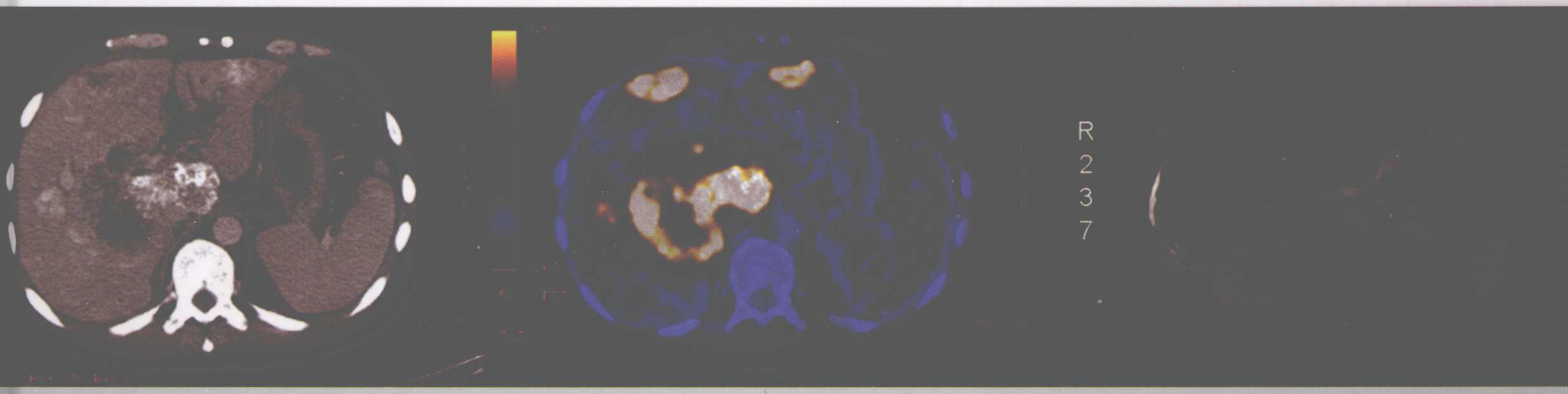
MALIGNANT LIVER TUMORS

Current and Emerging Therapies

THIRD EDITION



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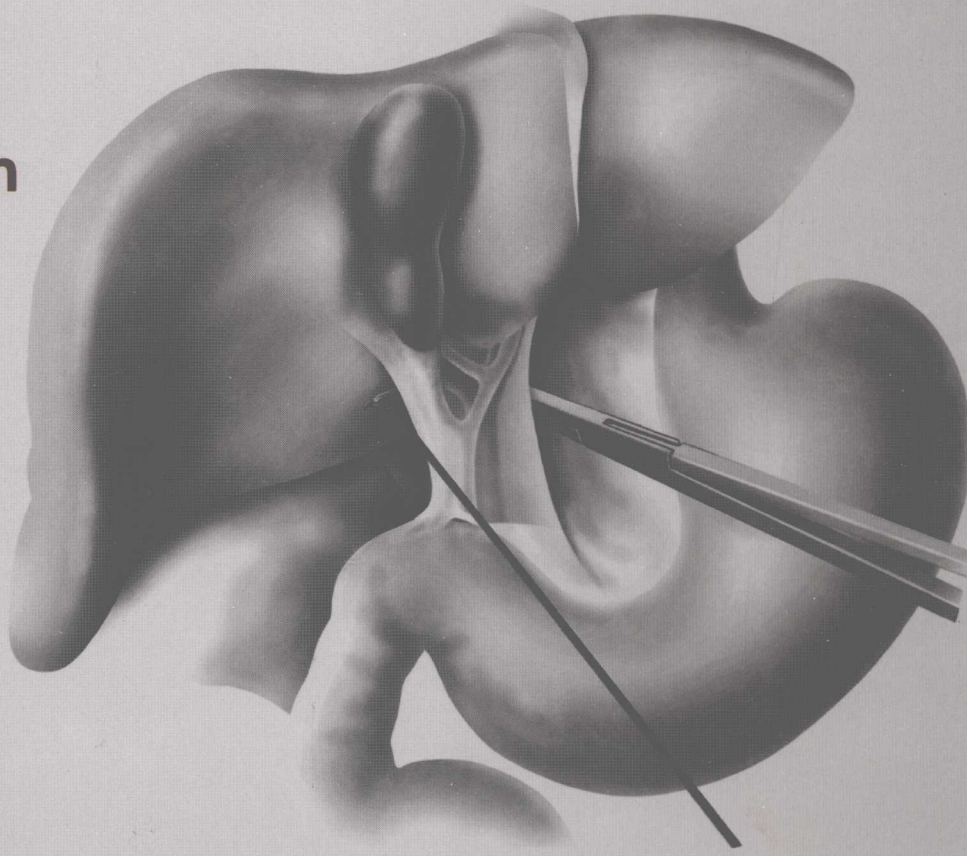

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Preface

Very few areas in medicine offer as many controversies as the management of liver tumors. Since the publication of the first two editions of the book, in 1999 and 2004 respectively, many novel diagnostic and therapeutic tools have become available. This has brought tremendous excitement and hope for curing previously lethal diseases. However, the recent proliferation of innovative and competitive approaches, often marketed prior to conclusive demonstration of their efficacy, has also brought confusion about which therapeutic modalities to select for a particular case [1].

Today, the success of treating a patient with hepatic malignancy is often linked to the appropriate use of various treatments, combining neoadjuvant and adjuvant modalities with surgery. Thus, the best approach for a patient with an hepatic tumor is achieved by a multidisciplinary team comprising a medical oncologist, hepatologist, hepatic surgeon, radiotherapist, and interventional radiologist. The availability of such specialists in a center *per se* is not enough for success. Of vital importance is the daily interaction of those specialists, which is mandatory in order to provide optimal treatment for each patient presenting with a complex liver malignancy [2].

Since most innovative approaches are still experimental and often technically demanding, patients presenting with hepatic tumors should optimally be managed in centers with a strong commitment to research. Patients often need to travel long distances to reach such centers. Therefore, for adequate long-term management of these patients, it is imperative to establish a close collaboration between specialized centers and local oncologists, as well as other physicians.

To this end, the third edition of *Malignant Liver Tumors* has been extensively revised compared to the two previous editions, including a new format, new associate editors, and 16 new chapters containing guidelines for the treatment of each specific type of malignancy. However, the goal remains similar in providing a comprehensive and critical approach to current and established therapeutic modalities, while critically evaluating promising new avenues. The book was written by a multidisciplinary panel of international experts, each with extensive experience in this population of patients. Each chapter was reviewed by the Editor, Deputy Editor, two Associate Editors, and at least one external reviewer to achieve comprehensive and balanced coverage of each topic, to minimize redundancy among chapters, and to provide appropriate cross-references. While each chapter can be read separately, the book was written with the intention that the chapters be read sequentially.

The first and second editions received many positive comments published in several surgical, oncologic, and gastrointestinal journals, testifying to the interdisciplinary interest in the field. Besides many eulogistic comments, such as "best book in the area" [3], the most relevant criticism of the second edition appeared in the *New England Journal of Medicine*: "If I were a physician who was consulting this book for advice on how to treat my patient, I would be impressed by how many treatment options my patient had, but I would have no idea how to pick up the best one" [4]. To address this pertinent comment we added an entire new section (Section 5) on "Guidelines for liver tumor treatment," covering the most common liver malignancies: hepatocellular carcinoma (HCC), cholangiocarcinoma (CC), gallbladder cancer, and colorectal liver metastases. These guidelines were prepared by the Associate Editors, taking into account other guidelines prepared by international or national societies, which should now offer a specific strategy to treat a patient with a specific condition through algorithms.

Each chapter has been updated, often by the original authors. Sixteen new chapters have been added. The book starts with a new chapter (Chapter 1) on the history of liver tumors and their therapies. The next chapter (Chapter 2) is also new, covering the liver anatomy and the consensus terminology for the various types of liver resection. A new emphasis is also given to histologic changes in the liver related to underlying conditions such as steatosis and cirrhosis, as well as neoadjuvant chemotherapies, which are increasingly used in clinical practice (Chapter 4). Three new chapters (Chapters 5–7) cover the epidemiology and the natural history of HCC, CC, and colorectal liver metastases, respectively. Novel developments have occurred in the field of internal radiation therapy of liver tumors, which is

covered in Chapter 12. Strategies for liver resection are newly covered in two separate chapters (Chapters 16 and 17), one for HCC and gallbladder cancer, and another for colorectal metastases. Among the emerging therapies, novel therapies, targeted at specific signaling pathways, appear to be the most promising, and a new chapter has been included which covers relevant signaling pathways in liver tumors (Chapter 31). Finally, a new chapter has been included to cover the economic aspects of the treatment of liver tumors (Chapter 44).

This book also has an important educational purpose, and therefore we include 5–10 questions after each chapter. This will enable the reader to test his or her understanding of the main information in each chapter.

I hope that this third edition of *Malignant Liver Tumors: Current and Emerging Therapies* will prove useful, and will provide timely information and guidelines for the management of this difficult population of patients.

P.-A.C.

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Abbreviations

5-FU	5-fluorouracil
AFLD	alcoholic fatty liver disease
AFP	alpha-fetoprotein
AFU	alpha-L-fucosidase
AIDS	acquired immunodeficiency syndrome
Akt	protein kinase B
APAF-1	apoptosis protease activating factor
ASH	alcoholic steatohepatitis
ATP	adenosine triphosphate
BMI	body mass index
BSC	best supportive care
CAG	chronic atropic gastritis
CASH	chemotherapy-associated steatohepatitis
CBA	cost-benefit analysis
CC	cholangiocarcinoma
CEA	cost-effective analysis
CEUS	contrast-enhanced ultrasound
CGH	comparative genomic hybridization
CK	cytokeratin
CLM	colorectal liver metastasis
CRC	colorectal cancer
CSI	chemical shift imaging
CT	computed tomography
CTAP	computed tomography during arterial portography
CTHA	computed tomography during hepatic arteriography
CTNNB1	catenin (cadherin-associated protein), beta
CTV	clinical target volume
CUA	cost-utility analysis CEA, carcinoembryonic antigen
CUSA	cavitron ultrasonic surgical aspiration
CyA	cyclosporin A
DFS	disease-free survival
DRG	diagnosis-related group
ECC	extrahepatic cholangiocarcinoma
ECM	extracellular matrix
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
ERC	endoscopic retrograde cholangiography
ERCP	endoscopic retrograde cholangiopancreatography
ERK	extracellular signal-regulated kinase
FDG	fluoro-2-deoxy-D-glucose
FLR	future liver remnant
FNH	focal nodular hyperplasia
FSE	fast spin echo
FUDR	floxuridine
GRE	gradient recalled echo
GSK-3β	glycogen synthase kinase 3 beta
GTV	gross tumor volume
H&E	hematoxylin and eosin
HAC	hepatic artery chemotherapy
HAI	hepatic arterial infusion
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
HEHE	hepatic epithelioid hemangioendothelioma
HNPCC	hereditary nonpolyposis colorectal cancer
HIV	human immunodeficiency virus
HPB	hepato-pancreatico-biliary
HSC	hepatic stellate cell
IAP	inhibitor of apoptosis protein
ICC	intrahepatic cholangiocarcinoma
ICER	incremental cost-effectiveness ratio
ICG	indocyanine green
IGF	insulin-like growth factor
IHP	isolated hepatic perfusion
IL	interleukin
IMTP	intensity modulated radiation therapy
IOUS	intraoperative ultrasound
ITV	internal target volume
IVC	inferior vena cava
LDLT	living donor liver transplantation
LMET	liver metastases from endocrine tumor
LOH	loss of heterozygosity
LSF	lung shunt function
MAPK	mitogen-activated protein kinase
MDCT	multidetector-row computed tomography

MEK	mitogen-activated protein kinase
MELD	model for end-stage liver disease
MEN	multiple endocrine neoplasia
MIP	maximum intensity projections
MMAC	mutated in multiple advanced cancer
MMF	mycophenolate mofetil
MNET	metastatic neuroendocrine tumor
MRC	magnetic resonance cholangiography
MRCP	magnetic resonance cholangiopancreatography
MRI	magnetic resonance imaging
mTOR	mammalian target of rapamycin
MWA	microwave ablation
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
NCNEM	noncolorectal nonendocrine metastases
NET	neuroendocrine tumor
NIH	National Institutes of Health
NO	nitric oxide
NSF	nephrogenic systemic sclerosis
OLT	orthotopic liver transplantation
PAAI	percutaneous acetic acid injection
PAS	periodic acid–Schiff
PEI	percutaneous ethanol injection
PET	positron emission tomography
PFS	progression free survival
PHoT	percutaneous hot saline therapy
PHP	percutaneous hepatic perfusion
PI3K	phosphoinositid-3-kinase
PKC	protein kinase C
PSC	primary sclerosing cholangitis
PTC	percutaneous transhepatic cholangiogram
PTEN	phosphatase and tensin homolog
PTV	planning target volume
PVE	portal vein embolization
PVT	portal vein thrombosis
QALY	quality adjusted life year
RAD	radiation absorbed dose
RECIST	response evaluation criteria in solid tumor
RFA	radiofrequency ablation
RILD	radiation-induced liver disease
RLN	regional lymph node
RTK	receptor tyrosine kinase
SBRT	stereotactic body radiotherapy
SEER	surveillance epidemiology and end results
SIRT	selective internal radiation therapy
SMA	superior mesenteric artery
SNP	single nucleotide polymorphism
STAT	signal transducers and activators of transcription
TACE	transarterial chemoembolization
TAE	transarterial embolization
TART	transarterial radionuclide therapy
TGF	transforming growth factor
TKR	tyrosine kinase receptor
TLV	total liver volume
TNF	tumor necrosis factor
TNM	tumor/node/metastasis
TPP	time to progression
UPA	urokinase-type plasminogen activator
VEGF	vascular endothelial growth factor
VOD	veno-occlusive disease
ZES	Zollinger–Ellison syndrome

Contents

1 Introduction

1 From Promethean to Modern Times

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From myths to mysteries

In the dark ages of our ancestors, liver surgery was inexistent and the organ was a source for myths, legends, and spirituality. During the Babylonian era (~3000–1500 BC), the liver was thought to bear the soul. Priests used hepatoscopy in animal livers as a tool for divine connection, predicting the future. Clay models of sheep livers, probably used for teaching or divination, still exist from this period.

The famous legend of Prometheus was written by Hesiod (750–700 BC), recounting very ancient times (Figure 1.1). Prometheus stole fire from Zeus, the godfather of ancient Greece, and gave it to mankind. For this infringement, the angry Zeus chained him to a rock and sent an eagle to devour his liver. Prometheus was captured in eternal pain. The liver regenerated and gained its normal size overnight, and the hungry eagle returned daily to its victim. Over 2000 years later, the amazing regenerative capacity of the liver is no longer a mystical tale, but the basis for current hepatobiliary surgery and a promising topic of surgical research [1].

Probably the first anatomist to describe the liver was the Alexandrian Herophilus (330–280 BC). Although his written work has not survived, another famous scientist cited him. This was the Greek Galen (130–200 AD), who dominated medical literature for the following centuries. He made accurate descriptions of the lobar anatomy and the vasculature, interpreting the liver as the source of blood. In contrast to his empirical anatomic insights, he propagated a humoral basis of medicine. Originating from the theories of Hippocrates (460–380 BC), diseases were based on an imbalance of the four humors: black and yellow bile, blood and phlegm. However, in the following years and centuries of the Middle Ages, theories became traditions and knowledge moved forward very little. Brilliant exceptions were Leonardo da Vinci's drawings of the extra- and intra-hepatic portal and venous vessels.

In 1640, Johannis Walaeus, from Leiden, Netherlands, reported a common tunic, surrounding the branches of the choledochal duct, the celiac artery, and the portal vein. In 1654, Francis Glisson, from Cambridge, England removed the liver parenchyma by cooking the organ in hot water and explored the hepatic blood flow with colored milk [2]. He discussed the intrahepatic anatomy and topography of the vasculature (Figure 1.2). The growing knowledge of liver anatomy was one of the substantial preconditions for the development of liver surgery. However, this was still far from realization, and the liver remained a fragile bleeding mystery. We would like to refer to the comprehensive overview by McClusky *et al* for the fruitful interaction between anatomists and pioneers of liver surgery [3].

Of inquisitive anatomists and courageous surgeons

In 1842, Crawford W. Long used ether as a surgical anesthetic for the first time in the United States. This was a fundamental step in the development of abdominal surgery. In 1867, Joseph Lister from Glasgow, Scotland, introduced antiseptic techniques against bacterial infections after Louis Pasteur, from Paris, France, had discovered the dangers of bacteria.

Before this period, only anecdotal records exist of descriptions about the removal of protruding liver tissue after trauma. Among these surgeons were Ambroise Paré from Paris, France, J.C. Massie from the United States, Victor von Bruns from Germany, and many others. However, liver trauma at this time was generally managed without operation. It took many years before any courageous surgeon was successful in the first attempt of a planned liver resection.

Carl Langenbuch from Berlin, Germany (Figure 1.3), who was among those to perform the first cholecystectomy, reported the first elective and successful hepatic resection in 1888 [4]. William W. Keen from Philadelphia performed the first liver resection in the United States in 1891. He used the "finger-fracture" technique to divide the liver parenchyma. By 1899, the first case series were being reported in the

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