Elevated Alpha-Fetoprotein

Differential Diagnosis - Hepatocellular Carcinoma and Other Disorders

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KEYWORDS

- Hepatocellular carcinoma • Alpha-fetoprotein • Chronic hepatitis C virus infection
- Chronic hepatitis B virus infection
- *Lens culinaris* agglutinin-reactive fraction of alpha-fetoprotein
- Des-gamma-carboxy prothrombin

KEY POINTS

- The incidence of cirrhosis-related hepatocellular carcinoma (HCC) is rising in the United States, with the associated disease burden expected to grow through 2020.
- Surveillance with alpha-fetoprotein (AFP) in combination with abdominal ultrasonography every 6 months was once widely recommended for HCC surveillance.
- Increased AFP is seen in chronic liver disease without HCC, nonhepatic malignancies, and normal pregnancy; thus, AFP levels must be interpreted within the context of the clinical presentation.
- Results of cross-sectional HCC screening studies show the benefit of diagnosing additional cases of HCC with AFP, but highlight the lack of cost-effectiveness owing to the increased false-positive results.
- US Food and Drug Administration guidelines for HCC risk assessment include using *Lens culinaris* agglutinin-reactive fraction of alpha-fetoprotein (AFP-L3) with des-gamma-carboxy prothrombin (DCP), or the combination of AFP-L3 with AFP and DCP.

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INTRODUCTION

Globally, up to approximately 800,000 new cases of hepatocellular carcinoma (HCC) are diagnosed annually.[1,2] The incidence of cirrhosis-related HCC is rising in the United States, with approximately 34,000 cases diagnosed each year as of 2014. The disease burden associated with HCC is expected to grow through 2020. The incremental increase in the incidence of HCC in the United States is largely a reflection of the natural history of chronic infection with hepatitis C virus (HCV) and the emerging epidemic of nonalcoholic steatohepatitis.[3,4] It is estimated that as many as 1 to 2 million patients with chronic HCV infection in the United States will develop cirrhosis and related complications in the near future.[3,4] Currently, HCV-related HCC is the leading indication for liver transplantation in patients with HCC in the United States [4] Recent data have demonstrated that nonalcoholic steatohepatitis is the fastest growing etiology of chronic liver disease among HCC-related liver transplantations in the United States.[5] It is estimated that nonalcoholic steatohepatitis–related cirrhosis and its complications will peak in the United States in the next 10 to 15 years.[5] Chronic infection with hepatitis B virus (HBV) is the most common cause of HCC worldwide; it contributes to HCC prevalence in the United States as a result of increasing immigration from high-prevalence regions of the world.[1] Curative surgical options, including hepatic resection and liver transplantation, are available, with acceptable outcomes if HCC is diagnosed at an early stage. The 5-year tumor-free survival is 15% to 40% with resection and up to 80% with liver transplantation.[6–10] Therefore, it is important to establish screening and surveillance protocols for HCC with a focus on diagnosing HCC at an early stage.

In this review, we discuss the differential diagnosis of increased serum biomarker levels and the role of these markers in the early diagnosis of HCC and in HCC surveillance programs. The impact of newly cleared risk biomarkers for HCC and their use in conjunction with serum alpha-fetoprotein (AFP) is reviewed.

SURVEILLANCE FOR HEPATOCELLULAR CARCINOMA

The goal of any screening and surveillance program is to effectively identify disease at an early stage such that potentially curative treatment options can be offered, and this principle is true for HCC screening and surveillance. Surveillance strategies with the goal of increasing the rate of early detection of HCC are needed to optimize the management of these patients by providing them with potentially curative surgical options, including hepatic resection and liver transplantation, as well as locoregional therapies, including ablation therapy, that can include thermal and transarterial ablation, and a reliable mechanism to follow the response to therapy.[6–10]

Evolution of Surveillance Guidelines

In the past, the combination of serum AFP level and an abdominal imaging study was recommended for HCC surveillance.[11] However, recent data have shown conclusively that the low sensitivity of serum AFP and its high false-negative rate and suboptimal discriminatory impact impair the diagnosis of HCC.[12] The low sensitivity and specificity of AFP for HCC diagnosis is complicated additionally by variations in tumor-specific and patient-specific heterogeneity, which further reduces its positive and negative predictive values.

The sensitivity of combined serum AFP level and abdominal ultrasonography to detect early stage HCC varies from 40% to 65%.[12–15] Owing to the lack of sensitivity and specificity of serum AFP, its use was withdrawn from the American Association for the Study of Liver Diseases (AASLD) guidelines for HCC surveillance.[16] However, the Asian Pacific Association for the Study of the Liver (APASL) and the National