nacional de Enfermedades Neoplásicas*) a total of 574 cases of Melanoma were reported in the period 2000-2004, when reviewing the frequency per year, an ascending curve of the cases is observed as in many countries of Latin America 54% of the cases were registered in the department of Lima and the other cases in other cities of the country. This high frequency would be the reflection of the geographic accessibility that the inhabitants of Lima have when the INEN is located in the same department, likewise it might be thought that there are cases of cutaneous melanoma existing in other departments that have not yet been reported. There was a greater number of cases in female, which has also been observed in other countries.

The age of presentation frequency includes patients of very early ages as it has been the case of children of four years of age, nevertheless a marked increase in the frequency was observed from the 45 years in men and women.

The location of the lesions registered in the INEN bears a resemblance to that observed in other countries where the most frequent place is in the lower extremities.

Colombia

The National Institute of Cancerology has a record of melanoma cases between 2006 and 2010. A total of 599

patients were included, of which 57.4% were women (n = 344) and 42.6% men (n = 255). The average age of diagnosis was 60.8 years.

Most of the cases were from Bogotá with 56.3% (n = 329). The urban area was more frequent as a site of habitual residence with 83.4% (n = 500). The average annual frequency was 115 new cases per year. The most frequent location was acral, with 42.2% (n = 253), followed by head and neck 31.0% (n = 186). Consistent with the location, the most frequent subtype was acral lentiginous melanoma with 43.7% (n = 262), followed by the malignant lentigo with 24% (n = 144).

In terms of depth, an equal frequency of melanomas *in situ* and melanomas with Breslow > 4 mm were observed, both with 19% of cases. It was found that most of the lentigo maligna, 75% (n = 108) presented a Breslow *in situ* or were microinvasive melanomas (Breslow ≤ 1 mm); On the other hand, lentiginous acral and nodular ones presented a Breslow > 4 mm more frequently (with 26.3% n = 69 and 45.4% n = 10, respectively). The most frequent stage was III with 26.2% of the cases (n = 157).

There was a higher percentage of melanomas in women and a higher frequency of acral melanomas. A difference was found with that reported in other Latin American series. A significant number of patients were placed in an advanced stage, so greater actions are required for the early detection of this disease.

Brazil

The Brazilian population is made up of multiple races, with many people of more than one racial heritage, therefore, a large range of skin colors. The population is frequently exposed to UV radiation.

In Brazil, an estimated 6,000 new cases occur each year, resulting in 1,300 deaths. In a retrospective study of 15 years in a reference cancer center, a total of 1,073 patients were analyzed, with an average age of 56.7 years. Men and women experienced a similar prevalence, and 91.2% of patients had white skin. The most prevalent subtype was superficial dissemination, and the most prevalent anatomical location was the trunk (32.2%), followed by the lower extremities (28%). Of all the cases, 567 (52.9%) were assigned to clinical stages I and II, while 382 (32.6%) were stages III and IV.

The high prevalence of advanced cases reinforces the importance of strategies to diagnose melanomas in the early stages. There is a need for future multi institutional prospective studies to achieve a better understanding of the possible socioeconomic and other influences on survival among melanoma populations in Brazil and Latin America. (RAMC)

Venezuela

To date, there are few population based studies reporting melanoma incidence rates and no reliable registry data reporting melanoma mortality rates for Venezuela. However, the Venezuela Cancer Registry (RNCV - *Registro Nacional de Cáncer de Venezuela*) created an electronic Internet version of a database originally established by the Multidisciplinary Group on Melanoma Study (GMMM - *Grupo Multidisciplinario y Multicéntrico para el Estudio del Melanoma*) in 2004 for the cities of Caracas and Valencia as part of a pilot project. The database categorizes patient cases based on clinical and histological characteristics, surgeries performed, and adjuvant treatment. The seven-year pilot project currently has three Venezuelan institutions (with nine medical centers) as registered users.

In December of 2009, according to data from GMMM, there were 701 patients in the database; of these, 54.9% were women, and the median age of presentation was 56 years. The annual reported number of skin cancer cases was 116. Fifty seven percent (57%) of the patients with melanoma had a previous history of sunburn. The most frequent localization site for primary melanoma was the limbs (53.2%), followed by the trunk (32%) and the head and neck areas (14.8%). Most cases were recorded as invasive melanoma (84.4%).

Venezuela is a country of great racial diversity. The majority of the current population is *mestizo*, with the remainder mainly of European (primarily German, Italian, Portuguese, or Spanish) descent. Blacks account for an estimated 8% to 10% of the population, and Amerindians represent about 2%. Arabs also represent part of the overall populace. Based on data from GMMM, most patients with melanoma had fair skin tone and light-colored eyes, and those with light skin had relatively high levels of pigmentation.

Panama

The Republic of Panama has 4 million inhabitants, with the particular historical-geographical circumstance that

70% is composed of a mixture (“genetic pool”) of the original indigenous inhabitants, with the Europeans who arrived at the Isthmus of Panama, during the discovery of America in the fifteenth century, Asians and West Indians (Antilleans), in the nineteenth century; who participated in the construction of roads, the transisthmian train (“during the California gold rush”), the Panama Canal and the large airports during World War II.

In the Republic of Panama, we give special attention to the original inhabitants, the American Indian group, among them, the “Gunas”, with great exposure to ultraviolet rays for its outdoor activities and the closest proximity to the equatorial line.

The Gunas have the highest incidence of albinism (> 1 Albinos: 165 Gunas) in the whole world, and a splice site mutation is the cause of the high prevalence of ocular-cutaneous albinism type 2 in the Guna population; and develop amelanotic melanoma.

In Panama, we have a low cancer registry, but as in the rest of the world, we have, according to statistics, an increase in the incidence of Cutaneous Melanoma, since 2012.

National Oncology Institute (ION – <i>Instituto Oncológico Nacional</i>)	
Statistics Department. Dra Nedelka Pinzon Solé	
2012	31
2013	25
2014	42
2015	46
2016	57
2017	50
TOTAL	251

Chapter 49

Clinical Diagnosis of Cutaneous Melanoma

Carlos Alonso, MD
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Clinic and Diagnostic Methods

Although melanoma accounts for only 4% of all dermatological cancers, it accounts for 80% of deaths from skin cancer.

The number of cases of melanoma in the world is growing faster than those of any other cancer, which constitutes a significant and growing burden on health systems. In any case, it presents a high rate of cure if it is detected at an early stage, related to its predictable sequence of tumor progression that allows the possibility of diagnosis in the pre-metastatic phase.

Almost thirty years ago, dermatologists at the Langone Medical Center at the University of New York, USA, developed and then refined the acronym “ABCD” that provides criteria for diagnosing melanoma.

- A** represents Asymmetry; one half is different from the other half.
- B** represents the Border; irregular, wavy or ill-defined edge.
- C** represents Color; variation from one area to another; different shades of brown and black; sometimes white, red or blue.
- D** represents the Diameter: greater than 6 mm.

Some researchers have extended the ABCD criteria by adding letter “E” enlargement, elevation or evolution (i.e. enlargement, changes in thickness and bleeding).

This acronym has been widely used in clinical practice and as a population education tool ^(1,2)

Another algorithm is that of Glasgow, which consists of seven basic points divided into three major criteria and four minor ones. The major criteria are changes in size, irregular shape and color. The minor criteria are diameter greater than 7 mm, inflammation, bleeding or eczematous skin, and moderate pruritus or altered sensitivity. In adults, a pigmented lesion with one of the major criteria is considered to be resected, while gathering minor criteria helps increase clinical suspicion.

Another clinical finding associated with melanoma is the “ugly duck sign”, this refers to a mole that differs significantly in appearance from other moles in the patient. ^(2,3)

These algorithms are criticized in various scientific fields, since they are not usually effective to detect nodular, acromic and less than 6 mm melanomas.

Although these diagnostic criteria were widely used for years, due to the development and progress of other diagnostic methods, fundamentally dermatoscopy, the clinical diagnosis is relegated to a population education tool. ⁽¹⁻³⁾

Dermatoscopy

Dermatoscopy, also called epiluminiscence microscopy, is a non-invasive technique that, by means of an optical instrument, called “dermatoscope”, allows to examine

the lesions below the cutaneous surface by amplifying the suspicious image *in-vivo*, once the phenomena of refraction and reflection of the light on the skin have been eliminated. ⁽⁴⁾

Dermoscopy has increased the ability to diagnose pigmented lesions in 10 to 30% compared to clinical evaluation and has a sensitivity of 60 to 95% depending on the degree of experience of the examiner and the diagnostic difficulty of the lesion. ⁽⁴⁾

Dermoscopy, which is now an evaluation standard, has greatly improved the diagnostic accuracy of pigmented and non-pigmented lesions. Meta-analyzes performed in experimental and clinical settings have shown that it increases the sensitivity and specificity of the diagnosis, favors the recognition of benign lesions of the malignant ones and consequently, the biopsy rate of benign lesions decreases. In addition, the dermatoscope is easy to manipulate and does not prolong observation times. ⁽⁵⁾

The first method of dermoscopic evaluation was introduced by Pehamberger in the late 1980s, who established the localized and global patterns associated with melanomas. **(Table 49-1)** The multicomponent pattern, which combines three or more different characteristics, it is usually the most recognized. However, the recognition of dermoscopic patterns requires training, and diagnostic algorithms, more structured forms of evaluation, may be useful for physicians who are just beginning in dermoscopy. The Stoltz algorithm,

also known as the dermoscopic ABCD rule (asymmetry, borders, colors, dermoscopic structures), defines benign, suspicious and malignant lesions according to a quantitative score, whereas the Menzies method is based on the absence of two negative criteria and the presence of at least one positive criterion to distinguish malignant melanoma. In addition, the Argenziano seven-point checklist, which consists of three main criteria and four minor criteria to identify benign or malignant lesions, based on a score, was the first to incorporate the vascular pattern into a score. ^(6,7)

A virtual meeting of Consensus Net Meeting on dermoscopy, in which 40 experienced professionals participated, concluded that, in comparison with algorithms, pattern analysis was the most sensitive and specific diagnostic method to distinguish benign from malignant melanocytic lesions. Beginners in dermoscopy can first become familiar with the diagnostic algorithms and, once they are completely trained, they can change to pattern recognition. ⁽³⁻⁷⁾

Digital Dermoscopy

The combination of total body photography and digital dermoscopy, called “two-step method”, allows tracking of all lesions and their evolution over time.

The first step in digital follow up is to obtain full body photographs or body maps in standardized poses of all body segments. This step is very important during digital follow-up since it allows identifying the appearance of new lesions during subsequent follow-ups. The second step is to obtain digital dermoscopic images of the most atypical lesions or lesions considered necessary to follow up. When performing digital follow-up it is important to identify the predominant dermoscopic pattern in the patient (pattern observed in more than 30% of the lesions), which will allows to identify as a suspicious lesion that which deviates from the patient’s usual pattern. ⁽⁸⁾

This is particularly important because nevi, including atypical nevi tend to be stable, while melanomas show changes in size, color and / or dermoscopic structures over time. In addition, de novo lesions can be identified and monitored. Therefore, the “two-step method” is more useful in patients with multiple nevi, those with a personal or family history of melanoma, or in those with a strong genetic susceptibility to developing melanoma. ⁽⁹⁾

The importance of detecting new lesions was highlighted in a prospective surveillance study conducted in 618

Table 49-1
Local Parameters Associated with Malignancy
• Pigmented reticulum prominent or atypical • Irregular spots and blood cells • Irregular projections • Blue-gray or blue-white veil • Destructured areas • Regression structures • Vascular structures associated with malignancy
Global Patterns Associated to Malignancy
• Atypical Reticular • Atypical Globular • Starburst • Homogeneous • Parallel pattern of the crest • Multi-component • Non-specific

patients with high-risk melanoma (11,396 lesions) from 1999 to 2008; Of the 1152 excised lesions analyzed, 32.4% (373/1152) corresponded to de novo lesions. In general, the majority of lesions (63.2%; 728/1152) were excised due to changes in the dermatoscopic patterns, with asymmetric enlargement being the most frequent change (57.4%, 418/728). Particularly, it was discovered that melanomas occur at any time during 10 years of surveillance, which supports the need for long-term monitoring of high-risk patients. These data were confirmed in a meta-analysis of two short-term and 12 long-term studies with sequential digital dermatoscopy to track 52,739 melanocytic skin lesions. ^(9,10)

Teledermatology

Teledermatology is the remote diagnosis of lesions evaluated and registered with dermatoscopy. Access to dermatologists for the detection of skin cancer is a growing problem worldwide. Teledermatology offers the possibility of an immediate detection of skin cancer by transmitting medical information to a dermatologist for remote evaluation. It has acceptable accuracy compared to a face-to-face clinical examination in the diagnosis of skin cancer and is a useful alternative for patients with limited access to medical care. ⁽¹¹⁾

There are two main types of remote consultation, synchronous or live and asynchronous also called store and forward.

In the first one, the patient and the dermatologist can interact in real time. It requires coordination in time and more expensive equipment. In the second one, the images of the lesions are stored to be sent for evaluation at a later time. This option has gained popularity in recent years due to its practicality and lower operating cost. ⁽¹²⁾

Teledermatology has shown in several studies an acceptable concordance with the standard of face-to-face evaluation, in the order of 78 to 92%, and this increase when the information of the lesion evaluated is more accurate and detailed. One of the main limitations is the possibility of not registering and evaluating lesions not considered important by the referring physician. Another issue is the lack of telemedicine legislation in general and the depersonalization of the medical act. ⁽¹³⁾

Confocal Microscopy

Confocal microscopy or RCM is a non-invasive technique that allows real-time examination of skin tumors at a

resolution at cellular level (0.5-1 μm) and provides serial optical sections of the lesion from the epidermis to the papillary dermis (200-300 μm deep). It has been shown that this method is excellent for the evaluation of suspicious melanocytic lesions, reducing the number necessary for the removal of benign tumors and thus improving the diagnostic accuracy. ⁽¹⁴⁾

Melanin provides endogenous contrast in the MCR images of melanocytic lesions, delineating the architecture of the lesion at different levels of the skin and illuminating the cytoplasm of the cells. Because the architectural and cytological characteristics are recognizable, benign and malignant tumors can be contrasted in the presence or absence of these characteristics. In this way, the degree of architectural disorder, the presence of pagetoid distribution cells and the type of nests can be recognized. In general, melanocytic nevi are characterized by the presence of bright and monomorphic cells, with dark nuclei, and grouped in dense nests. On the other hand, the typical characteristics of melanoma in MCR include architectural disorder of the spiny layer with keratinocytes of ill-defined edges (focal or diffuse). In addition, cytologic atypia it is recognized by the presence of complex dendritic structures within the epidermis. ^(14,15)

The latest generation equipment also incorporates high resolution dermatoscopy camera. This camera allows to make a dermoscopic record of the lesion or skin area to be evaluated and to perform the confocal microscopy examination using the dermoscopic image as a parameter. ^(15,16)

Optical Coherence Tomography (OCT)

OCT, based on the principle of interferometry, uses a low coherence light source with a relatively long wavelength to obtain non-transparent tissue images. In contrast to the RCM, the conventional OCT allows the examination of the skin lesions with a structural resolution (approximately 10 μm) and generates serial axial images that reach the reticular dermis (a depth of approximately 2 mm). This newer technique has been used to analyze non-melanocytic tumors, with a large number of basal cell carcinoma studies. OCT of variance by points (SV-OCT) has been recently developed and has been shown to be capable of detecting microscopic vascular changes that occur in melanocytic lesions and other skin tumors. ^(17,18)

The technology is still under development for the analysis of melanocytic tumors. It has been investigated if the specific OCT patterns could be associated with benign versus malignant melanocytic lesions. One study showed that the nevi compounds presented a hyporeflective band in the dermis and visualization of the collagen was preserved, while in situ melanomas characterized by epidermal shadows (eight out of ten cases). It was also reported that shadows and loss of bright collagen were specific to invasive melanomas compared to compound nevi. ^(19,20)

Artificial Intelligence

Artificial Intelligence tries to get computers to simulate human intelligence in a certain way. It goes to their techniques when it is necessary to incorporate into a computer system, knowledge or characteristics of the human being.

In recent years, different diagnostic algorithms for skin cancer have been developed, with the aim of reaching levels of acceptable sensitivity and specificity. In principle, they have shown promising results; however, there are different objections to their implementation and results. ⁽²¹⁾

All the studies that compared the diagnosis of melanoma by AI with the diagnosis in humans were made in an experimental setting. These studies were conducted in front of a computer, tablet or smart phone and were based on the evaluation of the images. None of these algorithms has been tested in a real clinical setting. In addition, most algorithms feed on images of lesions diagnosed histopathologically. Therefore, histopathology is always taken as a point of reference and presupposes that the histopathological diagnosis was correct. However, it is well documented that the interpretation of the histopathology, especially for borderline melanocytic lesions, is far from what one would expect from a “gold standard” and it is known that the interobserver variability in this type of lesions is very wide. ⁽²²⁾

Therefore, at present the AI is in full development and its potential for the future may be broad, but at the moment it is not even a complement to be used in daily practice and should be reserved only for areas of research.

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Chapter 50

Treatment of Primary Cutaneous Melanoma

Cesar J. Restrepo, MD

Clinical Staging of Skin Melanoma

A major development in recent years has been the release of the updated eighth edition of the American Joint Committee on Staging melanoma staging system based on a database of over 46,000 patients from 10 major international centers.⁽¹⁾ The advantages of having an accurate staging system to facilitate directed and validated patient care cannot be underestimated. This new staging system takes

into account developments in treatment such as sentinel biopsy and improved imaging.

Highlights of the new staging system include improved stratification of thin (T1, 0 - 1.0 mm) melanomas, classification of stage III disease by lymph node disease burden and refinement of staging for patients with distant recurrence. Details of the staging system and stage grouping with representative survivals is shown in **Tables 50-1 – 50-5**. An intriguing observation from the AJCC database has

Table 50-1. AJCC Cancer Staging Manual 8th, edition

T Category	Thickness	Ulceration Status
TX: primary tumor thickness cannot be assessed (e.g., diagnosis by curettage)	Not applicable	Not applicable
T0: no evidence of primary tumor (e.g., unknown primary or completely regressed melanoma)	Not applicable	Not applicable
Tis (melanoma <i>in situ</i>)	Not applicable	Not applicable
T1	≤1.0 mm	Unknown or unspecified
T1a	<0.8 mm	Without ulceration
T1b	<0.8 mm 1.0 mm	With ulceration With or without ulceration
T2	>1.0–2.0 mm	Unknown or unspecified
T2a	>1.0–2.0 mm	Without ulceration
T2b	>1.0–2.0 mm	With ulceration
T3	>2.0–4.0 mm	Unknown or unspecified
T3a	>2.0–4.0 mm	Without ulceration
T3b	>2.0–4.0 mm	With ulceration
T4	>4.0 mm	Unknown or unspecified
T4a	>4.0 mm	Without ulceration
T4b	>4.0 mm	With ulceration

Table 50-2. Definition of Regional Lymph Node (N)

Extent of regional lymph node and/or lymphatic metastasis		
N Category	Number of tumor- involved regional lymph node	Presence of in- transit, satellite, and/or microsatellite metastases
NX	Regional nodes not assessed (e.g., SLN biopsy not performed, regional nodes previously removed for another reason)	No
	Exception: pathological N category is not required for T1 melanomas, use cN.	
N0	No regional metastases detected	No
N1	One tumor-involved node or in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes	
N1a	One clinically occult (i.e., detected by SLN biopsy)	No
N1b	One clinically detected	No
N1c	No regional lymph node disease	Yes
N2	Two or three tumor-involved nodes or in-transit, satellite, and/or microsatellite metastases with one tumor-involved node	

Table 50-3. Extent of Regional Lymph Node and/or Lymphatic Metastasis

N Category	Number of tumor-involved regional lymph node	Presence of in-transit, satellite, and/or microsatellite metastases
N2a	Two or three clinically occult (i.e., detected by SLN biopsy)	No
N2b	Two or three, at least one of which was clinically detected	No
N2c	One clinically occult or clinically detected	Yes
N3	Four or more tumor-involved nodes or in-transit, satellite, and/or microsatellite metastases with two or more tumor-involved nodes, or any number of matted nodes without or with in-transit, satellite, and/or microsatellite metastases	
N3a	Four or more clinically occult (i.e., detected by SLN biopsy)	No
N3b	Four or more, at least one of which was clinically detected, or presence of any number of matted nodes	No
N3c	Two or more clinically occult or clinically detected and/or presence of any number of matted nodes	Yes

Table 50-4. Definition of Distant Metastasis (M)

M0	No evidence of distant metastasis	Not applicable
M1	Evidence of distant metastasis	See below
M1a	Distant metastasis to skin, soft tissue including muscle, and/or nonregional lymph node	Not recorded or unspecified
M1a(0)		Not elevated
M1a(1)		Elevated
M1b	Distant metastasis to lung with or without M1a sites of disease	Not recorded or unspecified
M1b(0)		Not elevated
M1b(1)		Elevated
M1c	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease	Not recorded or unspecified
M1c(0)		Not elevated
M1c(1)		Elevated
M1d	Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease	Not recorded or unspecified
M1d(0)		Normal
M1d(1)		Elevated

Suffixes for M category: (0) LDH not elevated, (1) LDH elevated.

No suffix is used if LDH is not recorded or is unspecified.

Table 50-5. Stage Groupings and 10-year survivals for Stage 1-3 cutaneous melanoma (AJCC 8th edition 2017).

Stage		10 yr. survival
Stage 1 – 2 Node Negative		
1a	T1a	98%
1a	T1b	96%
1b	T2a	92%
2a	T2b	88%
2a	T3a	88%
2b	T3b	81%
2b	T4a	83%
2c	T4b	75%
Stage 3		
3a	T1a/b, T2a and N1a/b	88%
3b	T1a/b and N1b/c or N2b	77%
3b	T2b/T3a and N1a-N2b	77%
3c	T1a-T3a and N2c or N3a/b/c	60%
3c	T3b/T4a and N2-N3	60%
3c	T4b and N1c-N2c	60%
3d	T4b and N3a/b/c	24%

been the significance of both tumor thickness and ulceration on outcome. Patients with stage 2c melanoma that is thick, T4 or > 4mm, sentinel lymph node negative melanoma have worse outcomes than patients with thinner melanomas and sentinel lymph node involvement. Among patients with stage III disease that is patients with lymph node spread, the presence of the primary tumor characteristics thickness and ulceration indicates significantly worse outcomes.

For patients presenting with a pigmented lesion suspicious for melanoma and no evidence of regional or distant spread on physical examination, a complete excision with a 1- 2 mm margin as noted above is recommended. ⁽²⁾ A complete excision provides the best possible sample for the pathologist to evaluate and facilitates appropriate treatment planning. Partial biopsies including superficial shave and punch biopsies may underestimate tumor thickness et cetera in up to 25% of cases. ⁽³⁾

Larger lesions not suitable for complete excision may be considered for partial biopsies by targeting multiple sites and the most aggressive or suspicious areas. In addition to the tumor thickness other important features to be obtained from the pathology report include the type of melanoma, presence of histological ulceration, the presence of perineural or lymphatic/vascular invasion, microsatellites, mitotic rate and adjacent *in situ* melanoma. The current consensus on margins of excision of primary melanomas is discussed below but in a small proportion of cases wider margins may be considered. Desmoplastic melanoma which accounts for less than 2% of cases particularly if there is perineural invasion present require considerably wider margins due to an increased risk of local recurrence. The presence of microsatellites is also an indication for wider margins than might normally be required for similar reasons.

The aim of complete wide local excision of a primary melanoma is complete eradication of the melanoma and for patients with T1A melanomas, the 10-year survival is 98%. In general, local recurrence is a very uncommon phenomenon in patients treated with an appropriate margin of excision. **(Table 50-5)** Over the last 150 years, the margin of excision has reduced serially from the extensive resections recommended by Handley based on his case study of a patient with a very advanced melanoma. The finding of “atypical” cells around primary melanoma was subsequently used to justify wide excisions for many years however, the consensus view is now that most local recurrences are due to progression of in-transit deposits or microsatellites already present at the time of diagnosis and located away from the primary lesion with a potential for local recurrence and regional and distant spread. ^(4,5)

Most patients with a local recurrence are salvaged by wide excision and in both the Intergroup and Swedish studies there was no difference in survival following a local recurrence between patients who received a wider margin compared to those who had a thinner margin of excision. The margin of excision should therefore reflect a balance between complete resection and the potential for wound morbidity.

The current national guidelines for margins of excision for primary cutaneous melanoma are summarized in **Table 50-6**. All agree that T1 melanomas should be excised with a 1 cm margin. For melanomas greater than 1 mm in thickness, the margins of excision remain controversial despite seven randomized trials, multiple retrospective studies, three meta-analyses and a Cochrane review. ⁽⁶⁻¹⁴⁾ This situation is highlighted by the significant variation in recommended margins by current national guidelines. **(Table 50-7)**

Margins of excision for *in situ* melanoma have never been formally studied although most authorities would agree a 5 mm margin is appropriate in most cases. Lentigo maligna or *in situ* melanoma occurring in sun damaged skin may be associated with widespread changes and in certain instances a wider excision margin may be necessary. For thin melanoma (≤ 1 mm, T1), the evidence is quite clear that a 1 cm margin is appropriate. Three studies have addressed margins for T2 melanomas (>1 - ≤ 2).

The WHO study (1 v 3 cm margin) founded similar outcomes to the Intergroup and French studies which employed wider margins (2 cm versus 4 or 5 cm). The WHO study found a slightly higher local recurrence rate for T2 melanomas (but not worse survival) than T1 melanomas which has led some to recommend 2 cm margins for higher risk e.g. ulcerated T2 tumors.

The situation is even more complex for T3 melanomas (>2 - ≤ 4 mm). The Swedish and Intergroup studies found no difference in local recurrence or survival for 2 versus 4 cm margins.

The UK study found an acceptable risk of local recurrence but no difference in survival for 1 versus 3 cm, although the final report from this study suggested that a 1 cm margin may not be appropriate.

All of the international guidelines recommend at least a 2 cm margin for T4 melanomas (> 4 mm). In recent years several comprehensive non-randomized studies have supported the use of 1 cm margins and as a consequence there is now a randomized trial of 1 cm versus 2 cm margins of excision for T2b -T4 melanoma (MELMART,

Table 50-6. Current national guidelines for excision margins for primary cutaneous melanoma

Thickness	UK (2010)	USA (2010)	Australia + New Zealand (2017)	Dutch (2008)	German (2013)
≤ 1 mm	1 cm	1 cm	1 cm	1 cm	1 cm
1.01 – 2.0 mm	1- 2 cm	1- 2 cm	1- 2 cm	1 cm	1 cm
2.01 – 4.0 mm	2 – 3 cm	2 cm	1 - 2 cm	2 cm	2 cm
> 4.0 mm	3 cm	2 cm	2 cm	2 cm	2 cm

Table 50-7: Summary of Randomized Trials of Excision Margins

Previous Trials (Year)	Sample Size	Margin (cm)	Thickness (mm)	Primary Site	Follow up (years)	Local Recurrence	Survival OR p
WHO No 10 1988 ⁽⁷⁾	612	1 v 3	< 2	Trunk Limbs	7.5	0.5%	0.83 NS
Intergroup 2001 ⁽⁸⁾	740	2 v 4	1 - 4	Trunk prox Limb	7.6	2%	1.46 NS
Swedish MSG 2000 ⁽⁹⁾	989	2 v 5	0.8 - 2	Trunk Limbs	11	0.8%	0.63 NS
French 2003 ⁽¹⁰⁾	337	2 v 5	<2	Digital ALM excluded	16	1.5%	NS
UK 2004 ^(11,12)	900	1 v 3	≥ 2	Trunk Limbs	5	3.1%	0.99 NS*
Sweden 2011 ^(13,14)	936	2 v 4	≥ 2	Trunk Limbs	20	2.2%	1.05 NS

ClinicalTrials.gov, NCT02385214). Anticipated benefits of a 1 cm margin include reduced need for skin grafts and complex reconstruction, reduced pain particularly long-term neuropathic pain, improved cosmesis and functional outcomes and quicker return to normal daily activities and employment as well as substantial health economic benefits.

Management of the regional lymph nodes in patients with clinically localized disease has evolved from an aggressive policy of prophylactic or elective lymphadenectomy to the current status of sentinel node biopsy.

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Chapter 51

Ocular, Mucosal, Subungual and Leptomeningeal Melanoma

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Ocular Melanoma

Ocular melanoma is the most common primary intraocular malignancy. Approximately 1,500 new cases are diagnosed in the United States each year. ⁽¹⁾ Ocular melanoma is the second most common type of melanoma after cutaneous melanoma. Melanomas of the uveal tract i.e. choroid, ciliary body and iris are distinguished from conjunctival melanoma which arises from melanocytes situated in conjunctival membrane. Although rare, melanoma may arise from melanocytes located in the orbit. Uvea is the most frequent site of origin of ocular melanomas and comprises 82.5%, while conjunctival melanoma is far less common. ⁽²⁾ The Great majority of ocular melanomas are primary, however, metastatic melanoma from primary cutaneous sites can also occur, it accounts for less than 5% of all metastases to the eye and orbit. ⁽³⁾

Ocular melanoma is still rare, and accounts for 3.7% of all melanoma cases. ⁽²⁾ In the United States the incidence of ocular melanoma is 6 per million, compared with 153.5 for cutaneous melanoma. ⁽²⁾ Ocular melanoma is more common among men, with an incidence of 6.8 per million, compared with 5.3 per million in women (male to female rate ratio 1.29). ⁽²⁾ In Australia ocular melanoma rates are higher, with an incidence of 8 per million in men, and 6.1 per million in women. ⁽⁴⁾ Ocular melanoma rates are 8-10 times higher among whites compared with blacks, but although obvious this difference is less pronounced compared to cutaneous melanoma which is 16 times higher rates among whites. ⁽²⁾

In contrast to uveal tract melanomas, conjunctival melanoma rates are 2.6 times higher in whites than in blacks, which is similar to mucosal melanomas. ⁽⁵⁾ The incidence of ocular melanoma increases with age, with a peak in seventh and

eight decade of life. ^(2,4) In contrast to uveal melanoma which has remained stable over last three decades, ⁽¹⁾ the incidence of conjunctival melanoma has increased, especially among white men and older than 60 years. ⁽⁶⁾

In an Australian population a higher incidence of ocular melanoma was found among men older than 65 years. ⁽⁴⁾ Iris melanoma is considerably less frequent than choroidal or ciliary body melanomas, usually with a better prognosis, and a lower potential for metastatic spread (approximately 3-5% risk). ⁽⁷⁾ Melanoma of uveal origin has an incidence rate of approximately 5 to 7 new cases per 1 million persons per year. ⁽⁸⁾

A variety of risk factors have been identified, including the presence of lighter colored eyes, fair skin, an inability to tan, ocular melanocytosis, dysplastic nevus syndrome, and *BAP1* mutations. ⁽⁹⁻¹²⁾ Interestingly, patients with uveal melanoma (UM) have an 11% higher risk of second malignancies, such as cutaneous melanoma and renal cell carcinoma, than the general population, which may be driven by the presence of germ-line *BAP1* mutations. The role of sun exposure as a risk factor for UM is unclear. Both light eye color and sunlight may be independent risk factors associated with different anatomic and mutation profiles. ⁽¹³⁾

The clinical presentation of ocular melanoma depends on the size and location of the tumor and may vary from asymptomatic to painless loss or distortion of vision.

Loss of vision is usually caused by tumor involvement of the macula or by exudative retinal detachment. At diagnosis, most ocular melanoma patients are asymptomatic, with the tumor identified on routine ophthalmic screening. Chronic conjunctivitis may also be a referring diagnosis. Rarely, a blind eye or one with a dense cataract may harbor an

occult melanoma.⁽¹⁴⁾ Ciliary and choroidal melanomas usually present with gradual visual loss and potentially pain. On the iris, general presenting symptoms are a new or growing pigmented lesion, elevated intraocular pressure, and decreased vision.⁽¹⁵⁾

Patients with suspicious pigmented lesions should be assessed by an ophthalmologist with clinical expertise in ocular tumors. Diagnostically small melanomas need to be differentiated from benign nevi. Diagnosis of these types of lesions is usually done based on physical findings, with biopsy not taking place until the time of definitive therapy (i.e. brachytherapy, enucleation). Rarely biopsy is used to confirm the diagnosis. The Collaborative Ocular Melanoma Study (COMS) had a greater than 99% diagnostic accuracy for eyes enucleated with typical features.⁽¹⁶⁾ Echography is the most useful diagnostic means available to the clinician. Most are dome shaped, but a collar stud or ‘mushroom’ configuration is highly suggestive of melanoma.⁽¹⁷⁾ Specifically when certain clinical and echographic findings are present the diagnostic accuracy is upwards of 99%.⁽¹⁸⁾

Surgery with enucleation remains a reasonable option for very large tumors and in cases where radiotherapy is likely to be complicated by severe ocular and visual complications. Exenteration, surgical removal of the globe and adjacent orbital contents, is infrequently indicated. It is limited to advanced tumors and palliative care. Surgery offers the most comprehensive histopathologic evaluation and can confirm microscopic extraocular extension.⁽¹⁹⁾

Radiation therapy is the most common globe salvaging approach used by ocular oncologists. No statistically significant difference was identified in melanoma-related mortality between ocular melanoma treated with enucleation or brachytherapy.⁽²⁰⁾ Most clinicians agree both modalities have high rates of local tumor control reported as high as 98% in some series.⁽²¹⁾

Despite excellent rates of local disease control with surgery or radiotherapy, up to 50% of patients will ultimately develop metastatic disease, with the most common initial sites being the liver (60.5%), the lung (24.4%), skin/soft tissue (10.9%), and bone (8.4%).⁽²²⁾ The overall rate of survival from initial diagnosis is 69% at 5 years, 55% at 15 years, and 51% at 25 years; however, following the development of metastatic disease, median overall survival is approximately 13.4 months, with only 8% surviving 2 years.^(23–25)

Mucosal Melanoma

Mucosal melanoma is a rare subtype of melanoma, accounting for only 0.03% of new cancer diagnoses, and has a distinct behavior from melanomas that develop at other sites in the body. It is originated from the malignant transformation of melanocytes present in the mucous membranes of the respiratory, gastrointestinal and urogenital tracts. They are epidemiologically and genetically distinct from cutaneous melanoma and they differ in how they interact with the immune system and respond to various forms of therapy.

In the United States, the incidence of mucosal melanoma has remained stable.⁽²⁶⁾ The distribution of mucosal melanoma is heterogeneous. It can develop within any mucosal membrane, although the incidence is greater in head and neck regions (31% to 55%), anorectal (17% to 24%), and vulvovaginal (18% to 40%) regions.^(2,27) The epidemiology of mucosal melanoma is distinct from cutaneous melanoma. Mucosal melanoma tends to develop at advanced age. The median age at diagnosis is 70, while cutaneous melanoma is 55 years.⁽²⁾ Mucosal melanoma is more often diagnosed at an advanced stage of disease and is associated with worse outcomes.⁽²⁾

The 5-year overall survival rate for mucosal melanoma is 25% and is related to advanced disease at diagnosis.⁽²⁷⁾ The male-to-female ratio is 1:1.87 and may be explained by the higher rates of genital tract melanomas in women.^(2,28,29) The racial distribution is heterogeneous. Although it is rare among Caucasians populations (1-2%), mucosal melanoma account for 5% to 13% of melanoma in black patients and 23% of Chinese patients.^(4,8) These differences are reflective of the lower incidence rates of cutaneous melanoma in non-white groups. While cutaneous melanoma is associated with exposure to ultraviolet (UV) radiation, no clear environmental risk factors have been identified for mucosal melanoma.⁽³⁰⁾ For vulvovaginal and anorectal mucosal, family history maybe an important risk factor.⁽³¹⁾

Unfortunately, for primary mucosal melanoma of the head and neck, because of the lack of visibility and relative asymptomatic nature of small lesions, mucosal melanoma of this region is often diagnosed at more advanced stages. The most common symptoms are unilateral nasal obstruction, mass lesion, and epistaxis.⁽³²⁾ In advanced stages pain and facial distortion can occur, and rarely proptosis and diplopia.

It is infrequently diagnosed accidentally because of its occult location, and patients with epistaxis are usually referred to physicians earlier than those with obstructive symptoms. Macroscopically, the majority of tumors appear as polypoid,

brown or black pigmented mass, often ulcerated. Tumors can also be amelanotic, mimicking other more common tumors.⁽³³⁾ For laryngeal lesions, the most common presenting symptom is hoarseness, followed by throat irritation. Other presenting symptoms include discomfort, dysphagia, neck swelling, and pain.⁽³⁴⁾

Mucosal melanoma of the oral cavity is rare, and is usually asymptomatic, presenting as flat, macular, or slightly elevated and irregular pigmented lesion. In later stages symptoms such as swelling, ulceration, bleeding, pain and tooth mobility occur, and the lesion can become elevated. Satellite lesions and areas of pre-existing melanosis can be present around the lesion.⁽³⁵⁾ For mucosal melanoma of the esophagus, symptoms include dysphagia, retrosternal pain, weight loss, hematemesis and melena.⁽³⁶⁾ For melanoma of the stomach, symptoms are unspecific and include abdominal pain, weight loss, upper gastrointestinal bleeding and anemia.^(37,38)

Primary melanoma of the small intestine is rare. Symptoms are non-specific and include anorexia, gastrointestinal bleeding, abdominal pain, weight loss, nausea and vomiting. When located at anorectal region, symptoms of mucosal melanoma include rectal bleeding, pain and prolapse of tumor.⁽³⁹⁾ Although rare, melanoma can arise in almost any part of the urogenital tract, including vulva and vagina, uterine cervix, urethra and urinary bladder. The most common presenting symptoms are bleeding, lump or vulvar mass, pruritus, pain or irritation, miction discomfort and discharge.⁽⁴⁰⁾

Vaginal melanoma most often occurs in the lower third and anterior wall of vagina. The most common presenting symptoms are vaginal bleeding and discharge, presence of mass lesion, and less common pain.⁽⁴¹⁾ Melanoma of the cervix is rare and majority of patients are symptomatic on diagnosis, with vaginal bleeding being the most common symptom followed by vaginal discharge.⁽⁴²⁾ Melanoma of the urethra can be easily misdiagnosed for urethral polyps, caruncle, mucosal prolapse, chancre or urothelial tumors.⁽⁴³⁾ Melanoma of the urinary bladder is uncommon, and is usually advanced at diagnosis. The most frequently symptoms are hematuria and dysuria.⁽⁴⁴⁾

The diagnosis of mucosal melanoma is usually delayed, and many lesions are thick and ulcerated at diagnosis. The paucity of symptoms and occult lesions are the most important reasons for this, especially in some sites on which it rarely arises. It is important to consider metastatic lesions from occult primary cutaneous melanoma or ocular melanoma. The most important criteria to distinguish primary lesions

from metastases is the presence of radial growth phase and intact epithelium overlaying invasive melanoma.^(45,46)

An amelanotic appearance, which is not rare among mucosal lesions, makes diagnosis even more difficult. Macroscopically pigmented lesions are always highly suspicious for melanoma, but when pigment is absent even microscopic diagnosis can be difficult. Immunohistochemical staining positive for protein S-100, HMB-45, Melan-A, Mart-1 and tyrosinase support a diagnosis of melanoma.

Surgery remains the gold standard intervention for mucosal melanoma. Complete resection offers the best chance for prolonged overall and disease-free survival. Unfortunately, wide negative margins is not easy to achieve in mucosal melanoma due to anatomic constraints, disease multifocality, and/or a lentiginous growth pattern.^(47,48) Lymph node evaluation, including sentinel nodes, may be considered in selected patients.⁽⁴⁰⁾ Radiotherapy is used for irresectable disease in case of locally advanced mucosal melanoma, and as adjuvant therapy after surgical resection. Radiation therapy is associated with complete response ratio in approximately 30% of mucosal melanoma of head and neck, with local control in 40%.⁽⁴⁹⁾ Adjuvant systemic therapy in patients with mucosal melanoma is not well defined. There is a general lack of efficacy for chemotherapy in the treatment of mucosal melanoma. Temozolomide with cisplatin and interferon alfa-2b, are options that have been used.^(50,51) Therapies targeted against C-KIT activating mutations, identified in many mucosal melanomas, are emerging as promising treatments.⁽⁵²⁾ The role of immunotherapy with immune checkpoint inhibitor therapy has been described but in general the results are less effective than are seen for cutaneous melanoma. Mutation in BRAF are very uncommon in mucosal melanomas.

Mucosal melanoma has an aggressive behavior and the prognosis is poor. The stage at diagnosis and anatomic site are the most important factors. The 5-year overall survival is 20%. Early detection, which is difficult because of the occult anatomic locations in which these tumors occur, allows the best hope for cure. Considering the poor prognosis for all stages of mucosal melanoma, dermatologists should incorporate examination of the oropharynx and genitalia in the full body skin exam.^(26,40,53)

Subungual Melanoma

Alexis Boyer first described subungual melanoma in 1834. It rises from under the nail bed and is a rare but well documented form of malignant melanoma. Little is known

about the risk factors, and ultraviolet (UV) radiation is unlikely to be a determinant factor. Some authors suggest that trauma may be a risk factor.⁽⁵⁴⁾

Prior studies have reported that subungual melanoma comprises anywhere from 0.7% to 3% of all cases of cutaneous melanoma.^(55–57) The peak incidence is in the 5th to 7th decades of life.^(55,58–60) The fact that the population, and even health professionals, lack awareness about rare diseases, coupled with the difficulties in mobilization and access to health services, may lead to a delay in the diagnosis of elderly patients in particular with subungual melanoma (SM). While cutaneous melanoma has been found to be more common in Caucasians, subungual melanoma is thought to occur disproportionately more often in dark skinned individuals.⁽⁵⁹⁾ SM distribution by ethnicity is interesting in that it occurs in great proportions in groups with low occurrence of cutaneous melanoma (CM).

It seems that there is no difference in the occurrence rates among various ethnic groups, and the SM ratio difference is due to the low frequency of CM in these groups.⁽⁶¹⁾ While very little has been published on risk factors, some suggest an association with a history of nail trauma in addition to sun exposure.⁽⁵⁴⁾ In Latin America, the available data are mostly from hospital-based studies. There are few population-based cancer records in our continent, conferring a lack of accurate and reliable information to be analyzed and used for early diagnosis and preventive actions.⁽⁶²⁾ Although, it seems there was no difference in the occurrence rates related to gender,⁽⁶³⁾ the F:M ratio was slightly higher in some series.^(58,60,64)

Clinically, subungual melanoma tumors present with local symptoms, as nail color changes, ulceration, mass, bleeding, and pain. The most common sites of subungual melanoma are the thumb (34%), great toe (25%), and the middle finger (14%).⁽⁵⁸⁾ In 1886, Sir Jonathan Hutchinson called it “melanotic whitlow” because it often resembled infection.⁽⁶⁵⁾ Hutchinson’s sign is the presence of a longitudinal pigmented line in the nail bend, which has usually been related with subungual melanoma. These lesions have been mistaken for hematomas, blisters, and nevi.⁽⁵⁹⁾ To confuse matters, studies have shown that the presence of amelanosis in subungual melanoma may be higher than in other forms of cutaneous melanomas and can represent anywhere from 15–50% of cases.^(55,66) As such, a delay in diagnosis has resulted in advanced lesions at presentation.^(66,67)

Time between onset of symptoms and diagnosis ranged from 1.4 to 2.2 years^(15–18) and it was made when the disease was already advanced at the primary site.^(58,64,66) Unlike

the significant improvement in the diagnosis of cutaneous melanoma, the diagnosis of subungual melanoma has shown little, if any, improvement over the years. The widespread adoption of the ABCDs of cutaneous melanoma has helped increase public and physician awareness, and thus helped increase the early detection of cutaneous melanoma; the same criteria cannot be applied to the examination of the nail pigmentation. Early recognition of clinical signs and symptoms, together with punch biopsy of the nail bed is essential in suspected lesions.

The most common histological subtypes of subungual melanoma are thought to be acral lentiginous and nodular.^(55,58,60,66) Optimal diagnosis is made by punch biopsy of the nail bed but has its limitations because accurate measurement of depth of invasion is often challenging. This is in part due to the poor interface between the papillary and reticular dermis and the paucity of subcutaneous fat in the subungual area, with only dermal collagen separating the nail matrix from the underlying bone. The nail matrix also lacks a granular layer, which further complicates this measurement.⁽⁶⁶⁾

Diagnosis of subungual melanoma is very difficult to establish merely on the basis of clinical examination due to the resemblance of subungual hematoma to melanocytic nevus, fungal or bacterial infections. Dermoscopy seems to be the ideal diagnostic tool in the differential diagnosis of this life-threatening disease.

Dermoscopy is a safe, easily repeatable diagnostic method, and knowledge of basic dermoscopic patterns of developing melanoma in subungual localization, along with the differential diagnosis of other diseases within the nail plate, will help not only dermatologists, but also the professionals of other specialties, such as surgeons, oncologists, orthopedists, and general practitioners. Dermoscopy provides valuable information for the diagnosis of subungual hemorrhage and aids in the differential diagnosis from nail-unit melanoma. In a series of 16 cases of nail-unit melanomas, Hutchinson’s sign, longitudinal irregular bands or lines, triangular shape of bands, vascular pattern, and ulceration were found in 100%, 81%, 25%, 6% and 81% of cases, respectively. In contrast, these features were not found in subungual hematoma.⁽⁶⁸⁾

Amputation is the conventional treatment for malignant subungual tumors to obtain the recommended clear surgical margins. However, controversy exists in respect to the level of amputation, and only a few limited studies have investigated the optimal surgical treatment. Functional surgery consisting of wide local excision (WLE) of the

nail unit alone can preserve function without modifying prognosis in some cases. In SM, even though there was no consensus in the literature regarding the choice between radical surgery and functional surgery, there was a trend toward conservative procedures for thin and possibly intermediate thickness lesions.

Studies, most of them on small series of cases, reported better aesthetic and functional results without any effect on overall survival (OS) or relapse free survival (RFS).^(69–76) The surgical margin is an important predictive factor when positive, re-excision is indicated. In several studies, the margin was positive in the first surgical approach in about 8.0% of the cases.^(60,77)

In most series of SM the lesion was relatively thick (1.75 to 6.0 mm) which could explain the worse prognosis compared to CM.^(58,60,64,78,79) Most series report a 5-year OS of approximately 60.0%.^(58,60) Some authors in the past considered Clark's invasion level IV/V as a poor prognostic factor for OS and RFS compared to Clark levels II/III.⁽⁸⁰⁾ Although Clark's level was not considered an important variable in the 8th edition the melanoma staging manual,⁽⁸¹⁾ it is routinely described in histopathological records. The survival rate in patients with an ulcerated tumor is lower than in those with a tumor without ulceration at the same stage "T" and is equivalent to those with a non-ulcerated tumor at a higher stage T.⁽⁸¹⁾

Some series showed an association between the presence of ulceration and survival, and the ulceration rate ranged from 30% to 34%^(58,60,64,79). In CM the status of the regional lymph nodes is an important prognostic factor for CM.^(81–83) Few studies have evaluated the role of SLNB in patients with SM. However, all of them revealed that SNB involvement indicate poorer RFS and OS.^(60,84–86) Usually, SLNB is performed for patients with performance status (PS) 0 – II, with Breslow thickness greater than 1.0 mm or for those with other worse prognostic factors such as ulceration or elevated mitotic rate and without clinical evidence of regional distant metastasis similar to CM.⁽⁶⁰⁾

Leptomeningeal Melanomas

Melanoma of the leptomeninges is a very rare malignant neoplasm that develops after a malignant transformation of melanocytes normally located in the leptomeninges, diffuse leptomeningeal melanocytosis, benign melanocytoma, and malignant melanoma. Melanocytic tumors of the central nervous system (CNS) are usually metastatic in origin. However, metastatic tumors are frequently multifocal and

located at the junction of the grey and white matter and rarely present with leptomeningeal involvement.⁽⁸⁷⁾

Primary leptomeningeal melanoma is a rare and aggressive tumor with an annual incidence of approximately one per 10 million people.⁽⁸⁸⁾ Peak incidence occurs in the fourth decade of life. Because of its rarity, the related literature primarily consists of individual case reports.^(89–92)

The initial symptoms were primarily neurologic, including seizures, psychiatric disturbances, and signs of increased intracranial pressure (headache, vomiting, and deterioration of consciousness). The variability of neurologic symptoms and signs on treatment also influenced exact diagnosis.⁽⁹³⁾

The diagnosis of primary CNS melanoma was made according to criteria proposed by Hayward, which include an absence of melanoma outside of the CNS, an absence of lesions in other areas of the CNS, and histologic confirmation of melanoma.⁽⁹⁴⁾ The CT findings for primary CNS melanocytic tumors include an extra-axial or superficially located mass which is iso- to hyperintense and has homogeneous enhancement with contrast agent. Leptomeningeal involvement is also occasionally found. The high attenuation on the precontrast images is related to melanin or intratumoral hemorrhage. MRI is the imaging method of choice for diagnosis. The paramagnetic properties of the melanin provide melanocytic neoplasms of the CNS their distinctive appearance on MRI. The typical characteristics include hyperintensity on T1-weighted images and isointensity to hypointensity on T2-weighted images. Variable imaging characteristics are often due to different degrees of paramagnetic effects of the stable free radicals in the melanin and/or hemorrhagic products.⁽⁹⁵⁾ Prompt surgical intervention for tissue biopsy is important in making the final diagnosis. The diagnosis can be confirmed through histopathological examination, immunohistochemistry, and electron microscopic examination. Expression of the malignant melanoma antibody (HMB-45) and S-100 protein but absence of meningothelial cell markers (such as epithelial membrane antigen) indicate melanocytic tumor and exclude melanotic meningioma.

The optimal treatment for primary CNS melanoma is complete resection of the tumor. Local recurrence has been reported even after complete resection. Consequently, adjuvant radiation therapy may be advised after surgery.⁽⁹⁶⁾

The prognosis for patients with primary malignant melanoma of the CNS is better than for those with metastatic melanoma, with reports of survival up to 9 and 12 years after presentation. The presence of leptomeningeal spread

reveals a worse prognosis. Recurrence after surgery tends to be localized and distant metastases are rarely seen in primary CNS malignant melanomas.⁽⁹⁷⁾

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Chapter 52

Past, Present and Future of Melanoma Sentinel Lymph Node Surgery

Stanley P. L. Leong, MD, FACS

Introduction

Historically, it was assumed that cancer usually spread from the primary site to the regional lymph nodes, then to the distant sites. Since the primary site and the nodal basins are anatomic sites that can be resected, surgical extirpation of primary cancer and the regional nodal basin became the standard procedure for the treatment of primary cancer. Thus, Halstad developed radical mastectomy and axillary lymph node dissection for breast cancer ⁽¹⁾ and Snow developed *en bloc* resection of the primary melanoma together with a radical lymph node dissection for the regional nodal basin. ^(2,3)

The Halsted influence was so profound that radical lymph node dissections were developed for various types of cancer such as esophagus, gastric, colon, gynecological cancers and others. However, despite the adequate resection of the primary site and radical regional lymph node dissection, the systemic recurrence rate was still high. Thus, Cady asserted that the lymph node was the marker but not the governor of cancer progression. ⁽⁴⁾

Furthermore, when the practice of radical regional lymph node dissection was introduced to resect the microscopic nodal disease, it was found that over 80% of the time, the lymph nodes were negative. If they were negative, why should we subject our patients to a significantly morbid procedure of a radical lymph node dissection with over 80% of the time, the patients probably would receive no benefit with a negative lymph node dissection. Therefore, there was an urgency to develop a technique to assess the nodal basin and yet not to dissect it out radically. The development of

sentinel lymph node (SLN) biopsy to solve this dilemma forms the basis of this chapter.

Past Development of the Concept of Sentinel Lymph Node

In the pre-SLN era, the question was whether the spread of the primary cancer site was random to any lymph nodes in the regional nodal basin or was it an orderly process to selective lymph nodes in the nodal basin. In 1960, Gould and colleagues developed the concept of a sentinel node in the cancer of the parotid gland ⁽⁵⁾ Gould *et al.* have found that when the node so called sentinel node was negative, the rest of the parotid nodal basin would also be negative.

In 1977, faced with the dilemma of dissecting bilateral inguinal lymph node basins, Cabanas proposed the identification of anatomically defined lymph nodes in the inguinal basin based on preoperative lymphangiography with contrast materials. ⁽⁶⁾ Based on 100 cases with penile cancer using lymphangiograms, according to Cabanas, the SLN was visualized on the antero-posterior view, at the junction of the femoral head and the ascending ramus of the pubis and was part of the lymphatic chain accompanying the superficial epigastric vein. Fifteen out of 46 SLN biopsies were positive for metastatic disease. An inguinofemoroiliac dissection was performed in these 15 patients and in 12 cases there were no positive lymph nodes. Cabanas noted that there were no lymphatic channels draining into the iliac lymph nodes without first draining into the SLN. Also, the inguinal-femoral lymph nodes were not involved

with metastasis in the absence of SLN involvement. Thus, Cabanas recommended preliminary bilateral SLN biopsy should be done first. Inguinofemoroiliac dissection was recommended only when SLN was positive. When SLN biopsy was negative for metastatic disease, no additional dissection was immediately indicated. The follow-up data showed that 5-year survival was 90% for a negative SLN biopsy. When the SLN alone was positive, the 5-year survival dropped to 70%. The 5-year survival was 50% when both SLN and other inguinal nodes were involved. When iliac metastases were also present, the 3-year survival was only 20%. Subsequent works by others, ⁽⁷⁾ although limited, could not validate Cabanas' findings.

It was Wong *et al.* in 1991 with the feline model ⁽⁸⁾ and Morton *et al.* ⁽⁹⁾ in 1992 with a study of patients with primary melanoma, the physiological basis of the SLN being identified by the blue dye was firmly established. In Morton's study, 223 patients were enrolled between 1985 and 1989. The patients received intradermal injection of vital blue dye around the primary melanoma and then underwent regional lymph node dissection to identify blue stained node(s). Lymphazurin or isosulfan blue, as a lymphatic tracer, when injected around the primary melanoma had been observed that it would drain into the SLN. Using this technique, Morton *et al.* identified SLNs successfully in 82% of the patients with primary melanoma and found 21% of these patients with micrometastasis. Only in 2 patients was occult metastasis found in the non-SLNs for a false negative rate of <1%. ⁽⁹⁾

Later, radiotracer was used to identify SLNs by Krag *et al.* ⁽¹⁰⁾ Thus, with a hiatus of 32 years since the publication by Gould, the sentinel lymph node era for staging the regional nodal basin for cancer has begun. To date, multiple studies have confirmed the validity and the prognostic significance of SLNs in melanoma and other types of solid cancer. ⁽¹¹⁻¹⁴⁾ In this chapter, it is devoted primarily to melanoma sentinel lymph node surgery.

A more personal account of the development of the concept and technique has been summarized by Balch ⁽¹⁵⁾ in his Donald L Morton Memorial Lecture at the 7th International Symposium on Cancer Metastasis. ⁽¹⁶⁾ **Figure 52-1** shows the seminal publication by Morton *et al.* in the Archives of Surgery in 1992 being cited for 209,248 times in the biomedical literature.

Of interest, Balch described the historical fact that the development of SLN concept in melanoma did not occur in a vacuum, but rather through a series of painstaking research and clinical trials as Morton *et al.* first developed the lymphoscintigraphy technique using radio-labeled colloidal gold. ⁽¹⁷⁾ Subsequently, Balch developed the first cutaneous lymphoscintigraphy using Tc99 as the radiotracer, which soon became the standard isotope for cutaneous lymphoscintigraphy for melanoma ⁽¹⁸⁻¹⁹⁾ and later for other types of cancer in the detection of SLNs.

Although both Cabanas and Morton developed the concept that SLN represented a selected lymph node or group of lymph nodes within the regional nodal basin to which the

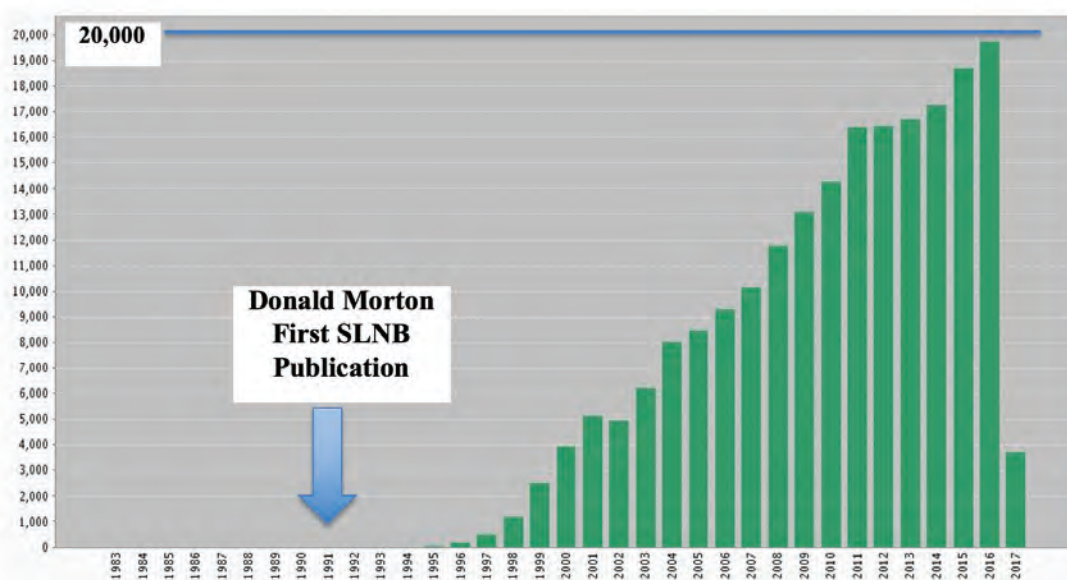


Figure 52-1. Citations each year on sentinel lymph node articles with total citations 209,248 times up to 2017. (Courtesy of Charles Balch, MD).

primary cancer cells would selectively spread there, their approach was independently different, Cabanas was based on anatomical localization of the SLNs and Morton was based on the physiological flow of the lymph through the lymphatic channels. Both pioneers have demonstrated that cancer spread to the regional nodal basin is a non-random process and that the SLN is the first lymph node receiving the arrival of cancer cells from the primary site that drains to that lymph node. The clinical implication is significant in that a radical lymph node dissection with increased morbidity can be spared if the SLN is negative for metastatic disease.

Present Experience of Melanoma Sentinel Lymph Nodes

Techniques for Identification of Sentinel Lymph Nodes

SLNs may be detected in singular or multiple nodal basins, such as the popliteal basin, in addition to the inguinal basin from a distal lower extremity primary site; epitrochlear basin, in addition to the axillary basin from a distal upper extremity primary site; and multiple sites including the lower neck, bilateral axillae and groins from a truncal primary site. Since primary melanoma may arise from any site of the body, it is mandatory to have preoperative lymphoscintigraphy to map out the exact locations of the nodal basins draining the primary melanoma site. **Figure 52-2** shows the various patterns of lymphatic drainage to different nodal basins. ⁽²⁰⁾

The initial tracer used was the blue dye (Lymphazurin) ⁽⁹⁾ and later a radiotracer was added ⁽¹⁰⁾ to localize the SLN. In the earlier days, both vital blue dye and radiotracer were used as the blue dye added the visualization of the SLN being blue. The identification of sentinel nodes was reported to be increased to 97% to 99%. ^(21,22)

To date, radiotracer such as Technetium sulfur colloid (99mTc) is used as it serves both purposes for preoperative lymphoscintigraphy and intraoperative localization of the SLNs. Radioactive SLNs are identified by a gamma probe intraoperatively with or without the use of vital blue dyes. Successful mapping of SLNs over 95-98% has been achieved. ^(23,24)

We and others have studied a novel radiotracer, Technetium-99m-labeled Tilmanocept (Lymphoseek, Cardinal Health, Dublin, Ohio) to detect SLNs. ^(25,26) It binds to technetium

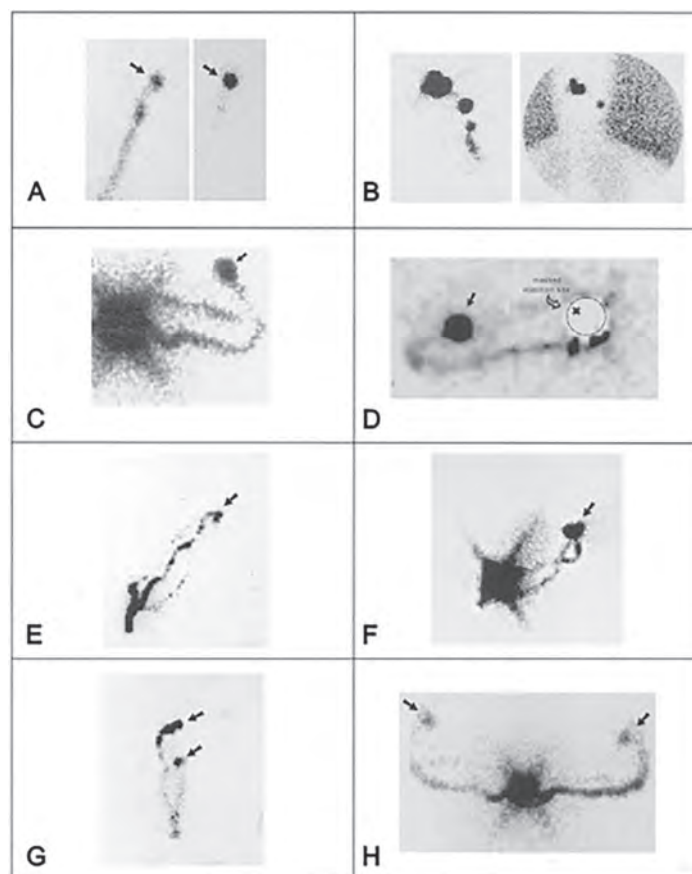


Figure 52-2. Pre-operative lymphoscintigraphy demonstrates varying lymphatic channel patterns in patients with primary melanoma. **(A)** Drainage of a single channel from the right upper arm leading to one SLN in the right axilla. **(B)** Drainage of a single channel from a posterior midline neck lesion to multiple contiguous nodes in the right posterior neck. **(C)** Confluent channels drain from the upper back to a single SLN in the left axilla. **(D)** Multiple channels from the left upper back draining to a single SLN in the left axilla. **(E)** Single primary site drainage source from the right arm, diverting into several channels and leading to a single SLN in the right axilla. **(F)** Multiple drainage channels from a lesion in the left anterior chest wall to one SLN in the left axilla. **(G)** Parallel simple channels from the right lower extremity, each draining to a single SLN, each in the same basin in the right groin. **(H)** Multiple channels from the midline back draining to multiple SLN(s) in different basins, the right and left axilla. This figure has been previously published by our group in *Clinical Nuclear Medicine* 30(3):150-158, 2005.

for its radioactivity and it also binds to mannose receptors to become internalized into the cell. These membrane receptors are expressed on the surface of the reticuloendothelial cells such as macrophages which are present in the lymph nodes.⁽²⁶⁾ Once the Tilmanocept reaches the lymph node, it is readily picked up by the macrophages and dendritic cells with the draining lymph nodes. Based on the efficacy of Tilmanocept in a phase III study that it identified more SLNs in melanoma⁽²⁷⁾ and breast cancer⁽²⁸⁾ patients and also more positive SLNs when compared to Lymphazurin, this was approved by the FDA for its clinical indication to detect melanoma SLNs by lymphoscintigraphy.

Other tracers such as indocyaninegreen (ICG) and superparamagnetic iron oxide tracer,⁽²⁹⁻³¹⁾ have been introduced to detect SLNs. ICG may be useful intraoperatively. But, to date, the standard for preoperative lymphoscintigraphy for melanoma is the radiotracer such as Technetium sulfur colloid or Tilmanocept.

To aid more precise anatomic localization of the SLNs particularly in the head and neck region with complication lymphatic drainage patterns, single photon emission computed tomography with integrated computed tomography (SPECT/CT) has been included in the imaging process to localize the SLNs with better anatomical precision. Several studies have shown a benefit of using SPECT/CT for preoperative evaluation and aiding decision-making during surgery.⁽³²⁻³⁵⁾

It has been debated whether lymph nodes with radioactivity lower than the highest count should be removed to avoid missing the positive nodes with lower counts. To date, multiple studies have supported the 10% rule, which states that a lymph node with a radioactive count $\geq$ 10% of the highest count node may potentially contain micrometastasis.^(23, 36-37)

False Negative Rate of SLN Biopsy

In order to make SLN biopsy a reliable staging procedure for patients with primary melanoma, it is important to minimize the false negative rate. False negative patients are those with a negative SLN biopsy who develop a nodal recurrence in the SLN basin due to a missed SLN which contains microscopic disease. The false negative rate is defined by the number of false negative cases divided by the total number of true positives as confirmed by histology plus false negatives multiplied by 100.

Valsecchi *et al.*⁽²⁴⁾ have performed the largest meta-analysis of SLN biopsy to date data from 71 studies and including over 25000 patients. The false negative rate (FNR) ranging from 0% to 34% in this extensive study, with a weighted summary rate of 12.5%. Multiple factors such as preoperative imaging methods, intraoperative techniques, pathologic analysis and length of follow-up may contribute to increased false negative rate.

Since the establishment of the SLN biopsy procedure by Morton *et al.*,⁽⁹⁾ the false negative rates of SLN biopsy worldwide have been published to range between 4.0 and 20%.⁽³⁸⁻⁴²⁾ The false negative rate increased with longer follow-up.⁽²⁴⁾ Failure to detect retained SLNs, which may contain micrometastasis (**Figure 52-3**) may be caused by a breakdown in preoperative imaging, identification of SLNs by surgeons intraoperatively, and pathological evaluation of the SLNs. It is important for the experienced pathologist to distinguish metastatic melanoma versus capsular nevus (**Figures 52-4 and 52-5**) in the SLN.⁽⁴³⁾

Although MSLT-II trial showed no therapeutic benefit by completion lymph node dissection versus observation following a positive SLN biopsy, SLN status continues to be an excellent predictor of the outcome of primary melanoma patients.⁽⁴⁴⁾ Thus, it is critical to identify melanoma SLNs as accurately as possible to reduce the rate of unidentified positive SLNs.⁽⁴⁵⁾

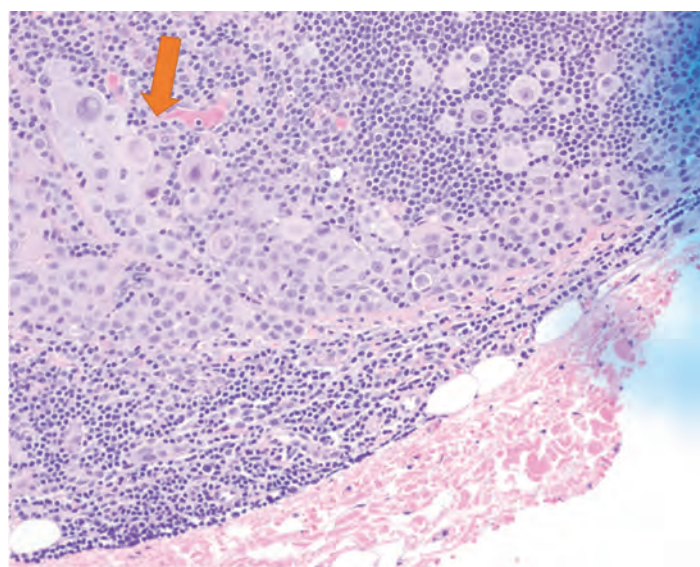


Figure 52-3. Metastatic melanoma, sentinel lymph node, 200x, H&E.

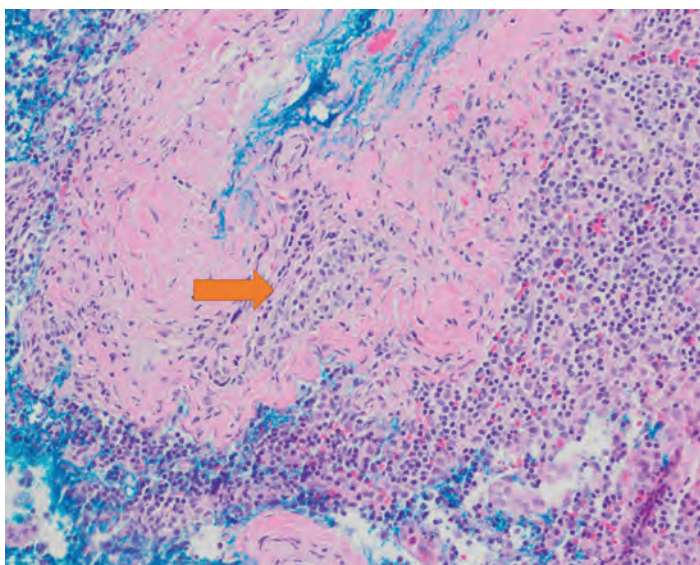


Figure 52-4. Bland melanocytes present in the capsule, consistent with nevus, 200x, H&E.

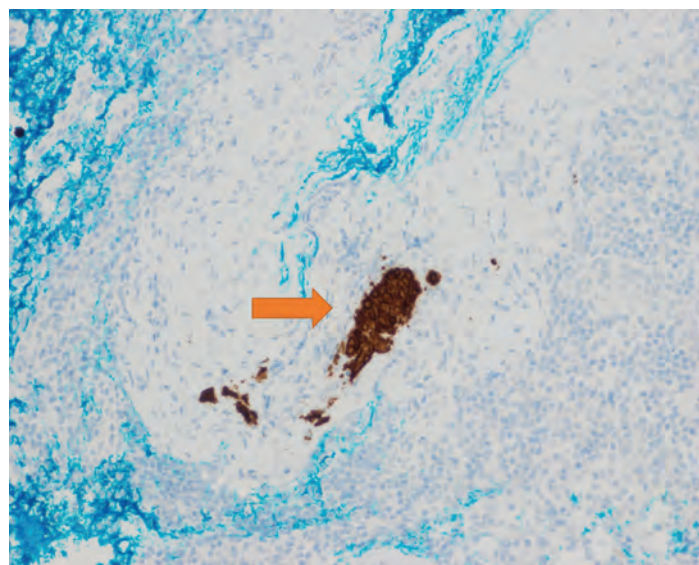


Figure 52-5. Melan A immunohistochemical stain of same area highlighting nevus cells, 200x.

Vidal-Sicart *et al.* have found that an intraoperative gamma camera has been quite helpful in difficult melanoma cases.⁽⁴⁶⁾ In a recent prospective Institutional Review Board-approved study, we have investigated whether an intraoperative portable gamma camera (Sentinella, improves SLN detection over the gamma probe.⁽⁴⁷⁾ We have found that the portable gamma camera (Sentinella S102, Oncovision S.A., Valencia, Spain) has detected 23% of SLNs (additional 89 SLNs) more than the gamma probe alone. Micrometastasis was identified in 4 of these 89 SLNs in 4 patients. In two of them the only tumor-positive SLN was identified by the portable gamma camera. Thus, two false-negative cases were prevented. Since completion lymph node dissection may be performed less often as the recently published MSLT-II study showing no therapeutic benefit of completion lymph node dissection as noted below,⁽⁴⁴⁾ increased detection of positive SLNs such as the application of intraoperative portable gamma camera becomes more important, not only for its prognostic value, identification of positive SLNs may have a significant impact in deciding whether adjuvant systemic therapy should be given, such as nivolumab⁽⁴⁸⁾ and a combination of dabrafenib and trametinib.⁽⁴⁹⁾ Thus, accurate staging by SLN biopsy is crucial in not only offering accurate staging of melanoma patients but also allowing them to receive effective adjuvant therapy.

Complications from sentinel node biopsy

SLN biopsy is a less morbid procedure with complication rate of about 5%⁽⁵⁰⁾ as compared to full lymph node dissection of as high as over 50%.⁽⁵¹⁾ The morbidity associated with a full lymph node dissection include wound separation, cellulitis, hematoma/seroma, lymphedema, and nerve injury, with some studies citing a complication rate as high as 65%.⁽⁵¹⁻⁵³⁾

In a clinical trial setting, the Sunbelt melanoma trial compared the complications in patients undergoing SLN biopsy alone with patients with a positive SLN biopsy being followed by a completion lymph node dissection.⁽⁵⁰⁾ In the SLN biopsy alone group, the overall complication rate was approximately 5% with hematoma, seroma and wound infection as the most frequent complications. For patients with SLN biopsy being followed by complete lymph node dissection, the complication rate increased to about 23% with the most frequent complications including lymphedema, wound infection, hematoma, seroma, and sensory nerve injury. As expected, the difference in complications was much more accentuated for patients undergoing inguinal lymph node dissection (31.5%) as compared with those undergoing axillary lymph node dissection (4.6%). Similarly, in the Multicenter Sentinel Lymphadenectomy Trial (MSLTII),⁽⁴⁴⁾ the complication rate for patients who

had SLN biopsy alone was about 12% as compared with the nearly 40% rate of complications noted in patients who also had a completion lymph node dissection with a positive SLN biopsy.

Although complications such as lymphedema, pain, and nerve injury from SLN biopsy are much less than those from completion lymph node dissection, major nerves are still exposed during the SLN biopsy for different nodal basins such as the facial nerve in the preauricular area, spinal accessory nerve in the posterior neck; thoracodorsal and long thoracic nerve in the axilla; ulnar, median, and radial nerves in the deep epitrochlear basin; femoral nerve in the groin; and sciatic nerve in the popliteal basin. The nerves may be more difficult to identify in these nodal basins due to the limited operative field in SLN biopsy. For both procedures of SLN biopsy and completion lymph node dissection, it is imperative to identify the nerve so that it will be carefully preserved during dissection. We have found that the Checkpoint Stimulator is an excellent tool to assist in localizing these nerves prior to visualization. The ability to repeatedly stimulate the nerves by the stimulator without causing any damage to the nerve makes it a valuable tool to allow the surgeon to repeatedly confirm nerve function, thus, enabling him or her to avoid nerve injury throughout the procedure. It is particularly helpful in the SLN procedure with a limited exposure of the anatomical structures.⁽⁵⁴⁾ For example, during SLN biopsy of the posterior neck and the popliteal fossa, it is crucial to identify the spinal accessory nerve and the sciatic nerve respectively, as the consequence of injury to these nerves is disastrous.

Several large confirmatory studies, including prospective randomized trials, have provided a wealth of convincing information regarding the SLN with respect to its accuracy and prognostic value.⁽⁵⁵⁾ Therefore, SLN biopsy identifies, with a high degree of accuracy, patients with early stage melanoma without nodal metastases (over 80%) who can be spared from a morbid radical lymphadenectomy. For detailed technical issues of SLN biopsy, several major references are included herewith.⁽¹¹⁻¹⁴⁾

Summary of the MSLT I and MSLT II Clinical Trial

Not only was the development of SLN concept and technique revolutionary, the most important contributions by Morton and Associates are the completion of MSLT I⁽⁵⁶⁾ and MSLT II.⁽⁴⁴⁾ It is important to keep the false negative

rate as low as possible to ensure the accuracy of the result of a SLN biopsy. For this reason, all the investigators have been trained and reached an acceptable level of competence to participate in these clinical trials. The goal of the MSLT I was to compare the clinical outcome of primary melanoma patients who underwent wide local excision only versus wide local excision and SLN biopsy. The final report of MSLT I demonstrated that the positive SLN rate in the intermediate thickness group (1.2 to 3.5 mm) was 16%. The 10-year disease-free survival (DFS) rates were significantly higher in the SLN biopsy group when compared with the nodal observation cohort ($71.3\% \pm 1.8\%$ vs $64.7\% \pm 2.3\%$, respectively; HR = 0.76; 95%CI: 0.62-0.94; P = 0.01). However, there were no significant differences in 10-year melanoma-specific survival (MSS) or overall survival (OS) between the SLN biopsy group and the nodal observation arm. In the subgroup with thick melanoma, the positive SLN rate was 32.9%. There was significant difference in 10-year DFS between the SLN biopsy cohort and the observation group with $50.7\% \pm 4.0\%$ vs $40.5\% \pm 4.7\%$, respectively (HR = 0.70; 95%CI: 0.50-0.96; P = 0.03). However, there were no significant differences in MSS and OS between the SLN biopsy and observation arms as shown in the intermediate thickness group.^(41, 56)

Survival analyses could not be performed in patients with thin melanoma as the number of patients was too small for analysis. The study confirmed and established the value of SLN status as the most significant prognostic factor for survival in patients with primary melanoma. Patients with a positive SLN biopsy had a significantly worse 10-year MSS ($62.1\% \pm 4.8\%$) when compared with patients having a negative SLN biopsy ($85.1\% \pm 1.5\%$; HR = 3.09; 95%CI: 2.12-4.49; P < 0.001).

The study concluded that the status of a patient's SLN was the most powerful prognosticator in patients with intermediate thickness and thick melanomas. Although it was not included as an end point in the clinical trial, one of the observation from MSLT-I is that treatment of nodal disease at the microscopic level may result in a survival advantage as compared with resection of nodal disease at the macroscopic or clinically palpable level in the intermediate thickness group. The 10-year MSS in the positive SLN biopsy group with microscopic nodal disease followed by a completion lymph node dissection was $62.1\% \pm 4.8\%$. This was significantly higher than the group with only wide local excision with a lymph node dissection being performed when clinically palpable lymph node was

detected upon follow-up with a 10-year MSS of $41.5\% \pm 5.6\%$ (HR = 0.56; 95%CI: 0.37-0.84; P = 0.006). On the other hand, such a difference was not noted in the thick melanoma group. Thus, these findings are consistent with previous studies showing a survival benefit for immediate lymph node dissection when compared with a delayed lymphadenectomy in the intermediate thickness group.⁽¹⁵⁾

Although a positive SLN biopsy in melanoma patients with intermediate thickness (1.2 to 3.5 mm) is associated with decreased melanoma-specific survival, the therapeutic benefit of completion lymph-node dissection is not clear. Therefore, Morton *et al.* launched the MSLT II clinical trial⁽⁴⁴⁾ to randomize patients with a positive SLN biopsy to immediate completion lymph node dissection or no lymph node dissection (observation group). In the per-protocol analysis of 1755 patients, the mean 3-year rate of melanoma-specific survival was similar in the dissection group and the observation group ($86 \pm 1.3\%$ and $86 \pm 1.2\%$, respectively; P = 0.42 by the log rank test) at a median follow-up of 43 months. In the immediate completion lymph node dissection group the positive rate was 11.5%, which was a significant independent prognostic factor for recurrence (hazard ratio, 1.78; P = 0.005).

In a separate German phase III randomized study, melanoma patients with a positive SLN biopsy were randomly enrolled (1:1) to undergo complete lymph node dissection versus observation. The primary endpoint was distant metastasis-free survival and the patients were analyzed by intention to treat. Between 2006 and 2014, 5547 patients were screened with SLN biopsy and 1269 patients (23%) were positive for micrometastasis. Of these, 483 patients (39%) were enrolled into the clinical trial with 241 patients being randomized to the observation group and 242 to the complete lymph node dissection group. The trial was closed early due to difficulties enrolling and a low event rate. Despite the fact that trial was closed prematurely, the study showed no difference in survival in patients from the two different groups. The authors recommend that complete lymph node dissection should not be performed in patients with melanoma with lymph node micrometastases of at least a diameter of 1 mm or smaller.⁽⁵⁷⁾

In a recent retrospective multicenter study by the Sentinel Lymph Node Working Group,⁽⁵⁸⁾ 953 positive SLN patients from a multicenter Sentinel Lymph Node Working Group database were analyzed. There were 831 patients (87%) who had completion lymph node dissection. The positive completion lymph node dissection rate was 17% (141

patients). The positive patients were associated with worse overall and melanoma specific survival (both P < 0.001). No significant differences were noted between completion lymph dissection versus no lymph node dissection both in overall and melanoma specific survival. Completion lymph node dissection provides prognostic information but is not correlated with a survival benefit.

In a separate study by Teixeira *et al.* with retrospective review of 221 melanoma patients,⁽⁵⁹⁾ for SLN positive patients, the 5-year survival rates were 53.1% and for SLN negative patients, they were 88.2%. Breslow thickness and the SLN status were independent predictor for overall survival. The risk factors for a positive SLN biopsy were similar to those being published. The authors have emphasized the importance of SLN biopsy for staging patients with primary melanoma.

As expected, lymphedema in MSLT -II was noted in 24.1% of the patients in the lymph node dissection group and in 6.3% of those in the observation group. Since no survival benefit was shown in immediate completion lymph node dissection over the observation group the routine use of completion lymph node dissection following a positive SLN biopsy has been questioned.⁽⁶⁰⁻⁶²⁾

From retrospective studies, the positive rate of a completion lymph node dissection following a positive SLN biopsy ranges from 15 to 20%.⁽⁶²⁻⁶⁴⁾ For those patients with a positive completion lymph node dissection, not only is the residual disease removed with better local control, the positive status is also marker for a worse prognosis.⁽⁶²⁻⁶⁴⁾ On the other hand, about 80% of the patients would probably not need a lymph node dissection since their lymph nodes are negative and, thus, can avoid the major morbidity of the procedure such as lymphedema. Therefore, an attempt has been made to search for a factor or factors which can predict the outcome of a completion lymph node dissection. To date, no reliable markers are available to make such an assessment. With the published data from the MSLT-II that there is no therapeutic benefit in the lymph node dissection group, if the tumor burden in the sentinel lymph node is low, such as 0.6 mm, which was the mean size of the tumor in the SLN in the MSLT-II, then, most of us would probably not recommend a complete lymph node dissection. This approach is particularly appropriate in the current landscape of melanoma treatment with availability of effective adjuvant therapy^(48, 49) based on the SLN staging information. Of course, the patient with a positive SLN biopsy without a completion lymph node dissection will be

followed closely and if recurrent disease is found in the nodal basin, a therapeutic lymph node dissection should be done. These studies have been adequately summarized in a recent review article by Han *et al.* ⁽⁶⁵⁾

Current Practice Guidelines of Melanoma Sentinel Lymph Node Surgery

Based on the 8th Edition of the American Joint Committee on Cancer for staging of melanoma, ⁽⁶⁶⁻⁶⁷⁾ the 2018 update of joint guidelines from the American Society of Clinical Oncology (ASCO) and Society of Surgical Oncology (SSO) includes the following recommendations: ⁽⁶⁸⁾

1. Routine SLN biopsy is not recommended for patients with thin melanomas that are T1a (non-ulcerated lesions < 0.8 mm in Breslow thickness).
2. SLN biopsy may be considered for thin melanomas that are T1b (0.8 to 1.0 mm Breslow thickness or < 0.8 mm Breslow thickness with ulceration) following a thorough discussion with the patient of the potential benefits and risk associated with the procedure.
3. SLN biopsy is recommended for patients with intermediate-thickness melanomas (T2 or T3; Breslow thickness of >1.0 to 4.0 mm).
4. SLN biopsy may be recommended for patients with thick melanomas (T4; > 4.0 mm in Breslow thickness), after a discussion of the potential benefits and risks.
5. In the case of a positive SLN biopsy, completion lymph node dissection or careful observation are options for patients with low-risk micrometastatic disease, with appropriate consideration of clinicopathologic factors. For higher-risk patients, careful observation may be considered only after a thorough discussion with patients about the potential risks and benefits of a completion lymph node dissection.

Furthermore, as the landscapes of treatment of melanoma are getting more and more complex, it requires the expertise from a multidisciplinary team including pathology, radiology, dermatology surgical oncology, medical oncology and radiation oncology to render the best treatment options for the melanoma patient. Thus, it is important to have a melanoma center to conduct a weekly Melanoma Multidisciplinary Tumor Board to develop the best care for our melanoma patients.

Future Perspectives of Melanoma Sentinel Lymph Node Surgery

The SLN biopsy procedure has been well established. All the current surgical oncology training programs have trained their residents well to perform the procedure for the staging of patients with primary melanoma. It is important to note that this procedure is a multidisciplinary approach involving the preoperative imaging of the sentinel lymph nodes by Nuclear Medicine, intraoperative identification of sentinel lymph nodes by surgical oncologists and subsequent pathological examined by trained pathologists. The surgical oncologist should take a leading role to ensure that such a procedure is efficiently executed and the patient gets the best surgical care. The intraoperative gamma camera (Sentinella) as described above in addition to the gamma probe may increase the detection of retained sentinel lymph nodes. The accurate identification of sentinel lymph nodes in the post MSLTII era have become increasingly important as completion lymph node dissection is less being performed for a small tumor burden in the SLN. However, the role of SLN biopsy remains important to stage melanoma patients accurately as the SLN status remains to be the most reliable prognosticator for melanoma disease-specific and overall survival. Also, more effective adjuvant therapy using check point inhibitors and targeted therapy are now available for the adjuvant treatment of stage III disease including micrometastasis in the SLNs. Furthermore, SLN status has been incorporated and utilized in the stratification of melanoma patients for adjuvant clinical trials.

The biology of metastasis from the primary melanoma biopsy site to the SLN and beyond is still poorly understood. Since 2005, we have conducted the biennial cancer metastasis conferences to understand the molecular mechanisms of cancer metastasis. ^(16, 69-70)

Melanoma remains one of the most aggressive cutaneous malignancies. Significant challenges still exist including diagnosis of controversial melanocytic lesions, correct prognostication of patients, selection of appropriate adjuvant and systemic therapies, as well as prediction of response. However, progress has been made in the areas of nucleic-acid based biomarkers being assayed from histologic tissue specimens. FISH, CGH and Decision Dx to enhance overall predictability have been described. ⁽⁷¹⁾ Other multi-marker assays have been used to study the molecular mechanisms of melanoma progression. ⁽⁷²⁾

It is not the intent of this chapter to cover the biomarkers of melanoma, but it is important to emphasize that, perhaps, the combination of SLN status and these melanoma biomarkers may enhance the prognostic and predictive power of therapeutic responses for the diagnosis and treatment of melanoma.

As mentioned above, the SLN appears to be the major gateway for melanoma metastasis. Therefore, it is important to understand the microenvironment of melanoma as it arrives in the SLN from the primary site and progresses into a metastatic colony with subsequent spread beyond to the systemic sites. ⁽⁷³⁻⁷⁴⁾

The cancer microenvironment exerts a selective force to favor the development of aggressive clones to metastasize further to the systemic sites, akin to Darwin's concept of natural selection. ⁽⁷⁵⁾ The immune system may play a major role in modulating the growth and progression of melanoma in the primary site, the SLN and beyond.

In general, the SLN may be the initial gateway for the cancer cells to spread to. However, in some cases, cancer cells may bypass the SLNs and directly enter the vascular channels. During its growth at the primary site within the melanoma microenvironment, its entry to the SLNs, its residence in the SLN and its final spread to the systemic sites

(**Figure 52-6**), the process involves complex biochemical and molecular mechanisms being influenced by the host microenvironment. Melanoma, being heterogeneous, allows it to evolve into more aggressive clone or clones to survive and proliferate. With respect to the host influence, in particular, the immune system exerts an effort to abate cancer growth. When the immune system fails, the melanoma cells proliferate and become clinically detectable. Thus, it is important to collect clinical, pathological and genomic characteristics of melanoma and its microenvironment for comprehensive analysis, perhaps, using new computer techniques of artificial intelligence ⁽⁷⁶⁻⁷⁷⁾ in order to develop unique melanoma profile of each patient so that specific personalized cancer therapy may be rendered with increased specificity and therapeutic benefit. ⁽⁷⁸⁾ These issues were discussed in detail in the 2019 8th International Congress on Cancer Metastasis through the Lymphovascular System held in San Francisco, CA, from October 25–27, 2019. ⁽¹⁶⁾

Summary

Most patients with cutaneous melanomas are adequately treated with wide local excision. However, given that 15% to 20% of patients will develop regional nodal metastasis and the results of prospective randomized trials showing

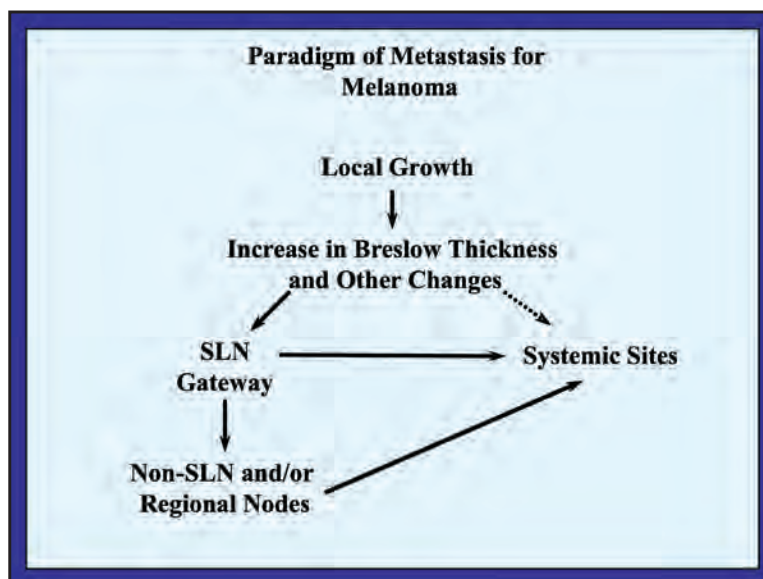


Figure 52-6. The figure depicts progression of melanoma from the primary site to the SLN, then to non-SLN or regional nodes and distant sites. Local growth and proliferation result in increase thickness associated with nodularity and other changes such as ulceration, increased mitotic rate and other invasive characteristics. Occasionally, cancer cells may bypass by lymph nodes and spread to distant sites through vascular channels. In the majority of the cases (up to 90%), the SLN is the gateway for cancer spread (bold arrow pathway in figure).

clearly the excellent prognostic value of SLN status, SLN biopsy, being less morbid, has remained the standard of care for staging patients with primary melanoma. Over 80% of melanoma patients with a negative SLN biopsy will be spared of a more morbid completion lymph node dissection. Furthermore, MSLT-II have shown that patients with a positive SLN biopsy with a tumor burden of less than 0.6 mm show no therapeutic benefit with the observation group. Therefore, even melanoma patients with a positive SLN biopsy with a low tumor burden may be spared of a completion lymph node dissection. However, staging information may allow those patients with a positive SLN biopsy to be eligible for more effective adjuvant therapy using check point inhibitors or targeted therapy. Future molecular and genomic studies of the melanoma microenvironment and SLN micrometastasis may give us a better understanding of the molecular mechanisms that promote spread of melanoma cells to SLNs and beyond. Thus, more specific personalized treatment may be offered to patients with high risk melanoma.

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Chapter 53

Management of Locoregional and Distant Recurrence

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Locoregional Disease

Clinically Apparent Regional Lymph Node Spread

The regional lymph nodes are the commonest first site of spread from the primary site and present in up to 80% of patients who develop metastatic disease sometime during their illness. The median time to development of regional lymph node metastasis is 18-24 months, however, this is shorter for patients with thicker lesions (T4 melanomas: 9 months) compared to those with thinner lesions (T3 melanomas: 19 months). Approximately 20% of patients presenting with palpable lymphadenopathy will have evidence of distant metastatic disease and therefore staging with whole-body CT or PET/CT scan and an MRI or CT brain scan is appropriate. Diagnosis should be confirmed by image guided fine needle aspiration cytology, usually using ultrasound, rather than open or core biopsy which risks the possibility of local tumor spill.

Patients with palpable lymphadenopathy and no evidence of metastasis are staged as stage IIIB, stage IIIC or stage IIID based on number of nodes involved and presence/absence of in-transit lesions. Appropriate surgical management of patients with palpable lymphadenopathy results in long-term control in approximately 50%. Five-year melanoma-specific survival for stages IIIB, C, D is 83%, 69% and 32%, respectively. Other factors influencing survival include the length of time since original diagnosis and the primary tumor characteristics, such as thickness and presence of ulceration.

Surgical Management

In the absence of metastatic disease, patients should proceed to a standard radical lymphadenectomy. Axillary lymphadenectomy should include lymph nodes in levels 1, 2 and 3 and incorporate the intercosto-brachial nerve. Many authorities recommend removal of the pectoralis minor to facilitate exposure of the upper axilla. Options for patients with cervical lymphadenopathy include radical lymphadenectomy which includes removal of levels I-V along with the accessory nerve, jugular vein and sternomastoid muscle, extended radical lymphadenectomy which includes in addition parotidectomy, modified radical lymphadenectomy which involves preservation of all or some of the accessory nerve, internal jugular vein and sternomastoid muscle or selective lymphadenectomy which generally involves a function preserving procedure removing less than levels I-V. Selective procedures may be considered for patients with small-volume disease. For patients with parotid lymph node involvement, the risk of upper cervical lymph node involvement is approximately 20%, indicating the need for an *en bloc* upper neck dissection incorporating at least levels 1B and 2-4. Unlike cervical lymph node involvement by squamous cell carcinoma, which tends to infiltrate the local tissues, melanoma tends to be more circumscribed, justifying the use of function preserving procedures for suitable patients. None of these procedures have been formally compared. Inguinal lymphadenectomy is the standard procedure for groin lymphadenopathy. In the absence of imaging detected pelvic lymph node involvement, there is no strong indication to combine the inguinal lymphadenectomy with a pelvic lymphadenectomy. Again, these two procedures have not been formally compared, but many authorities

would recommend pelvic lymphadenectomy in addition to the inguinal lymphadenectomy for patients with large (>5 cm) or multiple involved inguinal lymph nodes.

Approximately 10% of patients with clinically detected lymph node involvement will have no previous history of a primary melanoma. If anything, the outcome for these patients may be superior to patients with a known primary and they should be managed with a standard lymphadenectomy as noted above.

Adjuvant Radiotherapy

For patients with palpable lymphadenopathy, the risk of further lymph node field relapse is approximately 20% and is higher for patients with multiple nodes or extra capsular extension of tumor. Adjuvant radiotherapy has been shown to reduce the risk of lymph node field relapse by 50% but with no effect on overall survival and not insignificant toxicity and regional symptoms. On that basis, and particularly given the efficacy of newer systemic agents, adjuvant radiotherapy is not indicated.

Adjuvant Systemic Therapy

As at least 50% of patients will develop distant recurrence, effective adjuvant therapy has long been a goal. The first major adjuvant therapy, Interferon alpha 2B, was associated with a very small improvement in survival and significant toxicity, leading to minimal uptake in clinical practice internationally.

Evidence of efficacy of newer systemic treatments in advanced melanoma, specifically immunotherapy and targeted therapy, has led to trials investigating these agents in the adjuvant setting. With improvements seen in recurrence free survival, adjuvant treatment for stage III melanoma with these agents has now become standard of care.

Adjuvant systemic therapy should be considered for all fully resected stage III and IV disease, except for those with low volume stage IIIA disease where the overall low risk of recurrence should be balanced against toxicity risk with adjuvant systemic therapy. PD-1 inhibitors, including both pembrolizumab and nivolumab, have been shown to reduce the risk of recurrence by 40% compared to placebo and ipilimumab, respectively, with longer follow-up required to determine survival benefit. Both BRAF mutated and wild-type patients benefited from treatment. Again, these agents are associated with irAEs at rates similar to that seen in the

metastatic setting. Appropriate patient selection is essential, especially in the adjuvant setting as treatment toxicities may be serious.

Ipilimumab, at a higher dose of 10mg/kg, has also been studied in the adjuvant setting and shown to decrease the risk of recurrence and improve survival. However, the toxicity associated with this treatment was significant, with 54% grade 3 or 4 adverse events and five treatment-related deaths. As such, this regimen is not recommended.

For patients with a mutation in the V600 codon of the BRAF proto-oncogene, adjuvant treatment with dabrafenib and trametinib has been shown to reduce risk of recurrence by 50% compared to placebo. This is also associated with an improvement in survival, though the data remains immature. Treatment with targeted therapy has not been compared to immunotherapy in the adjuvant setting. Treatment choice should be based on patient characteristics and the toxicity profile of the different treatments.

For all adjuvant treatment, therapy is continued for a total of one year after resection. Surveillance for recurrent disease should continue post-operatively. For those that recur during or within 6 months of adjuvant treatment, therapy choices in the metastatic setting are complex, and consideration should be made for enrolment into a clinical trial. New strategies under investigation include combination immunotherapy in the adjuvant setting and neoadjuvant treatments, with pre-operative systemic treatment showing promising results in early-phase studies.

Local and In-Transit Recurrence

Under the new AJCC 8th edition staging system, no difference is made between local recurrence, satellite recurrence or in-transit recurrence, as they almost certainly represent the same process, namely persistence of intra lymphatic disease. Adverse primary tumor characteristics such as tumor thickness, the presence of ulceration, mitotic rate, lymphovascular invasion, micro-satellite deposits of tumor adjacent to the primary lesion and lymph node involvement are all associated with local and in-transit recurrence. The lower limb and elderly patients are overrepresented among patients with in-transit recurrence.

In the new AJCC staging system, local and in-transit recurrence (classified as stage IIIC or IIID) have five-year survivals of 69% and 32%, respectively. In a large study of 505 patients who had developed in-transit metastases, it was the first site of recurrence in one third. Local recurrence

preceded the development of in-transit metastases in 11%. Regional recurrence occurred in over 40% over the course of the patient's illness.

The course of in-transit recurrence is highly variable and there is limited data on how it should be managed. Generally, it is recommended that patients be staged at the time of presentation with local, satellite or in-transit recurrence to exclude the presence of distant disease. Many patients can be managed effectively by limited surgical excision which may be repeated, but most patients eventually will require more extensive treatment. Alternatives to surgery include: topical therapies such as imiquimod and diphenylcyclopropenone; intralesional therapy with BCG, interleukin 2 and Rose Bengal; or radiotherapy. Whilst most of these therapies are relatively effective, long-term control is unusual. Isolated limb perfusion and more recently the technically less demanding procedure of isolated limb infusion report complete response in approximately one third and partial response in a further one third. Isolated limb perfusion is slightly more effective than isolated infusion but at the cost of much greater risk of toxicity. Isolated infusion can be repeated as necessary and is generally preferred over isolated perfusion. Recently, intralesional Talimogene laherparepvec, a genetically modified oncolytic herpesvirus engineered to produce GM-CSF, has been shown to be relatively effective. In a small proportion of patients it may induce an abscopal or beneficial effect on distant metastatic disease. Given the efficacy of newer treatments, systemic therapy is increasingly being considered over extensive surgical resection or other local therapies for recurrent in-transit disease.

Advanced Melanoma

Introduction

Until recently, the development of metastatic disease indicated a very poor prognosis; the median survival was less than 12 months and fewer than 5% of patients survived five years. The standard chemotherapeutic approach included dacarbazine (DTIC) based protocols which at best achieved a 15% response rate with a median duration of response of approximately three months. Not surprisingly, surgical resection of limited metastatic disease was advocated. However, in reality all but a few patients were suitable operative candidates, and even fewer benefitted from the intervention.

In the last few years, the management of advanced melanoma has changed dramatically with the introduction of immune checkpoint inhibitors and therapies targeting the mitogen activated phosphate (MAP) kinase pathway. The initial wave of studies confirming the effectiveness of these therapies has now matured into more detailed examination of patient and treatment selection, drug combinations, timing and sequencing of treatments and management of the not inconsiderable toxicities. Surgery still has a role in the management of patients with limited metastatic disease and the patient with a surgical emergency. In the future, surgery may be incorporated into adjuvant or neoadjuvant approaches for patients with metastatic disease or resection of isolated progressive or residual disease following systemic therapy.

Surgery for Metastatic Disease

All the major studies which have investigated the role of surgery were conducted in the era prior to effective systemic treatment for advanced melanoma. In summary, patients with a disease-free interval of at least 12 months, preferably one but certainly three or fewer sites of metastasis, and patients with favorable sites such as subcutaneous deposits and lymph node metastases, are more likely to benefit. A prospective evaluation of surgical management of metastatic disease was a small study of 63 patients. At four years the overall survival was 31%, however relapse-free survival was only five months. Long-term follow-up of 496 patients randomized to receive a cancer vaccine after surgical resection of metastatic disease reported 5 and 10-year survivals of 39% and 33%, respectively. While these results are considerably better than reported for standard chemotherapy, there was considerable selection bias. In comparison, the outcomes after treatment with immune checkpoint inhibitors or targeted therapy appear to be at least as good and therefore these agents should be considered as first line treatment for patients with advanced metastatic melanoma.

In principle the patient with a disease-free interval of at least 12 months and limited disease burden in surgically accessible sites may be considered for surgical resection with close follow-up subsequently and the option to consider systemic therapy at the time of recurrence. It is unknown whether this approach compromises care, but it does offer the opportunity to delay or avoid commencing patients on prolonged treatment with checkpoint inhibitors,

which as will be discussed below can have life altering consequences. Increasingly, a small proportion of patients successfully managed with either immune checkpoint inhibitor or targeted therapies are found to have either isolated persistent or progressive disease after a period of control. These patients may be considered for surgical resection; however, the long-term results of this strategy are currently unknown.

Undeniably a role for surgery in advanced melanoma is in the management of patients with a surgical emergency, such as symptomatic gastrointestinal hemorrhage, which can be severe and unremitting, or bowel obstruction due to intussusception of GI metastases. In this instance, surgery can provide effective palliation and the opportunity to continue with systemic therapy.

Brain Metastases

Metastases to the brain are a unique subset and have proven to be difficult to treat. Approximately 10-20% of patients presenting with stage IV disease have evidence of brain metastases and approximately 50% of patients with advanced disease will develop brain metastases during their illness. In general, small isolated metastases will be considered for surgical resection. Stereotactic radiotherapy is preferred for larger lesions, metastases located in critical areas of the brain and suitable patients with multiple brain metastases. Whole brain radiotherapy is appropriate for patients with extensive intracranial disease. However, the use of radiotherapy, including when it is indicated and the sequencing with other treatments, has become more complex with effective systemic therapies with CNS activity and is an area of active research. Multidisciplinary management, with involvement of neurosurgeons, radiation oncologists and medical oncologists, is recommended.

Systemic Therapy

As mentioned, the treatment of advanced melanoma has changed dramatically over the last decade. As a result of developments in the areas of immunotherapy and targeted therapeutics, chemotherapy is now reserved for patients who have progressed through all other treatment options.

Immunotherapy

Ipilimumab, a monoclonal antibody against CTLA-4, was the first agent to demonstrate an overall survival benefit

in patients with advanced melanoma in a paradigm-changing phase III trial published in 2010. CTLA-4 affects the priming phase of T-cell activation and functions as a negative regulator of T cell function, binding to ligands on antigen-presenting cells and inducing cell-cycle arrest and T-cell anergy. Ipilimumab has an overall response rate of 11% in melanoma (Hodi 2010) and pooled analysis has shown a three-year survival rate of 22%, a vast improvement compared to historical figures.

Subsequent trials involving PD-1 inhibitors pembrolizumab and nivolumab demonstrated improved response rates and reduced toxicity compared to ipilimumab and chemotherapy, respectively. The PD-1 immune checkpoint pathway primarily functions during the effector phase of the T-cell response in the peripheral tissue. Tumor cells exploit this pathway by expressing PD-L1, which binds to PD-1 and inactivates T cells. Blocking this interaction can lead to an enhanced anti-tumor T cell response. PD-1 inhibitors have an overall response rate of approximately 40%, five-year survival rates of 34% and a median overall survival of 24 months, which increases to 39 months in those who were treatment-naïve. Desmoplastic melanoma, a rare subtype of cutaneous melanoma, is particularly responsive to immunotherapy, with a response rate of 70% to PD-1 inhibitors.

Combination treatment with ipilimumab and nivolumab has been shown to have enhanced efficacy, including a higher response rate of 58% and improved progression free survival, compared to single-agent PD-1 inhibitor. This is particularly true for tumors with lower PD-L1 staining and those with BRAF V600 mutations.

Prospective studies have shown intracranial activity for both monotherapy with PD-1 inhibitors and combination treatment with nivolumab and ipilimumab. The intracranial response rate is highest for the combination at 46 to 56%, including a complete response rate of 17 to 26%. However, this is applicable mainly to patients with fairly low volume, asymptomatic intracranial metastases, and decreases substantially if they have been pre-treated with targeted therapy.

Responses to immunotherapy may develop slowly and can be preceded by a transient enlargement of metastatic lesions, termed pseudo-progression. Development of immune-related phenomenon, such as sarcoidosis, can also mimic disease progression and should be considered. Responses induced by immunotherapy are durable; the median duration of response for pembrolizumab has not been reached after five years of follow-up. This is especially true of patients who achieve a complete response, including ongoing

complete responses in patients who come off treatment. Certain tumor features, including PD-L1 expression and tumor mutational burden, correlate with response, but further research into predictive biomarkers is needed.

Immunotherapy has been shown to be effective in both BRAF mutated and non-mutated patients, making the selection of first-line treatment controversial for those harbouring a BRAF driver mutation. Targeted therapy is often favoured in patients with high volume disease who require rapid disease response, those with high volume intracranial disease, or patients with contraindications to immunotherapy.

Immunotherapy is associated with unique immune-related adverse events (irAEs) due to immune system over-activity and damage to normal tissue. This includes autoimmune phenomenon involving virtually any organ system. Most commonly, this involves fatigue, rash/pruritus, arthritis, hypothyroidism, hypophysitis, hepatitis, pneumonitis, nephritis and diarrhea/colitis. Rare but serious irAEs include myocarditis, CNS toxicity such as encephalitis, and development of Type 1 diabetes mellitus. The rate of serious grade 3 to 5 irAEs varies significantly according to the treatment; monotherapy with ipilimumab or a PD-1 inhibitor has a rate of 10-15%, which increases to 60% with combination therapy with ipilimumab and nivolumab. These toxicities can be fatal, and early recognition with prompt initiation of treatment, typically involving glucocorticoids or other immunosuppressants, is crucial to the appropriate management of irAEs. Multidisciplinary care and involvement of the appropriate subspecialists, such as gastroenterologists, is also essential.

Targeted Therapy

Approximately 40-50% of patients with metastatic melanoma harbour a driver mutation in the V600 codon of the BRAF proto-oncogene encoding the BRAF kinase, leading to constitutive activity of the mitogen activated phosphate (MAP) kinase pathway. BRAF inhibitors, specifically dabrafenib and vemurafenib, are small molecule inhibitors that selectively block mutated forms of the BRAF kinase, thereby inhibiting tumor cell growth. Combination with MEK inhibitors, which block downstream signalling in the MAP kinase pathway, leads to more durable disease control and improvement in overall survival. Thus, combination treatment has replaced the use of single-agent BRAF agents.

BRAF/MEK inhibition leads to rapid tumor regression in most patients, with an overall response rate of approximately 70% and a median progression free survival of approximately 12 months. Treatment with vemurafenib/cobimetinib or dabrafenib/trametinib is considered to be equally efficacious, with treatment decisions based on the differing toxicity profiles of the combinations. Generally, these combinations are well tolerated, with common side effects including fatigue, skin toxicity, nausea, diarrhea and arthralgias/myalgias. Dabrafenib/trametinib is associated with non-infective fevers/chills that can often be successfully managed which short treatment interruptions. Vemurafenib/cobimetinib is associated with severe sun sensitivity, requiring the patient to be vigilant regarding sun exposure. Rare side effects to both combinations include uveitis, cardiotoxicity and squamous cell carcinomas.

Encorafenib and binimetinib are second-generation BRAF and MEK inhibitors, respectively, with longer dissociation half-lives that enable sustained target inhibition. A phase III trial recently showed a median progression-free survival of 15 months with this novel combination, outperforming results from previous trials of combination BRAF/MEK inhibition. Approval of this combination is pending in several countries but given evidence of enhanced efficacy it may be the combination of choice in the future.

Future Directions

Several unanswered questions remain, including the optimal sequencing of targeted therapy and immunotherapy for patients harbouring a BRAF driver mutation. This remains to be investigated in a prospective manner, and treatment choices should be individualized to the patient, based on volume and sites of disease, LDH level and co-morbidities.

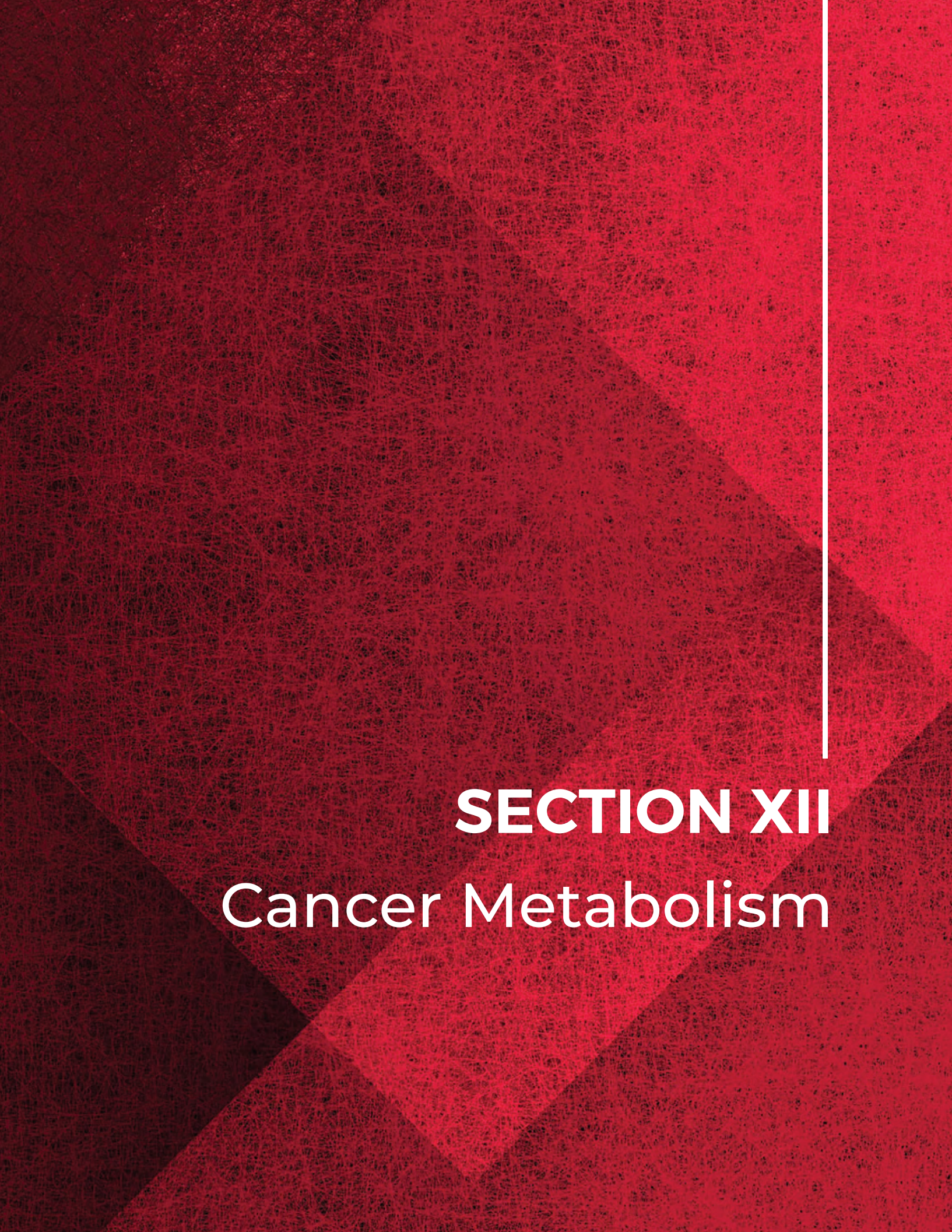
Currently several new treatments are under investigation, including inhibitors that target alternative checkpoints in the immune system response, such as LAG-3, and novel combinations of immunotherapy and targeted therapy.

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SECTION XII

Cancer Metabolism

Chapter 54

Targeting Cancer Metabolism

Tomas Koltai, MD

Abstract

The wealth of knowledge on cancer metabolism acquired since the days of Otto Warburg to the present, has led to better understanding of metabolic reprogramming, its causes and consequences.

In the past 25 years it has become evident that in addition to a different metabolism there is also a significant metabolic flexibility in cancer cells, in response to glucose, serine, glycine, glutamine, and oxygen deprivation or overproduction of reactive oxygen species. Complex bioenergetic relations among cancer cells and between cancer cells and stromal cells are emerging concepts that show the involvement of symbiotic and parasitic mechanisms on one side and metabolic heterogeneity on the other.

Enhanced cell survival, cell proliferation and metabolic changes are shared responses to oncogenic stimuli. No malignant tumor or metastasis can survive without triggering metabolic adaptations and tumor cell is one of the most adaptable creatures.

Cancer seems to use an awkward metabolism if we do not analyze it thoroughly. But when we take a better look, the intrinsic logic behind what seemed awkward starts to become clearer. And the conclusion is that cancer metabolism is not strange at all, on the contrary, it is the best metabolism a cell can develop when it needs to proliferate swiftly in a very harsh environment. At the same time, the fact that cancer metabolism is different from that seen in normal cells, transforms it in a targetable weak spot.

There are many drugs that can attack these metabolic changes. The Food and Drug Administration's (FDA)

approved pharmaceuticals for indications other than cancer (repurposed drugs) are particularly considered in this chapter. Natural products and drugs under investigation with possible anti-cancer metabolism activities are also briefly discussed. The last twenty years have seen the emergence of metabolism as a target for treatment, however, little has been entered the mainstream medical practice.

Introduction

Metabolism is the basis of cellular life. It is the mechanism that cells use to break down nutrients like glucose, fatty acids, and amino acids to produce the energy and building blocks needed for life. Cells accumulate this energy mainly in ATP molecules (high energy molecules) or macromolecules like glycogen, starch, etc. And it is also the building of molecules necessary for appropriate functioning and adaptation to changing environmental conditions.

The main source of energy is glucose and there are two different mechanisms for glucose breakdown: aerobic and anaerobic. At the beginning of life on earth, even within the uncertainty of our knowledge about the matter, ⁽¹⁾ we can assume that there was no fully developed atmosphere with adequate oxygen supply. Therefore, the first living organisms could only use the anaerobic pathway that required no oxygen. When photosynthesizing organisms, like cyanobacteria appeared, this low oxygen atmosphere slowly changed. ⁽²⁾

In this way, when the earth's atmosphere acquired a stable oxygen level, new organisms developed through natural selection, containing mitochondria (these probably appeared through a process of Endobiotic association: mitochondria were originally independent organisms that established symbiotic associations within host cells). ⁽³⁻⁴⁾

Organisms with mitochondria could generate energy in a more effective way through aerobic metabolism (oxidative phosphorylation metabolism or OX-PHOS). However, mitochondria introduced also some disadvantages, like the production of toxic reactive oxygen species (ROS) that produce mutations, diseases and ageing. ⁽⁵⁾

In both cases, aerobic and anaerobic, the initial molecule of the metabolic pathway is glucose, which is broken down to pyruvate in 10 enzymatic steps (the process is known as glycolysis). Each step needs a specific enzyme. Nine of these 10 enzymes are controlled by HIF-1 α (Hypoxia Inducible Factor 1 α). ⁽⁶⁻⁷⁾ From pyruvate on, the two metabolisms follow different routes. If there is adequate oxygen supply the pathway is the aerobic (oxidative) pathway. If the supply is inadequate, pyruvate is converted into lactic acid (anaerobic pathway).

Since the pioneering works of Otto Warburg in the 1920s, ⁽⁸⁻⁹⁾ we have known that the metabolism of tumors is quite different from that of normal cells. Warburg discovered that malignant cells preferentially break down glucose to lactic acid (glycolytic metabolism) instead of metabolizing it to CO₂ and H₂O (oxidative phosphorylation) as normal cells usually do. The consequence of this behavior was that significantly less energy (2 molecules of ATP) was obtained in comparison with normal cells (36 ATPs per each molecule of glucose). This low production of ATP in malignant cells, was compensated by an increased (2 to 20-fold) uptake of glucose.

The increased rate of glucose uptake allows tumors to be visualized by positron emission tomography (PET) using a positron emitting radionuclide like fluorine 18 attached to deoxyglucose (18 fluo-2deoxyglucose), a glucose analogue.

Warburg thought that this phenomenon was due to a mitochondrial disease and that this was the cause of cancer. Now, we know that it is not so. ⁽¹⁰⁾ Glycolytic cancer cells do not loose their ability to use the oxidative pathway. ⁽¹¹⁾

Glycolytic metabolism also takes place in normal tissues when they are under poor oxygen conditions, but when the oxygen levels return to normal, non-malignant cells return to oxidative phosphorylation (the mechanism is known as anaerobic glycolysis). This does not happen in malignant cells, they continue with their glycolytic metabolism even with normal oxygen supply. This “abnormality” was called the Warburg effect or aerobic glycolysis or glycolytic metabolism. ⁽¹²⁾ The Warburg effect implies a high production of lactic acid (60 times more than in normal cells) because much more glucose is used. When the lactic acid is extruded

from the cells, it creates a highly acidic microenvironment. (We also know now, that lactic acid is not the main cause of extracellular acidosis). ⁽¹³⁻¹⁴⁾

Normal cells: Glucose $\Rightarrow$ Pyruvate $\Rightarrow$ Acetyl CoA $\Rightarrow$ Krebs cycle
Malignant cells: Glucose $\Rightarrow$ Pyruvate $\Rightarrow$ Lactic acid $\Rightarrow$ Extrusion

For the next half-century this was the mainstream knowledge we had on tumor metabolism. In the last 30 years, it was found that the metabolic differences between normal and malignant cells were not only in carbohydrate metabolism but went far beyond those described by Warburg: lipids, amino acids and proteins, enzymes, nucleic acids, water, ROS, ions, and acid-base balance all behaved differently. The glycolytic phenotype was only one, in a group of metabolic alterations. The changes showed by malignant cells were called the “metabolic switch”.

Cancer development is an extraordinary metabolic challenge where the biomass needs to double with each mitotic cycle. This requires major energetic changes and nutritional resources. Therefore, until quite recently, the scientific community wondered why a tumor that needed a significant amount of energy for accelerated growth and proliferation was using an inefficient metabolism like aerobic glycolysis.

For a moment, let’s suppose that the tumor does not develop a different metabolism of its own. What would happen?

The energy requirements are high because the tumor needs to duplicate its biomass in a short time. Therefore, it would increase glucose uptake and the mitochondrial oxidative pathway’s activity would be correspondingly increased. Energy production would be augmented. And now two vital problems threatening the tumor’s life would appear:

1. The oxygen requirements for the oxidative metabolism would be increased. But the tumor is embedded in a hypoxic environment due to excessive proliferation without a correspondingly efficient vascular supply. This means that there is not enough oxygen available for oxidative metabolism. ⁽¹⁵⁻¹⁶⁾
2. A highly increased oxidative metabolism would produce an important amount of ROS which are highly toxic for the cell ⁽¹⁷⁻¹⁸⁾ and creating an increased oxidative stress. ⁽¹⁹⁾

Thus, in order to grow and proliferate quickly, tumor cells need to develop a different metabolism, one that needs

little or no oxygen and produces low amounts of ROS. The response to these needs is aerobic glycolysis, that requires no oxygen and by avoiding the mitochondrial activity reduces ROS production. Tumors use an ancestral metabolism present in nature since the beginning of life: anaerobic metabolism, but they do so also in the presence of oxygen, that is why it is called aerobic glycolysis or simply glycolysis.

And, what about the low energy production of aerobic glycolysis? An important increase of glucose uptake compensates the low energy efficiency of glycolysis.

Increased glucose uptake, predominance of glycolytic metabolism, increased fatty acid synthesis, increased role of glutamine, and pH gradient inversion are the main characteristics of these changes. The metabolic changes (metabolic switch) are part of the hallmarks of cancer ⁽²⁰⁾ and are essential for tumor survival. This makes malignant cells vulnerable to drugs that target their peculiar metabolism.

Even if the metabolic changes are a highly integrated process, for the sake of a better understanding, we shall analyze them separately.

1. The glycolytic phenotype

Two mechanisms are involved in the metabolic switch:

1. Oncogenic mutations and
2. Hypoxia

One or more oncogenic mutations are the starting point of the malignant process. There is an intimate association between oncogenic mutations and glycolytic metabolism. Protooncogenes, like PI3K, AKT, RAS, c-Myc, promote glycolysis while tumor suppressors tend to inhibit glycolysis. ⁽²¹⁾ The up-regulation of the PI3K/Akt pathway, (which is common to many cancers) promotes glycolysis by diverse mechanisms:

1. Akt phosphorylation (activation) increases the expression of Gluts (glucose membrane transporters) and of glycolytic enzymes like phospho-fructokinase and hexokinase II.
2. Akt increases Hypoxia inducible factor-1 (HIF-1) activation that induces over-expression of glycolytic enzymes ⁽²²⁻²³⁾ and represses pro-oxidative enzymes like PDH (pyruvate dehydrogenase). ⁽²⁴⁾

Hypoxia stabilizes HIF-1 α (hypoxia inducible factor-1 alpha) allowing its dimerization with HIF-1 β , migrating to the nucleus and acting as a transcription factor. (Figure 54-1)

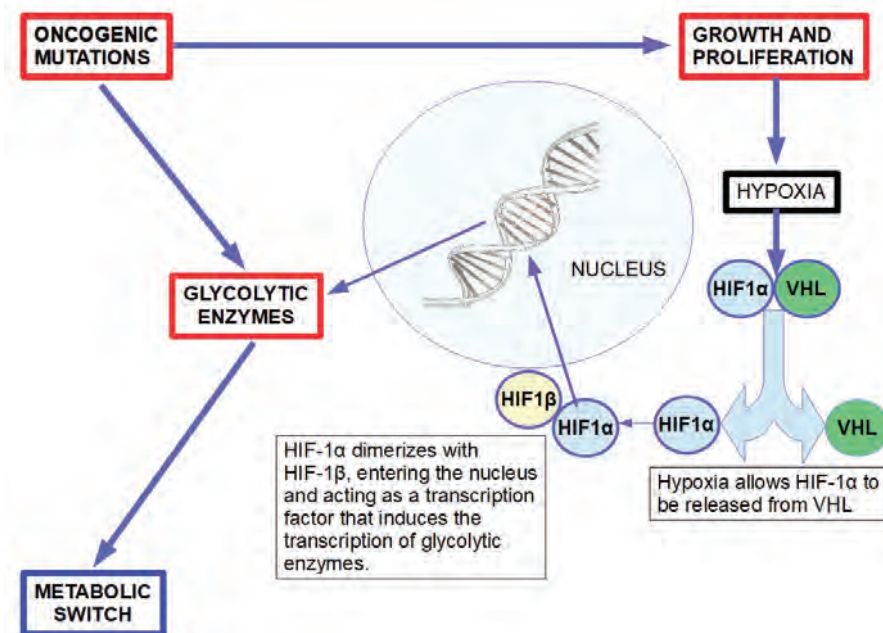


Figure 54-1. Cancer's glycolytic phenotype is the consequence of oncogenic mutations that initiate proliferation and hypoxia which develops due to excessive growth uncompensated by an increased and effective vascular supply.

Over-expression of cMyc in cancer cells enhances PKM2's (pyruvate kinase isoform M2) activity whereas in normal tissues the PKM1 isoform predominates. ⁽²⁵⁾ This modification retards the glycolytic process permitting increased deviation towards the PPP (pentose phosphate pathway) that is necessary for an increased synthesis of nucleotide sugars ribose and deoxyribose.

Another situation leading to the glycolytic phenotype is the loss of tumor suppressor genes. For example, mTOR (mammalian target of rapamycin) is negatively regulated by AMPK (AMP activated kinase) which is positively activated by Liver kinase B1 (LKB1) and the increase of the AMP/ATP ratio. AMPK promotes oxidative phosphorylation. Loss of tumor suppressor LKB1 promotes tumorigenesis, decreases AMPK signaling, enhances mTOR signaling and promotes a glycolytic phenotype. ⁽²⁶⁾ p53 on the other hand, down-regulates the glycolytic phenotype. ⁽²⁷⁻²⁸⁾ Another frequent finding is the loss of function of Pten (a protein that down-regulates the oncogenic PI3K/Akt pathway). (Figure 54-2)

Figure 54-3 is a summary that shows the metabolic hallmarks of cancer, explaining the extracellular acidity and the proton gradient inversion that will be discussed in this chapter.

These metabolic changes are essential partners for cancer's progression, and they may vary according to type of tumor, the driver gene, environment and evolution of the tumor. The predominant oncogenic pathway of a tumor and the tissue type determine the metabolic phenotype. When the driver gene is cMyc the metabolic behavior may be different from that found with cMet as a driver. And different metabolic behavior is possible with the same driver but in a different cancer cell line. ⁽³⁹⁾

Tumors are metabolically heterogeneous. ⁽⁴⁰⁻⁴²⁾ Most tumors show cells with different metabolic profiles, (glycolytic hypoxic areas coexisting with oxygenated oxidative areas). ⁽⁴³⁾

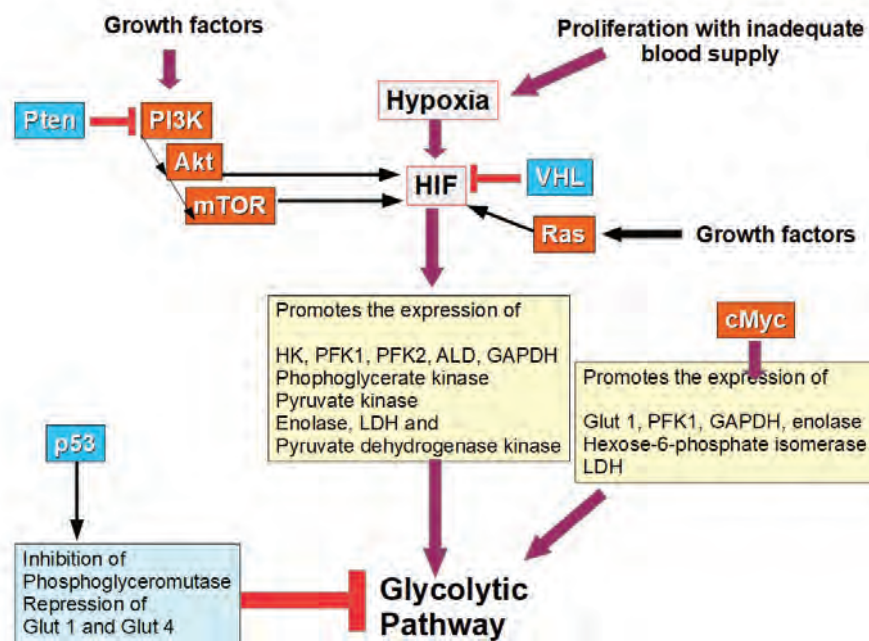


Figure 54-2. Relation among proto-oncogenes, tumor suppressor genes, metabolic enzymes, and glycolysis ⁽²⁹⁻³⁸⁾ (VHL: Von Hippel Lindau protein; HK: hexokinase; Glut: glucose transporters; LDH: lactate dehydrogenase; PDH kinase: pyruvate dehydrogenase kinase). (Tumor suppressor genes/proteins in blue, oncogenes in red).

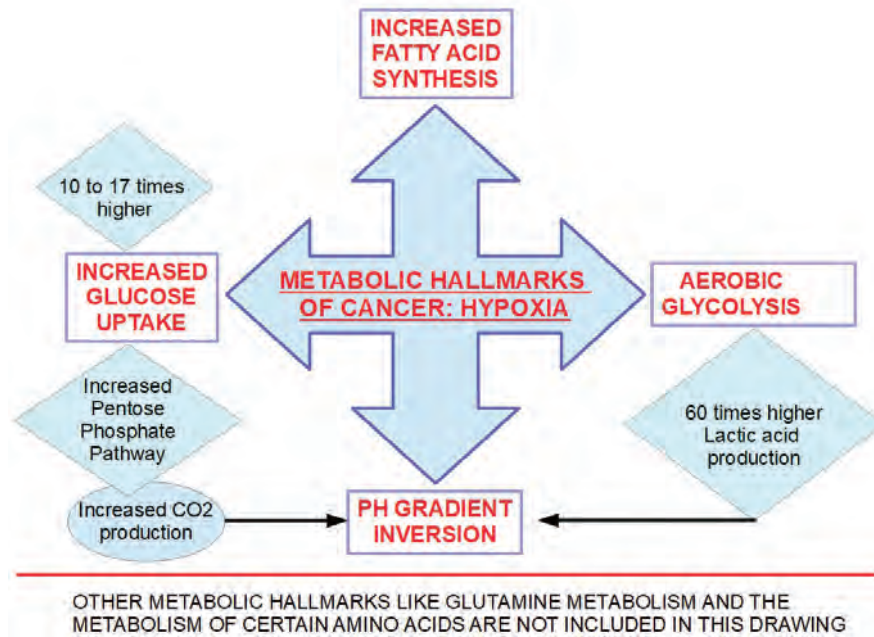


Figure 54-3. Metabolic hallmarks of cancer.

The metabolic switch provides a competitive advantage

Metabolic changes are a progressive process: not all the cells in a cancer adopt the same metabolic changes at the same time, but as a tumor progresses the metabolic changes become more evident and are increasingly modified with respect to normal.

The metabolic portfolio that may be partially or completely present in cancer consists of:

1. Hypoxia
2. High energy requirements.
3. Increased consumption of nutrients.
4. Aerobic glycolysis (Warburg effect) (glycolytic phenotype).
5. Increased synthesis of fatty acids (lipogenic phenotype).
6. Increased consumption of glutamine (glutaminolytic phenotype).
7. Symbiotic and/or parasitic behavior (lactate shuttle).

Oncogenic pathways and hypoxia create the basic elements for the metabolic switch. (**Figure 54-3**)

Figure 54-4 shows the glycolytic pathway. It takes place in the cytoplasm. When the metabolism is oxidative, pyruvate enters the mitochondria as acetyl Coenzyme A (acetyl CoA) where it incorporates to the Krebs cycle. When the metabolism is glycolytic (also known as fermentative), pyruvate is transformed into lactic acid without entering the mitochondria. The lactate is extruded from the cell by the action of transporters like the monocarboxylate transporters (MCTs).

The direct consequence of the metabolic switch is the increased acidity of the extracellular matrix (ECM). For many years, ECM acidity was considered the natural effect of the significant extrusion of lactic acid from the cell. This classical view seems to be partially wrong, because ECM in tumors is acidic even when lactic acid is experimentally eliminated. Increased CO_2 production is probably one of the main culprits of the abnormal ECM's pH through the production of CO_3H_2 (carbonic acid) mediated by the presence of carbonic anhydrases on the cell surface. Of course, lactic acid is still a contributory factor to this acidity.

ECM's acidity is a very important factor in tumor migration, invasion and eventual metastases⁽⁴⁴⁻⁴⁵⁾ because it activates proteolytic enzymes that degrade surrounding tissues and

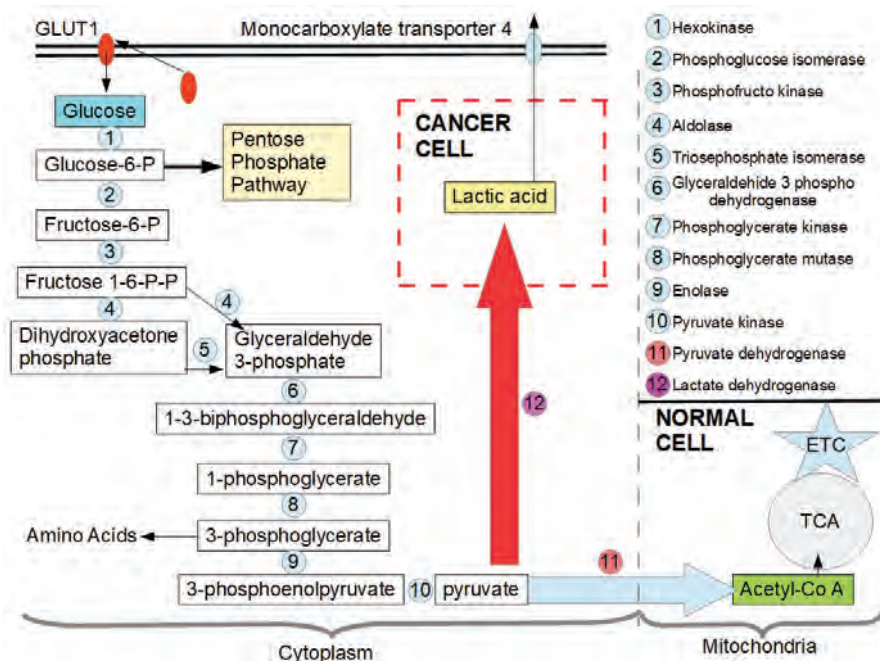


Figure 54-4. The glycolytic pathway in cancer cells finishes in lactic acid, that is extruded from the cell through the action of monocarboxylate transporters. Normal cells, on the other hand, transform pyruvate into acetyl-Co A that enters the tricarboxylic cycle (TCA) and the electron transport system (ETC) generating energy, ROS, and the end products: CO₂ and H₂O. The “metabolic decision point” is located at the pyruvate level and controlled by PDH (pyruvate dehydrogenase). This enzyme is usually inhibited in cancer cells. Therefore, pyruvate does not enter into the mitochondria, but is transformed into lactic acid.

allow migration. It also acts as a barrier against immunodefensive systems and impedes the activity of certain chemotherapeutic drugs like doxorubicin and weak bases in general. ⁽⁴⁶⁻⁴⁹⁾

The utilization of the aerobic glycolytic pathway has been frequently found during embryonic development. ⁽⁵⁰⁾ After birth, probably due to an adequate oxygen supply, a metabolic change is triggered in the hepatocytes that adopt oxidative phosphorylation.

The glycolytic pathway found in cancer cells maintains clear differences with the glycolytic pathway found sometimes in normal cells. Certain glycolytic enzyme isoforms are over-expressed only in cancer cells. This is the case of pyruvatekinase isoform M2 (PKM2). PKM2 is less active than PKM1, and this slower activity down-regulates phosphoenolpyruvate catabolism to pyruvate. The direct consequence of this down-regulation is an accumulation of intermediate products of glycolysis upstream of phosphoenolpyruvate that makes it possible to use them to produce other molecules that are necessary for proliferation, like amino acids, nucleic acids and lipids. ⁽⁵¹⁻⁵³⁾

What is the goal of tumor cells when they adopt the energetically inefficient glycolytic phenotype? Possible answers:

1. The energy inefficiency is adequately compensated by higher flux of glucose.
2. Down-regulation of PK activity through its less active isoform PKM2 slows down the whole process and accumulates intermediaries needed for the synthesis of other molecules (ribose for nucleotides, lipids for membranes and other uses, amino acids). PKM2 is pro-glycolytic while PKM1 is pro-oxidative. ⁽⁵⁴⁾
3. The malignant cell in a hypoxic/anoxic environment requires less oxygen. This creates an increasing resistance to permanent or transitory hypoxia.
4. The glycolytic phenotype generates an acidic extracellular matrix that is necessary for activation of enzymes taking part in extracellular matrix remodeling, migration and invasion. ⁽⁵⁵⁻⁶⁸⁾
5. The increased lactic acid activates translocation of Glut1 and Glut4 to the plasmatic membrane increasing glucose uptake. ⁽⁶⁹⁾

6. The down-regulation of OXPHOS generates less ROS. ⁽⁷⁰⁻⁷¹⁾

In summary, a reduced OXPHOX capacity is favorable for rapid growth and increased invasiveness with low ROS production.

Targeting glycolytic enzymes in cancer

Normal cells use the glycolytic pathway in very limited circumstances (during embryonic development, ⁽⁷²⁾ muscle efforts, ischemia and T cell activation and proliferation). ⁽⁷³⁻⁷⁴⁾ But under normoxia, normal tissues do not employ the glycolytic pathway. Therefore, in theory, the glycolytic pathway may be targeted at very low cost for normal cells.

The Warburg effect is addictive for cancer cells and they depend on it for generating ATP and biosynthetic building blocks. Inhibition of the glycolytic pathway results in slowing down proliferation and invasion and eventually in cell death. The multiplicity of enzymes involved in the glycolytic pathway highlights many different targets to be considered and the possibility of combining drugs and attacking more than one target simultaneously.

The possible targets

GLUTs are a family of membrane proteins that transports glucose from the extracellular to the intracellular matrix. Due to the high glucose requirements of cancer cells, its transport across the cell membrane is the first rate-limiting factor in carbohydrate metabolism. ⁽⁷⁵⁾

Fourteen GLUT isoforms have been identified and many of them are over-expressed in cancers with bad prognosis. GLUT1 seems to be the most important in the group and a potential target for anti-cancer therapy. ⁽⁷⁶⁾ In breast and prostate cancer Glut12 has emerged as an important glucose transporter. ⁽⁷⁷⁾ **(Figure 54-5)**

GLUT1 is regulated by insulin, and also by HIF-1 α , ⁽⁷⁸⁾ growth factors like EGF and VEGF, ⁽⁷⁹⁾ hormones, like estrogens in breast cancer, ⁽⁸⁰⁾ cMyc protooncogene, ⁽⁸¹⁾ and indirectly by Ras. p53 is a GLUT1 and GLUT4 down-regulator. ⁽⁸²⁾

Inhibition of GLUTs, particularly GLUT1 and GLUT2 with phloretin ⁽⁸³⁻⁸⁴⁾ have shown apoptosis in breast, colon and hepatic cancer cell lines. GLUTs are also down-

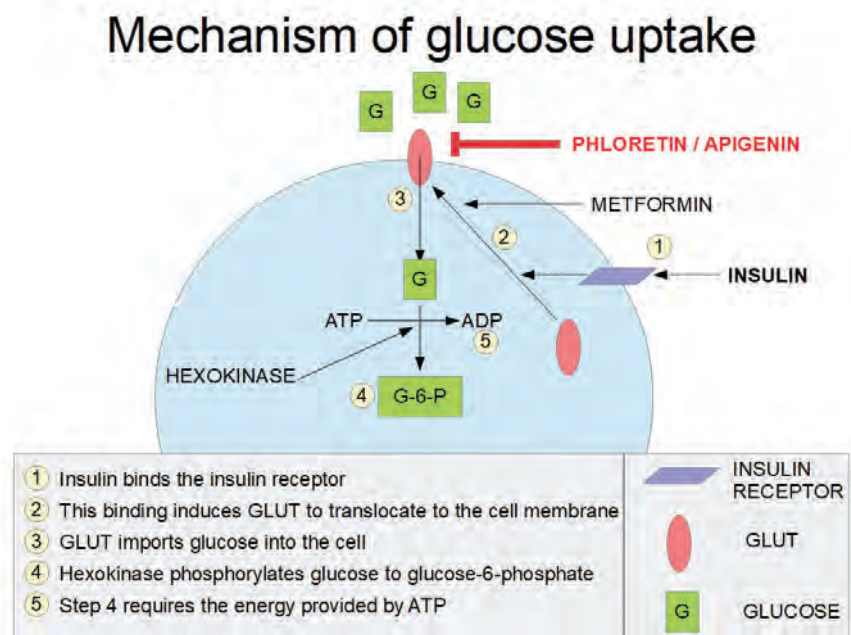


Figure 54-5. Glucose uptake mechanism (G-6-P = Glucose-6-Phosphate). Phloretin and apigenin are inhibitors of glucose uptake.

regulated by other natural compounds such as resveratrol, quercetin, ⁽⁸⁵⁾ sylimarin, ⁽⁸⁶⁾ apigenin, ⁽⁸⁷⁾ compounds like caffeine, theophiline, pentoxifilline and antidiabetics like thiazolidenediones. ⁽⁸⁵⁾ GLUT5 is a fructose transporter that has not been extensively studied in the cancer context.

Hexokinase: Cancer cells preferentially express Hexokinase II (HK-II) mainly due to gene amplification ⁽⁸⁸⁾ which catalyzes irreversible glucose phosphorylation to glucose-6-phosphate. HK-II is bound to the mitochondrial outer membrane, decreasing apoptosis through inhibition of cytochrome c release. HK II over-expression increases the glycolytic rate. ⁽⁸⁹⁻⁹¹⁾ HIF-1 and cMyc induce HK-II over-expression. ⁽⁹²⁾ Krushna *et al.* showed that deleting HK-II targets cancer cells. ⁽⁹³⁾

HK-II has been targeted with an alkylating agent like 3-bromopyruvate (3-BP) with interesting results. ⁽⁹⁴⁻⁹⁶⁾ 3-BP is undoubtedly a glycolytic inhibitor, but the exact mechanism of action is difficult to identify because 3BP is also an alkylating agent. Lonidamine an anti-spermatogenic with low human toxicity is an inhibitor of HK-II that has been tested in cancer patients. ⁽⁹⁷⁻⁹⁸⁾ Lonidamine is potentiated by diazepam in human glioblastoma cells. ⁽⁹⁹⁾

2 deoxy-glucose (2dg) is an inhibitor of hexokinase through a competitive mechanism with glucose. **(Figure 54-6)** This glucose deprivation reduces ATP production and markedly interferes with the glycolytic pathway. ⁽¹⁰⁰⁾ The good results as an anticancer molecule found in the laboratory ⁽¹⁰¹⁻¹⁰⁴⁾ could not be reproduced in the few and limited clinical trials performed with this drug. ⁽¹⁰⁵⁻¹⁰⁶⁾ When 2dg is associated with certain other drugs, like metformin or autophagy inhibitors, cytotoxicity becomes more relevant. ⁽¹⁰⁷⁾

PFK (Phosphofructokinase): This enzyme irreversibly commits the glucose molecule to the glycolytic pathway. Increased PFK-1 activity in cancer is a frequent finding in glycolytic cells and is the consequence of direct oncogene signaling and/or HIF-1 activity. ⁽¹⁰⁹⁻¹¹⁰⁾ PFK phosphorylation is a highly controlled step that is dependent on fructose 2-6 biphosphate.

Enolase: Isoform 1 is increased in multiple cancer tissues. In glioblastoma, isoform 2 is up-regulated because the enolase 1 gene is usually deleted. ⁽¹¹¹⁾ Phosphonoacetate-hydroxamate has shown selective toxicity against enolase 1 deleted cells.

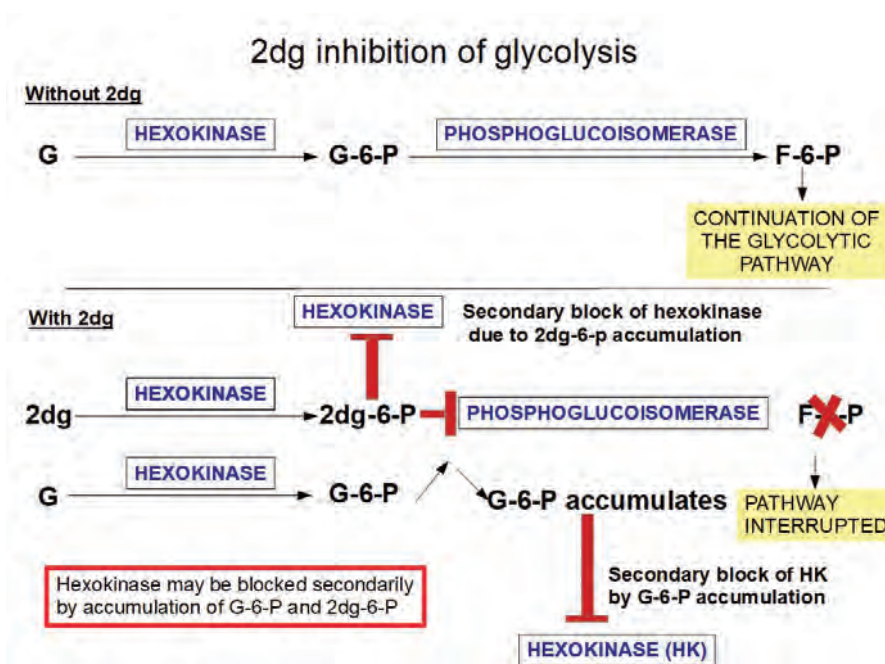


Figure 54-6. Mechanism of action of 2dg: primary block is at the level of phosphoglucoisomerase. ⁽¹⁰⁸⁾ The accumulation of non-metabolized 2dg-6-P and glucose 6 phosphate secondarily inhibit hexokinase.

Pyruvate kinase (PK): Myc induces over-expression of isoform M2. PKM2 slows down the phosphoenolpyruvate to pyruvate transformation allowing the build up of intermediate products needed for anabolic processes. So, it makes sense to activate this rate-limiting enzyme. This theory has been experimentally proved: activation of PKM2 inhibits growth of cancer xenograft experimental models.⁽¹¹²⁾ In the absence of serine, sulfonamide-quinoline activators decrease tumor growth. PKM2 has and maintains a close relationship with HIF-1 α where PKM2 is a HIF-1 α target gene, interacting with it, and regulating HIF-1 α transcriptional activity through a feedback loop. The interaction between these two proteins plays a fundamental role in the glycolytic phenotype.⁽¹¹³⁾ **(Figure 54-7)**

Lactate dehydrogenase (LDH): LDH-A plays a role in cancer cell survival under severe hypoxia. Isoform A favors the pyruvate to lactate pathway and LDH-B, the backward process.⁽¹¹⁴⁾ Gossypol and sodium oxamate have been tested as LDH inhibitors but their use is limited to the experimental setting.⁽¹¹⁵⁾ By targeting LDH-A, the number of tumor initiating cells were significantly reduced.⁽¹¹⁶⁾ No adequate inhibitor has yet been found.

According to Armstrong *et al.*⁽¹¹⁷⁾ “serum LDH is a prognostic and a predictive biomarker for the survival benefit conferred by TORC1 inhibition in poor-risk RCC (renal cell carcinoma)”.

Pyruvate dehydrogenase (PDH): PDH is a crossroad enzyme complex that is indirectly controlled by protooncogenes. When this enzyme is inhibited, the metabolism becomes glycolytic because the pyruvate cannot enter into the Krebs cycle (TCA) and is metabolized to lactic acid by lactate dehydrogenase. PDH is inhibited through phosphorylation by PDK (pyruvate dehydrogenase kinase). PDK's activity is strongly increased in glycolytic malignant cells. Thus, PDH is inhibited and oxidative metabolism is impeded.

CPI-613 is a novel anti-cancer agent described as a PDH inhibitor, decreasing pyruvate's access to the mitochondrial metabolism. It is in phase II clinical trial (NCT01832857 and NCT00741403).⁽¹¹⁸⁾

Dichloroacetate (DCA) is an inhibitor of pyruvate dehydrogenase kinase that inhibits PDH through

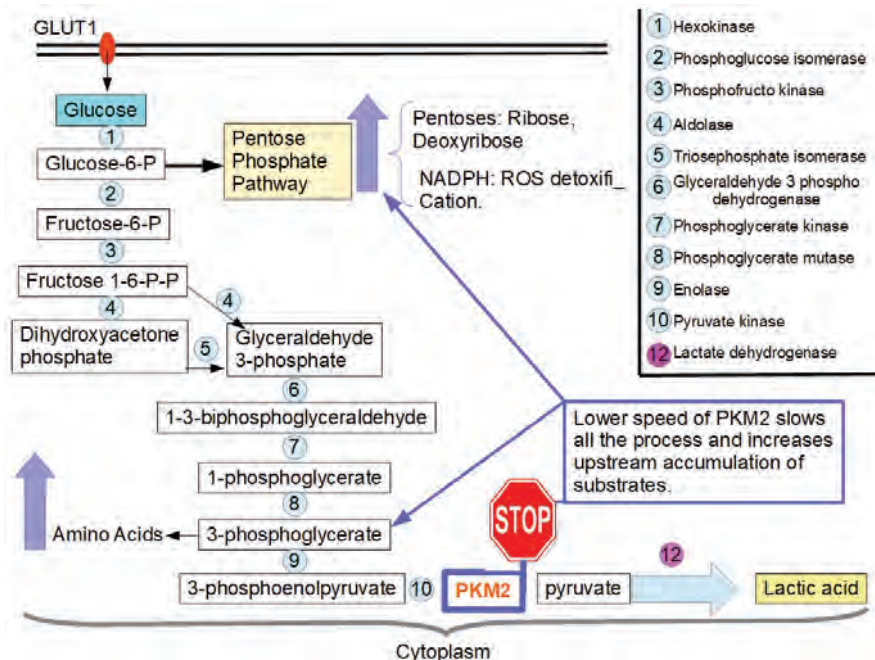


Figure 54-7. PKM2 slows down glycolysis, upstream substrates accumulate, and PPP is increased with high production of nucleic acid sugars and NADPH. The later has a key role in ROS detoxification. Increased 3-phosphoglycerate enhances amino acid production.

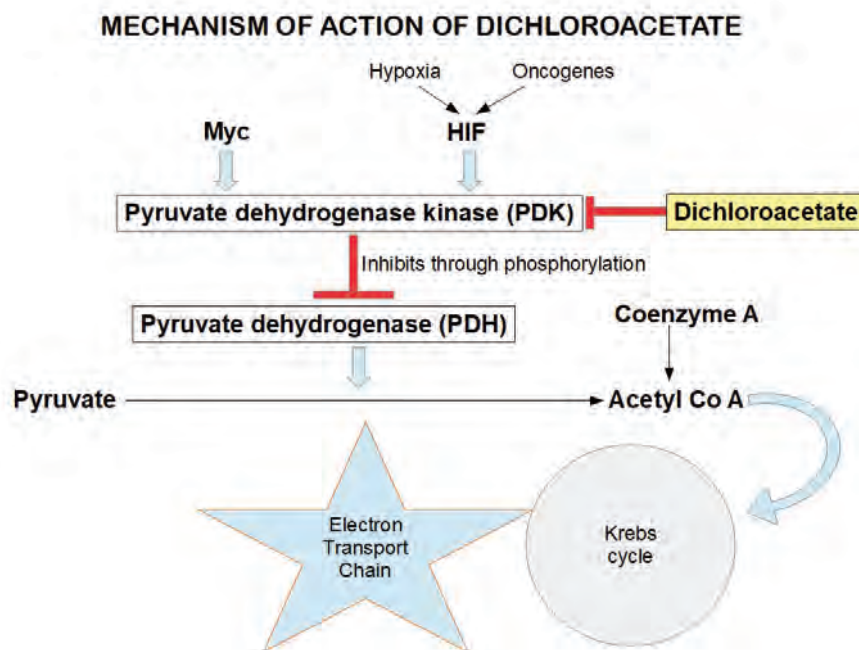


Figure 54-8. PDK phosphorylates PDH, inactivating it. Dichloroacetate by inhibiting PDK, activates PDH which restores oxidative metabolism.

phosphorylation. The inhibition of the inhibitor activates PDH. **(Figure 54-8)** It introduces modifications in tumor metabolism by “forcing” pyruvate into the mitochondria, increasing oxidative phosphorylation. Dichloroacetate alone has only modest anti-tumor effects. In the experimental setting with Lewis lung carcinoma, it did not show growth arrest, but there was significant anti-metastatic activity⁽¹¹⁹⁾ and synergy with radiotherapy in glioblastoma.⁽¹²⁰⁾

The lactate shuttle⁽¹²¹⁾

Advanced tumors are very heterogeneous, not only morphologically but also in their genotype and metabolism. Regarding glucose metabolism, this heterogeneity shows the presence of two different types of malignant cells: glycolytic and oxidative. The oxidative cells, usually located in better oxygenated areas of the tumor, are able to use the lactic acid produced by glycolytic cells as fuel for their own metabolism.⁽¹²²⁻¹²³⁾ Many tumors develop a shuttle system in which the uptake of lactate by the oxidative cells become an important source of energy (reversed Warburg effect).⁽¹²⁴⁾ We have called these cells as lactophagic cells. This mechanism can be considered as a symbiotic system in

which a group of cells produce lactic acid that serves as an energy source for lactophagic cells. Furthermore, it is quite common to find stromal cells surrounding the tumor that are “enslaved” by the malignant cells and induced to produce lactic acid to feed the lactophagic cells.⁽¹²⁵⁾ This resembles a parasitic system. Monocarboxylate transporters are over-expressed in cancer cells, and they are of paramount importance in the symbiotic and parasitic systems.⁽¹²⁶⁻¹²⁸⁾

The lactate shuttle allows the tumor to save glucose to be used by the less oxygenated areas, while feeding the more oxygenated ones with lactate. This is a mechanism that is also found in normal tissues like muscle and brain. The lactate shuttle is a sign of poor prognosis.⁽¹²⁹⁻¹³⁰⁾

2. The lipogenic phenotype

In 1994 Kuhajda *et al.*⁽¹³¹⁾ identified OA-519 antigen, a marker of poor prognosis in breast and prostate cancer, as Fatty Acid Synthase (FAS). Abnormal fatty acids (FA) synthesis and FAS up-regulation are common features of cancer.⁽¹³²⁻¹³⁴⁾

FA comes mainly from external sources (food), but *de novo* synthesis is also a source that becomes very important in many types of cancer. ⁽¹³⁵⁻¹³⁶⁾ The regulators of this synthesis are the master transcriptional regulators Sterol Regulatory Element-Binding Protein 1 (SREBP-1) transcription factors. ⁽¹³⁷⁾

Fatty acid synthase

FAS is a key enzyme complex in FA synthesis from acetyl-CoA and malonyl-CoA, in the presence of NADPH, into long-chain saturated FAs ⁽¹³⁸⁾ and is expressed at high levels in liver and adipose tissues, and at low levels in other tissues. Under a diet with a relatively high fat content (40 %), and even after a carbohydrate-rich diet for three days, FAS activity remained low in humans. Under normal dietary conditions, *de novo* lipogenesis in man is negligible. ⁽¹³⁹⁾

FAS is the single human enzyme complex responsible for the conversion of dietary carbohydrate to fat and it is the only eukaryotic enzyme capable of synthesizing palmitate, the precursor for the majority of nonessential FAs. It is down-regulated in most normal cells, except in lipogenic

tissues such as liver, lactating breast, fetal lung, and adipose tissue. Conversely, several human cancers, over-express FAS, which has been associated with poor prognoses.

FAS is not a single enzyme but a whole enzymatic system composed of two identical 272 kDa multifunctional polypeptides, with seven functional domains each, in which substrates are transferred from one functional domain to the next. ⁽¹⁴⁰⁻¹⁴⁴⁾ (Figure 54-9)

FAs are aliphatic acids fundamental for energy production and storage, building blocks for cellular structures as membranes and as intermediates in the biosynthesis of hormones and other biologically important molecules.

Metabolism and homeostasis of FAS is transcriptionally regulated by Upstream Stimulatory Factors and sterol regulatory element binding protein-1c (SREBP-1c) in response to feeding/insulin in living animals. ⁽¹⁴⁷⁻¹⁴⁸⁾

FAS has been investigated as a possible oncogene. ⁽¹⁴⁹⁾ Increased aggressiveness in retinoblastoma was associated with FAS activation and Camassei postulated that FAS

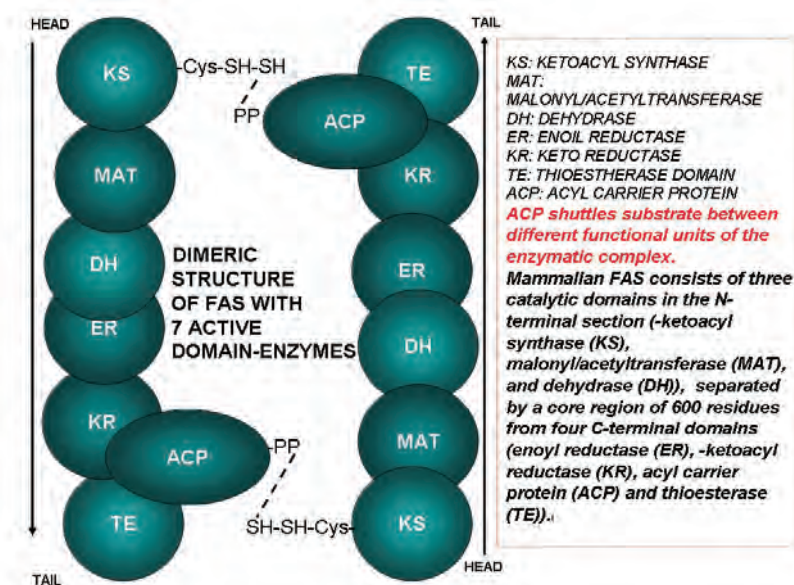


Figure 54-9. Structure of FAS showing the dimeric arrangement and the seven enzymes that form part of the complex. ⁽¹⁴⁵⁻¹⁴⁶⁾

inhibition could represent an alternative treatment strategy in advanced and resistant retinoblastoma. ⁽¹⁵⁰⁾ Chirala *et al.* ⁽¹⁵¹⁾ generated FAS knockout mice. The heterozygous mutant mice were ostensibly normal; however, levels of FAS mRNA and activity were approximately 50% and 35% lower, respectively, than those of WT mice. When the heterozygous mutant mice were interbred, no null mice were produced; thus, FAS is essential during embryonic development.

A molecular link was identified between FAS and the HER2 oncogene, a marker for poor prognosis that is over-expressed in 30% of breast and ovarian cancers. Pharmacologic FAS inhibitors were found to suppress p185(HER2) oncoprotein expression and tyrosine kinase activity in breast and ovarian cancers that over-express HER2. ⁽¹⁵²⁾ Similar suppression was observed when FAS gene expression was silenced by RNA interference.

Metformin is not usually considered a FAS inhibitor, but metformin administration blocks the stimulatory effect of a high energy diet on colon carcinoma growth *in vivo* and is associated with a reduction of FAS expression. ⁽¹⁵³⁾ Energy deficiency induced by metformin inhibits lipogenesis in prostate cancer cells. ⁽¹⁵⁴⁾ Wahdan-Alaswad *et al.* ⁽¹⁵⁵⁾ found that MIRNA 193b is induced by metformin and it inhibits FAS through a posttranslational block of the 3' UTR region of the transcript.

Known inhibitors of FAS are cerulenin, C75 ⁽¹⁵⁶⁾ (a derivative of cerulenin), orlistat, ⁽¹⁵⁷⁾ flavonoids (epigallocatechin-3-gallate, luteolin, quercetin, kaempferol, apigenin, and taxifolin). ⁽¹⁵⁸⁾ They have all shown pro-apoptotic effects in malignant cells.

3. Glutaminolytic phenotype

In 1955, Eagle ⁽¹⁵⁹⁾ studying the nutritional requirements of cells in culture found that many cells exhibited high glutamine consumption that significantly surpassed the consumption of other amino acids. These cells could not maintain growth in the absence of glutamine and some lost viability. This was a surprising issue because glutamine is not an essential amino acid, and there was no explanation at that time.

Glutamine is a major energy source through the production of α -ketoglutarate, which enters into the Krebs cycle contributing to the production of citrate. Now, there is evidence indicating that it may be an “essential” amino

acid in certain cancer cells when they become “addicted” to glutamine ⁽¹⁶⁰⁾ and synthesis cannot keep pace with demand. ⁽¹⁶¹⁾ Not all cancer cells show glutamine dependency. ⁽¹⁶²⁾ The addicted cells cannot survive without an exogenous supply of glutamine. Under glucose limitation, cancer cells are able to reprogram the fuel required by TCA and feed solely on glutamine, generating citrate. ⁽¹⁶³⁾ Glutamine in cancer cells is not only a fuel for the TCA cycle but it is also a nitrogen donor and activator of mTORC1. ⁽¹⁶⁴⁾

Glutamine analogues have been tested as inhibitors of the glutaminolytic pathway, but toxicity was too high. ⁽¹⁶⁵⁾ DON (6-diazo-5-oxo-L-norleucine) a glutamine analogue has shown important anti-cancer and anti-metastatic abilities with low toxicity in mice. ⁽¹⁶⁶⁾

4. The acid-base balance in malignant tumors

Normal cells have a slightly alkaline intracellular pH ($pH_i = 7.1-7.3$) and a more alkaline extracellular matrix ($pH_e = 7.3-7.4$). The difference between the two pH levels is the gradient. ⁽¹⁶⁷⁾

The first step in the cancerization process is an increase in the intracellular pH ($pH_i = 7.4-7.5$) to the point that the intracellular milieu becomes more alkaline than the extracellular one. ⁽¹⁶⁸⁾ Simultaneously, the ECM receives an acidic burden that is extruded from the malignant cells and it becomes acidic (pH_e less than 7). ⁽¹⁶⁹⁻¹⁷¹⁾ Proton production in malignant cells is 65 to 100% higher than in normal cells. ⁽¹⁷²⁾ This is known as the inversion of the pH gradient, representing an important step in tumor development. ⁽¹⁷³⁾ Intracellular alkalinity is essential for the proliferative phenotype and resistance of apoptosis. ⁽¹⁷⁴⁾ Extracellular acidity is necessary for the activation of proteolytic enzymes (for the degradation of the extracellular matrix), migration, invasion, metastasis, ⁽¹⁷⁵⁻¹⁸⁸⁾ and impairment of the host's immunological defenses against malignant cells. ⁽¹⁸⁹⁾

The increased intracellular pH is the result of the activity of certain membrane proteins and channels like:

1. NHE-1 (sodium/hydrogen antiporter) that extrudes protons and imports sodium in an equimolecular fashion.
2. Carbonic anhydrases 9 and 12 (CAIX and CAXII) that catalyze the conversion of the excessive CO₂ production of cancer cells into carbonic acid which ionizes into bicarbonate and a proton on the cell surface. This proton and the one extruded by NHE-1 are the main cause of the extracellular acidity.

3. Sodium/bicarbonate co-transporter (NBC) that imports the bicarbonate ion, participating in the intracellular alkalinization.

Caloric restriction (CR)

In 1909, Moreschi ⁽¹⁹⁰⁾ found that tumors transplanted to undernourished rats had poor growth or no growth at all. This led to investigations showing that CR had a negative effect on the growth of naturally occurring cancers. It has been well known for more than 80 years that laboratory animals under a calorie-restricted diet live longer and have less cancer than their normally fed counterparts. ⁽¹⁹¹⁾ CR means a reduction of 20 to 40% in total energy intake, without undernourishment. There is epidemiologic and experimental evidence showing that CR has anti-tumor effects. Obesity is associated with an increased risk for cancer ⁽¹⁹²⁾ and with cancer recurrence. ⁽¹⁹³⁾ In an experimental model of chemically induced breast carcinoma in rats a mild CR inhibited tumor growth. ⁽¹⁹⁴⁾ Okinawa inhabitants who usually consumed a lower calorie diet than Japanese living in the mainland had lower cancer rates. ⁽¹⁹⁵⁾

There are three theoretical explanations of this concept:

1. CR decreases secretion of hormones and growth factors such as insulin and insulin-like growth factor. ⁽¹⁹⁶⁻¹⁹⁸⁾
2. CR decreases oxidative damage.
3. The sirtuin pathway. ⁽¹⁹⁹⁻²⁰²⁾

The need for nutrients is extremely enhanced in cancer, therefore, nutrient deprivation and CR may be a useful method for slowing cancer growth. However, when the PI3K-Akt axis is constitutively activated, CR does not show anti-cancer effects. ⁽²⁰³⁾ This finding confirms that the main anti-cancer activity of CR is the down-regulation of factors stimulating the PI3K-Akt axis, and it seems to hint that inhibiting mTOR through the activation of AMPK and of sirtuins are insufficient to have anti-cancer effects by CR. The proof of this concept comes from a research by Dunn *et al.* ⁽²⁰⁴⁾ where, after decreasing tumor progression in a chemically induced urothelial cancer in mice (where down-regulation of IGF-1 was obtained through a 20% CR), treatment with a recombinant IGF-1 restored tumor growth and cell proliferation. **(Figure 54-10)**

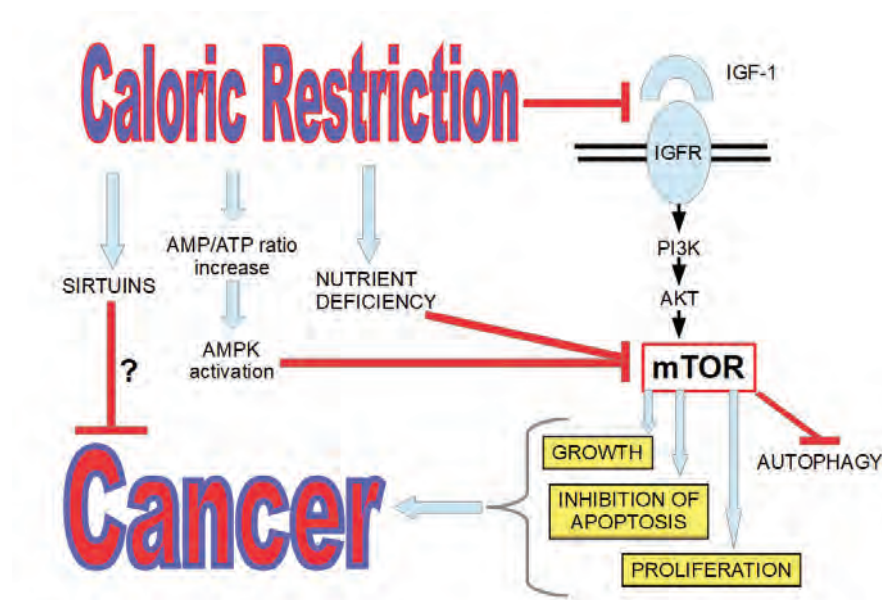


Figure 54-10. The central role of the PI3K-Akt-mTor axis is the main pathway that is down-regulated by CR and nutrient deficiency through inhibition of IGF-1/IGFR signalling. The inhibition of mTOR may enhance autophagy in order to preserve cellular survival under energetic stress. The exact role of sirtuins is yet to be established.

Therefore, in patient with moderate to high overweight, a caloric restriction of 15-20% of caloric needs may improve the treatment results.

The ROS problem

Intense anabolism, such as in cancer tissues, means high ROS production. ROS are cytotoxic for normal and cancer cells. The over-production of ROS by chemotherapeutic agents is precisely one of the mechanisms used by radiotherapy and chemotherapy to achieve cancer cell's apoptosis and/or necrosis. Cancer cells defend themselves from ROS through different mechanisms:

1. Adopting the glycolytic phenotype that produces less ROS than OXPHOS,
2. Importing glutamine as a glutathione precursor.
3. Increasing the PPP (Pentose Phosphate Pathway) that produces NADPH.

Glutathione and thioredoxin are ROS scavengers that require NADPH for their activity. (Figure 54-11)

NADPH production is essential for cancer cells so that it becomes another targetable point in cancer metabolism⁽²⁰⁵⁾

6 Amino-nicotinamide (6-AN) is an anti-metabolite that has been known for over 60 years and is one of the most potent antagonists of NADPH. ⁽²⁰⁶⁾ In experimental conditions 6-AN has shown strong anti-cancer effects in mice with mammary carcinoma, rat lymphosarcoma, mouse melanoma, walker carcinoma, and mouse glioblastoma. The problem with 6-AN was that at clinically tolerable dosage (0.2 mg/Kg of body weight) tumoricidal properties were lost. ⁽²⁰⁷⁾ Used alone in different advanced tumors the clinical results were poor. ⁽²⁰⁸⁾

Patients under chemotherapy treatment should avoid anti-oxidants because these compounds reduce ROS production or increase ROS scavenging, thus, reducing the effectiveness of the treatment. Therefore, it is important to reduce ROS scavengers during chemotherapy.

Metabolic treatment of cancer

Many “metabolic” treatments have been attempted. Almost all of them, are not stand-alone treatments, and should be used as complementary to mainstream protocols. We shall here only summarize a few of them that are based on FDA approved drugs for other purposes (repurposed drugs) and some experimental drugs that have been tested against cancer. (Table 54-1) (Figure 54-12)

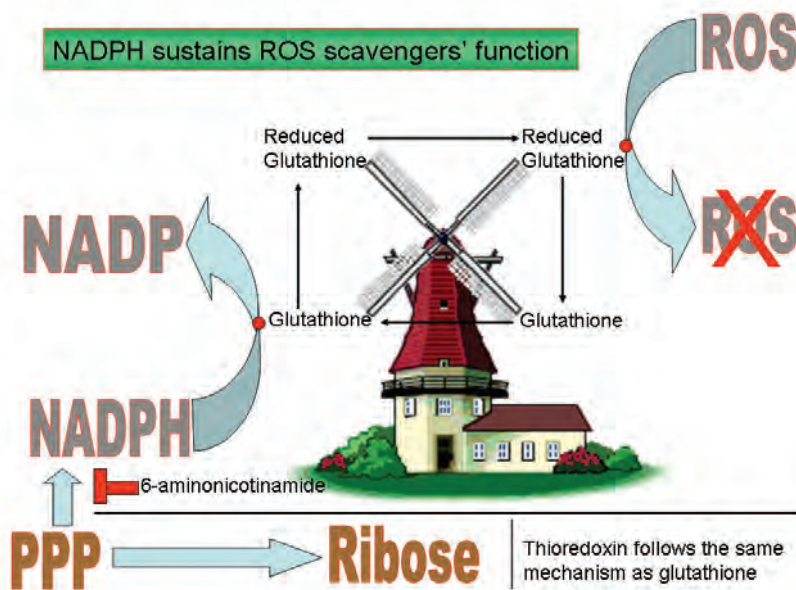


Figure 54-11. The ROS scavenging activity depends from NADPH availability. NADPH is produced in the PPP (Pentose Phosphate Pathway). NADPH reduces glutathione that scavenges ROS.

Table 54-1. Drugs repurposed for “metabolic treatment” of cancer.

Drug or compound	Effects
2-deoxyglucose	Inhibits glucose uptake and glycolysis.
Metformin	Induces AMPK, indirectly inhibit mTOR, promotes cellular acidification through inhibition of mitochondrial complex I.
Proton pump inhibitors (esomeprazol, lansoprazole, etc.)	Decrease extracellular acidity and improve chemotherapy treatments based on doxorubicin.
Acetazolamide	Inhibits carbonic anhydrase, decreases intracellular alkalinity.
Sylimarin compounds	Promote intracellular acidification and inhibit other pathways.
Dichloroacetate	Inhibits glycolysis.
Topiramate	Promotes intracellular acidification, inhibits voltage gated sodium channels.
Nelfinavir	Inhibits of FAS and Akt/mTOR pathway. ER stress.
Alpha-lipoic acid	Increases oxphos and decreases glycolysis.
Celecoxib	COX2 inhibitor decreases angiogenesis and inhibits Sp1 that is an inducer of NHE1, HIF, and carbonic anhydrases.
Amiloride and cariporide	Inhibits NHE1 causing intracellular acidification.
Tolfenamic acid	Inhibits Sp1.
DON	Reduces glutamine availability.
Artemisinin derivatives	Increases ROS production.
Fenofibrate	Down-regulates FAS.
Resveratrol	Down-regulates FAS, and GLUT1. However, stimulates glutamine metabolism.
Quercetin	Promotes intracellular acidification and inhibits FAS.
Evodiamine	Inhibits Src at the invadopodia reducing migration.

Four drugs and one purpose: apoptosis

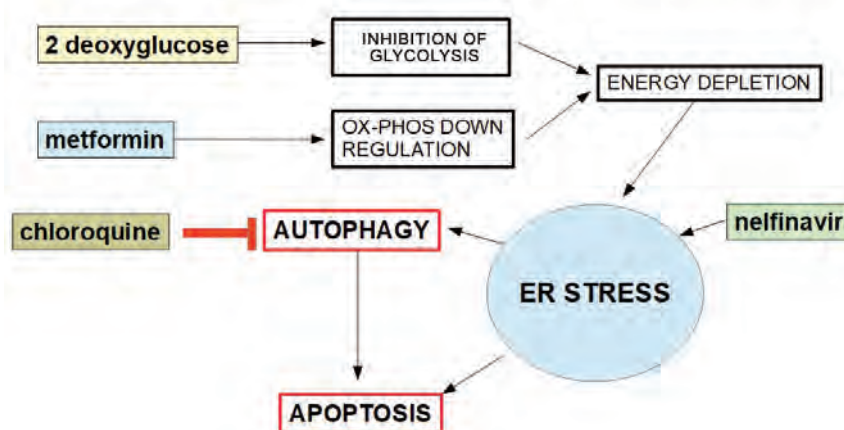


Figure 54-12. An example of the combination of “anti-metabolic” repurposed drugs that can achieve results that individual drugs are unable to achieve alone. (ER: endoplasmic reticulum.) ⁽²²⁰⁻²²²⁾

Skulachev *et al* have established that when the intracellular ATP level drops to 1/3 of normal, cells go into the apoptotic pathway. ⁽²⁰⁹⁾

Interesting results were obtained with the association of a glycolytic down-regulator like 2dg or oxamate and mitochondrial respiratory complex-I inhibitors like biguanides; this kind of treatment reduces intracellular ATP.

Kroon, Van den Bogert and De Vries published a series of seminal works in which they described that mitochondrial RNA and protein synthesis can be inhibited by many antibiotics commonly used in everyday practice, like cloramphenicol and tetracyclines. They presented the hypothesis that this inhibition may induce proliferation arrest. ⁽²¹⁰⁻²¹⁴⁾ Further investigations confirmed this hypothesis in the experimental setting. Onoda *et al.*, ⁽²¹⁵⁻²¹⁶⁾ found apoptosis in human colon cancer cells, with clinically achievable concentration of doxycycline when associated with a cicloxygenase-2 inhibitor. Doxycycline produced apoptosis in pancreatic cancer cells, ⁽²¹⁷⁾ leukemia cells ⁽²¹⁸⁾ and in skin metastasis of human malignancies. ⁽²¹⁹⁾

In theory a mitochondrial complex I inhibitor like metformin and a glycolytic inhibitor like 2DG should achieve synergistic anti-cancer effects when associated with doxycycline and celecoxib.

Conclusions

Although there may be very important differences among cancers, most of them share metabolic abnormalities. Metabolic targeting is just beginning. Ninety years have elapsed since the pioneering investigations of Warburg, who established that blocking one of the two possible metabolic pathways of energy (aerobic glycolysis or oxidative respiration) was not enough to kill tumor cells and that it was necessary to block both. This concept seems to be valid even today.

The combination of different “anti-metabolic” drugs that are wisely selected, may achieve interesting results in cancer treatment. And if we intend to target cancer metabolism we must first determine which metabolic pathways are preferentially used by the tumor, due to its metabolic heterogeneity and flexibility. Metabolic reprogramming makes cancer cells more aggressive and this fact fully justifies targeting it as part of an integral approach because cancer requires metabolic reprogramming in order to evolve.

We believe that targeting cancer metabolism has an important role as an adjunct to classical treatments, and that it will become reality sooner than later. Using well-known repurposed drugs against cancer bioenergetics is still a little-explored field, and yet there is a wealth of pharmaceuticals with strong potential that practicing oncologists could harness as complementary treatments for their patients.

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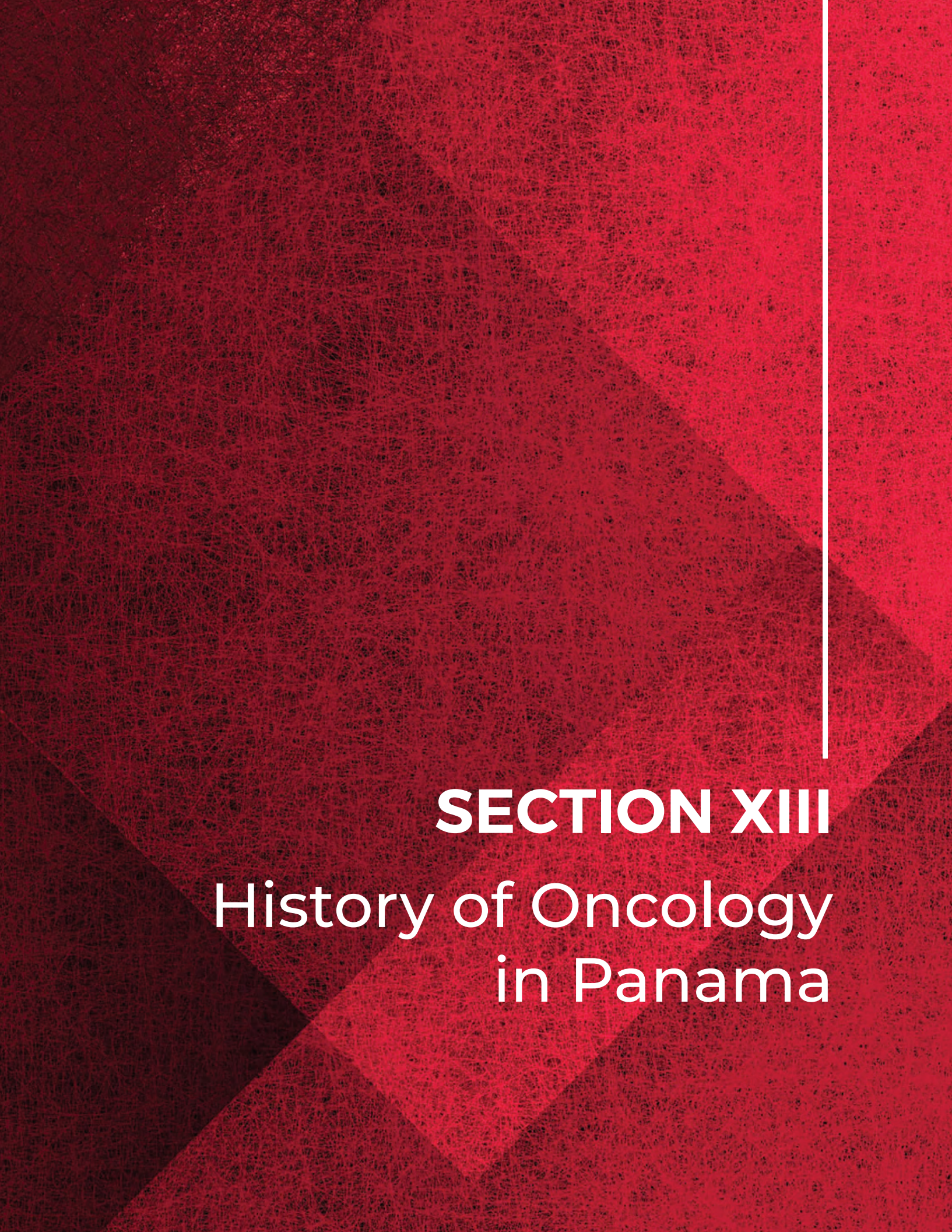
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SECTION XIII

History of Oncology in Panama

Chapter 55

History of Oncology in Panama

César J. Restrepo, MD
Plinio Valdés, MD

“Those who do not know their history are doomed to repeat it.”

This is a phrase from George Santayana (although others say it is from Napoleon Bonaparte, even from the Chinese philosopher Confucius).

“There is an untold story, which is also true.” CR

Abstract

This history, is an example for everyone, beginning with the historical challenges of Charles V in the XV century, to join the two big oceans, to the French Ferdinand de Lesseps of the Suez Canal, to the interaction with the North Americans (with the sanitation of malaria yellow fever), who with their genius, finished the Panama Canal originally started by the “Compagnie Universelle du Canal Interocéanique de Panama” (the French Company of the Panama Canal). The North Americans, in conjunction with our local inhabitants and citizens from all the civilized world, created an infrastructure to finish the Panama Canal, with the best hospitals; from where the pioneers of Panama medicine began since 1905.

Currently with the leadership of the main cancer centers in other countries including, USA, Mexico, Costa Rica, Brazil, Argentina, Italy, Portugal, England, Australia, Israel, Ireland, and the Caribbean.

Panama, thanks to its geopolitics and mixtures of races (a genetic group) became a place to analyze multiple

diseases, including cancer, that in conjunction with the main international oncological guidelines, adjusted (“tropicalize”) the local conditions and resources, to obtain, the best individualizes oncology services.

History

This History of Oncology in Panama is written, with the guide and testimony, of the oldest and still alive protagonists:

- Plinio Valdés, Medical Oncologist
- Enero Avilés, Surgical Oncologist
- Daisy Ferrari, Surgical Oncologist
- Alonso Young, Radiotherapist
- Sonia Ehlers S, daughter of Dr. Alfredo Ehlers Prestán, the First Surgical Oncologist in the Republic of Panama.

Since the beginning of this country of ours, due to our geopolitics and history, we have been in contact with the strongest and largest nations of the Civilized World, as well as with the evolution of Medicine, including Oncology.

In his essay “Historical traces and some anecdotes of Panamanian oncology”, Dr. Plinio Valdés begins as follows: In 1877, The Star and Herald publishes a Record of deaths in Panama with 44 different diagnoses, of the most frequent: hit by train 6, cancer 9 (3 men, 6 women), injured in street fights 19, fever 34, malaria 35, dysentery 40, tuberculosis 61, there were also epidemics of cholera, smallpox and yellow fever of which we have no data. Thus, at the end of the 19th century, cancer was not a major problem in Panama, infectious diseases killed people and penicillin had not been discovered (Fleming in 1928).

Contribution of the North Americans to the Medicine in Panama

The efforts of the United States of America to preserve the health of the Panama Canal workers, profoundly influenced the evolution of our nation's medicine (our independence history, the sanitation of the canal area and medicine intermingle). The entry, to allow Americans to our nation the health system, was granted in section VII of the Hay-Bunau Varilla Treaty when Panama ceded sanitary control of the cities of Panama and Colon to the United States of America.

The greatest contribution of the North Americans to Panama includes not only the medicine, buildings, the Panama Canal, a transoceanic bridge, they brought more importantly, their culture and human quality. Brilliant Doctors and Nurses decided to come to work in Panama, not only to fight infectious diseases but also to work in other areas of Medicine.

We will mention a few of the long list of these distinguished professionals:

Dr. William Crawford Gorgas, Chief Surgeon of the American Armed Forces in Europe during World War I; an entire team of nurses; Doctor Henry Rose Carter, one of the main protagonists in the conquest of yellow fever in this continent in conjunction with Jesse Lazear, one of the four members of the US Army Yellow Fever Commission headed by Dr. Walter Reed, that in 1900 led the team that confirmed the theory (first exposed in 1881 by the Cuban Doctor / Scientist Charles Finlay), that yellow fever is transmitted by mosquitoes, rather than by direct contact. This vision opened completely new fields in epidemiology and biomedicine and directly allowed the resumption and completion of the work of the United States in the Panama Canal (1904-1914).

Dr. Alfred B. Herrick and Dr. Raymond Runyan, celebrity Surgeons who years later would be one of the Founders of the "Hospital Panama" (first and only private facility for many years); Dr. Samuel Taylor Darling, discoverer of histoplasmosis in Panama ("Darling's disease"); Dr. Lawrence H. Dunn, expert in Chagas disease; Dr. Theodore Lyster and Dennis W. Reeder, renowned specialists in Otolaryngology; Dr. James Simmons, considered one of the greatest experts in malaria and eventual Dean of the School of Public Health of Harvard; Dr. Elbert de Coursey, future Head of the Institute of Pathology of the North American Armed Forces; Dr. Lawrence Getz bacteriologist and

pathologist; Dr. C. D. Briscoe, Scholar of diseases of the Heart and kidneys; Dr. William James, General practitioner.

These professionals generated an intellectual climate and a discipline in medical practice that raised to a high level the quality of medicine in our Isthmus. In the articles published in the journal of the "Medical Association of the Isthmian Canal Zone" and in other scientific journals, we see the excellence levels reached by these individuals and the encouragement they gave to Panamanian Doctors.

Dr. Alfred B. Herrick, Head of Surgery at the "Ancon Hospital", (the first building constructed in this area was a model hospital with 500 beds, built by the French in 1882, at an elevation between 39 and 55 meters above sea level, on the slopes of Cerro Ancón (L'Hopital Central du Panama). It had an excellent view of Panama City and the Pacific Ocean. This hospital offered something more than compassion to the patients of yellow fever and malaria, since at that time the cause or cure was unknown. It passed into American hands in 1904 and was immediately repaired and renamed "Ancon Hospital". From this date until 1909, almost one million dollars were invested and a complex of 96 buildings with 1170 beds and a staff of almost 500 people is obtained. By 1914, the United States finished the construction of the Panama Canal and Dr. (Colonel) William Gorgas completed his work. Because the original structure of the hospital and support buildings was made of wood, some with more than 30 years and the workforce of the Canal would be much smaller, permanent and specialized, it was decided to build a modern hospital with 800 beds, in the same site, at a cost of two million dollars.

Dr. Alfred B. Herrick reported in 1913 the number of the largest number of surgical cases were the orthopedic and second group in frequency, were cases related to venereal diseases. If we estimate that the average number of employees in those years was 50,000, we see that 10% of the workforce was disabled each year by an orthopedic problem. Dr. Alfred B. Herrick reported in 1908 one of the first experiences in the medical literature what we now know as after abdominal surgery as paralytic ileus. Dr. Alfred B. Herrick described this surgical procedure carried out in the Ancon Hospital in the years 1911 to 1913, described the high mortality produced by this surgical complication and its easy handling with a "tube that sucks the contents of the stomach". His co-worker, Dr. Raymond Runyon, reported 200 appendectomies made by him in 6 months with a mortality of 0.5%. Dr. Carlos Brin reported on 113 cases made by him in a year with the new surgical technique called vaginal hysterectomy. Dr. Herbert C. Clark (first Director for the Gorgas Memorial Laboratory), reports the result of

4,806 autopsies carried out between 1904 and 1916. In these figures we see the importance of tuberculosis and trauma as causes of death. Only 269 cases of cancer death occurred in that period and it is interesting that the most common cancer was “Stomach Cancer”. Colon Cancer and Prostate Cancer occupied the 5th and 6th place, probably due to the short life expectancy in those years.

Panamanian Pioneers

The Panamanians also contributed, with excellent publications. We can see an example of these publications in the report of 6,229 cases of spinal anesthesia by Dr. Augusto S. Boyd, the report of the treatment of hyperthyroidism with thyroidectomy by Dr. Joaquín José Vallarino and the surgical reports of Dr. Carlos Brin. The impetus of this force continued for many years carried forward by new Doctors and especially by Doctors who since 1905 were trained at the Hospital of Ancon (later known as Gorgas Hospital).

Examples of achievements made by Panamanians on the fight against tuberculosis and other lung diseases by Dr. Amadeo Vicente Mastellari and the two excellent Doctors who continued their work, Dr. Rodolfo V. Young and Dr. José Filós Díaz. Innovations in Cardiology by Dr. Eduardo De Alba, Dr. Guillermo Cedeño. C. in leprosy, Dr. Juan Luis Correa in Gastroenterology, Dr. Benjamin Boyd in Ophthalmology, the influence in Surgery of Dr. Rogelio Arosemena, the precise work in pathology by the Dr. Ferucchio Bértoli, Dr. Gil Sánchez and Dr. Carlos Briceño.

Foundation of Radiological Institute

In 1939 there were a series of important events, we were in World War II, the President of the Republic of Panama was Dr. Juan Demóstenes Arosemena, one of his “compadres”, Dr. Ernesto Zubieta, a Panamanian Doctor, prepared in the United States of America, attending the teachings of Dr. George T. Pack, world-renowned oncologist surgeon; (remembered among other things because he traveled to the Argentine Republic to operate Evita Duarte de Perón, wife of the President of that nation; General Juan Domingo Perón). “Evita” died at the age of 33 years, secondary to cervical Cancer.

Dr. Plinio Valdés wrote: “As Dr. Zubieta told me”: upon his return to the country, he (Dr. Ernesto Zubieta) was assigned to the Maternity ward of the Santo Tomás Hospital (HST). There, in the outpatient clinic, he was surprised

by a large number of very young women with advanced cervical cancer. He was so genuinely impressed that in a meeting with his “compadre”, the Panamanian President, Dr. Juan Demóstenes Arosemena, informed him about the observation and asked him to consider the creation of a Hospital for the care of Cancer patients.

President Dr. Juan Demóstenes Arosemena took the request very seriously and submitted it to the consideration of his six medical advisors; among them Dr. Amadeo Vicente Mastellari. After one month, the result was three consultants in favor and three in disagreement (because according to those who did not support the construction of the hospital for the care of patients with cancer, it would be better to build a hospital for venereal diseases); to which, the President, Dr. Juan Demóstenes Arosemena said: as my advisers do not have an even agreement, I have to decide, and since my “compadre Ernesto,” (Dr. Ernesto Zubieta) wants a hospital to treat cancer patients, this will be done, and I have the budget (a budget initially planned, to build a bridge).

On September 18, 1940, the Radiological Institute, Dr. Juan Demóstenes Arosemena was inaugurated, (named after the President, who had died the previous year.) The honor fell to Dr. Augusto Samuel Boyd, Surgeon, First Vice President, who supported the project. The name changed to Dr. Juan Demóstenes Arosemena Cancer Institute and finally, by law 11 of June 4, 1984, it is called the National Institute of Oncology Dr. Juan Demóstenes Arosemena (ION).

In preparation for the inauguration of the Radiological Institute, some Physicians had been sent to the United States, including Dr. Ernesto Icaza, who would be the Head of Laboratory and Dr. Roberto Sandoval Radiologist, to direct the Radiotherapy application, since the Hospital had a 400,000 volt radiotherapy machine, a 250,000 volt radiation machine and 850 mg radium for local application. “I think,” said Dr. Plinio Valdés, “that for both, the government and the population, the tumor that first attracted attention (due to its frequency and ravages) was cancer of the uterine cervix, in addition to the fact that the patients were generally young women with young children.”

In 1960 the Panamanian League Against Cancer was born. In 1965, with a more direct title, related to women, the National Association for the Prevention of Cancer of Women. On June 29, 1970 the two Societies merged to form the National Association Against Cancer (ANCEC), had the enthusiasm and work of Dr. Aristóbulo Carrizo Villarreal (Gynecologist), Mrs. Isabel Jáuregui de Núñez and Mr. Frank De Lima (Panamanian entrepreneur), its First President.

Remodeling of the Dr. Juan Demóstenes Arosemena Cancer Institute

In the years 1965-1972, the work was truncated, the Dr. Juan Demóstenes Arosemena Cancer Center, became a section of the Department of Obstetrics and Gynecology of the Santo Tomás Hospital. That was related with the *coup d'état* of the President of the Republic Dr. Arnulfo Arias Madrid. In 1972, the Cancer Center Dr. Juan Demóstenes Arosemena, served as a section of Obstetrics at the Hospital Santo Tomas. In 1978, during the administration of the President, Engineer Basilio Lakas, remodeling began, at that time, Dr. Manuel Fernández Díaz (recently deceased, mid 2018) served as Director of the Department.

In 1979, President Aristides Royo requested the support of the government of Japan. Dr. Kito Young, (ION Surgical Oncology chief for 15y, in charge of the training of ION residents, worldwide recognized and member of multiple local as well as international societies and associations), and was chosen to administer, the donations from the Japanese Government to the surgical team, radiology, and clinical pathological laboratory to ION, Panama). The remodeling of the Dr. Juan Demóstenes Arosemena Cancer Institute ended in 1982, during the administration of President Ricardo De La Espriella.

On June 4, 1984, the Panama National Cancer Institute Dr. Juan Demóstenes Arosemena (ION); was created during the administration of President Jorge Illueca. The National Institute of Oncology was transferred to the premises of the old "Gorgas Hospital", by the act performed on June 24 of the same year, when the Official Buildings 242 and 254 were delivered. On July 23, 1999, the National Oncology Institute moved from its location on Avenida Justo Arosemena, to the facilities of the former Gorgas Hospital, (named after the US Army, General William Gorgas).

How and Who Treated Cancer in Panama

At the beginning the General Surgeons were in charge of operating the tumors that justified it, we want to highlight the work of:

- Dr. Rolando De la Guardia
- Dr. Rogelio Arosemena
- Dr. Elías Córdoba
- Dr. Elías Nevah
- Dr. Gaspar García de Paredes
- Dr. Keith Arthur
- Dr. Rolando De la Guardia G., in Panama city.

- Dr. Samuel Cattán, Senior, in the province of Chiriquí.
- Dr. Jaime Trejos performed the first abdominoperineal resection, at the Manuel Amador Guerrero Hospital in the province of Colón.
- Dr. José Trinidad Castellero, in the province of Herrera.
- Dr. Adolfo Name in Santiago, in the province of Veraguas
- Dr. Domitilo "tilín" Castillo Durán from the province of Los Santos.

In the 1960s, Dr. Alfredo Ehlers Prestán, the First Panamanian Surgeon Oncologist, returned to his native province Colón, after having trained in Mexico, he settled in Colón; there, he dedicated to assisting cancer patients.

The Metropolitan Hospital Complex, (CHM) Dr. Arnulfo Arias Madrid, of the Social Security System, (CSS) had established a series of scholarships to prepare Doctors, of the Specialties necessary for the Institution and after the basic residence, with the support of Dr. Guillermo González Barrientos (one of the First Cardiologists in Panama, until the early 1950s), Medical Director of the Hospital (CHM), they were sent to important Hospitals abroad. Dr. Enero Avilés was sent to the Memorial Sloan Kettering Cancer Center in NY. (MSKCC, NY), for his training in Oncological Surgery.

National Institute of Oncology - ION	
Medical Directors	Period
Dr. Ernesto Zubieta, Founder	1940 - 1963
Dr. Aristóbulo Carrizo	1964 – 1969
Dr. Enero Avilés	1970 – 1971
Dr. Manuel Fernández Díaz	1971 - 1976
Dr. Rubén Dario Rojas	1977 – 1978
Dr. Rosa María de Britton	1979 – 1987
Dr. Rodrigo Testa Paredes	1987 – 1988
Dr. Sergio Fuentes	1988 – 1989
Dr. Rosa María de Britton	1989 - 1991
Dr. Jorge Díaz	1991 – 1994
Dr. Fernando Cebamano	1994 – 1999
Dr. Juan Pablo Barés W.	1999 – 2004
Dr. Roberto I. López	2004 – 2007
Dr. Jorge Lasso de la Vega	2007 – 2008
Dr. Aníbal Villa-Real	2008 - 2019

Then, we see that two teams are being formed, some for the National Institute of Oncology, (ION), and others for the General Hospital (CHM) of the Social Security System: Dr. Enero Avilés, Dr. Daisy Ferrari, Dr. José Manuel Fábrega and Dr. Cesar Restrepo. Currently, there are Surgeons Oncologists, dedicated exclusively to the private practice: Dr. Luis Felipe Mosquera, Dr. Carlomagno Castellero Pinilla and Dr. Pablo Duran.

Other Oncological Surgeons arrived in Panama, after their training in International Cancer Centers, among them:

Panamanian Oncologist Surgeons
Dr. Alberto De Sedas (MSKCC, NY)
Dr. Benigno Rodríguez
Dr. Carlomagno Castellero Pinilla (INCan, Mexico)
Dr. Carlos Aguilar
Dr. César Restrepo (MD Anderson Houston, TX)
Dr. Jorge Díaz, Oncology Urology
Dr. José Manuel Vialette
Dr. Julio García, Oncology Urology
Dr. Kito Young (MSKCC, NY)
Dr. Luis Luzcando (ION)
Dr. Moisés Cuckier (Canada)
Dr. Olivia El Acthar (ION)
Dr. Oriel González, Oncology Urology
Dr. Ricardo Pereira
Dr. Roberto García (ION)
Dr. Stephany Torres (ION)
Dr. Yamileth Pereira

As we have said, the one that began the fight against cancer in Panama; Dr. Ernesto Zubieta, who was in charge of the surgical part, from the beginning, opted for gynecology, then followed, Dr. Aristóbulo Carrizo, who devoted much of his life to the fight against gynecological cancer.

Here, (said Dr. Plinio Valdés) “I will include a Doctor, who in his short existence, dedicated it with ardor to the Gynecologic Oncology, and who told me, that he had used a device that is in the ION, that never had been used, a device that allowed a microscopy of the uterine cervix.” Unfortunately, being still very young, Dr. Sergio Núñez died while driving his car on the road to Ocu (place of family residence), due to an acute heart attack.

In 1924, in the new Hospital Santo Tomás (HST), an X-ray diagnosis and treatment equipment was installed, replaced in 1929 by an exclusively diagnostic equipment.

In 1940, the first Radiotherapy machines were installed in the Radiological Institute Dr. Juan Demóstenes Arosemena, (that was the name of the Panama National Oncological Institute at that time).

In 1959 Dr. Rogelio Ávila and Dr. Manuel Roy returned to Panama, from the United States, with the title of Radiologists and Radiotherapists. They were appointed at the Hospital of the Social Security System. In 1962 they installed the Radiotherapy team, brand Simmons, of 250 kV in 1962 at the Hospital San Fernando.

The first “cobalt bomb” in Panama was installed in Gorgas Hospital, for the attention of soldiers and inhabitants of the former Panama Canal Zone. Years after Dr. Roberto Sandoval (already mentioned), was sent to the United States for his specialization

The first Hematologist in the Social Security System, in the Metropolitan Hospital Complex, Dr. Arnulfo Arias Madrid. (“CHM-CSS”), Dr. Marciaq Altafulla, administered the treatments to patients with leukemia, lymphoma, myeloma, and was the first to administer it to patients with solid tumors.

The First Medical Oncologist, in the Republic of Panama, is our esteemed Professor and Friend Dr. Plinio Valdés, after his training as a Medical Oncologist, at the Mexican Institute of Social Security; under the direction of Dr. Jaime de La Garza, returned to Panama, and dedicated his whole life, to teaching, as a Professor in the School of Medicine. He was the First Medical Oncologist of the Metropolitan Hospital Complex (CHM), of the Social Security System (CSS), helped to develop the Pediatric Oncology, which had started in the children’s hospital, with Dr. Luis Espósito, (who treated the children with leukemia,) while the others were treated by Dr. Plinio Valdés, then came Drs. Napoleón Chen, Jaime Boyd and Sabina Achú.

Another contribution of Dr. Plinio Valdes, to Oncology in Panama, is the Creation of the Panamanian National Cancer Registry, it began on January 01, 1974. The most frequent tumor was cervical uterine cancer: 384 cases, of which 157 were in situ, and 227 were invasive, mostly women between 20 and 60 years. Then, skin cancer continues, especially basal cell cancer, which is frequent, in a tropical country like ours, where the sun is intense. Even, adds Dr. Plinio Valdés, “with a sub-record” from the beginning, they have kept high figures, Breast Cancer, Stomach, Prostate, Rectum, Colon.

The National Cancer registry began in a rudimentary way, with Dr. Plinio Valdés and a Secretary, Myrna Fitzgerald, everything was done manually and was based on pathology reports. At that time there were relatively few pathologists in the Republic of Panama, 10 in total; by province: 7 in Panama capital, 1 in Chiriquí, 1 in Azuero and 1 in Colón. Dr. Plinio Valdés, Medical Oncologist, visited each one of them and broke down the cases of cancer one by one. In the capital, all reports were reviewed, by Institution, including those of the child's Hospital. Private clinics were not included.

In the National Oncological Institute (ION), Dr. Alfredo Hidrovo Clinical Oncologist was the one who initiated the treatments of solid tumors.

Other medical oncologists with training in the United States, (Specialist in Internal Medicine and Medical Oncologists) are: Dr. Adán Ríos, Dr. Julio Santamaría and Dr. Rubén Darío Fábrega.

From the Italian School of Oncology, Dr. Fernando Cebamanos; from England, Dr. Roberto Iván López; from the Brazilian School, Dr. Fernanda Picardi.

From the Mexican School, Dr. Enrique Díaz, Dr. Juan Pablo Bares W., Dr. Juan Alcedo. Gynecology Oncology Dr. Julio César Godoy, Dr. Gustavo De Obaldía, Dr. Erasmo Martínez and Dr. Ángel Díaz, current Head of the Service.

The Pediatric Hematology Oncology in the Metropolitan Hospital Complex began with Dr. Margarita Grain de Roy. The Oncological Surgery was performed by Dr. Gonzalo Sosa and Dr. Carlos García de Paredes at the Child's Hospital.

Pediatric Oncology Surgery at the Child's Hospital, began with Dr. Enero Avilés, as a consultant to the service, later Dr. Honorina Espinosa, Dr. Benjamín De Los Ríos (current Chief) and recently Dr. Zaida Castellero, Pediatric Surgical Oncologist, trained with the renowned Pediatric Surgeon Dr. Pablo Lezama.

Multiagent Chemotherapy

In the 1970s, multiagent chemotherapy was administered, which had replaced chemotherapy, with a single drug, such as 5-Fu, which was used predominantly in the treatment of gastric, pancreatic and colon cancer, with a duration of up to a year.

Then Adriamycin, and Tamoxifen, which were administered in Panama, rather than in the United States, because we

received it directly from England; when it had not yet been approved by the FDA. Even, the patients of the United States acquired it in Panama and took it to the United States.

From these "brush strokes", we must add Drs. Luis F. Chen and Dr. José B. Moreno, from Nuclear Medicine; Dr. Rafael Barletta, Medical Oncologist in La Chorrera; Hematologists Dr. José Franceschi, Dr. Carlos Rodríguez, Dr. Dimas Quiel, Dr. Natalie Buitron, Dr. Heidy Cedeño; Dr. Eliecer Cherigo, Infectious Diseases Specialist, and Dr. Alberto Saenz Cardiologist.

Currently, they reach more than 95 well-trained doctors from all over the civilized world, in comparison to the 4 Doctors who started the ION in 1940. In his review, Dr. Plinio Valdés says that "he will not touch the History of the Oncology Nurse, or Palliative Care." Excludes mention of the administrative part, acquisition of devices.

Dr. Plinio Valdés Anecdotes

At the end of his writing, Dr. Plinio Valdés clarifies: "there are still issues to be developed: You could easily write several volumes with the Panamanian Oncology History."

Now, says Dr. Plinio Valdés, "I want to add some anecdotes, in relation to the information that appears on the Internet, ...that the Panama National Cancer Institute (ION) at its base had two Radiotherapy machines, that nitrogen mustard was administered, and radio needles were used". Dr. Plinio Valdés states categorically: "There were two radiotherapy machines, the Nitrogen Mustard was not available, (Nitrogen Mustard- Mustargen was released in 1949) is related to a World War II event: The John Harvey, a ship owned by the United States, with a secret cargo of 1,350 tons of mustard gas bombs, docked in the port of Bari, Italy; was attacked by German aircraft, which resulted in a large death of civilians and military, was observed in the survivors, in addition to skin lesions, **leukopenia**, which led to the use of mustard nitrogenated Mustargen®, in Oncology. Dr. George T. Pack, (already mentioned), sent this product (Mustargen®), to Argentina, for the treatment of Doña Evita Duarte Perón."

The National Cancer Institute (ION), is a Tertiary Hospital, which has had changes since its inception, to this day.

When the Dr. Juan Demóstenes Arosemena Radiological Institute started, it had four Doctors, three Nurses, assistants and forty (40) beds; everything designated by the Santo Tomás Hospital.

Radiotherapy is the oldest of all the Oncological Therapies, especially because of the most frequent cancer of the uterine cervix, Drs. Ernesto Zubieta and Dr. Generoso Guerra were involved in these treatments. They did implantation with a radio needle, injections of nitrogen mustard. The treatments were palliative.

From the year 1965 an active battle against cancer is developed, applying the latest advances in medicine, for the detection and treatment of this disease. The National Radiological Institute was named Dr. Juan Demóstenes Arosemena Cancer Center, in recognition of the work done by this President. In the administration of Dr. Aristóbulo Carrizo Villarreal, the Cobalt Bomb 60 was incorporated.

Dr. Daisy Ferrari, spent 2 years at the ION, working with Dr. Enero Avilés, and Dr. Aristóbulos Carrizo, later on, she traveled to the Royal Marsden. (RM) in London to further increase her training as Oncology Surgeon, returned to Panama and worked with dedication to the patients and on the training of General Surgeons.

We definitively were influenced (as she says, contaminated), by her extraordinary examples, and became Surgical Oncologist (Dr. José M. Vialette, Dr. Luis Luzcando and Dr. Cesar Restrepo). In her clear and straight way of talking add Dr. Ferrari: "If Dr. Enero Avilés had remained at the ION, the ION would have become an MSKCC or a RM type of Cancer Center, but politics involved, it did not happen."

Reorganization of Radiotherapy Service at ION

Dr. Alonso Young returned to Panama in 1971, after doing 3 years of Residency Training on Radiotherapy, at the National Oncological Institute of Madrid, title endorsed by the Universidad Complutense de Madrid. Dr. Alonso Young was the First full trained Radiotherapist in Panama. In 1971, the ION, was a Department of the Santo Tomas Hospital, the Chief was Dr. Manuel Fernandez Diaz (first Breast Cancer Surgeon in Panama).

The Chief of the Radiotherapy Service was Dr. Generoso Guerra, Obstetrician-Gynecologist. (Dr Ernesto Zubieta, remained attending the unit, as the senior staff.) Physics: Prof. Ricardo Lajon, Prof. Denek Hlasivek – Czechoslovak nuclear physicist sent to Panama by the International Atomic Energy Agency (IAEA), United Nations Organization (UN) to reorganize and modernize the Radiotherapy Service at ION.

Physics Assistant: Cecí Eliecer Cedeño, PhD. Technicians: Judith Reyna, RN. Doris Murillo, RN. Teresa De Gracia, RN. – Head of the Radiotherapy Chirophobe and Custody of the Radioactive Deposit. Radiotherapy units: Unit of Cobalt 60, a load of 5000 Ci, bought by the government of Panama during the Presidency of Mr. Marcos Robles, by request of the ladies of ANCEC. Unit of Orthovoltage of 250 Kv. Radioactive isotopes: Radio 226 tubes and needles. Radioactive deposit: a "safe box, for commercial use". Hand carrying of the radioactive charges, from the storage room to the operating room. Physics Laboratory and Workshop: Dosimetry Equipment, Water Fantoma, a Geiger counter. Utensils to melt lead and wax. Equipment to cut plexiglass and foam.

Tele Therapy or External Radiotherapy: The therapeutic dose was expressed in Rads and then changed to Gray. The irradiation technique was mainly done, through direct fields; parallel and opposite fields; tangential Crossfire techniques are then introduced; Of Arc and Pendular; Box technique; Moving strip. Planning was done by taking radiographic films and using Fluoroscope. Taking of corporal contours by means of Flexicurve; Anatomical Atlas on slides and determination of tumor dose by manual tracing of isodose curves. The use of bolus and lead blocks for protection begins. Intracavitary brachytherapy or Curie Terapia: apply directly, manually, under anesthesia, in a minor chiropractic room.

The rooms were adequately enabled. The X-rays were taken with portable equipment. The dose was expressed in milligrams per hour and the main indications were Cervix Uterine Cancer, Endometrium Cancer, Vagina Cancer. This technique was modernized, and the Afterload Technique was used thanks to the financial contribution of ANCEC, for the purchase of intrauterine applicators in tandem; Fletcher Colpostatos, Plastic tubes, etc. in the style of MD Anderson of Houston. Cesium 137 tubes and lead blocks are purchased to build a deposit of radioactive material. The dose was expressed in rads mainly at the level of the cervix or vaginal vault and at the level of parametrium through the use of radiographic plates and pelvic grams, according to the Manchester technique.

The first brachytherapy is performed in nasopharyngeal Cancer, the first contact brachytherapy in Cancer of Skin and palate. The first radioactive implants are made with the needles of Ra 226 mainly in the Tongue. A homemade portable radioactive deposit is made, to transport the radioactive charges from the warehouse to the operating room. The metabolic brachytherapy program based on I

131 starts in Thyroid Cancer. Radiological Protection: The Radiological Protection Program is organized. New Radio-oncology Doctors arrived years later: Dr. España De la Rosa, Dr. Ricardo Britton and Dr. Andrevis Berroa. New Physics: Years later, arrived the technicians in radiotherapy Olivia Saldaña and Alvaro Mejía. It is decided to train technicians New Technicians: in Radiotherapy.

Dr. Plinio Valdés adds that the ION has Medical Oncologists, Gynecologic Oncologists, Radiotherapists, specialists in palliative medicine and reconstructive Surgery. In the words of Dr. Alberto De Sedas: “Cesar, before, the Oncology Surgeons, we did everything from the complex resection of tumors in the Head and Neck, the Thorax and the extremities, and also the reconstructions, were | endless hours of hard work; now we have reconstructive surgeons”.

In recent years, the field of Surgical Oncology has expanded at ION : with the help of Drs. Camilo Rodríguez of the (CHM), Social Security System, (CSS) a Cardiovascular and Thoracic Surgeon, who helped us at ION, in the resection of Thoracic and Hepatic lesions, complex resections of Soft Tissue Sarcomas of the extremities, which required *en bloc* resection of the femoral artery and immediate vascular replacement and Dr. Alejandro Arango Restrepo Orthopedic Surgeon, from the CHM,CSS; treating Bone tumors.

Chemotherapy Treatment

Dr. Plinio Valdés explicitly states that “he, will not refer to the development of the history of Oncology Nursing, only mentions that at the beginning, a nurse, usually the Head nurse of the pavilion, without any special preparation applied chemotherapy at the Panama National Oncological Institute ION.

The local efforts, characteristic of our countries, led them to obtain, from an official school nearby: two chairs for “left-handers” and two chairs for “rights”, the chemotherapy was administered in room # 29 of the National Oncological Institute, initially by the head nurse Lic. Zobeida Ríos. The oncologist doctor administered the chemotherapy, initially in his office. Later, in the Emergency room of the Metropolitan Hospital complex. Dr. Arnulfo Arias Madrid, Social Security System, later in the medicine ward of this same premise.

Other ION Specialists that were Arriving

Reconstructive Surgeons Dr. Jorge Selles, Dr. Adalberto Mayorga (current Chief of the section, trained in Mexico under Dr. Fernando Ortiz Monasterio), Dr. Roberto Tribaldos, Dr. Abraham Malca, Dr. Luis Miguel Samudio.

Dr. Dolores Tamez, ENT, Head and Neck Surgeon. Radiotherapist: Eliecer Cherigo, Keith Britton, Rafael Araúz, Dr. Yasir Ruiz. Dr. Eliecer Cherigo Senior, Infectious Disease Specialist.

Dental Doctors Dr. Francisco Martínez and Dr. Rene Luciani (Head), who help us with the reconstructions of the Head and Neck area, in addition to the comprehensive evaluation of all Oncological patients before starting radiotherapy and or Chemotherapy.

During the last years of the military dictatorship, after years with 4 Surgical Oncologists in the Metropolitan Hospital Complex, and 3 Medical Oncologists. We all were rearranged (the Medical Oncologists were transferred to the National Institute of Oncology before 1986), in 1989 Dr. Enero Avilés retired and move to the Medical School as Dean, Professor, Head of the Department of Surgery, Dr. José Manuel Fábrega, moved to private practice, Dr. Daisy Ferrari to Mexico and Dr. Cesar Restrepo went to Gorgas.

After a decade, working as Surgeon General and Oncologist, consultant in Hyperbaric Medicine in Gorgas Hospital, US Army Community Hospital, and the US Air Force. (In the Howard Base.), another decade, at ION and a year at the Luis “Chicho” Fabrega Hospital, in the city of Santiago, my hometown. I returned to the Metropolitan Hospital Complex, Dr. Arnulfo Arias Madrid in 2008, since then, I have been working with the Heads of the General Surgery Service (Dr. Javier Díaz, Dr. César De Leon, Dr. Luis Mendieta, Dr. Guillermo Bailey, Dr. Edgardo Campana, Dr. Nicolás Saval Robles, Dr. Joaquín Perurena, Dr. José Miguel Cabada Lee). Endocrine Surgeon and Head and neck specialists (Dr. Gabriela Ganci, Dr. Eliecer Tello, Dr. Jorge Calvo). Surgeons trained in Advanced Laparoscopy, who perform GI cancer operations (Dr. Mario Quiel, Dr. Rogelio Naranjo, Dr. Herbert García, Dr. Alonso Alvarado, Dr. Roberto Sing, Dr. Mauricio Rodríguez).

Coloproctologist (Dr. Félix Filos, Dr. Roger Vega, Dr. Edgar Alemán, Dr. José Luis Rios). Specialist, who performed the first liver Transplantation in Panama, and treat GI cancer,

(Dr. Leonardo Santamaría, Dr. Lizka Richards). Also, a transplantation specialist who is deeply involved in teaching in our General Surgery Service at the CHM, CSS. Dr. Melissa Menendez, Urologists (Dr. Juan Materno Vásques, Dr. David Crespo).

Otolaryngologists (Dr. Maximiliano Romero, Dr. Francisco Rozas, Dr. Carlos de la Rosa, Dr. Moises Torrijos, Dr. Francisco Tejeira.) Neurosurgeons (Dr. Luis Fernando Pitty, Dr. Avelino Gutierrez, Dr. Ricardo Bermúdez.) Plastic Reconstructive Surgeons (Dr. Julio Moltó, Dr. Sergei de la Rosa, Dr. Edgar Terán, Dr. Gerardo Garrudo).

Gynecologic Oncologists: Dr. José Luis Gonzales, Dr. Ana I. González P., Dr. Miguel Cáceres, Dr. Georgios Karnakis Kosmas, Dr. Noel De Obaldía, Dr. Thais Atoche). Orthopedic Oncologist (Dr. Alejandro Arango Restrepo, Dr. Alan Rios).

A Tumor Board Committee was established, Head by César Restrepo, with the administrative support and participation of the, Gynecologic Oncologist. ENTs. Pathologist: Dr. Jaime Arias, Dr. Gabriela Martínez, Dr. Giselle Aguirre and Dr. Moises Espino. Radiologist: Dr. Elba García, Dr. Mario Miranda, Dr. Gilberto Chanis, Jr., Dr. Baltazar Isaza, Jr.; and Dr. Amhed Vielgo, Medical Director of the Metropolitan Hospital Complex, Dr. Arnulfo Arias Madrid, of the Social Security Fund. We have agreements to refer patients to the National Oncology Institute, patients with the cancer that we operate with more frequency, that require receiving neo and / or adjuvant therapies.

The future is promising, on the other hand, in private environments, several oncological units have been established over the years, the Hematology Oncology Center (integrated by Drs. Ricardo Díaz, Dr. José Luis Franceschi, Dr. Juan Carlos Alcedo, Dr. Julio Santamaría, Dr. Juan Pablo Barés, Dr. Alejandro Crismatt, Dr. German Espino, Dr. José Moreno, Dr. José Luis Amador, Dr. Lineth López, Dr. Dimas Quiel, Dr. Benito Castillo). There are other Oncology Clinics and Service in the Paitilla Medical Center, Clínica Hospital Nacional and Hospital Punta Pacífica.

The Pediatric Oncology in Panama, at the Panamanian Children's Hospital, continues to develop, with the recent arrival of Dr. Zaida Castellero, First Pediatric Surgical Oncologist, some provinces have an Oncologist in Public and Private practice, Dr. Américo Abadía, Surgical Oncologist, Dr. Reinaldo Isaacs and Dr. Luis Caballero Medical Oncologist, in the Chiriquí Province.

At the Metropolitan Hospital Complex of the Social Security System, in the last 10 years, we have the arrival of Dr. Noel De Obaldía and Dr. Miguel Cáceres, Oncological Gynecologist, Neurosurgery and Orthopedics.

During this same time, we have the opportunity to find Dr. César Díaz, a 2nd year Resident of Surgical Oncology at the National Oncology Institute of Panama; Dr. Erick Santos, a 5th year Resident of General Surgery; a 3rd year General Surgery Resident, Dr. Martin Alpírez; 2nd year Residents, Dr. Ale You, Alfredo Orillac De Obaldía and Dr. Laura Rodríguez Barrios; Second year In-house Doctors Dr. Tiffani Ashley Lara Gómez, Dr. Emilia Fábrega Fontane, Dr. María Alejandra Marcucci Stanziola, Dr. Laurence José Conway Restrepo); that could be a “generational replacement”.

Recommended Bibliography

We exhort the History student, genuinely interested in deepening knowledge of the History of Panamanian Oncology, to consult the Libraries and information from sources such as ANCEC, with special interest in the Thesis of Dr. Doménico Melillo; The Joaquin José Vallarino Library at the National Institute of Oncology of Panama (ION), “Traces of the History of Oncology in Panama” by Dr Plinio Valdés. The Panama Canal “Roberto F. Chiari” Library. Lottery cultural magazine # 435 March / April 2001. Medicine and the Panama Canal, Jorge A. Motta, MD. Salud Publica y Saneamiento en la Zona del Canal de Panama: Un Recuento Historico, 1880-1915 Carlos A. Guardia’ Bol Of Sanit Pamm 95(1), 1983. Medical Association of the Isthmian Canal Zone. Walter G. Nelson, M.D. JAMA. 1953;152(17):1652. doi:10.1001/jama.1953.03690170066026. The Panama Canal Zone; an epochal event in sanitation by Adams, Charles Francis, 1835-1915.

As we mentioned at the beginning of this manuscript, in Panama we have the singularity of having been trained under the influence of Oncologists from the main countries of the world, at the most reputable Cancer Centers. For those, who have learned “the hard way” and, therefore, have “a lived experience”, enjoy reviewing every detail of this historical legacy of Panama, to the North Americans, Latin Americans and the Caribbean countries; to the Whole World.

¡We are fighting Cancer “from the battlefield”,

Comprehensive Clinical **ONCOLOGY**

CURRENT PRACTICES

I am very pleased to release this Comprehensive Clinical Oncology: Current Practices book with the valuable collaboration of prestigious oncologists from Argentina, Australia, Brazil, Costa Rica, Guatemala, Israel, Italy, Mexico, Panama, Portugal and the United States; all of them experts in their field and members of international surgical oncology societies.

This book is designed for both practitioners who specialize in oncology, as well as for more general practitioners, and medical students and residents in training to help address this deficit in compiled oncology information. Although this book is not intended to replace any of the great existing texts, it does fill a space between them and the realities we see in our developing countries.

Comprehensive Clinical Oncology: Current Practices has 55 Chapters, its format is designed to provide immediate access to key information needed to establish an informed therapeutic relationship between caregivers and patients. A brief list of pertinent and contemporary references is included in each chapter.

The incidence of mortality in our developing countries exceeds that of developed countries. After many years of working with people and for people, after consulting in Panama and abroad, thank God, we are able to see this project come to fruition. It is hoped that this very focused volume will prove to be useful to readers.

I would like to thank those who made this book possible.



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