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Hcpatoccllular Carcinoma : Diagnosis and Management

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Abstract

The incidence of hepatocellular carcinoma (HCC) has been increasing in the world mainly because of the rising incidence of hepatitis C. Currently 3 to 4 million persons are infected with hepatitis C .It is estimated that 5% to 30% of these patients will develop chronic liver disease and of these, 30% will progress to cirrhosis. Once patients develop cirrhosis, the risk of hepatocellular carcinoma is 1% to 2% per year. The latency period between hepatitis B or C exposure and the development of hepatocellular cancer varies between 30 and 50 years. Various procedures are used to treat HCC such as liver transplantation, alcohol injection, radiofrequency curative ablation and hepatic artery catheterization. The hepatologist's role in HCC is mainly in the diagnosis, to assess the liver disease status, to decide appropriate treatment, surveillance for HCC and to manage the liver disease. We will review various advances in the diagnosis and management of HCC, which have made possible the discovery of HCC at potentially treatable stage.

Keywords: Hepatocellular carcinoma, Hepatitis C, Hepatitis B, Liver Transplantation.

Introduction

Hepatocellular carcinoma is the most common primary malignant tumor of liver. It is the seventh most common cancer in the world and the most common cancer diagnosed in men, with a male- female ratio

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of 7:1 in high- incidence regions, such as China and Korea (1). It is also one of the most deadly, with a 5-year survival rate of 25% without treatment. It is especially prevalent in Asian and sub-Saharan African regions. The incidence peaks in the fifth to sixth decade of life in western countries but 1 to 2 decades earlier in regions of Asia and Africa. The principal reason for the high incidence of HCC in parts of Asia and Africa is the frequency of chronic infection with hepatitis B and Hepatitis C virus infection. The risk of liver cancer in a cirrhotic liver is ~3% per year and 60-90% of these tumors occur in patients with macronodular cirrhosis. The onset of HCC occurs one to two decades earlier in those with lifelong hepatitis B than in persons with adult acquired hepatitis C. The annual incidence of HCC in cirrhotic patients with chronic hepatitis C is 1.5 to 4%. Any agent or factor that contributes to chronic, low-grade liver cell damage and mitosis makes hepatocyte DNA more susceptible to genetic alterations. Therefore, chronic liver disease of any type is a risk factor and predisposes to the development of HCC. These conditions include alcoholic liver disease, nonalcoholic fatty liver disease (NAFLD) related cirrhosis, Alpha-1 Antitrypsin deficiency, hemochromatosis, primary biliary cirrhosis and cryptogenic cirrhosis. In Africa and southern China, Aflatoxin B_1 is an important public health hazard. Hormonal factors also believed to play a role and HCC may occur with long-term androgenic steroids administration, with exposure to thorium dioxide or vinyl chloride and possibly, with exposure to estrogens in the form of oral contraceptives.

Clinical Features

HCC should be considered in any patients with chronic liver disease whose clinical status indicates sudden decompensation. The most common presenting symptoms and physical findings are summarized in Table 1.

Table 1 : Common presenting symptoms and physical findings in HCC

Findings	Average incidence (%)
A. Symptoms	
a. Abdominal pain	91%
b. Abdominal swelling	43%
c. Weight loss	35%
d. Weakness	31%
e. Feeling of fullness and anorexia	27%
f. Vomiting	08%
g. Jaundice	07%
B. Physical Examination	
a. Hepatomegaly	89%
b. Spleenomegaly	65%
c. Ascites	52%
d. Jaundice	41%
e. Fever	38%
f. Hepatic bruit	28%

Paraneoplastic syndromes are associated and are as given in Table 2.

Table 2 : Paraneoplastic syndromes in HCC

- Erythrocytosis
- Hypercalcemia
- Hypoglycemia
- Carcinoid syndrome
- Dysfibrinogenemia
- Cryoglobulinemia
- Hypercholesterolemia
- Polymyositis
- Acquired porphyria
- Dysfibrinogenemia
- Cryofibrinogenemia
- VIP associated diarrhea
- Thyrotoxicosis
- Osteoporosis
- Thrombophlebitis migrans

Surveillance of HCC

Surveillance for HCC is widely practiced and can generally be recommended at risk groups. HCC detected after the onset of symptoms has a dismal prognosis (5-year survival of 0%-10%) in contrast to small HCC, which can be cured with appreciable frequency. Since major advances in our ability to treat HCC are less likely to come from treating end stage disease, it is therefore important to detect the disease at an early stage. Accordingly, patients at high risk for developing HCC should be entered into surveillance programs; and patient on the transplant waiting list should be screened for HCC because failure to screen for HCC means that patients may develop HCC and progress beyond listing criteria without the physician being aware.

Surveillance is recommended for the following groups of patients

Table 3 : Group of patients needing surveillance

A. Hepatitis B carriers
Asian males ≥ 40 years
Asian females ≥ 50 years
All cirrhotic hepatitis B carriers
Family history of HCC
African ethnicity and age > 20 years

For non-cirrhotic hepatitis B carriers not listed above, the risk of HCC varies depending on the severity of the underlying liver disease and current and past hepatic inflammatory activity. Patients with high HBV/DNA concentrations and those with ongoing hepatic inflammatory activity remain at risk of HCC.

B. Non-hepatitis B cirrhosis
Hepatitis C
Alcoholic cirrhosis
Genetic hemochromatosis
Primary biliary cirrhosis

Although the following groups have an increased risk of HCC no recommendations for or against surveillance can be made because of lack of data precludes an assessment of whether surveillance would be beneficial

Alpha1-antitrypsin deficiency
Non-alcoholic steatohepatitis
Autoimmune hepatitis

Surveillance Tests and Interval

Surveillance of HCC should be performed using ultrasonography (USG) and alpha-fetoprotein (AFP). AFP alone should not be used for screening unless ultrasound is not available. Patients should be generally screened at 6 to 12 months interval and the interval need not be shortened for patients at a higher risk of HCC.

Diagnosis of HCC

Anyone with chronic liver disease whose clinical profile and/or hepatic function status is declining should be assessed for HCC. The most common presenting features are abdominal pain with detection of an abdominal mass in the right upper quadrant. A friction rub or bruit may be heard over the liver.

1. **Basic laboratory evaluation**: It should include a complete blood count, blood chemistry, transaminase levels, albumin levels and prothrombin time. Jaundice is rare, unless significant deterioration of liver function or mechanical obstruction of the bile duct occurs. Serum elevations of alkaline phosphatase and cholesterol (11-38% of pt) are common. Paracentesis should be performed if imaging studies or physical examination reveals ascites. Bloody ascites is found in 20% of patients with hepatocellular carcinoma and during paracentesis, fluid can be obtained for cytological evaluation.
2. **Tumor Markers**: Alpha-fetoprotein levels > 500 mg/L are found in about 70-80% of patients with HCC. Two third of HCCs less than 4 cm however have AFP levels less than 200 ng/ml and up to 20% of HCC do not produce AFP, even when very large. High levels of serum AFP (>500-1000 µg/L) in an adult with liver disease and without an obvious gastrointestinal tumor strongly suggests HCC. Besides AFP, other markers elevated in HCC include Des-Gamma-Carboxy prothrombin, ß-HCG (ß-Human Chorionic Gonadotropin) and alpha-fucosidase.
3. **Imaging Studies**: Imaging modalities used to detect liver tumors include ultrasound, CT-Scan, MRI and Hepatic artery angiography. Ultrasound is frequently employed to screen high-risk populations and should be the first procedure if HCC is suspected. It is less costly than CT/MRI scans, is relatively sensitive and can detect most tumors > 3cm. Helical CT and MRI (Hyperintense T2- weighted imaging) scans are being used with increasing frequency and have higher sensitivities. Currently emerging studies support multiple phasic abdominal CT as the imaging procedure of choice, despite current high costs and limited availability. Magnetic resonance imaging is less sensitive than angiographically assisted helical CT in diagnosing HCC

and is currently used to further characterize the disease within a nodular liver.

4. **Liver Biopsy**: Percutaneous liver biopsy can be diagnostic if the sample is taken from an area localized by ultrasonography or CT. The risks for liver biopsy include hemorrhage and seeding the needle track with malignant cells.

Thus, the basic tests commonly used to diagnose HCC include radioimaging, biopsy and AFP serology.

The sequence of the tests used for the diagnosis depends upon the size of the lesion.

a) Lesions > 2 cm in diameter

Detection of a hepatic mass within a cirrhotic liver is highly suspicious of HCC. If AFP is greater than 200 ng/ml and the radiological appearance of the mass is suggestive of HCC, the likelihood of HCC is higher and biopsy is not essential (2,3).

Higher chances of HCC are there if

a) Patient has cirrhotic liver.

b) Lesion > 2 cm.

c) Large and multifocal disease.

d) Arterial hypervascularity is present.

The European association for the study of liver disease (EASL) conference has recommended that the diagnosis of HCC can be made without biopsy in patients with cirrhosis who have a mass > 2 cm, that shows characteristic arterial vascularization that is seen in two imaging modalities i.e. triphasic CT scan and MRI (4). If the vascular profile on dynamic imaging is not characteristic and the AFP is less than 200 ng/ml a biopsy is recommended.

b) Lesions 1-2 cm in diameter

Lesions between 1-2 cms in a cirrhotic liver found during surveillance have a high likelihood of being HCC. Lesions between 1-2 cm found on USG screening of cirrhotic liver should be investigated further with two dynamic studies. The EASL conference recommended that these lesions should be biopsied irrespective of their vascular profile (4). A high rate of diagnosis of HCC is found when small lesions found on ultrasound are biopsied. Recently a distinction has been made between "very early HCC" and "small HCC". Early HCC as defined by Japanese pathologist is generally hypervascular and has ill-defined margins. In contrast, small HCC have well defined margins on ultrasound and exhibit the typical patterns of HCC on CT and histology.

c) Lesions < 1 cm in diameter

Lesion < 1 cm on ultrasound, particularly in a cirrhotic liver has a low likelihood of being HCC.

Staging and Prognosis

Accurate staging is critical for determining the prognosis and therapeutic approach in HCC. Historically, HCC has been classified by the TNM or Okuda staging (5). Recently Marrero et al (6) and Grieco et al (7) have compared all the systems available and validated the Barcelona-Clinic Liver Cancer (BCLC) Staging System. It includes variables related to tumor stage, liver function status, physical status and cancer related symptoms. The main advantage of BCLC staging system is that it links staging with treatment modalities and with an estimation of life expectancy.

Based on BCLC staging system hepatocellular carcinoma can be classified into following stages:

Early Stage Disease: It includes

a) Preserved liver function (Child Pugh A or B)

b) Solitary HCC or upto 3 nodules = 3 cm in size

The 5-year survival of these patients ranges from 50-75%. These patients can be effectively treated by resection, percutaneous ablation and liver transplantation with a possibility of a long-term cure.

Intermediate Stage:

It consists of Child Pugh A and B with large/multifocal HCC who do not have

a. cancer related symptoms

b. macrovascular invasion or extrahepatic spread

The 3-year survival of these patients may reach 50%. These are ideal candidates for transarterial chemoembolization.

Advanced Stage:

Patients who present with

a. cancer symptom

b. cancer symptom and/or with extrahepatic spread

are included in the advanced stage. These patients have a shorter life expectancy (<50% survival at one year) and are candidates to enter therapeutic trials with new agents.

End Stage

Patients with extensive tumor involvement and/or major impairment of liver function are considered end stage with medium survival of less than 3 months.

Prognosis of HCC

For best assessment of prognosis of HCC, the staging system should take into account tumor stage, liver function, physical status and the response to treatment when estimating life expectancy. Currently the BCLC system is the only staging system that accomplishes these aims.

Treatment of Hepatocellular Carcinoma

A. Curative Treatment:

I. Surgical Resection

Patients who have single lesion can be offered surgical resection, if they are non-cirrhotic or have cirrhosis but still have well preserved liver function, normal bilirubin and hepatic vein pressure gradient < 10 mmHg. Pre or post resection adjuvant therapy is presently not recommended.

II. Liver Transplantation

Liver transplantation is an effective option for patients with HCC corresponding to the Milan criterion i.e. solitary tumor ≤ 5 cm or upto three nodules < 3 cm (8). The 5-year survival of these early stage patients exceeds 70%. Living donor transplantation can be offered if the waiting time is long.

III. Percutanous Ablation Therapy

Patients who are not candidates for transplant or resection due to inadequate liver reserve, large or multiple lesions in multiple lobes, fibrosis or cirrhosis can benefit from minimally invasive ablation therapy. These therapies use either extreme heat or cold to destroy liver tumors.

It is usually done under ultrasound guidance using percutaneous ethanol injection (PEIT) or radiofrequency ablation. The ideal patient for radiofrequency invasive ablation therapy generally has not more than three lesions and that are not greater than 5 cm in size. Local ablation is safe and effective therapy for patients who cannot undergo resection or as a bridge to transplantation. Alcohol injection and radiofrequency are equally effective for tumor < 2 cm. However, the necrotic effects of radiofrequency are more predictable in all tumor sizes and in addition, its efficacy is clearly superior to that of alcohol injection in larger tumor.

B. Non curative Treatment:

I) Transarterial Embolization and Chemoembolization (TACE)

TACE is recommended as a first line non-curative therapy for non-surgical patients with large/multifocal HCC who do not have vascular invasion or extrahepatic spread (9). The response rates for HCC are 60-80% with an average duration of one year. This therapy can be repeated multiple times before transplantation with excellent disease free survival. This techniques combines selective arteriography precise targeting), chemotherapeutic drugs (produce necrosis), Lipoidal agents (concentrates chemo drugs) and embolization (produces ischemia, prevent washout). Complications can occur in form of postembolization syndrome (Fever, chill, abdominal pain, nausea, vomiting and leukocytosis) and transient (but occasionally irreversible) hepatic decompensation. Variation of TACE in form of theraspheres (using Glass Microspheres) and Iron/activated charcoal can also be used. Future evolution of TACE includes

anti vascular endothelial growth factor (VEGF) antibodies in combination with TACE.

II) Chemotherapy

No conventional chemotherapy is considered effective. The best single agent is doxorubicin with response rates of 10-15%. More aggressive combination regimes show no improvement in response rates and may even produce reduction in survival of treated patients.

III) Role of Radiotherapy

Standard Radiotherapy is ineffective, as liver does not tolerate radiation. Novel approaches, which may limit liver injury, include proton beam radiotherapy, carbon ion radiotherapy and intensity modulated radiotherapy are being tried.

C. Treatments not recommended

Tamoxifen, antiandrogens, octreotide, hepatic artery ligation / embolization of systemic or selective intra-arterial chemotherapy are not recommended. In addition radiolabelled Yttrium glass beads, radiolabelled lipoidal or immunotherapy cannot be recommended as standard therapy for advanced HCC outside clinical trial.

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