

Hepatocellular Carcinoma: Diagnosis and Therapeutic Options

Khairy Hammam Morsy¹, Mahmoud Saif-Al-Islam¹, Esraa Maher Ibrahim²

¹Tropical Medicine and Gastroenterology Department, Faculty of Medicine, Sohag University. ²Sohag Cancer Center, Sohag, Egypt.

Abstract

Hepatocellular carcinoma (HCC) is the most common primary neoplasm of the liver and a significant cause of mortality in patients with cirrhosis. Aim of this review is to summarize the new methods of diagnosis and therapeutic options.

Background

HCC has become the third most common malignancy worldwide with very poor prognosis, rendering it the fourth highest cause of cancer related deaths^{1, 2}. The distribution of liver cancer varies by region and more than 80% of cases and deaths occur in developing countries³. In Africa, liver cancer has been ranked as the fourth common cancer, and most of liver cancers are HCC⁴.

Epidemiology

HCC represents 85%-90% of primary liver cancers accounting for 3.5% and 7.5% of all cancers among women and men respectively, and accounts for half a million deaths per year. In Middle Eastern countries, liver cancer is a major concern among men, especially in certain countries such as Egypt and Saudi Arabia, and to a lesser extent in other countries of this region. Recent reports demonstrate that the incidence of HCC has increased sharply in the last 5–10 years, with an especially high incidence in Egypt⁵.

Risk factors

The major risk factor for the development of HCC is cirrhosis of the liver. However, about one quarter of HCC cases diagnosed in the United States do not have any known predisposing risk factors. The major known risk factors for HCC are viral (chronic hepatitis B and hepatitis C), toxic (alcohol and aflatoxins), metabolic (diabetes and non-alcoholic

fatty liver disease, hereditary haemochromatosis) and immune-related (primary biliary cirrhosis and autoimmune hepatitis)⁶. Recently, the geographical variability in the incidence of HCC has been attributed to the changing distribution and the natural history of Hepatitis B virus (HBV) and Hepatitis C virus (HCV) infection⁷.

Diagnosis of HCC

• *Clinical presentation*

In most HCC cases, clinical signs and symptoms may occur several months after development, when therapy cannot be curative. Clinical signs and symptoms of hepatic cirrhosis that is often present in patients with HCC usually mask the presence of an underlying early hepatocellular carcinoma. Symptoms and signs of cirrhosis are often the only expression of the disease. Because of this, patients affected by HCC usually present at an advanced stage of the disease with clinical signs as jaundice, ascites, peripheral edemas, neurologic manifestations of hepatic encephalopathy, and bleeding⁸.

• *Laboratory diagnosis*

Since the early diagnosis of primary liver cancer (PLC) is particularly critical for the treatment efficacy and long-term survival, early screening and early surveillance should be emphasized. The routine screening includes alpha-fetoprotein (AFP) every

six months for men ≥ 40 years and women ≥ 50 years who belong to the high-risk populations that have a history of HBV/HCV infection, alcoholism, and/or diabetes and a family history of liver cancer. It is generally believed that AFP is a relatively specific tumor marker for HCC; the continued AFP increase usually is a risk factor for HCC⁹.

Other tests include:

1. Des-gamma carboxyprothrombin (DCP)

DCP is an abnormal prothrombin protein that is found in the serum of patients with HCC and in patients with vitamin K-deficiency or on warfarin therapy¹⁰.

1. Glypican-3 (GPC3)

It is an oncofetal protein expressed in fetal liver and HCC. A clinical trial using a GPC3 peptide vaccine in patients with advanced HCC has been carried out, denoting that it serves not only as a tumor marker but also as a therapeutic target¹¹.

2. Squamous cell carcinoma antigen (SCCA)

SCCA is physiologically expressed in the skin and other squamous epithelial cells¹². It has been reported to be overexpressed in HCC tissue and in serum from patients with HCC¹³.

3. Golgi protein 73 (GP73, also known as Golp2)

It is a protein expressed by biliary epithelial cells in normal liver. It is up-regulated in patients with acute hepatitis, cirrhosis and HCC¹⁴.

4. Hepatocyte growth factor (HGF)

HGF has been used as a prognostic marker in HCC. Serum HGF levels greater than or equal to 1.0 ng/mL have been associated with poor survival in HCC patients¹⁵.

•Imaging diagnosis

Imaging studies for diagnosis of HCC can fall into one of two main categories: routine non-invasive studies such as US, CT, and MRI, and more specialized invasive techniques

including CT during hepatic arteriography, iodised oil-CT, and CT arterial portography in addition to the conventional hepatic angiography¹⁶.

1. Abdominal ultrasonography (US)

Abdominal US allows the recognition of tumours as small as 1 cm in size¹⁶. US offers many signs that raise the suspicion of malignant transformation, including the presence of intrahepatic venous thrombosis, a mass protruding from the hepatic surface or dilated intrahepatic bile duct, even in the absence of a definite liver mass¹⁷.

2. Multislice-helical (spiral) CT

Abdominal multiphase perfusion CT is the technique of choice for diagnosis of HCC with an excellent performance in the early detection and staging of hepatic focal lesions¹⁷. The gold standard imaging modality for evaluating the response after loco-regional intervention of HCC is Spiral CT¹⁸.

3. Magnetic resonance imaging (MRI)

The advantage of MRI over CT is obtaining images of the liver of high-resolution without using ionizing radiation or nephrotoxic contrast agents. MRI has an equivalent diagnostic accuracy as helical CT in the early detection and diagnosis of HCC¹⁹.

Therapeutic options

HCC therapies are categorized as curative and palliative, which depend upon the tumor features, hepatic reserve, and presence or not of extrahepatic metastasis or vascular invasion. Manifold current treatment choices include: Surgical resection, liver transplantation, radiofrequency ablation (RFA), microwave ablation, percutaneous ethanol injection (PEI) or acetic acid ablation, transcatheter arterial chemoembolization (TACE), radioembolization, cryoablation, radiation therapy (RT), stereotactic radiotherapy, systemic chemotherapy, molecularly targeted therapies like sorafenib²⁰, and viscum fraxini²¹

Summary and conclusion

HCC is one of the commonest cancers worldwide. It is a major health problem and its incidence is increasing. More than 600,000 people die from it each year. The presence of cirrhosis is the major risk factor and this is largely due to chronic HCV and HBV infection.

Worldwide research on the disease needs to be intensified in both the medical and pharmaceutical fields, especially with a focus on providing help to areas where resources are limited.

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