CURRENT ONCOLOGY
A Canadian Cancer Research Journal

REVIEW ARTICLE

Hepatocellular carcinoma: epidemiology, screening, and assessment of hepatic reserve

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ABSTRACT

Hepatocellular carcinoma is a leading cause of cancer-related mortality worldwide. This review summarizes the epidemiology and causes of the disease, and the roles of screening and surveillance for early tumour detection. It also highlights the important role of assessment of hepatic reserve in consideration of appropriate staging and treatment.

Key Words Hepatocellular carcinoma, epidemiology, risk factors, screening, surveillance

Curr Oncol. 2020 November:27(S3)138–143 www.current-oncology.com

INTRODUCTION

The landscape of hepatocellular carcinoma (HCC) has been rapidly evolving in the past few years. Hepatocellular carcinoma accounts for approximately 75% of all primary liver malignancies[1]. Based on data from the Canadian Liver Foundation's commissioned liver disease report in 2013[2], the incidence and mortality of HCC was rising in Canada, with rates being highest in Quebec[2]. Recent data from Statistics Canada showed a HCC incidence rate in Canada of 6.3 per 100,000 population[3] (excluding Quebec), with approximately 3000 individuals having been diagnosed with HCC in 2019[3].

In Canada, a Statistics Canada analysis showed that the age-specific 5-year net survival for liver cancer for individuals aged 15–99 was 18 months in 2007–2009[4]. Care for patients with HCC demands a multidisciplinary approach, requiring input from surgery, hepatology, interventional radiology, and medical oncology. In addition to updates in the surgical and locoregional liver-directed management of HCC, considerable advances have been made in systemic therapy for patients with the disease. Although sorafenib had been the mainstay of treatment for well over a decade, a considerable armamentarium is now available, including lenvatinib, cabozantinib, regorafenib, and immunotherapy. In this article, we summarize the current epidemiology and risk and the role of screening and surveillance in HCC. We also review the assessment of hepatic reserve for patients with HCC, given that treatment is guided by both tumour characteristics and hepatic capacity.

DISCUSSION

Epidemiology

Hepatocellular carcinoma is the 7th most common cancer worldwide and the 2nd most common cause of cancer-related death[5]. The HCC incidence shows substantial global variation, largely attributed to differences in HCC risk factors such as viral hepatitis and exposure to co-carcinogens. The highest incidences of HCC are seen in sub-Saharan Africa and Southeast Asia[6,7]. Based on GLOBOCAN 2018 data, the estimated cumulative incidence risk for HCC in 2018 was 6.6 per 100,000 men and 3.4 per 100,000 women in North America[5]. The projected HCC incidence in Canada is estimated at 12 per 100,000 population[2]. Overall, the incidence of HCC has plateaued or declined in most developed countries, but it continues to increase in low-HCC-rate areas[1].

As noted in a recent review by McGlynn *et al.*[8], the incidence and mortality of HCC are interconnected and almost equivalent. That finding reflects the high case fatality rate for this disease, which is often diagnosed at a late stage. The HCC-related global death rate was 8.5 per 100,000 person–years in 2018[5], and the prognosis for HCC is poor throughout the world. Median age at HCC diagnosis in the United States is 60–64 years for men and 65–69 years for women[9].

In the United States, HCC incidence rates are higher by a factor of between 2 and 4 in men compared with women, and the difference between the incidence rates for men and women is even more pronounced in Europe[1]. The sex difference in HCC incidence might be related to a

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protective effect of estrogens and lower exposure to HCC risk factors in women. In 2016, the incidence of HCC was highest in the American Indian/Alaskan Native population (11.4), followed by the Hispanic population (9.8), the Asian/Pacific Islander population (9.1), the non-Hispanic black population (8.1), and the non-Hispanic white population (4.6)[9].

Specific Risk Factors

Viral Hepatitis

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are still the most common risk factors for HCC, causing 80% of cases worldwide[6,10]. Overall, the annual incidence of HCC is 2%–5% in patients with cirrhosis from chronic HBV or HCV infection[11]. Based on Canadian Liver Foundation data from 2013, approximately 500,000 people are infected with HBV or HCV in Canada[2]. Data from the Canadian Notifiable Disease Surveillance System and the Enhanced Hepatitis Strain Surveillance System show that the incidence of acute hepatitis B is falling in Canada (although those data represent only 41% of the population).

Hepatitis B virus is a known direct liver cancer carcinogen, given its ability to intercalate into the host genome in the form of covalently closed circular DNA[12,13]. Multiple studies have shown a relationship between HBV infection and HCC development in patients with or without cirrhosis[14–16]. The annual incidence of HCC in patients with chronic HBV infection without cirrhosis is 3.2 per 100 person–years, and the lifetime risk of HCC among carriers of HBV ranges from 10% to 25%[12]. Patients at higher risk of developing HCC have a high viral load (HBV DNA > 10^6 U/mL), positivity for the hepatitis B e-antigen, inactive chronic HBV, HBV genotype C, male sex, or hepatis delta co-infection. Clearance of hepatitis B surface antigen is associated with a favourable prognosis, but HCC can still develop. Other non-modifiable factors that increase the risk of developing HCC are young age at HBV acquisition, alcohol or tobacco use, blood type B (in male individuals), and a family history of HCC. Some of those factors are incorporated into various societal HCC screening guidelines.

Vaccination against hepatitis B has dramatically reduced the incidence of HCC[17]. In addition, therapy for HBV in patients with a high viral load and evidence of necroinflammation or fibrosis has been shown to improve liver function and fibrosis stage. Antiviral therapy against HBV using older interferon regimens and nucles(t)ide analogues reduced the relative risk for HCC [interferon relative risk: 0.66; 95% confidence interval: 0.48 to 0.89; nucles(t)ide relative risk: 0.22; 95% confidence interval: 0.10 to 0.50][18]. Studies from the United States, Japan, and Taiwan have evaluated specific nucles(t)ide analogues, although no specific drug outperformed the others[19–21]. Increased awareness of HBV vaccination programs and decreasing costs of available antiviral therapy might affect the weight of the HBV risk factor on HCC rates. In Canada, the National Advisory Committee on Immunization advises universal vaccination either at birth or in adolescence, leading to a decreased incidence of HBV infection in immigrants to Canada[2].

Hepatitis C virus leads to HCC by creating an inflammatory milieu causing advanced liver fibrosis or cirrhosis, increasing the risk of HCC by a factor of between 10 and 20[22]. The annual incidence of HCC in patients with HCV cirrhosis ranges from 0.5% to 10%[23]. Remis[24] estimated that, in December 2007, approximately 242,500 people in Canada were infected with HCV and that about 7900 people became newly infected during that year. Intravenous drug use accounted for 58% of prevalent HCV infections in Canada; blood transfusion, for 11%; hemophilia, for 0.4%; and other modes of transmission, for 31%. Overall, it was estimated that, as of December 2007, about 192,000 of HCV-infected people living in Canada had been diagnosed (79%)[24]. Additional non-modifiable risk factors that increase the HCC risk in patients with HCV include male sex, Hispanic ethnicity, HCV genotype 3, longer duration of infection, co-infection with HBV or HIV, insulin resistance, obesity, diabetes, and tobacco or alcohol use. Many studies have shown a decrease in the rate of HCC in patients with HCV who are treated with direct-acting antiviral therapy. A sustained viral response to antiviral therapy lowers HCC incidence and mortality[25]; however, the risk for HCC remains even after a sustained viral response, and in certain instances, HCC screening is still advocated by societal guidelines when the incidence of HCC meets the screening threshold of 1.5% per year posited by Sarasin *et al.*[26].

Non-Alcoholic Fatty Liver Disease

Fatty liver disease is the most common HCC risk factor in the developed world and the 2nd leading cause of HCC-related liver transplantation in the United States[27,28]. Fatty liver disease is the most common liver disease in Canada, affecting 25% of the population[2]. Approximately 10%–20% of HCC cases in the United States are attributed to cirrhosis caused by non-alcoholic steatohepatitis (NASH)[27]. Of HCC cases caused by NASH, 20%–30% can be found in patients without cirrhosis[29], and NASH might confer a risk of HCC that is increased by a factor of 2.6[30]. The other components of the metabolic syndrome are also known risk factors for HCC[31]. Coffee use has been shown to be protective against liver diseases in patients with NASH[32] and to be protective against the development of HCC[33].

Alcohol

The rate of alcohol consumption is increasing in Canada. Per-capita rates rose to 8.2 L (18 g) daily in 2010 from 7.6 L (16 g) daily in 2000[2]. There is a clear relationship between the amount of alcohol consumed per country or region and the incidence of alcohol-related liver disease. It is postulated that the increase in alcohol-related liver disease increased the standardized cirrhosis death rates to 6.5 per 100,000 population in 2008 from 6 per 100,000 population in 2004[2]. Alcohol consumption follows NASH as a risk factor for HCC in both the United States and Europe. A population-based study of 3107 patients with cirrhosis in the U.K. General Practice Research Database (1987–2006) found that the risk of HCC was lower by a factor of 2–3 in patients with alcohol-related cirrhosis than in patients with cirrhosis from viral hepatitis[34]. There might be data to indicate that alcohol is a stronger risk factor for HCC in women than in men, possibly because of evolving alcohol consumption practices or the lower level of endogenous alcohol dehydrogenase present in the gastric mucosa in women[35].

Co-carcinogens

There is a known additive effect of multiple carcinogens on HCC rates. *Aspergillus*-derived aflatoxins proliferate in countries with warm or humid environments and contaminate maize, groundnuts, and tree nuts[8]. Of the 4 aflatoxin forms, aflatoxin B1 is the most common and potent. The International Agency for Research on Cancer has classified aflatoxin B1 as a group 1 human carcinogen[13]. Estimates suggest that aflatoxin B1 alone increases HCC risk by a factor of 6; HBV alone, by a factor of 11; and those two components together, by a factor of 54[36]. Smoking is also a known risk factor for HCC[37]. Data from 14 U.S. cohorts suggest that the risk for HCC in individuals who had quit smoking more than 30 years earlier was almost equivalent to the risk in individuals who were never-smokers (hazard ratio: 1.09; 95% confidence interval: 0.74 to 1.61), suggesting that the carcinogenic effect can be reversed[1].

Metabolic Liver Disease

Many inherited metabolic liver diseases such as hemochromatosis *(HFE)*, α_1-antitrypsin deficiency *(SERPINA1)*, glycogen storage diseases *(G6PC, SLC37A4)*, porphyria *(HMBS, UROD)*, tyrosinemia *(FAH)*, and Wilson disease *(ATP7B)* increase susceptibility to HCC[38–43]. The precise incidence of HCC in each of those populations is unknown, but is likely to be greater than 1.5% per year[44]. Multiple allelic HCC associations have been identified in the Asian HBV cohort[45]. In the United States, *PNPLA3* and the rs738409 single-nucleotide polymorphism have been shown to increase the risk of HCC in the white population with an odds ratio of 1.75[46,47].

HCC Screening and Surveillance

The main goals of a screening program for HCC are to prevent and detect cancer at an early stage so as to intervene, with measurable good outcomes[44]. Any screening program, including surveillance for liver cancer, is subject to lead-time bias[44]. Only one randomized controlled trial—by Zhang *et al.*[48] in 2004 in China—has evaluated a primary endpoint of mortality in patients undergoing HCC screening. In 19,200 Chinese patients with chronic hepatitis B (with or without cirrhosis) followed for 5 years, the mortality rate from HCC was 83 per 100,000 population in the screening arm compared with 132 per 100,000 population in the non-screening arm[48]. A 37% reduction in mortality was observed with implementation of a screening protocol of ultrasonography and alpha-fetoprotein (AFP) measurement every 6 months[48]. The study has been critiqued for using cluster randomization, and it is unclear whether data derived from this cohort of patients with hepatitis B can be generalized to other patients at risk for HCC.

Given that screening is now the standard of care in HCC management, additional randomized controlled trials are unlikely to occur, but other observational studies show that surveillance is associated with both early tumour detection and improved survival[49,50]. More than 58 studies have been pooled to calculate mortality rates in a HCC screening population, but the data about the benefits of screening are mixed[49,51].

Ten different societal HCC-related screening guidelines from four continents have been published[52]. Each guideline reflects the epidemiology and risk factors endemic to its region. Based on the available data, all the guidelines indicate that an incidence of 1.5% per year or greater warrants surveillance of HCC in cirrhosis[26]. With respect to screening in the non-cirrhotic population, the guidelines vary. Based on tumour doubling time, all societies use a 6-month screening interval (except for the Japan Society of Hepatology, which endorses 3- to 4-month follow-up for patients who are at high risk for HCC). The American Association for the Study of Liver Diseases (2017) recommends ultrasound-based HCC screening with or without AFP measurement, and the Canadian Association for the Study of the Liver (2014) recommends the ultrasound modality alone. Asian societies promote use of computed tomography and magnetic resonance imaging in high-risk populations and delineate an AFP cut-off of more than 200 ng/mL to reduce the rate of false positives. The European Association for the Study of the Liver recommends HCC screening for all patients with advanced (F3) fibrosis without defining the cause of that condition. The American Association for the Study of Liver Diseases and the Canadian Association for the Study of the Liver do not make specific recommendations about screening for patients with F3 disease. The American Association for the Study of Liver Diseases recommends avoiding screening in patients classified as Child–Turcotte–Pugh (CTP) C unless there is a route to liver transplantation. Asian societies state that screening should not be performed in patients with advanced liver disease for whom HCC treatment modalities cannot be pursued.

The data support a survival benefit with HCC screening. Median survival in newly diagnosed HCC was 52 months in Japan, where a screening program was in place; it was 17.8 months in Hong Kong, where no screening was performed. The most important factor influencing survival was stage at diagnosis.

Despite societal guidelines that recommend ultrasonography and AFP measurement as tools for screening and surveillance, the performance characteristics of those modalities have been relatively poor, with relatively low sensitivity, specificity, and positive predictive value. Several groups have been attempting to identify serum markers that could enable early detection of HCC, with varied success. A model that includes sex, age, AFP-L3, AFP, and des-gamma-carboxyprothrombin (GALAD score) combines several tumour markers to derive a composite score that has a high sensitivity (>60%) and positive predictive value for identifying early-stage HCC[53]. Another novel and recent analysis of viral exposure signatures in patients at risk for HCC unexpectedly showed excellent performance characteristics for such signatures in predicting and diagnosing HCC[54]. Validation of that screening strategy and others using serum gene expression profiles will hopefully improve the ability to detect and treat this tumour at an early stage.

Hepatic Reserve

In contrast to the many malignancies in which tumour characteristics influence treatment, prognosis and ability to treat patients with HCC are contingent on a combination of tumour characteristics, hepatic reserve, and the patient's functional status.

Common determinants of hepatic reserve include the CTP classification, which incorporates a score assigned based on serum albumin, prothrombin time, bilirubin, ascites, and hepatic encephalopathy. Patients with 5–6 points are categorized as class A; those with 7–9 points, as class B; and those with 10 or more points, as class C. The Model for End-Stage Liver Disease (MELD), which incorporates objective laboratory values (bilirubin, international normalized ratio, and creatinine) to remove the subjective bias inherent in the CTP system, has been developed for use in liver transplantation allocation. Both the CTP classification and the MELD score are useful for the assessment of hepatic reserve in patients with HCC and for guiding treatment decisions.

Developed in 2008, the Barcelona Clinic Liver Cancer staging system has emerged as the most prominent global staging system for HCC, and it is used worldwide to define treatment modalities for HCC[55]. The CTP classification and the Eastern Cooperative Oncology Group performance status are incorporated into that treatment allocation system.

Limitations inherent in the subjective nature of the CTP classification and the short-term prognostic value of the MELD have led to the development of a prognostic system that can be applied specifically to patients with HCC. The albumin–bilirubin score was developed using a multivariate analysis of prognostic variables from a large cohort of Japanese patients with HCC[56]. This prognostic system has been validated in other populations. Albumin–bilirubin grade I (score: –2.60 or less), grade II (score: greater than –2.60 to –1.39), and grade III (greater than –1.39) are associated with differences in overall survival; however, the albumin–bilirubin score might not necessarily influence decisions about treatment eligibility.

Hepatic Resection

Evaluation of hepatic reserve is important for patients with small tumours who could be eligible for curative surgical resection. Although the CTP classification and the MELD score are sometimes used for prognostication before surgical resection, those scoring systems do not correlate with the risk of hepatic decompensation after resection[57]. Based on data from Bismuth *et al.*[58], only 5%–15% of patients presenting with HCC will have adequate hepatic reserve to undergo resection. Patients with decompensated liver disease (defined as ascites, encephalopathy, or prior variceal bleeding) or those with portal hypertension associated thrombocytopenia or gastroesophageal varices should not undergo surgical resection. Many groups have moved toward using portal pressure measurement or a dual volumetric–technetium hepatobiliary scintigraphy approach to define liver synthetic function. Asian societies use indocyanine green at 15 minutes as a defining criterion for hepatic reserve. There is currently no definitive algorithm to assess hepatic reserve in North America, and a case-by-case discussion at a multidisciplinary tumour board is recommended.

Transarterial Therapies

Given the potential for hepatic decompensation and failure, treatment with transarterial chemoembolization and radioembolization is typically restricted to patients with CTP class A or B cirrhosis and a good performance status. Relative contraindications include serum bilirubin greater than 2 mg/dL, aspartate aminotransferase greater than 100 U/L, tumour burden involving more than 50% of the liver, and prior transjugular intrahepatic portosystemic shunting.

Systemic Therapies

Most studies of systemic therapies, including multikinase inhibitors or immunotherapies, have been limited to patients with CTP class A cirrhosis and a good performance status. Although there can be some flexibility for patients with CTP class B cirrhosis, a low threshold for dose adjustment or discontinuation should be maintained.

SUMMARY

We have summarized the key data regarding HCC epidemiology, screening, and hepatic reserve assessment. Ongoing studies will be needed in the next 5–10 years to determine whether changes in the incidence of viral hepatitis, new treatment modalities, and improved screening and surveillance tools can positively influence the HCC landscape.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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