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EDITORIAL

Autoimmune Hepatitis, Cirrhosis, and Hepatocellular Carcinoma (HCC)

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Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the third most common cause of cancer death. The success of treatment for HCC largely depends on the stage at which it is diagnosed, with 5-year survival rates of 70–75% in patients with compensated cirrhosis and early HCC [1–4]. As HCC usually arises in individuals with the clearly defined underlying risk factor of chronic liver disease, a focus on early detection through screening and surveillance programs in individuals with proven cirrhosis had been adopted by most clinicians [5, 6] despite an initial lack of supportive evidence. A randomised controlled trial of surveillance versus no surveillance performed in China in 2004 recruited nearly 19,000 patients having markers of current or past hepatitis B infection. Despite poor compliance, the HCC-related mortality in the surveillance arm was reduced by 37% [7]. It is not clear, however, whether screening is appropriate and cost effective for all aetiologies of cirrhosis.

The decision to enter a patient into a surveillance program is dependant on the risk of HCC development. There are a number of models which calculate cost-effectiveness dependant upon the incidence of HCC in a particular population, and the modality of screening used. A study published in 1996, which did not include orthotopic liver transplantation (OLT) as a treatment option, found that if the incidence of HCC was 1.5% per year, surveillance resulted in an increased longevity of approximately 3 months. If the incidence was 6% per year, the survival was increased to 9 months [8]. Using a similar analysis, Arguedas et al. [9] found that surveillance with computed tomography (CT) scanning (either alone or in combination with ultrasound) became cost effective when the incidence of HCC was greater than 1.4%. A more recent study published in 2004 by Lin et al. [10] demonstrated that surveillance with ultrasound (US) and alpha-fetoprotein (AFP) is cost effective regardless of HCC incidence. The cost-effectiveness largely depends on the outcomes of treatment, and so studies like the Chinese program, which lacked access to OLT, are not necessarily relevant to other centers where transplantation is the first-line treatment for patients with cirrhosis and a small tumour. The incidence of HCC in cirrhosis caused by non-viral aetiologies is still not accurately established due to many preliminary studies being performed prior to the discovery of the hepatitis C virus. Current guidelines of the American Association for the Study of Liver Diseases (AASLD) suggest that surveillance should be offered when the risk of HCC exceeds 1.5%/year [5, 6].

The optimal interval for US surveillance is still controversial. The Clinical Practice Guidelines for Hepatocellular Carcinoma 2005 (Japan) recommends US surveillance with an interval of 6 months for patients at a risk of HCC and surveillance every 3–4 months in those at extremely high risk [11]. In contrast, the guidelines proposed by the American Association for study of Liver Diseases (AASLD) proposes that US be performed at 6-month intervals for all patients at risk of HCC regardless of the magnitude of risk but based on expected tumour doubling times. Although the retrospective study by Zhang et al. used a surveillance interval of 6 months, [7] several other studies report that the likelihood of finding HCC at the single nodule stage is no different between 6- and 12-month surveillance intervals [12, 13]. One non-randomised prospective study in patients with hepatitis B

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has demonstrated that survival is greater when surveillance intervals are shortened to 6 months as opposed to 12 months [14]. The AASLD guidelines state that instead of having separate guidelines between hepatitis B and hepatitis C, a single guideline for surveillance every 6 months is recommended [5, 6]. The decision to provide surveillance for HCC in the first instance is dependant on the magnitude of risk for its development. However, the surveillance interval is determined by the tumour growth rate, not by the degree of risk. This means that surveillance intervals need not be shortened for patients who are thought to be at higher risk and vice versa.

Autoimmune hepatitis (AIH) is recognised as a multisystem disorder that can occur in males and females of all age groups and may coexist with other liver diseases. Without treatment, patients have a mortality of 10 years from disease onset even if asymptomatic. Chances of survival are significantly improved with corticosteroid treatment and life expectancy of those in treated remission is similar to that of an age- and sex-matched control population [15]. HCC has traditionally been considered as a rare complication of AIH; however, the true incidence is unclear due to a paucity of published data. Recent data suggests that the risk of HCC in AIH with cirrhosis may be significant enough to warrant surveillance. Yeoman et al. [16] performed a prospective study evaluating 243 patients with AIH and 15 cases of HCC were diagnosed over a 16-year period, all of whom had underlying cirrhosis (median time from confirmed cirrhosis to diagnosis of HCC being 102.5 months). In contrast, Teufel et al. reviewed a cohort of 278 patients with AIH (89 with cirrhosis); the median period of follow-up was 4.8 years per patient. During this time, none of their patients developed HCC; however, three additional patients were referred to their center for management of HCC suspected to have arisen secondary to AIH with cirrhosis [17].

The study by Wong et al. [18] described in this issue of *Digestive Diseases and Sciences* finds that HCC in the context of underlying AIH is a rare event but does occur in those who have AIH-induced cirrhosis. Using the Organ Transplant Tracking Record (OTTR), 322 patients with AIH were observed over a 10-year period, 50 of whom were either cirrhotic at diagnosis or developed cirrhosis at a later date. Five patients in the cirrhotic group (1 of whom had an overlap syndrome between AIH and primary biliary cirrhosis; AIH post-treatment score 11) went on to develop HCC. A sixth patient is also described as having HCC detected simultaneously at time of diagnosis of AIH with cirrhosis. Diagnosis of HCC was made via radiological means (CT, magnetic resonance imaging or US) in all cases, histological confirmation being obtained in three patients. In this large study cohort, the overall estimated HCC risk was less than 0.2%; however, the prevalence among patients with cirrhosis due to AIH rose to 1.9%, comparable to the HCC risk in cirrhosis caused by viral hepatitis (see Table 1) [2]. The authors also note that AIH commonly affects women more than men, but despite this the occurrence of HCC was still comparable with other causes of cirrhosis.

Table 1 Groups for whom hepatocellular carcinoma (HCC) surveillance in recommended (in the context of established liver cirrhosis) or in whom the risk of HCC is increased, but in whom efficacy of surveillance has not been demonstrated [5, 6]

Population group	Incidence of HCC (%/year)
Cirrhotic hepatitis B carriers	2.5–8
Hepatitis C cirrhosis	2–8
Stage 4 primary biliary cirrhosis	3–11
Genetic haemochromatosis and cirrhosis	3–4
Alpha 1-antitrypsin deficiency and cirrhosis	Unknown, but probably >1.5

Many early epidemiological studies regarding the incidence and prevalence of HCC in liver cirrhosis were performed prior to the sequencing of the hepatitis B genome and full characterisation of the hepatitis C virus. As a result, much data regarding the incidence of HCC in other etiologies of cirrhosis may have been inaccurate as occult viral hepatitis would not have been included. The finding of HBV DNA sequences in tumor samples from individuals negative for hepatitis B surface antigen is well documented indicating that previous hepatitis B exposure may be a risk factor for the development of HCC even in individuals who do not have evidence of active infection or cirrhosis [19]. Any epidemiological study of HCC needs to take account of this factor, and in this series patients were screened for antibodies to not only hepatitis C but also hepatitis B core antigen.

The limitations of this observational study revolve around all data being collected from a large, single, tertiary referral center in the United States. Given the nature of a specialist center, it may be that more complex patients, perhaps those refractory to immunosuppressive therapy may have been selected inadvertently and hence more prone to develop HCC. Data from such a cohort may be difficult to generalise and further studies would clearly be useful in this area. Compared to AIH patients without HCC, those with HCC had a lower absolute platelet count and lower serum albumin; however, there was no difference between bilirubin, international normalized ratio for prothrombin time (INR) and overall model for end-stage liver disease (MELD) scores between the two groups. In addition, little information about other illnesses has been provided. Concurrent autoimmune diseases such as hypothyroidism and diabetes mellitus are not uncommon in AIH and both have been linked to an increased risk of liver and

other cancers [20]. Alcohol intake and obesity are also risk factors for progression of all liver disease but little data in this area is given.

This paper adds to the small but growing body of evidence regarding the risk of HCC in the context of AIH induced liver cirrhosis. In this study the presence of cirrhosis in AIH is associated with a risk of developing HCC approaching that observed in viral hepatitis. This has been acknowledged in the most recent AASLD guidelines which recommend surveillance in this group of patients. Centers which take up this recommendation will be able to provide prospective data on the incidence and outcomes in these patients to allow better cost-effectiveness models to be developed.

Key Points

- HCC is a rare occurrence in AIH
- The development of cirrhosis in AIH is associated with a greatly increased risk of HCC
- The incidence of HCC in individuals with AIH with cirrhosis is comparable to that of cirrhosis arising from other etiologies
- Further prospective studies are needed in order to evaluate the optimum interval for HCC in individuals with AIH-induced cirrhosis

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