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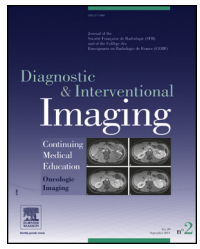

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Hepatocellular carcinoma in 2014: Current situation and future prospects

J.-C. Trinchet[a,b,c,*]

[a] *Department of Hepato-Gastroenterology, Jean-Verdier Hospital, AP—HP, avenue du 14-Juillet, 93140 Bondy, France*
[b] *Paris Public Hospitals Health Service and Research and Training Unit SMBH - Paris 13 University, Bobigny, France*
[c] *INSERM U674/UMR-1162, Paris, France*

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Abstract The leading causes of chronic liver disease associated with HCC are hepatitis B and C viruses throughout the world, and alcohol and NASH in France. After increasing for 20—30 years in France, the rise in the incidence of HCC appears to be slowing and the death rates appear to be falling. Screening for HCC by liver ultrasound is performed every 6 months. Assay of serum alpha-fetoprotein has no benefit. In developed countries, failure to identify patients with cirrhosis and inadequate adherence to guidelines greatly reduces the effectiveness of screening for HCC.

Epidemiology and risk factors

Epidemiology

HCC almost always develops in patients suffering from chronic liver disease, usually at the cirrhotic stage. Its epidemiology is therefore closely related to that of the causes of cirrhosis [1]: chronic viral hepatitis B (HBV) and C (HCV) infections, excessive alcohol consumption and nonalcoholic steatohepatitis (NASH).

Viral causes predominate throughout the world and approximately 80% of cases of HCC are found in areas where HBV is highly endemic (Asia and Africa), often associated with ingestion of aflatoxin B1, a potently carcinogenic mycotoxin. The incidence of HCC should be reduced by improving storage conditions for cereals and large-scale vaccination of newborns against HBV. This vaccination was set up in Taiwan almost 30 years ago and has produced a spectacular fall in the number of cases of HCC

* Corresponding author at: Department of Hepato-Gastroenterology, Jean-Verdier Hospital, avenue du 14-Juillet, 93140 Bondy, France.
E-mail address: jean-claude.trinchet@jvr.aphp.fr

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in children and young adults [2]. The epidemiology of HCC is very different in France, as the main cause of cirrhosis and HCC (two-thirds of cases) is excessive alcohol consumption [1]. NASH is increasingly responsible because of the increased prevalence of obesity and diabetes. The number of cases of NASH-related HCC currently appears to be similar to the number associated with HCV [3].

Although the incidence of HCC appears to be falling in Africa and Asia, the same does not apply in the Western world, where both its incidence and mortality rates have increased greatly over recent years. This rise appears to be due to patients infected with HCV in the 1970—1980s reaching the cirrhotic stage and to the reduction in mortality from the other complications of cirrhosis (gastrointestinal bleeds and bacterial infection) leaving patients exposed for longer to the risk of developing HCC [1].

Risk factors

Cirrhosis, regardless of its cause, is the main risk factor for HCC with an individual risk of 2 to 6% annually, which is influenced by many other factors [4]. Risk is greater in patients with HCV cirrhosis than in those with alcoholic or HBV cirrhosis. The risk from similar viral causes is higher in Asia than in the Western world and is also influenced by sex (male), age (> 55-years-old), severity of the liver disease, serum alpha-fetoprotein (AFP) concentration, and comorbidities (alcohol, obesity, diabetes and HIV). Simple clinical and laboratory scores can be used to separate patients suffering from cirrhosis into several groups at very different risks of HCC [1].

If cirrhosis is not present, the risk of developing HCC is extremely low in alcoholic and HCV disease and higher for HBV and NASH (40% of cases) [5].

Screening

Only a small HCCs (Milan criteria: a single nodule under 5 cm in diameter or 2 to 3 nodules under 3 cm in diameter) are amenable to curative treatment. As the tumors are asymptomatic, they need to be screened for by periodic monitoring in at risk patients [6].

Academic studies

These have clarified the screening methods [6]. The major target is patients suffering from cirrhosis regardless of cause, alcohol, HCV, HBV and NASH, and those with inherited hemochromatosis, autoimmune hepatitis and primary biliary cirrhosis. As the aim is to offer curative therapy, patients with contraindications to this are not therefore affected. Whilst there are many contraindications to surgery (transplantation and resection), percutaneous ablation therapies can be used in a large number of patients. Screening is not indicated if the cirrhosis is decompensated as the major prognostic indicator in this situation is the severity of the cirrhosis, unless the patient is awaiting transplantation, in which development of an HCC changes the transplant allocation rules.

Screening for HCC is still based on a standard liver ultrasound performed every 6 months [6]. There is no evidence to shorten this period, which is based on the aggressive nature of the tumor and not on actual risk [7]. Measurement of AFP is of little benefit as the majority of small HCC are not associated with a rise in serum AFP concentrations. If a focal lesion is found on screening, diagnostic investigations need to be performed with enhanced CT and/or MRI and possibly a guided biopsy. Unlike other solid tumors, HCC can be diagnosed without histological evidence (probabilistic diagnosis), if imaging shows typical appearance (hypervascularized nodule in the arterial phase with washout in the portal and/or late phase) [6]. This typical appearance is only rarely found if the nodule is small (under 10 mm in diameter). This is an important limitation as small nodules currently account for up to 40% of focal lesions found on screening [7]. If the nature of the nodule has not been established, it is essential to continue monitoring to detect any increase in size. Ultrasound cannot be performed in 10% of patients (because of obesity), in which case MRI is recommended.

Periodic screening detects up to 75% of tumors at a stage, which is amenable to curative treatment [7]. One randomized trial (of poor methodological quality) has shown improved survival in patients who were screened [8]. Interestingly, survival in patients undergoing the same screening methods increased over time, probably due to more effective curative therapy [9].

Studies in the general population

As in other countries, screening for HCC is not used sufficiently in France. One recent French study (the Changh observational study) showed that only 25% of patients received curative treatment and that only 20% of patients were screened before the diagnosis of their cancer [3], in contrast to the findings from the academic studies.

The effectiveness of screening relies on several successive stages: identification of patients suffering from cirrhosis, screening of these patients for HCC using recommended methods and the appropriate use of curative treatments. Identifying patients suffering from compensated cirrhosis, who are usually asymptomatic, can be facilitated by 'non invasive' methods such as blood tests (Fibrotest®, Fibromètre®) and the Fibroscan®. Even when cirrhosis is found, periodic screening appears to be used inappropriately: almost 40% of patients suffering from HCC have not had appropriate screening despite the fact that their cirrhosis was known [10], probably because of doctors not being aware of guidelines or being sceptical about the effectiveness of screening. The Changh study results also suggest that percutaneous ablation is still underused, as the proportion of patients treated with this method (which has few contraindications) was similar to the proportion of patients undergoing resection or transplantation (which have many contraindications) [3].

Treatment

The indications for treatment depend on the size and extension of the tumor, the condition of the non-tumor liver