Hepatocellular carcinoma surveillance in Australia: current and future perspectives

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Summary

- Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death worldwide, and is increasing in incidence in Australia.
- For most people with cirrhosis and chronic hepatitis B, HCC screening and surveillance is recommended with 6-monthly ultrasound. However, most patients with HCC are still diagnosed outside of surveillance with incurable disease.
- While HCC surveillance almost certainly reduces cancer-related mortality, the potential harms of surveillance are incompletely understood.
- Surveillance uptake remains suboptimal in many contexts, and stems from a combination of patient, clinician and system level barriers.
- Improved case-finding strategies may be required to identify high risk individuals in need of surveillance, as cirrhosis and viral hepatitis are often asymptomatic.
- HCC prediction models and novel surveillance tools such as biomarker panels, computed tomography and magnetic resonance imaging may have a future role in personalised HCC surveillance.
- Analyses suggest surveillance may be cost-effective, but Australian data remain limited.
- A centralised HCC surveillance program may ultimately have a role in delivering improved and more equitable care.

Hepatocellular carcinoma (HCC) represents the third most common cause of cancer-related death worldwide.[1] In Australia, the incidence of HCC is rising, and between 2001 and 2021, HCC increased from the fifteenth to the seventh most common cause of cancer-related death.[2,3] In the past few decades, both HCC mortality rates and the overall disease incidence have increased more than those of any other cancer in Australia.[4]

HCC predominantly occurs in people with underlying liver disease and particularly cirrhosis, with hepatitis C, alcohol misuse, hepatitis B, and non-alcoholic fatty liver disease/metabolic dysfunction-associated fatty liver disease (MAFLD) representing the dominant aetiologies.[5] The increasing burden of HCC in Australia is suspected to reflect revised diagnostic criteria as well as an increased at-risk population driven by migration, and metabolic risk factors such as a rise in obesity.[5-7]

The staging, treatment and prognosis of HCC are determined by the extent of disease, in addition to the individual's potential to tolerate treatment based on their underlying liver disease and performance status. This is reflected in a unique staging algorithm, the Barcelona Clinic Liver Cancer (BCLC) system (Box 1).[8-11]

Most cases in Australia are diagnosed at intermediate to late stage disease (BCLC stages B to D) where curative therapies are not attainable. In a Victorian dataset from 2012–13, only 26% of HCC cases were diagnosed with early stage disease (BCLC stage A), and only 40% were diagnosed in the context of surveillance.[12]

The challenges for HCC surveillance are multifaceted, and include barriers to surveillance uptake, an under-recognition of the at-risk population, and limited performance of existing surveillance tools.[10] There has been increasing recognition of the need to improve surveillance in Australia, and recently Cancer Council Australia was commissioned by the Department of Health and Aged Care to produce a roadmap for liver cancer control and clinical practice guidelines for HCC surveillance.[13]

In this narrative review, we performed an extensive search of the literature through Ovid MEDLINE, Embase and the Cochrane Central Register of Controlled Trials until 30 January 2023. We additionally reference checked HCC guidelines and review articles to formulate the discussion.

Current HCC screening and surveillance recommendations

The purpose of screening and surveillance is to identify early and subclinical disease, to potentially offer curative therapies and improve survival. When HCC is identified at a symptomatic stage, tumours are often advanced and untreatable, with a poor prognosis.[9,14]

Australian, Asian, North American and European society guidelines all endorse surveillance for HCC in high risk patients with ultrasound every 6 months, based on a median tumour doubling time of 4–5 months.[10,13,15-19] The serum biomarker α-fetoprotein (AFP) is frequently used in conjunction with ultrasound-based surveillance, although no guidelines mandate its use given limited sensitivity.

High risk patients are defined as individuals with cirrhosis of any aetiology as well as non-cirrhotic chronic hepatitis B in certain ethnic and age groups (Box 2).[10,15] Surveillance in people with the most advanced liver disease (Child–Pugh class C) is not recommended unless they are transplantation candidates, owing to an absence of treatment options and a poor overall prognosis dictated by their liver disease or other comorbidities.[10,15]

The evidence for HCC surveillance

The evidence for HCC surveillance was first supported by a randomised trial of patients with chronic hepatitis B in China, where ultrasound and AFP testing every 6 months resulted in a 37% reduction in HCC-related mortality after 5 years.[20]

There is no equivalent trial in people with cirrhosis of other aetiologies, although multiple observational studies have found similar outcomes.[12,21,22] The 2012–13 Victorian cohort

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1 Barcelona Clinic Liver Cancer system for prognosis prediction and treatment[10,11]

	0 Very early stage	A Early stage	B Intermediate stage	C Advanced stage	D Terminal stage
Definition					
Tumour burden	Single ≤ 2 cm	Single, or ≤ 3 HCCs ≤ 3 cm	Multinodular	Portal invasion and/or extrahepatic spread	Any
Liver function	Preserved	Preserved	Preserved	Preserved	End stage
ECOG PS	0	0	0	1–2	3–4
Treatment options	Ablation Resection Liver transplantation	Ablation Resection Liver transplantation	TACE Systemic treatment Liver transplantation (criteria dependent)	Systemic treatment	Supportive care
Treatment intent	Curative	Curative	Palliative (unless liver transplantation)	Palliative	Palliative
Prognosis	> 5 years	> 5 years	> 2.5 years	> 1 year	3–6 months

ECOG PS = Eastern Cooperative Oncology Group performance status; HCC = hepatocellular carcinoma; TACE = transcatheter arterial chemoembolisation. ◆

predominantly comprised participants with cirrhosis (83%), and participation in surveillance was associated with a significantly lower mortality.[12] However, outcomes in observational studies are inherently limited, given the potential for lead-time and length-time biases to overestimate survival benefit.[23]

Despite the low certainty of evidence, the current practice of HCC surveillance is endorsed by major guidelines and is established as a standard of care.[10,13,15-17] A previous Australian patient survey also detected low acceptability among patients with cirrhosis to participate in a randomised trial investigating HCC surveillance, with most instead preferring usual care with surveillance.[24] It is therefore unlikely that further randomised trials will be conducted to evaluate HCC surveillance.

Surveillance-related harm

Surveillance-related harm may consist of physical, financial or psychosocial harms. To date, three observational studies have investigated physical harms associated with HCC surveillance.[25-27] Although the use of ultrasound rarely results in direct harm, the downstream investigation of false-positive liver lesions may expose patients to radiation and contrast from other imaging modalities and even biopsies. This has been estimated to occur in 8–28% of patients across the three studies, with all finding the benefit of surveillance outweighs the risk of physical harm.[25-27]

Little is known about the financial or psychosocial harms that arise from HCC surveillance. Financial harms in other cancers have been documented, with evidence that false-positive cancer screens are associated with significant medical expenditure in prostate, lung, colorectal and ovarian cancer screening.[28] Psychosocial harms may also arise at any point in the surveillance cascade and negatively affect patients' quality of life. These include the frequent reminder to individuals that they are at risk of cancer, the anxiety associated with waiting for results, and false-positive findings. An observational study for breast cancer screening identified negative long term psychosocial consequences in women found to have false-positive findings.[29]

At present there are no published Australian data available for surveillance-related outcomes, including benefits or harms. Further research in this area across a range of subgroups in Australia is required, as ultimately the value of any cancer screening program is defined by the balance of benefits to harms. These data may also support improved surveillance algorithms to improve detection in high risk patients while minimising harm in lower risk patients.

Current surveillance uptake

One of the greatest limitations of HCC surveillance remains its limited uptake in many settings. A meta-analysis of 22 studies reported an overall adherence to HCC surveillance of 52% across a range of disease aetiologies and geographic regions.[30] While this is comparable to other cancer screening programs, the true surveillance rate is likely to be lower, with a rate of 39% noted within analysed retrospective studies, which may better reflect real-life clinical practice.[30]

Barriers occur at every step of the surveillance cascade and include patient, system, and clinician factors.

Patient barriers

Racial and socio-economic disparities are known to influence surveillance participation, with one United States study reporting significantly reduced surveillance participation among African Americans and underinsured patients.[31]

Although surveillance ultrasounds are funded by universal health care in Australia, marginalised groups continue to experience poor surveillance participation. Indigenous Australians in particular have a higher incidence of HCC, higher incidence of late stage disease at diagnosis, and poorer survival, which may stem from reduced access to screening in addition to socio-environmental inequality, cultural barriers, and a distrust in the health care system.[32-34] The 2023 Australian HCC surveillance guidelines specifically highlight the need to provide local access to culturally safe preventive care and surveillance within communities and on-Country where possible.[13]

System barriers

In contrast to other cancers, no centralised HCC surveillance and prevention programs exist in any Western country.[35] Coordination of surveillance is dependent on local protocols

2 Guideline recommendations for groups requiring hepatocellular carcinoma (HCC) surveillance

Guidelines	Recommendations for groups requiring HCC surveillance
Gastroenterological Society of Australia[10]	• All patients with cirrhosis, except Child–Pugh class C patients ineligible for transplantation • Chronic HBV infection without cirrhosis in: ▸ Asian men aged > 40 years ▸ Asian women aged > 50 years ▸ People born in sub-Saharan Africa aged > 20 years ▸ Aboriginal and Torres Strait Islander people aged > 50 years
European Association for the Study of the Liver[15]	• All patients with cirrhosis, except Child–Pugh class C patients ineligible for transplantation • Chronic HBV infection without cirrhosis in patients at intermediate or high risk of HCC • Patients without cirrhosis who have METAVIR stage F3 fibrosis, regardless of aetiology, may be considered based on individual risk assessment
American Association for the Study of Liver Diseases[16]	• All patients with cirrhosis, except Child–Pugh class C patients ineligible for transplantation • Chronic HBV infection without cirrhosis in: ▸ Asian men aged ≥ 40 years ▸ Asian women aged ≥ 50 years ▸ People with a family history of HCC ▸ All African/North American black adults
Asian Pacific Association for the Study of the Liver[17]	• All patients with cirrhosis, except Child–Pugh class C patients ineligible for transplantation • Chronic HBV infection without cirrhosis in: ▸ Asian men aged ≥ 40 years ▸ Asian women aged ≥ 50 years ▸ Africans aged ≥ 20 years ▸ People with a family history of HCC
Cancer Council Australia[13]	• All patients with cirrhosis, except Child–Pugh class C patients ineligible for transplantation • Chronic HBV infection without cirrhosis in: ▸ Asian or Pacific background men aged ≥ 40 years ▸ Asian or Pacific background women aged ≥ 50 years ▸ Sub-Saharan Africans aged ≥ 20 years ▸ Aboriginal and Torres Strait Islander people aged ≥ 50 years ▸ Aboriginal and Torres Strait Islander people aged ≥ 40 years with a high risk HBV genotype (testing not subsidised) ▸ Aboriginal and Torres Strait Islander people with a family history of HCC ▸ All other people aged ≥ 40 years with a family history of HCC

HBV = hepatitis B virus. ◆

and initiatives, but often is largely clinician driven through visit-based surveillance.

Conversely, Japan and South Korea have implemented centralised health promotion and surveillance programs. The Japanese program was implemented over 30 years ago, and includes public awareness campaigns, dedicated educators, and free hepatitis testing and surveillance.[35,36] Sixty-two percent of HCC cases in Japan are diagnosed at very early and early stage disease (BCLC stages 0 and A).[36]

In the absence of a centralised surveillance program, smaller scale health promotion and coordination initiatives may still improve surveillance. Reported interventions include primary care physician education, recall systems, nurse-led clinics, and mailed outreach invitations.[37-40] Most interventions are evaluated with before-and-after studies; however, a randomised trial in the US investigated mailed outreach invitations and patient navigation strategies.[40] This intervention resulted in a 16% higher rate of surveillance in the mailed outreach with patient navigation group compared with usual care, with consequently a higher rate of screen-detected HCC.

Two small Australian studies have described interventions to promote surveillance. One reported a nurse-led surveillance clinic, but did not describe the change in surveillance uptake following the intervention.[39] Another reported a before-and-after study of 22 patients with hepatitis C cirrhosis or hepatitis B, with the intervention consisting of improved doctor education, system redesign, and patient education.[41] This intervention resulted in an increase from no patients having appropriate surveillance (defined as four 6-monthly cycles of ultrasound and AFP over two years) to 64% post intervention.

Clinician barriers

In a meta-analysis of factors determining HCC surveillance, one of the most consistent correlates of surveillance participation was receipt of subspecialty care.[42] Surveillance participation was highest in patients enrolled in gastroenterology and hepatology clinics, followed by studies from centres including both subspecialty and primary care patients, and lowest among studies reporting population-based cohorts (73.7% *v* 29.5% *v* 8.8%; $P < 0.01$).

In Australia, very high surveillance rates have been reported among patients cared for through tertiary liver clinics in Melbourne, with a percentage of time up-to-date with surveillance of greater than 80%.[43,44] Primary care and population-based data on HCC surveillance are limited in Australia, although one retrospective study of patients with hepatitis B in primary care in Melbourne found that only 27% of patients had good adherence, which was defined as an average of ≥ 1 ultrasound every 7 months.[45]

The problems with surveillance in primary care may be multifactorial. A web-based survey of US primary care providers identified high rates of misconceptions and clinician barriers,

including not being up to date with surveillance recommendations, limited time in clinic, and competing clinical concerns.[46]

Identifying at-risk patients

Implementation of HCC surveillance differs from that for bowel and breast cancer as the at-risk population is significantly narrower. Identifying this cohort, however, may be challenging as cirrhosis and viral hepatitis may remain asymptomatic for many years. This challenge is highlighted in a US veteran study, in which 24.6% of patients with HCC and cirrhosis had unrecognised cirrhosis before their HCC diagnosis, and this group was significantly more likely to have advanced HCC.[47]

Improving HCC outcomes therefore requires case-finding strategies to better identify at-risk patients.[48] The use of hospital coding and administrative data has been demonstrated to have a high level of accuracy in identifying patients with cirrhosis, offering a potential opportunity for early detection.[49,50] In another novel example, a machine learning algorithm was developed to accurately detect cirrhosis through electrocardiogram changes.[51]

Hepatitis C is the most common aetiology of HCC in Australia and most Western countries.[12] In France and the US, universal hepatitis C screening has been proposed to allow for the institution of direct-acting antiviral therapy.[52,53] In addition to gaining access to treatment, however, expanded hepatitis C screening may also increase the identification of high risk patients who could be enrolled in HCC surveillance.

Health promotion initiatives also hold a central role given a limited public understanding of liver disease, its risk factors, and its complications.[54-56] This need is particularly acute in regional and remote Australia, where HCC age-standardised incidence rates are double those of urban centres.[4,57] Strategies may include targeted education campaigns, mobile liver screening services, and expanding access to point-of-care diagnostics such as transient elastography.[58,59]

Risk prediction models

Risk prediction models may have an expanded future role in targeting patients for HCC surveillance. These models may be particularly advantageous in groups who fall under grey areas within the guidelines or where inconsistency exists, such as individuals without cirrhosis who have hepatitis B, hepatitis C, or MAFLD.

For chronic hepatitis B virus infection, numerous models incorporating clinical and biochemical values now exist for predicting HCC, where they have an additional role in informing decisions regarding the initiation of antiviral therapy.[60] Most models were developed from Asian datasets, with only the PAGE-B score developed among patients of European ancestry, although this model only included patients treated with antiviral therapy.[61,62]

Another group of recent interest in HCC risk categorisation is patients with hepatitis C who have undergone viral elimination with direct-acting antiviral therapies. In a cohort mostly without cirrhosis, Tahata and colleagues produced a prediction model based on clinical and biochemical factors, following sustained virological response.[63] Semmler and colleagues similarly produced an HCC risk stratification algorithm for patients with hepatitis C following sustained virological response; however, this only included patients with advanced chronic liver disease.[64] Patients who undergo hepatitis C treatment may sometimes experience fibrosis regression following sustained virological response. The risk of HCC for this cohort is uncertain, with limited data to support decision making for surveillance.

The recognition that HCC may develop in MAFLD without cirrhosis presents a unique challenge for screening and surveillance.[65] Owing to the extremely high prevalence of MAFLD, risk categorisation algorithms and scores are a particularly desirable approach for guiding HCC surveillance. While there are no established HCC risk prediction scores for non-cirrhotic MAFLD at present, available observational data suggest that elevated alanine transaminase levels, male gender, smoking, and diabetes are risk factors for HCC.[66]

Biomarkers

Serum biomarkers present a possible alternative to ultrasound-based HCC surveillance. Inter-observer variability is non-existent for biomarkers, and they are more convenient and accessible for patients. These advantages could in theory promote improved outcomes through increased surveillance participation.

α-Fetoprotein

Serum AFP is the most utilised biomarker for HCC, and its use is discussed in all major clinical guidelines for HCC management.[10,13,15-17] In large scale prospective studies, AFP has a sensitivity of only 54% in detecting HCC at a cut-off of >20 ng/mL, and as such is not a desirable screening or surveillance test in isolation.[67] The addition of AFP to ultrasound surveillance improves the sensitivity of detecting early stage HCC, but at the trade-off of reduced specificity.[68] At present, the use of AFP as a complementary surveillance test to ultrasound therefore remains discretionary among the major HCC clinical guidelines.

Novel biomarkers

Des-γ-carboxy prothrombin (DCP) and lens culinaris agglutinin-reactive fraction of AFP (AFP-L3) are two novel biomarkers that are highly specific for the diagnosis of HCC.[69-71] Several clinical scores have been derived from these biomarkers, including the GALAD (gender, age, AFP-L3, AFP, DCP) and GAAD (gender, age, AFP, DCP) scores.[72,73] One prospective study found that longitudinal GALAD scoring may produce comparable sensitivity for HCC detection to ultrasound-based surveillance, while another study combined the use of ultrasound with GALAD scoring and found a superior diagnostic performance to either GALAD or ultrasound alone.[74,75] These findings require further validation in phase 3 or 4 biomarker studies to validate their performance in HCC surveillance and to allow further adjustments in score thresholds.[76]

Computed tomography and magnetic resonance imaging

Several studies have evaluated computed tomography (CT) and magnetic resonance imaging (MRI) for HCC surveillance. A single-arm study in South Korea,[77] in which high risk participants (>5% annual risk) underwent biannual ultrasound surveillance and two-phase low dose CT over 1.5 years, found that low dose CT showed a higher sensitivity and specificity than ultrasound, with fewer false-positive diagnoses.

A randomised trial in a US veteran population, comparing standard biannual ultrasound surveillance to annual triple phase CT, found that ultrasound demonstrated marginally superior sensitivity and was less costly for detecting early HCC.[78] This cohort was lower risk than that of the South Korean study,[77] with

most participants being white people with cirrhosis secondary to hepatitis C virus infection.

In another prospective Korean study in which high risk participants underwent simultaneous biannual ultrasound surveillance and contrast-enhanced MRI over 1.5 years,[79] the HCC detection rate was significantly higher for MRI than ultrasound (86% *v* 28%). MRI surveillance again resulted in fewer false-positive diagnoses.

Non-contrast MRI has also been evaluated in a recent meta-analysis, with the authors reporting a sensitivity of 79.2% (diffusion-weighted MRI) to 86.8% (multisequence MRI) for the detection of HCC.[80] However, prospective data in the surveillance setting are required.

While it is likely that CT and MRI have higher diagnostic performance than ultrasound for HCC surveillance, longer term studies are needed to assess the impact on HCC-related mortality and to address potential lead-time and length-time biases. The cost and resources required to deliver CT and MRI may also be prohibitive in a universal surveillance context. In the era of personalised medicine, however, there maybe a future role in delivering CT or MRI surveillance for certain high risk populations.

Cost-effectiveness of HCC surveillance

Cost-effectiveness is a key consideration in cancer screening programs. In Australia, an assumed willingness-to-pay threshold of AU$30 000–50 000 per life-year saved or quality-adjusted life-year saved is frequently reported to assess cost-effectiveness of cancer screening.[81]

There is evidence that HCC surveillance is cost-effective; however, this depends on the incidence of HCC. US guidelines indicate that surveillance is likely cost-effective in patients with cirrhosis if the risk of HCC exceeds 1.5% per year, but most referenced models are North American with an accepted willingness-to-pay threshold of US$50 000–100 000.[16] There is some evidence, however, that in patients with hepatitis B virus infection without cirrhosis, surveillance may be cost-effective once incidence exceeds 0.2% per year.[8]

In an Australian cost-effectiveness analysis for HCC surveillance, a biomarker risk-stratified approach was compared with a standard all-inclusive approach among patients with cirrhosis.[82] Both models were ultimately found to be cost-effective when compared with no screening at all, with an incremental cost-effectiveness ratio of AU$23 090 per quality-adjusted life-year for the standard surveillance approach. However, the model used data from international surveillance cohorts, given an absence of longitudinally reported outcomes for HCC surveillance in Australia. Future analyses should incorporate data from Australian surveillance outcomes, as well as the cost-effectiveness of alternative surveillance strategies including risk-based screening and biomarker panels.

Conclusion

Overall, the increasing disease burden of HCC presents a major public health challenge in Australia. The current surveillance strategy almost certainly improves outcomes, but there are multiple challenges that must additionally be considered in improving its delivery. This includes an enhanced understanding of surveillance-related harms, addressing barriers within the surveillance cascade, case finding of high risk patients, and considering novel prediction models and screening tests, such as biomarkers, CT, and MRI.

With time, a centralised surveillance program may be an effective way of delivering improved and more equitable care. The cost implications of such a program need to be evaluated, although it should be noted that the current model of clinician-driven surveillance already relies heavily on Medicare-funded care.

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