

## HEPATOCELLULAR CARCINOMA

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### **Disease Epidemiology**

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver. It represents the fifth most common cancer and the third most common cause of cancer death worldwide(4). It has a variable geographical distribution around the world. The incidence in developing countries is two to three times higher than in Western countries. For example, in Eastern Asia and Middle Africa the age-adjusted incidence rate (AAIR) ranges from 20-28 cases per 10,000 in men while it is about 1-3 per 100,000 in Northern Europe, Australia and North America. In the United States the incidence of HCC has increased from 1.4 per 100,000 population at the period from 1976-1980 to 2.4 per 100,000 population for the period from 1991-1995.

In Saudi Arabia, according to the National Cancer Registry, liver cancer accounts for 6.1% of all newly diagnosed cancers according to the most recent cancer registry covering the years 1999-2000. HCC was the second most common cancer affecting Saudi males and the eighth most common cancer affecting females with an overall age standardized rate is 4.5/100,000 population. Male to female ratio is 279:100. Of all liver cancers in Saudi Arabia, hepatocellular carcinoma accounts for 87.6% in Saudi Arabia. The median age at diagnosis is 65 years for males and 60 years for females.

This incidence of HCC in Saudi Arabia is not surprising given the high prevalence of the two major risk factors, namely hepatitis B and hepatitis C infections. In the large epidemiologic study by Al Faleh et al, 7% of Saudi children were found to be positive for HBsAg. Not until universal vaccination was applied in Saudi Arabia did this prevalence rate decrease to less than 0.3%. Since the initial epidemiologic studies showing high prevalence of hepatitis B were done on children who are now adults and with an estimation that about 20% of these patients will probably develop cirrhosis with an annual risk of 1-4% for HCC, the incidence of HCC is expected to increase dramatically in the Kingdom in the next 30 years. Hepatitis C is also common in Saudi Arabia with a prevalence rate of 1-3% of the population, which further increases the risk of HCC. More recently, the incidence of hepatitis C seems to have decreased to about 1.1%.

### **Risk Factors**

The development of cirrhosis is the major risk factor for the development of HCC regardless of the cause. The annual incidence of HCC in patients with compensated cirrhosis is about 3%.

Hepatitis B is considered the strongest epidemiologic factor associated with HCC in the majority of countries but more importantly in Asia and Africa. The carrier state of hepatitis B early in life carries a lifetime relative risk of developing HCC of over 100, while the annual incidence of HCC in hepatitis B patients with cirrhosis exceeds 2%. Hepatitis C is considered the most important risk factor for HCC in Western countries and Japan. Almost all HCC in patients with hepatitis C occurs in patients who have developed cirrhosis in which the yearly incidence varies between 3 to 8 %. Other less likely risk factors include Aflatoxin B1 derived from *Aspergillus flavus* and *Aspergillus parasiticus* which is an important risk factor for HCC in parts of Africa and Asia, hereditary hemochromatosis and Wilson's disease. Because of the significant increase in the prevalence of diabetes and obesity, it is estimated that non alcoholic fatty liver disease may be an important risk factor for development of HCC in the future.

### **Presenting Signs and Symptoms**

The classic features of HCC include right upper quadrant pain and weight loss. Weakness, abdominal swelling, nonspecific gastrointestinal symptoms, and jaundice are other presenting features. Special clinical scenarios should raise the suspicion of HCC. This includes acute deterioration of liver function in a patient with stable cirrhosis, new onset ascites, and acute intra-abdominal bleeding.

Physical findings vary according to the stage of the disease. If the tumor is small, no signs may be found except those related to cirrhosis. In more advanced disease, hepatomegaly is common with a possibility of feeling a mass or a hard irregular liver surface which may be tender. A bruit may be heard on the liver. Ascites is often found, most commonly as a result of the underlying cirrhosis leading to portal hypertension but rarely due to tumor invasion of the peritoneum. Muscle wasting is common and is usually progressive.

### **Screening Methods**

#### **Abdominal Ultrasound (US)**

While US has the advantage of being safe, commonly available, and cost-effective, its main disadvantage is its low specificity and its operator dependent nature. Newly discovered focal liver masses in patients with liver cirrhosis has a high likelihood of being HCC. Abdominal US is associated with a sensitivity and specificity of 20-51% and 92-96%, respectively for detecting lesions consistent with HCC in patients with cirrhosis. Detection rates for lesions between 2 and 3 cm and 1 and 2 cm with US are estimated to be as low as 20 and 13%, respectively. In spite of the limitations of US in diagnosing HCC, due to its low cost, safety, and availability, it is still considered the best first test to be performed when HCC is expected.

Triphasic CT scan of the liver as well as MRI are the diagnostic tests of choice in patients with HCC. Some studies are utilizing these tests in screening purposes as well especially in high risk patients but high cost and radiation, in case of CT, are significant limiting factors.

#### **Serum Alfa fetoprotein (AFP)**

AFP is an alfa 1 globulin that is normally present in high concentrations in fetal serum but in only minute concentrations in adults. Reported sensitivities are around 39-65%, specificities around 76-94%, but a poor positive predictive value of 9-50%. In a recent systematic review it was confirmed that AFP has a poor diagnostic ability to detecting HCC at any level of pretest risk. However, as a confirmatory test in patients with a mass on imaging studies, AFP determination remains clinically useful. AFP elevation lower than 500 ng/mL may be seen in patients with active necroinflammatory changes in the liver secondary to active hepatitis. A progressively rising AFP level even at low concentrations is highly suggestive of HCC. Elevations above 1000 ng/mL have a high specificity rate.

Other tumor markers are under investigation but none is ready for clinical use yet. These include Des-γ-carboxy prothrombin and alfa-l-fucosidase.

### **Summary of Management**

Different treatment modalities are available for patients with HCC. The decision on the best treatment modality should be based on the following factors:

- The number of lesions
- The size of lesions
- The status of the underlying liver
- The status of the portal vein
- The patient's performance status
- The local expertise
- The patient preferences

Current available modalities include: liver transplantation, tumor resection, alcohol ablation,

radiofrequency ablation, chemoembolization, radioembolization, chemotherapy or targeted therapy (Sorafenib).

The approach for the management of HCC must be multi disciplinary where oncology, hepatology, liver transplantation, liver surgery, interventional radiology, and palliative care specialists are involved.

## **Prevention**

### **Vaccination programs**

Vaccination is a very powerful measure to reduce the infection rate with hepatitis B and hence reduce the incidence of HCC. The nationwide hepatitis B vaccination program launched in Taiwan in 1984 led to a reduction of the hepatitis carrier rate in children from 10% to less than 1% and to a reduction in the incidence of HCC from 0.70 to 0.36 per 100,000 between 1986 and 1994. In Saudi Arabia, a routine hepatitis B vaccination of children was added as part of the extended program of immunization in 1989. A dramatic reduction was noted in the prevalence of hepatitis B from 6.7% in 1989 to 0.3% in 1997. No evidence is available yet on the effect of this reduction on the incidence of HCC.

### **Treatment of viral hepatitis**

If cirrhosis is the most important risk factor for the development of HCC, could the incidence of HCC be reduced by preventing cirrhosis or treating cirrhosis due to viral hepatitis with antiviral therapy? Many studies in hepatitis B and hepatitis C show that treatment of active hepatitis, especially when successful, may lead to a reduction in the incidence of HCC.

### **Screening**

Although many modeling data exist suggesting that screening can reduce HCC related disease specific mortality in a cost effective manner, there is only one randomized trial showing benefit while many other studies didn't. In the study showing benefit from China, 18,816 patients were screened with 6 monthly AFP and ultrasound showing a reduced mortality rate by 37% in the screened arm even though the adherence to the surveillance was only around 60%. The screened population in this study was patients with current or previous exposure to hepatitis B.

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Patients who are best candidates for enrollment in a screening program include patients with cirrhosis for whatever reason. Patients who have hepatitis B without cirrhosis, especially if above 45 in age or have a family history of HCC may also be candidates.

Most authorities (including the Saudi Gastroenterology Association) suggest screening with abdominal ultrasound and AFP every 6 months. Once a lesion is detected then a triphasic CT or contrast enhanced MRI is indicated for confirmation. In case of patients with cirrhosis who have a lesion larger than 2 cm detected by a contrast radiological study showing early arterial enhancement and rapid venous washout this is diagnostic for HCC and no further testing is recommended. If the lesion is less than 2 cm or the patient is not cirrhotic then a biopsy is indicated for confirmation.

### **Outcome**

The natural history of HCC depends on the stage of the disease but is poor in the majority of cases. Tumor size at presentation is an important factor in the natural history but its use as a sole predicting factor is hindered by the fact that this tumor doubling time may in fact be very variable. In some patients the tumor growth is slow doubling in size in twenty months or more, while in others the tumor grows much faster and doubles in less than 1 month. In symptomatic patients in China and Africa, death usually occurs within four months, while some reports suggest a longer survival and a more indolent course in Western countries. The most important factor in determining the natural history of HCC patients is the stage of the underlying liver disease.

## Recommendation of Hepatocellular Carcinoma Prevention and Early Detection

Population	Category	Recommendation
Primary Prevention	General population Patients with hepatitis	- Hep B vaccination - Prevention of hepatitis - Avoidance of alcohol - Treatment of hepatitis
Patients with cirrhosis	Early detection	Alpha fetoprotein and liver ultrasound every 6 months

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