Hepatocellular Carcinoma
Diagnosis, Management, and Prognosis

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KEYWORDS

• Hepatocellular carcinoma • Transplantation • Locoregional therapy
• Transarterial chemoembolization (TACE) • Sorafenib

KEY POINTS

- The progress made in the diagnosis and management of hepatocellular carcinoma (HCC) represents one of the growing successes in surgical oncology.
- Despite advances in HCC diagnosis and management, the incidence of HCC is still increasing, and HCC represents the fifth most common cancer and the third most common cause of cancer death worldwide.
- Over the last 20 years alone, advances have been made to elucidate the mechanisms of carcinogenesis, to diagnose disease at an earlier stage, and to improve local and systemic treatment of HCC.

INTRODUCTION

The progress made in the diagnosis and management of hepatocellular carcinoma (HCC) represents one of the growing successes in surgical oncology. Despite these advances, the incidence of HCC is still increasing, and HCC represents the fifth most common cancer and the third most common cause of cancer death worldwide.[1] Over the last 20 years alone, advances have been made to elucidate the mechanisms of carcinogenesis, to diagnose disease at an earlier stage, and to improve local and systemic treatment of HCC.

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CARCINOGENESIS AND DIAGNOSIS

Genetics

As technology has improved, the mechanisms for the generation of cirrhosis and subsequent HCC behave become better understood. The well-known environmental risk factors that may lead to underlying cirrhosis include hepatitis B virus (HBV), hepatitis C virus (HCV), exposure to toxins such as aflatoxin, and alcohol intake. For each of these causes of HCC, specific genetic mutations have been isolated.[2] In HCV-related HCC, mutations have been identified in p53, in the disintegrin and metalloproteinase domain–containing protein 22 (ADAM22), in the Janus kinase/signal transducer and activator of transcription (JAK) pathway, in the beta-catenin gene CTNNB1, in the transport protein particle (TRAPP), in the never in mitosis A–related kinase 8 (NEK8) gene, and in the AT-rich interactive domain 2 (ARID2) gene.[3] HBV-related HCC is associated with p53 mutations but also with exclusive mutations in ATPase family AAA domain–containing 2 (ATAD2) and interferon regulatory factor 2 (IRF2) genes. Although there is some overlap in the genetic mutations responsible for HCC in the background of HBV versus HCV, there are notable differences, with HCV being associated with increased CTNNB1 mutations and fewer p53 mutations.[4] Alcohol consumption has shown a correlation to mutations in the chromatin remodelers, which predispose to dysregulation and the development of HCC.[5] The mechanism for the development of aflatoxin-induced HCC has been genetically described by specific base substitutions, which can lead to HCC in the absence of any underlying liver disease.[6]

From a population-based perspective, specific patient polymorphisms have also recently been identified as potential risk factors for the development of chronic hepatitis and cirrhosis. Using genome-wide association analyses and single-nucleotide polymorphisms, subsets of patients have been identified at a specifically higher risk for the development of HCC, independent of the well-established external exposures.[7]

Molecular Mechanisms

The downstream pathways in which HBV and HCV promote HCC are becoming better understood. One such pathway is through promoting stem-cell activity,[8] which has been shown by the upregulation of the well-known stemness-associated marker epithelial cell adhesion molecule (EpCAM) and beta-catenin.[9] Other more recent markers to show stem cell–like properties in HCC include the NANOG transcription factor, octamer-binding transcription factor 4 (OCT4), sex-determining region Y box 2 (SOX2), and Kruppel-like factor 4.[9–11]

Another newly uncovered mechanism of HCC carcinogenesis is secondary to the relative hypoxia and subsequent angiogenesis incurred by the cirrhotic liver. At the macroscopic level, nodular cirrhosis leads to a decrease in hepatic vasculature, which is followed by a hypoxic environment. In the setting of hypoxia, there is upregulation of hypoxia inducible factor 1 alpha (H1F1α). Stimulation of this factor leads to upregulation of vascular endothelial growth factor (VEGF), cyclo-oxygenase 2, angiopoietin 2, and several matrix metalloproteinases.[12–14] These inappropriately upregulated angiogenic and inflammatory signals predispose the underlying parenchyma to damage, inhibition of regeneration, and subsequent HCC.[8] Specific mechanisms have also shown that both HBV and HCV have unique upregulation of the transcription factor HIF1α at the genetic level.[15] The downstream activation of these proangiogenic growth signals has shown promise in the systemic management of HCC, because some of these factors may be targeted and blocked with agents like sorafenib.[16]