

Hepatitis B related hepatocellular carcinoma

KEY POINTS

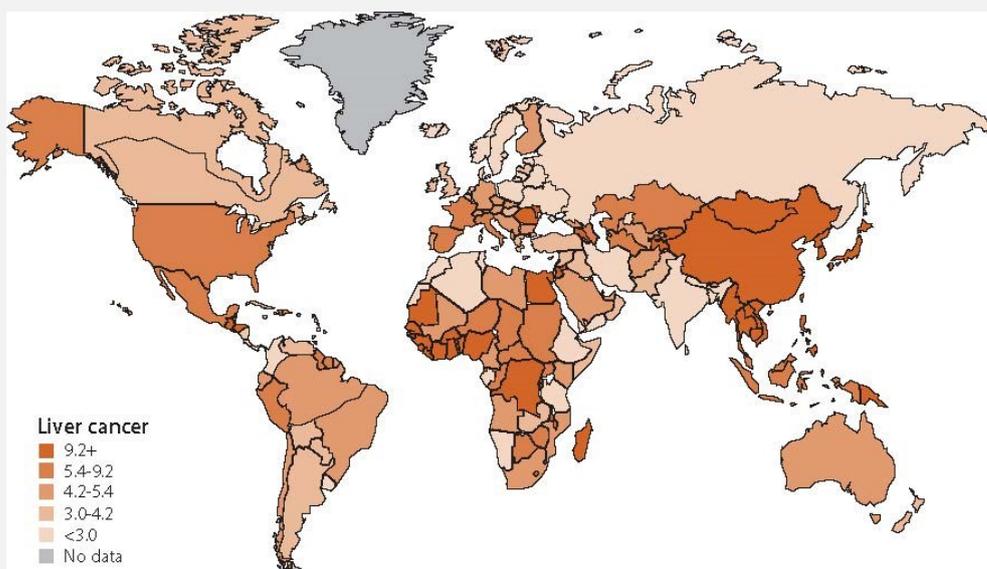
- Hepatitis B Virus (HBV) is an oncogenic virus that is globally the most important aetiological factor in the development of hepatocellular carcinoma (HCC).
 - Treatment of chronic hepatitis B (CHB) decreases, but does not completely eliminate, risk of HCC, underscoring the need for ongoing HCC surveillance in at-risk individuals.
 - HCC surveillance by 6-monthly ultrasound scanning, with or without alpha-fetoprotein level is recommended in patients with cirrhosis, and in patients with CHB who have additional risk factors.
 - Early diagnosis of HCC improves access to curative therapy and prognosis.
 - Curative therapies include liver transplantation, resection and local ablation.
 - Additional therapies that prolong survival include transarterial chemoembolisation and sorafenib.
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Hepatocellular carcinoma epidemiology

Liver cancer is the sixth most common cancer and the fourth most common cause of cancer-related death worldwide⁽¹⁾. Globally, over 54% of HCC is attributable to the combined effects of chronic infection with hepatitis B virus (HBV) and hepatitis C virus (HCV), which confers a 20 to 100-fold increased risk of developing HCC relative to those without viral hepatitis infections ⁽¹⁾. There are large geographic variations in HCC incidence, with the highest prevalence being in eastern Asia and middle or western Africa, where the estimated age-adjusted incidence rates of HCC are about 10 times greater than in Australia and New Zealand (Figure 9.1) ⁽²⁾. In 2016, there was an estimated 233,000 people living with chronic hepatitis B (CHB) in Australia ^(3,4), and primary liver cancer incidence rates have been rising faster than any other cancer (with the exception of thyroid cancer) ⁽⁵⁾. This increasing rate has propelled HCC from being a rare cancer to among the top 10 causes of cancer death overall in Australia: the sixth most common cause of cancer death in men and ninth most common cancer death in women ⁽⁵⁾. Furthermore, the economic cost associated with HCC are considerable and higher than that of other cancers ^(6,7).

In New South Wales (NSW), nearly 90% of hepatitis B related HCC occurs in people born overseas, in particular from countries with high HBV prevalence ⁽⁸⁾. Standardised incidence rates of HCC are at least six times higher in men born in China, Hong Kong, Indonesia, Korea, Macau and Vietnam, and in women born in China and Vietnam, than in the Australian-born population. This trend mirrors those in the Netherlands and the United States of America (USA), where rising rates of HCC are reported in migrants from Asia and the Pacific Islands that are disproportionate in comparison to the locally born populations ^(9,10). Aboriginal and Torres Strait Islander people are also disproportionately affected by CHB and related liver cancer: the prevalence of HBV in the Aboriginal and Torres Strait Islander population is estimated to be 3.9% ⁽⁵⁾, and, in some Aboriginal and Torres Strait Islander communities, rates of HCC are 5–10 times greater than in non-Indigenous Australians ^(11,12). (see: [Prevalence and epidemiology of hepatitis B](#)).

Figure 9.1 The global distribution of liver cancer (GLOBOCAN data) ⁽²⁾



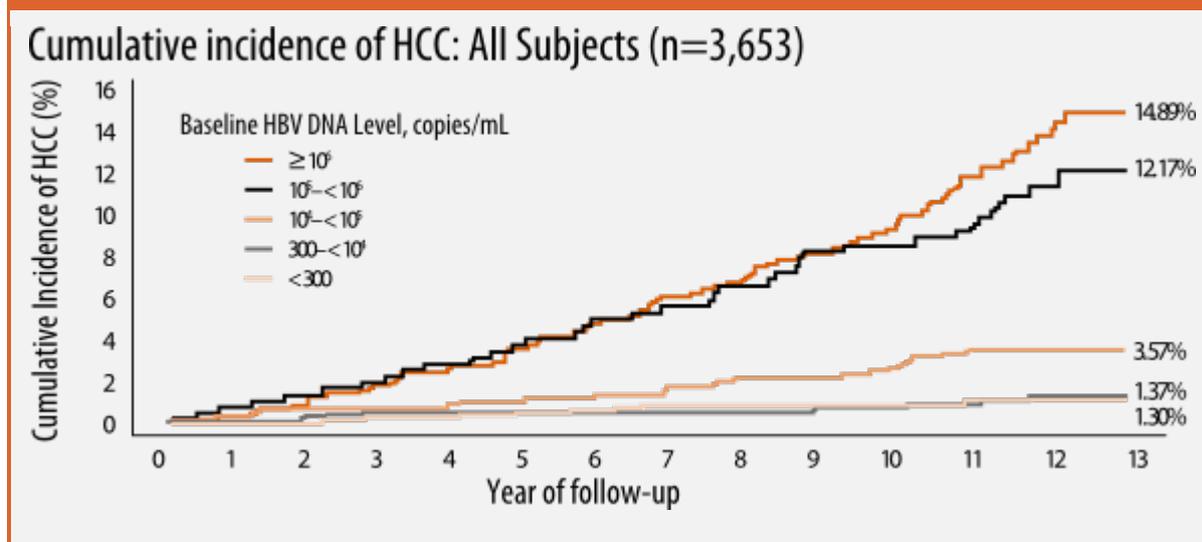
Risk factors

HBV is an oncogenic virus that increases the risk of HCC occurrence directly (by viral mechanisms) and indirectly (by liver inflammation and cirrhosis). Thus, persistently high HBV DNA and alanine aminotransferase (ALT) are strong independent predictors of HBV-related HCC (13). The significance of HBV replication in HCC pathogenesis was demonstrated in the REVEAL study, a community-based natural history study of CHB in Taiwan, which found that HCC risk increased proportionally to serum HBV DNA viral load (Figure 9.2) (14). Chronic replication of HBV increases the risk of progression to cirrhosis and HCC (15). In CHB patients without cirrhosis, the incidence of HCC is increased compared to the general population and varies with geographical region: ranging from less than 0.2% per year in Europeans to 0.4–0.6% per year in Asians (16). Presence of cirrhosis further increases HCC risk by over 10-fold. One-third of CHB patients with cirrhosis develop HCC in their lifetime. Among people with cirrhosis, the annual incidence of HCC is 2–3% in western countries and 6–11% in Asian populations (17,18). The incidence rates of HCC are two to three times higher in men than in women in all regions of the world (19). At each stage of chronic hepatitis, a positive family history (in first-degree relatives) increases HCC risk (20). Coexisting obesity, diabetes and non-alcoholic fatty liver disease (NAFLD) (21), together with alcohol and cigarette smoking (22), are additive risk factors for HCC development (see Table 9.1).

Table 9.1 Risk factors for hepatitis B-related hepatocellular carcinoma

Risk factor	Reference
Active HBV DNA replication or viral load	Chen et al (2006) (14)
HBV genotype C	Yang et al (2002) (23)
HBeAg-negative core promoter mutation	Yang et al (2002) (23)
Cirrhosis	Schiff et al (2006) (24)
Male sex	Bosch (1999) (19)
Asian, African, Aboriginal and Torres Strait Islander or Australian ethnicity	Fattovich (2003), Parker (2014) (17,11)
Coexisting NAFLD and diabetes	El-Serag (2001) (21)
Smoking, alcohol, obesity	Marrero (2005) (22)
Positive family history, first-degree relative	Loomba (2013) (20)
HBeAg: hepatitis B e antigen; HBV: hepatitis B virus; NAFLD: non-alcoholic fatty liver disease	

Figure 9.2 Viral load as a predictor of hepatocellular carcinoma risk (14)



Prevention

The most effective and practical means to control HBV infection and its long-term sequelae (cirrhosis and HCC) is to reduce or eliminate viral transmission by primary prevention. Secondary prevention aims to reduce progression to end-stage liver disease and HCC, by optimising medical management. This approach is intuitive, and is based on the close correlation between HBV replication and the risk of disease progression and liver cancer. Data suggest that effective suppression of viral replication reduces the risk of HCC by approximately 30% in patients with cirrhosis and up to 80% in non-cirrhotic patients (25,26).

HCC can progress rapidly and present at an advanced stage in the absence of symptoms. Hence, the aim of HCC surveillance is to detect tumours at an early stage, when curative treatment can be offered. However, the benefits of a surveillance strategy have to be balanced against the cumulative risk of developing the disease, and against the costs, sensitivity and specificity of the screening tests. The effect of lead-time bias (i.e. the period by which screening advances diagnosis of the disease) on survival leads to uncertainty about the cost-effectiveness of screening protocols and the effect that antiviral treatment may have on surveillance for HCC (14, 27). There is one large randomised controlled trial of over 18,000 Chinese subjects with CHB that showed a 37% reduction of mortality from HCC in people screened compared to those receiving usual medical care (28). Despite some ongoing uncertainties, current clinical practice guidelines recommend HCC screening by ultrasound scanning as being of benefit in all patients with cirrhosis (29).

Liver ultrasound is considered the HCC surveillance test of choice because it can detect tumours as small as 1–2 cm in diameter (sensitivity 94%); however, it is operator dependent and does not discriminate between HCC and other liver pathology (e.g. haemangiomas or regenerative nodules). Serum alpha fetoprotein (AFP) alone is inadequate for HCC surveillance because AFP is secreted by only approximately 50% of small HCC lesions, and levels may remain normal even in the setting of advanced disease. In HBV patients with complete viral suppression on antiviral therapy, in particular, the addition of serum AFP measurement increases detection of HCC, and elevation of AFP may precede the detection of HCC by ultrasound by 6 months (30). However, serum AFP may be significantly elevated in patients undergoing an HBV flare, and may not be a useful marker of HCC in that situation. While combined use of AFP and ultrasound for HCC surveillance may increase detection rates, false-positive rates and associated costs

are also increased. It is currently unclear whether the addition of AFP to ultrasound leads to improved survival. HCC screening using both ultrasound and AFP is recommended by the Asian Pacific Association for the Study of the Liver (31) and the Gastroenterological Society of Australia (GESA) (32), whereas the addition of AFP is not routinely recommended by US and European guidelines (29,33).

Target groups for HCC surveillance

Those with cirrhosis

Those without cirrhosis but with any of the following additional risk factors:

- Asian men over 40 years
- Asian women over 50 years
- Africans over 20 years
- Aboriginal and Torres Strait Islander people over 50 years
- Those with a family history of HCC.

The benefit of HCC surveillance in non-cirrhotic CHB patients is controversial, and there is currently no coordinated national program to improve HCC surveillance of high-risk groups in Australia. However, guidelines from both Gastroenterological Society of Australia (GESA) and the American Association for the Study of Liver Disease (AASLD) highlight some important sub-populations that may benefit from surveillance in the absence of cirrhosis. These include those with HBV infection who are Asian-born men over the age of 40, Asian-born women over the age of 50, African-born people over the age of 20 and those who have a family history of primary liver cancer (32-34).

Given that the individual annual risk of HCC in Aboriginal and Torres Strait Islander peoples with HBV infection over 50 years of age is estimated to be 0.34–0.86%, this population should also be included in HCC surveillance (11).

A negative screening result cannot reliably exclude the presence of a HCC; hence, enrolment in a regular surveillance program is required (35). Generally, a 6-month interval is recommended between screenings, which takes into consideration the estimated doubling time of HCCs smaller than 5 cm in diameter (36).

Several validated scoring systems have been developed to predict the risk of HCC in patients with CHB (e.g. GAG-HCC, CU-HCC, REACH-B and PAGE-B) (37). These HCC risk scores vary in their study cohorts in terms of patient population (Asian and European, untreated and receiving antiviral therapy, proportion with cirrhosis). Accordingly, the variables used and weighting assigned to each variable also differ between the risk scores. Although these scores consistently demonstrate high negative-predictive values (97-100%) to exclude HCC development in the next 3–10 years (hence permitting increased surveillance intervals), their use has not been widely adopted in Australia.

Diagnosis

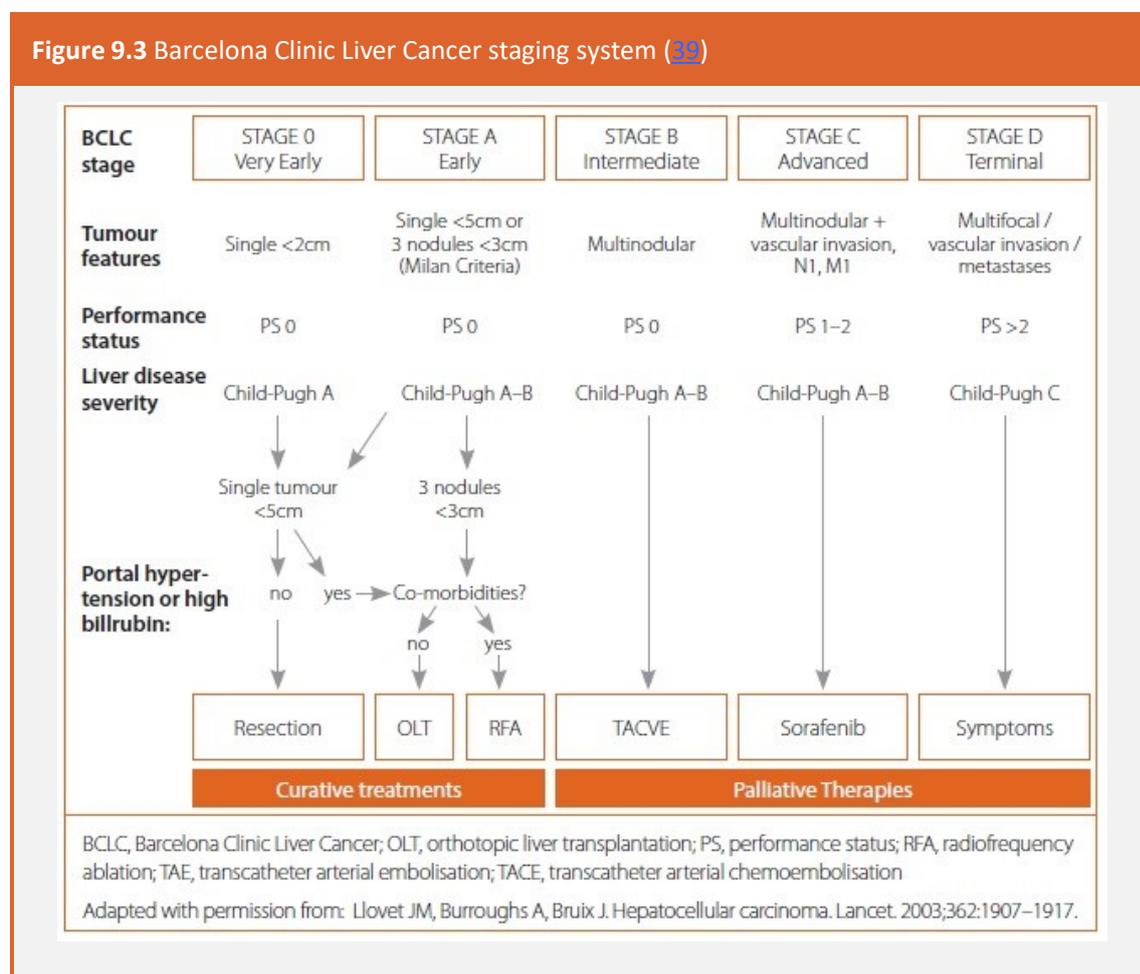
Unequivocal diagnosis of HCC is required if there is an abnormal screening test. Diagnosis of HCC can be made non-invasively through imaging, on the basis of its radiological hallmark, enhancement with contrast in the arterial phase and washout in the portal or delayed phase. Diagnostic imaging modalities include multiphasic computed tomography (CT) scanning, multiphasic magnetic resonance imaging (MRI) or multiphasic contrast-enhanced ultrasonography. While multiphasic MRI may be marginally more sensitive than CT in a pooled analysis of comparative studies, the differences in pooled diagnostic performance are insufficient to recommend MRI over CT (38). Contrast-enhanced ultrasound is not widely used in Australia.

Histological diagnosis by guided liver biopsy is not often required in cirrhosis, but is an investigative option for selected cases of hepatic nodules which appear inconclusive or atypical on imaging and in non-cirrhotic livers (39). Other options for further evaluation of indeterminate hepatic nodules include follow-up imaging, imaging with an alternative modality or alternative contrast agent.

Staging and treatment

Historically, HCC has been diagnosed in advanced disease stages, when prognosis is uniformly poor; with earlier detection, outcomes have been improving. Predictors of HCC prognosis include tumour-related factors (size, number, vascular invasion and metastases), AFP level, age, severity of liver disease (Child-Pugh classification) and the degree of existing functional reserve. The Barcelona Clinic Liver Cancer (BCLC) staging system incorporates these factors, and is now widely adopted to determine prognosis and allocate therapies (Figure 9.3) (33). Given its complexity, patients with HCC should be discussed and managed in a multidisciplinary setting.

Figure 9.3 Barcelona Clinic Liver Cancer staging system (39)



Very early HCC is defined as a single HCC of less than 2 cm with good performance status; however, less than 10% of all patients are diagnosed at this very early stage (40). They are amenable to curative treatments; these include orthotopic liver transplantation (OLT) and liver resection, which are associated with 5-year survival rates of over 80% and over 70%, respectively (41, 42).

Early HCC is defined as a single tumour less than 5 cm, or three nodules of less than 3 cm, performance status 0, and Child-Pugh class A or B. OLT is considered in cases where there is a single tumour less than

or equal to 5 cm, or up to three nodules less than or equal to 3 cm (Milan Criteria). OLT remains the only curative option for those with resectable tumours and decompensated cirrhosis, because it removes not only the tumour, but also the underlying liver disease. However, the lack of available livers for transplantation means that many of those on the waiting list may ultimately be denied transplantation, because of tumour advancement during the waiting period.

The local ablation of HCC is an acceptable alternative to resection for small liver cancers (< 3 cm) in Child-Pugh class A patients. Tumour ablation is also first-line treatment for unresectable, small HCCs with up to three nodules in Child-Pugh class A or B cirrhosis. Image-guided percutaneous ablation of tumours is generally performed with radiofrequency ablation (RFA) or microwave ablation, using extreme temperature to destroy tumour cells. Other ablation techniques that may be used include instillation of chemicals such as ethanol or acetic acid (43, 44), or the use of laser or cryotherapy. Choice of ablative therapies is determined by tumour position in relation to vascular structures, size and number, as well as the resources and expertise available. Local treatments provide good results with 5-year survival rates of 40–50% (42).

Transcatheter arterial embolisation (TAE) and transcatheter arterial chemoembolisation (TACE) may be indicated in non-surgical patients who are free of vascular invasion or extrahepatic tumour extension. These techniques aim to obstruct the blood supply to intermediate-sized tumours by using an embolising agent (e.g. gelfoam, starch microspheres or metallic coils) which, in the case of TACE, is combined with a chemotherapeutic agent (e.g. doxorubicin or cisplatinum).

Systemic therapies for HCC are recommended for the treatment of advanced stage patients who are not suitable for loco-regional therapies (e.g. due to multifocal disease, vascular invasion, metastasis or poor performance status) and who have good liver synthetic function. Cytotoxic therapies are not routinely recommended, but the multi-tyrosine kinase inhibitor sorafenib is commonly used, based on a demonstrated survival benefit in advanced HCC in phase III clinical trials. In the SHARP trial, sorafenib increased median survival to 10.7 months, compared to 7.9 months with placebo (45). This treatment is indicated for advanced HCC with well-preserved liver synthetic function, or for tumours that are progressing despite loco-regional therapies. Other therapies have emerged and shown promise for the treatment of advanced HCC. These include the use of an immune checkpoint inhibitor (nivolumab) (46) and radioembolisation with Yttrium-90 microspheres (47). Phase III studies comparing these therapies with sorafenib are currently ongoing. For patients with advanced HCC who have disease progression during sorafenib treatment, regorafenib (also a multi-tyrosine kinase inhibitor) was recently shown to be the only systemic treatment to provide survival benefit in this setting, improving median survival to 10.6 months compared to 7.8 months with placebo ($p < 0.0001$) (48).

Patients with advanced HCC, very poor performance status and/or Child-Pugh C cirrhosis have a poor prognosis, with a median survival of only 3–4 months. They should be offered the best supportive palliative care to alleviate symptoms.

Conclusion

Hepatitis B related HCC is an important global disease. Primary prevention of HBV infection remains the most effective long-term intervention; however, for those diagnosed with CHB, early detection and treatment of HCC has led to improved outcomes. HCC surveillance may increase the proportion being diagnosed at a curable stage. Although screening for HCC remains a topic for debate, earlier detection of these tumours has been associated with good results in the short and intermediate term. Disease recurrence and the treatment of advanced cancer remain a challenge. It is likely that the treatment of CHB infection will continue to make a significant impact on end-stage disease, and reduce the probability of developing liver cancer, but these benefits will take a long time to become apparent.

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