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Review

Hepatocellular carcinoma: From diagnosis to treatment

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ABSTRACT

Primary liver cancer is the sixth most common cancer overall and the second most common cause of cancer mortality worldwide. Hepatocellular carcinoma accounts for up to 90% of all primary hepatic malignancies and represents a major international health problem. While surgical resection and transplantation are the cornerstone of therapy in early-stage hepatocellular carcinoma, locoregional therapy and sorafenib are beneficial in those with more advanced disease or those who are not surgical candidates. At times, the integration of both surgical and locoregional therapy may be necessary. Hence, hepatocellular carcinoma requires a multidisciplinary approach to determine the most appropriate treatment as well as the timing of various treatments for optimal outcomes.

Contents

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Abbreviations

AFP	alpha-fetoprotein
BCLC	Barcelona Clinic Liver Cancer
DCP	Des-gamma-carboxy-prothrombin
EASL	European Association for the Study of Liver
ECOG	Eastern Cooperative Oncology Group
EGF	epidermal growth factor
FLR	future liver remnant
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HVPG	hepatic venous pressure gradient
IAT	intra-arterial therapy
IGFR	insulin-like growth factor receptor
IOUS	intraoperative ultrasound
LDLT	living donor liver transplantation
MDCT	multidetector computed tomography
MELD	Model for End-Stage Liver Disease
mRECIST	modified Response Evaluation Criteria in Solid Tumors
MRI	magnetic resonance imaging
MWA	microwave ablation
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
PEI	percutaneous ethanol injection
PSC	primary sclerosing cholangitis
PBC	primary biliary cirrhosis
PVE	portal vein embolization
RECIST	Response Evaluation Criteria in Solid Tumors
RFA	radiofrequency ablation
TACE	transarterial chemoembolization
TACE-DEB	transarterial chemoembolization drug eluting beads
UCSF	University of California, San Francisco
UNOS	United Network of Organ Sharing
VEGF	vascular endothelial growth factor
Y-90	Yttrium-90

1. Introduction

Primary liver cancer is the sixth most common cancer overall and the second most common cause of cancer mortality worldwide [1,2]. Unfortunately, the incidence of liver cancer has been on the rise globally, increasing to 782,000 new cases in 2012 [1,2]. Given the poor prognosis of primary hepatic malignancies, the mortality of primary liver cancer has also increased, reaching 745,000 deaths in 2012 and comprising 9.1% of all cancer deaths [1,2]. Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer, accounting for up to 90% of all primary hepatic malignancies [3].

HCC arises from hepatocytes comprising the liver parenchyma and is preceded by liver cirrhosis in 80% of the cases [4]. As the primary predisposing condition of HCC, liver cirrhosis is a consequence of chronic liver injury, leading to subsequent regeneration of liver cells and formation of abnormal structural nodules with surrounding fibrosis [5]. Common causes of cirrhosis include chronic viral hepatitis such as hepatitis C virus (HCV) and hepatitis B virus (HBV); metabolic liver diseases such as nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), hemochromatosis, α1-antitrypsin deficiency, and Wilson's disease; alcoholic liver disease; autoimmune diseases such as primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC), and autoimmune hepatitis; and environmental factors such as alfatoxins [5].

HCC represents a major international health problem. However, the incidence is unevenly distributed worldwide as a result of the wide variability in the prevalence of various etiologies of cirrhosis [3]. The burden of HCC is greatest (>80%) in sub-Saharan Africa and Eastern Asia, where HBV infection is endemic. In contrast, HCV infection is more predominant in the United States, Europe, and Japan, making it the major risk factor for HCC in these regions [3,6]. However, the geographic distribution of HCC is expected to change over time due to an increase in vaccination and early treatment of HBV in Asian countries, recent advancements in curative treatments of HCV, and the increase in NAFLD-associated HCC corresponding to a rise in obesity in Western countries [3,7]. Notably, NASH is the most rapidly growing indication for HCC-related liver transplantation with a 364% increase in the United States since 2001, compared to an increase of 225% with HCC-related liver transplantation for HCV [8].

Despite improved surveillance programs globally, the overall 5-year survival remains poor at 20%, correlating to delay in diagnosis and advanced stage at the time of diagnosis. Given that most HCC arises in the setting of liver cirrhosis, patient outcomes are not only based on the tumor itself but also the underlying cirrhosis. The Barcelona Clinic Liver Cancer (BCLC) staging system, one of the most commonly utilized staging systems for HCC, classifies patients based on tumor stage, liver function, performance status, and cancer-related symptoms [9,10]. Under the BCLC staging system, the patient stage is allocated to a specific treatment strategy [9]. In this article, we will review the current diagnostic modalities as well as these specific treatment strategies for HCC.

2. Diagnosis

Serologic testing, diagnostic imaging, and histology can all aid in diagnosing HCC. Alpha-fetoprotein (AFP) has been the most commonly tested biomarker for HCC, despite limited sensitivity and specificity [11]. Not only can AFP be elevated in a variety of conditions other than HCC, such as chronic liver disease, pregnancy, and other malignancies, but it can also be normal in a variant of HCC known as fibrolamellar carcinoma [12,13]. In addition, only a small portion of early HCC presents with an elevated AFP [14].

In an effort to improve the diagnostic performance of AFP, three different variants of AFP (AFP-L1, AFP-L2, and AFP-L3) have been studied. AFP-L3 has been found to be more specific for HCC than AFP [15]. The AFP-L3 to AFP relative percentage also has been demonstrated to be an indicator of prognosis [16]. In addition, Des-gamma-carboxy-prothrombin (DCP) has been investigated as a prospective biomarker for HCC [17]. Although these tumor markers have potential value in combination with one another for the diagnosis of HCC, they have not been accepted for clinical use in the United States [18]. In Asia however, DCP is routinely being used as part of both screening and surveillance after curative therapy.

Ultrasound surveillance every 6 months is currently the standard of care for at-risk patient populations [19–21]. However, the use of AFP has fallen out of favor in the surveillance of HCC in the United States given its limited sensitivity and specificity [11]. When a hepatic mass or nodule <1 cm in a cirrhotic liver is detected on surveillance ultrasound, repeat imaging with ultrasound is recommended at 3–4 month intervals as many of these lesion are not HCC [22]. If a hepatic mass or nodule >1 cm is detected in a cirrhotic liver, appropriate contrast enhanced dynamic imaging with either