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Epidemiology, risk factors and surveillance of hepatocellular carcinoma

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Abstract. – Hepatocellular carcinoma (HCC) is a challenging malignancy of global importance, it is associated with a high rate of mortality and its prevalence in the United States and in Western Europe is increasing. Cirrhosis is the strongest and the most common known risk factor for hepatocellular carcinoma, particularly cirrhosis related to hepatitis C virus (HCV) and hepatitis B virus (HBV) infections. The stage of cancer dictates the therapeutic choice, making early detection a primary objective. Early diagnosis of hepatocellular carcinoma is feasible because HCC develops in the background of well-known, readily identifiable and potentially avoidable environmental risk factors. Many observational studies have reported that HCC is diagnosed at an earlier stage in patients who received surveillance. Current guidelines advocate the use of abdominal ultrasound (US) at 6-12 months frequency to screen for HCC in high-risk patients. The use of AFP alone is strongly discouraged, and its use in addition to US is controversial. Patients with abnormal screening tests require additional investigation. Although the optimal methods of screening and the cost-effectiveness of surveillance for HCC remain to be established, systematic screening still offers the best hope for early diagnosis, treatment eligibility, and improved survival.

Key Words:

Hepatocellular carcinoma, Risk factors, Screening, Surveillance.

Introduction

Hepatocellular carcinoma (HCC) is a challenging malignancy of global importance. It is the sixth most common cancer, and the third most common cause of cancer-related death worldwide[1]. HCC accounts for between 85% and 90% of primary liver cancers. The geographic distribution of HCC is highly uneven: three geographic areas with different incidence rates (low, intermediate, and high) have been recognized. North America and Western Europe are generally considered to be low-incidence regions but in these regions the incidence of HCC is rising.

In oncology cancer prevention may be categorized as primary or secondary.

Primary prevention refers to the identification of genetic, biologic, and environmental factors that are etiologic or pathogenetic and subsequent alteration of their effects on tumor development. *Secondary prevention* refers to identification existing preneoplastic and early neoplastic lesions and to treat them thoroughly and expeditiously.

The stage of cancer dictates the therapeutic choice, making early detection a primary objective. The goal of cancer screening is to reduce mortality through a reduction in incidence of advanced disease.

Because symptomatic HCC seldom is amenable to radical cure and respond poorly to conservative treatments, a pressing need exists either to prevent the tumor or to diagnose it at early or very early stage, when curative treatments, as surgical resection, liver transplantation or percutaneous ablation, are still possible[2].

Risk Factors of HCC

Surveillance is not recommended for the general population given the low overall rate of HCC.

So, one of the important aspects of establishing a screening program for HCC is to define the at-risk population.

Generally, HCC develops on a background of chronic liver disease or inflammation and cirrhosis in 70-90% of all cases. All risk factors for liver cirrhosis play a role in the hepatocellular carcinogenesis and liver cirrhosis *per se* is a precancerous condition[3].

Major causes of cirrhosis in patients with HCC include hepatitis B, hepatitis C, alcoholic liver disease, and possibly nonalcoholic steatohepatitis. Less common causes include hereditary hemochro-

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matosis, α-1 antitrypsin deficiency and autoimmune hepatitis.

Because accurate serologic tests are available to detect viral hepatitis, and the presence of cirrhosis often is known in advance, patients at risk for HCC are readily identifiable.

HBV is the leading cause of HCC worldwide, particularly in Asia and Africa. Population in which HBV is endemic have high incidence rates of HCC. 70-90% of HBV-associated HCC develop in the setting of liver cirrhosis, but even in the absence of cirrhosis the infection is an important risk factor[4].

Hepatitis C infection is the main risk factor in Western countries and Japan. HCV increases the risk of HCC by promoting fibrosis and cirrhosis. In general, HCC develops only after two or more decades of HCV infection, and the increased risk is largely restricted to patients with cirrhosis or advanced fibrosis.

Markers of HCV infection are found in a variable proportion of HCC cases in Europe, with an increasing gradient from north to south. In some geographic regions, HCV has been shown to be the sole etiologic factor behind increases in the incidence of HCC[5].

HCC risk can further increase in the presence of cofactors known to accelerate progression of HCC like aflatoxin B1 in HBV carriers, and alcohol consumption[6], iron and overweight in hepatitis C virus (HCV) carriers.

Obesity and metabolic syndrome are considered risk factors for the development of nonalcoholic steatohepatitis (NASH) and NASH-related cirrhosis, and probably contribute to the increased prevalence of HCC[7,8]. Given the continuing increase in the prevalence of obesity and diabetes, the incidence of NASH-related HCC can also be expected to increase[9].

The at-risk groups according different guidelines[10,2,11] are identified in Table I.

The Screening and Surveillance Strategies

Surveillance tools include tumor marker assessment and US examination.

Ultrasound is the method of choice for screening, because it has adequate sensitivity, specificity, positive and negative predictive values[2].

A recent study generally indicates a >60% sensitivity, and >90% specificity when US is used as a screening test[12].

Tumor markers have been used widely and evaluated as a potential diagnostic tool, while their usefulness as for screening tool is less characterized. The most widely established tumor marker is alpha-fetoprotein (AFP). However, the serum assay AFP is no longer considered for screening and surveillance by AASLD[2] and EASL[10] because of the high rates of false-positive and false-negative results in patients with chronic liver disease.

The demonstration of the benefits of a surveillance policy should be derived from a randomized controlled investigation comparing surveillance versus no surveillance.

Table I. Groups of patients for whom HCC surveillance is recommended according to several Guidelines.

Guideline (year)	Chronic hepatitis	Cirrhosis
EASL (2001)[10]	HBV: not specified HCV: histological transition to cirrhosis	Child-Pugh A without any severe associated condition Child-Pugh B: controversial Child-Pugh C if LT is a treatment option
AASLD (2005)[2]	Asian males ≥ 40 years Asian females ≥ 50 years Family history of HCC Africans over age 20 Patients with high HBV DNA concentration and those with ongoing hepatic inflammatory activity HCV: controversial	Cirrhotic hepatitis B carriers Hepatitis C Alcoholic cirrhosis Genetic hemochromatosis Primary biliary cirrhosis Alpha1-antitrypsin deficiency Non-alcoholic steatohepatitis Autoimmune hepatitis
JSH (2007)[11]	High-risk population – Chronic hepatitis B – Chronic hepatitis C Increasing risk: alcohol	Super-high-risk population – Hepatitis B-related liver cirrhosis – Hepatitis C-related liver cirrhosis High-risk population Liver cirrhosis (causes other than hepatitis B or C virus)

There is a single, randomized control trial assessing the benefits of surveillance. It included Chinese patients with hepatitis B virus (HBV) infection and, despite several limitations (heterogeneity of the population, lack of adherence, lack of uniform treatment approach), survival was significantly improved in the surveillance cohort[13].

The remaining data supporting the benefits of surveillance for HCC in patients with cirrhosis come from cohort investigations and similar suboptimal assessments[12,14-18].

These studies suggest that survival is improved in patients who received surveillance. The studies focused on populations with variable baseline risk for HCC, used different surveillance methods, variable endpoints and reference standards. Thus, comparison among them is difficult. Furthermore, most have been observational and thus subject to several biases (such as lead time bias), leaving substantial uncertainty as to observed benefits. However, it is widely acknowledged that a proper randomized control trial is not feasible in settings where health care is of adequate quality.

A recent systematic review suggests that AFP is a better screening test for small HCC than ultrasound[19]. This is contrary to clinical experience, where it is unusual to find an elevated AFP in patients with lesions in the range of 1 to 2 cm in size (the size of lesion that should be identified by screening). Nevertheless, the analysis suggests that HCC screening is effective and cost-effective, although the authors found that adding US to AFP screening increased the cost considerably.

Surveillance Interval

The ideal surveillance interval is not known. A screening interval of 4 to 12 months has been proposed on the basis of tumor doubling times[20,21].

A multicenter retrospective study, conducted on 1051 consecutive patients with hepatocellular carcinoma, has demonstrated that survival, cancer stage and frequency of ablative treatments or chemoembolization are no different in patients screened at 6- or 12-monthly intervals[22].

A study in haemophiliacs chronically infected with HCV demonstrated similar efficacies for 6- and 12-month intervals of screening in the identification of potentially curable HCC[23].

Otherwise, two recent studies both published as abstracts, showed that semiannual surveillance resulted in the detection of HCC at an earlier stage[24,25], and improved survival compared to annual surveillance[25].

A recent randomised trial aimed at comparing two periodicities of surveillance (3 months vs. 6 months) in 1200 cirrhotic patients concluded that ultrasound-based screening performed every 3 months does not improve the diagnosis and treatment of small HCC[26].

Clearly, additional prospective studies are needed to validate the surveillance interval.

Conclusions

Hepatocellular carcinoma is an important public health problem with available screening tests, effective treatments, and a subclinical phase in identifiable high-risk groups of patients with cirrhosis and viral hepatitis. The disparity in outcomes between patients diagnosed with an early HCC compared with those with a more advanced tumour strongly supports screening for HCC. Although the optimal methods of screening and the cost-effectiveness of surveillance for HCC remain to be established, systematic screening still offers the best hope for early diagnosis, treatment eligibility, and improved survival.

At this moment we think is correct to follows the American Association for the Study of Liver Diseases Guidelines[2] suggestions: (1) surveillance for HCC should be performed using ultrasonography; (2) AFP alone should not be used for screening unless unless ultrasound is not available; (3) Patients should be screened at 6 to 12 month intervals; (4) the surveillance interval does not need to be shortened for patients at higher risk of HCC.

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