

# Contents

**Preface: Advances in Hepatocellular Carcinoma** **xiii**

Catherine Frenette

**The Changing Global Epidemiology of Hepatocellular Carcinoma** **535**

Allyce Caines, Ranya Selim, and Reena Salgia

Hepatocellular carcinoma is among the leading causes of morbidity and mortality. Owing to the current epidemic of metabolic syndrome, the population affected by nonalcoholic fatty liver disease/nonalcoholic steatohepatitis continues to increase and now comprises a significant portion with those with hepatocellular carcinoma. The World Health Organization goal of obtaining universal hepatitis B virus vaccination has led to a global effort to improve vaccination, prevent mother-to-child transmission, and implement linkage to care to avoid the development of hepatocellular carcinoma. In contrast with the decreased burden of chronic hepatitis C virus, there has been an increase in new-onset acute hepatitis C virus.

**Lifestyle and Environmental Approaches for the Primary Prevention of Hepatocellular Carcinoma** **549**

Tracey G. Simon and Andrew T. Chan

Patients with chronic liver disease are at increased risk of developing hepatocellular carcinoma (HCC). Most patients diagnosed with HCC have limited treatment options and a poor overall prognosis, with a 5-year survival less than 15%. Preventing the development of HCC represents the most important strategy. However, current guidelines lack specific recommendations for primary prevention. Lifestyle factors may be central in the pathogenesis of HCC, and primary prevention strategies focused on lifestyle modification could represent an important approach to the prevention of HCC. Both experimental and epidemiologic studies have identified promising chemopreventive agents for the primary prevention of HCC.

**Role of Biomarkers and Biopsy in Hepatocellular Carcinoma** **577**

Vincent L. Chen and Pratima Sharma

Hepatocellular carcinoma (HCC) is increasing in prevalence and is the third leading cause of cancer-related death worldwide. Unlike other malignancies, HCC can be diagnosed with dynamic imaging with very high accuracy, and tissue diagnosis is not needed for cancer therapy. There is a unique role of established as well as developing biomarkers in diagnosis, prognosis, and management of HCC. Sequencing HCC tumors has yielded substantial insights into HCC tumor biology and has raised the possibility of precision oncology in which therapy decisions are guided by cancer genetics. However, it is not ready for prime time yet.

**Hepatocellular Carcinoma: Role of Pathology in the Era of Precision Medicine** 591

Monika Vyas and Xuchen Zhang

Hepatocellular carcinoma (HCC) is a morphologically heterogeneous tumor with variable architectural growth patterns and several distinct histologic subtypes. Large-scale attempts have been made over the past decade to identify targetable genomic alterations in HCC; however, its translation into clinical personalized care remains a challenge to precision oncology. The role of pathology is no longer limited to confirmation of diagnosis when radiologic features are atypical. Pathology is now in a position to predict the underlying molecular alteration, prognosis, and behavior of HCC. This review outlines various aspects of histopathologic diagnosis and role of pathology in cutting-edge diagnostics of HCC.

**Surveillance for Hepatocellular Carcinoma** 611

Jorge A. Marrero

Patients with cirrhosis of the liver have a very high risk for developing hepatocellular carcinoma (HCC). Therefore, this group of patients should undergo surveillance to improve mortality. Better tools for stratifying the risk of HCC among patients with cirrhosis are needed. The best strategy for surveillance is the combination of alpha-fetoprotein and ultrasound of the liver every 6 months. This strategy shows a sensitivity of approximately 65% and a specificity of 90%, and importantly, has been shown to improve mortality in these patients. Balancing benefits and harms should be performed when deciding to proceed with surveillance.

**Imaging Diagnosis of Hepatocellular Carcinoma: The Liver Imaging Reporting and Data System, Why and How?** 623

Guilherme Moura Cunha, Kathryn J. Fowler, Farid Abushamat, Claude B. Sirlin, and Yuko Kono

The Liver Imaging Reporting and Data System (LI-RADS) provides standardized lexicon, technique, interpretation, and reporting of liver imaging in patients at risk for hepatocellular carcinoma (HCC). When applied to at-risk populations, LI-RADS achieves higher than 95% positive predictive value for the noninvasive diagnosis of HCC on computed tomography (CT), MRI and contrast-enhanced ultrasound (CEUS). This article focuses on similarities and differences between the CT/MRI diagnostic algorithm (CT/MRI LI-RADS) and the CEUS diagnostic algorithm (CEUS LI-RADS) to inform health care professionals for efficient and appropriate clinical decisions through the management of patients at risk.

**Surgical Resection: Old Dog, Any New Tricks?** 637

Yoshikuni Kawaguchi, Heather A. Lillemoe, and Jean-Nicolas Vauthey

Patients with hepatocellular carcinoma (HCC) have many treatment options. For patients with surgical indication, consideration of future liver remnant and the surgical complexity of the procedure is essential. A new 3-level complexity classification categorizing 11 liver resection procedures predicts surgical complexity and postoperative morbidity better than reported classifications. Preoperative portal vein embolization can mitigate the risk of hepatic insufficiency. For small HCCs, both liver

resection and ablation are effective. New medical treatment options are promising and perioperative use of these drugs may further improve outcomes for patients undergoing liver resection and lead to changes in current treatment guidelines.

## **The Impact of Allocation Changes on Patients with Hepatocellular Carcinoma** 657

Lavanya Yohanathan and Julie K. Heimbach

Since the establishment of the Milan criteria, liver transplantation (LT) has been identified as an optimal therapy for selected patients with early stage, unresectable hepatocellular carcinoma (HCC) complicating cirrhosis, although a major limitation is the critical shortage of available deceased donor liver allografts. This review focuses on the evolution of liver allocation for HCC in the United States and what the most recent revisions to the allocation system mean for patients with HCC.

## **Downstaging to Liver Transplant: Success Involves Choosing the Right Patient** 665

Kali Zhou and Neil Mehta

Hepatocellular carcinoma is a rising indication for liver transplantation in the United States. Downstaging, defined as the reduction of tumor burden using local-regional therapy into Milan criteria, opens an avenue to access cure through transplant for patients who traditionally would not qualify. Approaching the selection of downstaging candidates through an assessment of hepatic function, staying within a modest expansion of tumor burden, and incorporation of serologic/imaging markers for tumor biology provide the best chance for successful downstaging. Following well-defined downstaging protocols with built-in failure criteria ensures excellent post-transplant outcomes.

## **Locoregional Therapies for Hepatocellular Carcinoma: What Has Changed in the Past Ten Years?** 681

Anjana A. Pillai, Meera Ramanathan, and Laura Kulik

The evolution of locoregional therapies in the last decade has been refined with improved patient selection and a development of a more personalized approach. In doing so, there has been associated improved outcomes and less toxicity. With the rapidly changing landscape of systemic therapy, the role of locoregional therapies alone or in combination for downstaging and curative intent will continue to evolve.

## **Role of External Beam Radiotherapy in Hepatocellular Carcinoma** 701

Chien Peter Chen

External beam radiotherapy (EBRT) has improved efficacy and safety with advancements in technology and techniques. EBRT plays an important role in management of hepatocellular carcinoma (HCC). In resectable cases, EBRT serves as a bridge to transplantation or improves local control through adjuvant radiotherapy. In unresectable patients, EBRT offers high local control rates. In metastatic settings, EBRT provides effective palliation. This review presents an overview of radiotherapy treatment modalities used for HCC, current treatment guidelines for the role of EBRT in

HCC, clinical outcomes between various EBRT approaches and other locoregional treatments for HCC, and the future role of EBRT for HCC.

### **Tyrosine Kinase Inhibitors and Hepatocellular Carcinoma**

719

Leonardo G. da Fonseca, Maria Reig, and Jordi Bruix

Sorafenib was the first tyrosine kinase inhibitor (TKI) that showed success in extending survival in patients with advanced hepatocellular carcinoma (HCC). In recent years, additional TKIs have been shown to improve survival and expanded the armamentarium for treating this malignancy. The current landscape includes other classes of drugs, such as immune checkpoint inhibitors and monoclonal antibodies. The challenge is now placed on how to best select, combine, and sequence drugs with the goal of improving efficacy and minimizing toxicities to deliver better outcomes for HCC patients.

### **Immuno-oncology for Hepatocellular Carcinoma: The Present and the Future**

739

Samantha A. Armstrong and Aiwu Ruth He

Hepatocellular carcinoma is a highly prevalent and lethal cancer that many therapeutics are being tested for this disease. It has the potential to be a highly immune-responsive tumor given its inflammatory origins. The first immunotherapies were anti-programmed death-1 monotherapies, which improved response rates and survival. Novel immunotherapy combinations and immunotherapy show promise in frontline treatment. The novel antibody therapy combination of atezolizumab and bevacizumab may be practice changing. Although these landmark studies seem to offer new treatment options, the role of immunotherapy in the liver transplant setting is uncertain until the safety of this approach is defined.

### **Management of Side Effects of Systemic Therapies for Hepatocellular Carcinoma: Guide for the Hepatologist**

755

Adam C. Winters, Fatima Bedier, and Sammy Saab

Historically, systemic treatment of advanced hepatocellular carcinoma was limited to the tyrosine kinase inhibitor sorafenib. With the recent approval of several new agents the armamentarium of treatment options available to providers and patients has expanded. Although these promising advances offer hope for patients with advanced hepatocellular carcinoma, they also present new and challenging adverse effects that threaten to limit their efficacy. Immunotherapy with checkpoint inhibitors introduce immune-related adverse events, which may affect a wide array of organ systems. With prompt recognition, however, common side effects of systemic therapies for hepatocellular carcinoma are predictable, manageable, and many improve with appropriate intervention.

### **Multidisciplinary Team Management of Hepatocellular Carcinoma Is Standard of Care**

771

Dekey Lhewa, Ellen W. Green, and Willscott E. Naugler

Hepatocellular carcinoma (HCC) is a leading cause of cancer mortality, but unlike other leading causes of cancer death, HCC is increasing in mortality

and burden of management. Management of HCC is unique because it usually arises in a diseased liver, which itself may be a driver of mortality. Multidisciplinary teams (MDTs) for the management of complex diseases are becoming more common, but are especially needed in the management of patients with HCC. Liver cancer MDTs are used in most centers providing comprehensive care for patients with HCC, and should be considered the standard of care for these patients.