

# HEPATITIS B VIRUS-RELATED HEPATOCELLULAR CARCINOMA 9

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Links to: Chapter 1: Prevalence and epidemiology of hepatitis B  
Chapter 6: Clinical assessment of patients with hepatitis B virus infection

## KEY POINTS

- Worldwide, hepatocellular carcinoma (HCC) is the third most common cause of cancer-related mortality.
- In Australia, the HCC incidence has been increasing over the last 20 years.
- Hepatitis B virus (HBV)-associated HCC may occur in non cirrhotic and, more commonly, in cirrhotic patients.
- In NSW, the burden of disease is greatest in migrants from countries where HBV infection is endemic: people born in Southern and Eastern Asia are 6–12 times more likely to be diagnosed with HCC than Australian-born people.
- Traditionally, measuring serum alpha fetoprotein levels and performing liver ultrasound have been used for HCC screening.
- Despite a lack of agreement on whether screening improves disease-specific mortality, informal screening is widely practiced.
- Curative treatments for early stage HCC include surgical resection, liver transplantation and percutaneous ablation of tumours.
- Systemic chemotherapy has a low response rate, but targeted chemotherapy infused through the hepatic artery may be effective in select cases.
- The most effective prevention strategy is universal HBV vaccination.
- There are effective treatments for chronic HBV; they may alter the course of the disease and they may reduce the incidence of end-stage liver disease and liver cancer.

Worldwide, hepatocellular carcinoma (HCC) is the fifth most common cancer and the third most common cause of cancer-related death, with incidence rates two to three times higher in men than in women.<sup>1</sup> Over 80% of HCC worldwide is attributable to the combined effects of chronic hepatitis B and C infections. People with these infections have a 20 to 100-fold increased risk of developing HCC relative to those without these infections.<sup>2,3</sup> HCC prevalence is highest in Eastern Asia, middle Africa and some countries of Western Africa, with large variations in HCC incidence observed in different world regions. The estimated age-adjusted incidence rates of liver cancer per 100,000 men are approximately 10 times

higher in Eastern Asia, compared to the rates in Australia and New Zealand.<sup>4</sup> Hepatitis B is the most common cause of HCC worldwide and almost a third of all people with HBV infection live in China. Annually, 300,000 Chinese die from HBV-related conditions, including 180,000 deaths from HCC.<sup>5</sup>

In Australia, the liver cancer incidence ranks fifteenth in males and twentieth in females, but incidence and mortality figures have progressively risen over the last two decades. In NSW, primary liver cancer incidence rates have been rising faster than rates for any other cancer,<sup>6</sup> surpassing cancers of the lung, mesothelioma, and brain and thyroid cancer.<sup>7</sup>

The burden of liver cancer is greatest among populations born in countries with a high HBV prevalence. Standardised incidence rates (SIR) of primary liver cancer in NSW are at least six times higher in men born in Vietnam, Hong Kong and Macau, Korea, Indonesia and China, and in women born in Vietnam and China, as compared to the Australian-born population. This mirrors trends in the USA and the Netherlands, where rising rates of HCC are reported disproportionately in migrants from Asia and the Pacific Islands compared to the locally-born populations.<sup>8,9</sup>

While most HCCs occur in cirrhotic livers, tumours can also occur in livers with minimal histological changes. This phenomenon is more common in Southern Africa (where about 40% have minimal liver damage) than in Asia, America and Europe (where more than 90% are associated with cirrhosis).<sup>10</sup> Among people with cirrhosis, the annual incidence of HCC ranges from 2–3% in Western countries to 6–11% in Asian populations.<sup>11</sup>

### Screening assays for HCC

Traditional screening regimes for the detection of HCC have included measuring serum alpha-fetoprotein (AFP) levels and performing liver ultrasounds, used together in order to improve screening accuracy, as their individual sensitivity and specificity is relatively low, particularly among people with cirrhosis.<sup>11</sup> Generally, a six-month interval is recommended between screenings, which takes into consideration the estimated doubling time of HCCs smaller than 5cm in diameter.<sup>12</sup> As the serum AFP level is usually normal in early stage HCC, AFP is not a reliable indicator of early disease, although it can assist in ascertaining the individual level of risk for developing HCC or in monitoring patients following tumour removal.<sup>13</sup> The liver ultrasound is considered the screening test of choice, as it can detect tumours as small as 1–2cm in diameter, but it is operator-dependent and does not reliably discriminate between a HCC and other liver pathology (such as haemangiomas or cirrhotic nodules). Patients with abnormal screening tests need an unequivocal diagnosis reached through additional investigations, which may

include computed tomography (CT) scanning, magnetic resonance imaging (MRI) or liver biopsy.<sup>14</sup> As negative screening results cannot reliably exclude the presence of HCC, regular follow-up is required.<sup>15</sup>

One randomised controlled trial (RCT) enrolling over 18,000 people with chronic hepatitis B (CHB) infection has demonstrated a 37% reduction of mortality in people screened for HCC compared to those randomised to usual medical care.<sup>16</sup> More answers are needed regarding the appropriate targeting of mass screening programs, the cost-effectiveness of screening protocols and the effect antiviral treatment may have on screening and treatment algorithms for preventing HCC. Although rates of survival estimated by non-randomised studies are better for patients with HCC detected by screening compared to those detected clinically, many studies do not take into account the effect of lead time bias on survival (lead time is the period by which screening advances diagnosis of the disease), so the real benefits of surveillance remain the source of debate.<sup>11,17</sup> Currently there is no consensus on whether screening with AFP or a combination of AFP and ultrasound improves disease-specific or all-cause mortality for HCC.<sup>12,18</sup> Due to the low cure rate for symptomatically diagnosed HCC, (five-year survival rates less than 10%), and as cancers detected by screening are generally smaller in size and more likely to be unifocal, compared to those clinically detected,<sup>19</sup> screening is commonly used in clinical practice as a means to increase the proportion of cancers amenable to liver resection or liver transplantation.<sup>11</sup> Informal screening is widely practised, with a national survey of US gastroenterologists finding that 84% of the respondents screened their cirrhotic patients for HCC.<sup>20</sup>

Due to the limitations of existing HCC markers, the search for new prognostic markers continues. Several markers are currently under evaluation for their potential to predict disease prognosis and for their possible roles as targets for therapeutic interventions in the future.<sup>21</sup>

## Treatment of HCC

Traditionally, HCC has been diagnosed in advanced stages, when prognosis is uniformly poor, but with earlier detection, outcomes have been improving. Predictors of HCC prognosis include: the stage and size of the tumour at diagnosis;<sup>22</sup> the alpha-fetoprotein level;<sup>23,24</sup> age; the presence of liver cirrhosis and the degree of existing functional reserve;<sup>25</sup> and tumour-related factors, including size, number and the degree of tumour spread.<sup>26</sup>

Therapeutic options for early-stage disease (where cure is possible) include surgical resection, liver transplantation and percutaneous ablation. As no RCTs have compared the relative effectiveness of these three types of interventions, it remains unclear which should be the first-line treatment option for people with early disease.<sup>27</sup> Surgical resection for small tumours in people with normal liver function is associated with five-year survival rates in excess of 50%,<sup>28</sup> but disease recurrences are common, both locally and related to new tumour formations in a cirrhotic liver.<sup>23,29-31</sup>

**Orthotopic liver transplantation** remains the only option for those with resectable tumours and decompensated cirrhosis, as it not only removes the tumour but also the underlying liver disease.<sup>32</sup> Results of earlier surgical series were fairly poor, but later series demonstrated that in carefully selected patients, with single or relatively small cancers (tumours  $\leq 5$  cm in diameter, or  $\leq 3$  tumour nodules, each 3 cm or less in diameter—known as the Milan criteria) and without vascular invasion, five-year survival rates of 50–70% can be achieved, with low recurrence rates.<sup>30,33</sup> Although HBV infection can be associated with lower survival rates, combining transplantation with antiviral therapy achieved a five-year survival rate in excess of 75%.<sup>34</sup> However, the lack of available livers for transplantation means that a significant proportion of those on the waiting list may end up ultimately being denied transplantation, due to tumour advancement during the waiting period.<sup>35</sup>

**Percutaneous ablation** of tumours using chemicals (ethanol or acetic acid) has been successful in select case series, with best results achieved with small, solitary tumours.<sup>36,37</sup> Other means of destroying tumour cells include extreme temperatures, achieved using techniques such as radiofrequency ablation, microwaves, laser or cryotherapy.<sup>14</sup>

**Transcatheter arterial embolisation (TAE)** and transarterial chemoembolisation (TACE) may be indicated in non-surgical patients free of vascular invasion or extrahepatic tumour extension.<sup>14</sup> These techniques aim to obstruct the blood supply to intermediate-sized tumours and use an embolising agent (such as gelfoam, starch microspheres and metallic coils),<sup>38</sup> which in the case of TACE is combined with a chemotherapeutic agent (such as doxorubicin or cisplatin).<sup>14</sup>

Overall, systemic chemotherapy for advanced HCC has not been very effective, with response rates below 20% and significant toxicity in cirrhotic patients.<sup>28</sup> Targeted therapy using hepatic artery infusion of chemotherapeutic agents may prove useful for some patients with advanced HCC,<sup>39</sup> but validation in larger trials is awaited.

## Public health approaches for HCC prevention

The most effective and practical approaches to controlling HBV infection and its long-term sequelae are primary prevention approaches, which aim to reduce or eliminate viral transmission. Key interventions include universal vaccination against HBV, ensuring a safe blood supply (through screening of all blood donations), and harm minimisation approaches. To date, more than 100 countries have instituted HBV vaccination programs and there is strong evidence that infant vaccination is effective in reducing the incidence of liver cancer and the rate of chronic infection in children. Within 15 years from the commencement of mass immunisation against HBV in Taiwan, the rate of chronicity in children decreased from 9.8% to 0.7%<sup>40</sup> and was paralleled by a reduction of the incidence rate of HCC in children aged 6–14 years.<sup>4</sup>

However, due to the long latency period and the large burden of undiagnosed disease in the community, the overall impact of universal vaccination in reducing morbidity and mortality from liver disease is not expected for another 30 or more years. Experts of the Hepatitis Control Committee in Taiwan estimate that vaccination could result in 80–85% decreases in the incidence of HCC in all adults within three to four decades of vaccination.<sup>42</sup>

Secondary prevention aims to reduce the proportion of people progressing to end-stage liver disease and HCC by optimising their medical management. Emerging evidence suggests that reducing viral replication may reduce the risk of developing HCC and cirrhosis, so earlier identification and treatment for chronic HBV could be a valid cancer control option in well-resourced settings, such as Australia. One meta-analysis of RCTs using interferon for cancer prevention suggests that this agent may have a protective role for cancer development, but the trials have been performed mostly in people without advanced cirrhosis, so these findings are difficult to generalise.<sup>43</sup> The demonstration of a close correlation between HBV replication and the risk of disease progression and liver cancer,<sup>44-46</sup> coupled with data suggesting that effective suppression of viral replication may be associated with a reduced risk of HCC,<sup>44-47</sup> represent significant advances in our understanding of the natural history of CHB infection. However, long-term studies that evaluate the benefits of antiviral therapy or interferon-based therapies in reducing the incidence of HCC in people with chronic HBV infection are likely to present significant challenges, due to the prolonged course of HBV infection.<sup>43</sup>

Population-based HCC screening of high-risk groups is not practised uniformly in Australia. It has been recommended for Asian-born males over the age of 40, Asian-born females over the age of 50, African-born people over the age of 20, those with CHB-related cirrhosis (irrespective of age) and those with a family history of primary liver cancer<sup>48</sup> (see Table 6.4, Chapter 6: Clinical assessment of patients with hepatitis B virus infection).

Since 1999, New Zealand has had a targeted national screening and follow-up program for hepatitis B among Maori, Pacific and Asian people aged over 15 years, developed in response to the high morbidity and mortality and the significant economic impact of untreated HBV infection. The program provides active surveillance for more than 12,000 people and has identified approximately 100 people with HCC, with 65% of them amenable to curative resection or transplantation. Their five-year survival exceeds 50%, which compares to 0% in 150 people with chronic HBV-related liver cancer diagnosed during the same period, but not enrolled in a screening program.<sup>49</sup>

A similar initiative, the Asian-American Hepatitis B Program in New York City, aims to identify people with chronic HBV infection among the Asian and Pacific Islander communities; it provides a pathway for preventing the complications of chronic liver disease in those with the infection and offers HBV vaccination to susceptible contacts.<sup>50</sup>

In conclusion, hepatitis B-related HCC is a complex disease, with no ideal treatment currently available. Primary prevention remains the most effective intervention, but for those people diagnosed with chronic disease, early detection and treatment have led to improved outcomes. While screening for HCC remains a topic for debate, the earlier detection of these tumours has been associated with good short- and intermediate-term results. Disease recurrence and the treatment of advanced cancer remain a challenge. It is likely that the treatment of chronic HBV infection will 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. The burden of chronic HBV infection suggests that the incidence of liver cancer is likely to continue to rise over the next two decades.

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