Current issues in the prevalence, diagnosis and management of hepatocellular carcinoma in Australia

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Abstract
Hepatocellular carcinoma (HCC) is the commonest primary liver cancer encountered in the community and a leading cause of cancer morbidity and mortality. In Australia, there are several current important issues that need to be addressed in HCC management. There is a dramatically rising incidence of HCC in Australia with comparatively poorer outcomes in remote regions and in socioeconomic disadvantaged groups. Aboriginal people have a greater incidence of HCC on a background of increased liver disease prevalence and face several barriers to delivery of better healthcare outcomes compared to other Australians. The previously adopted use of imaging alone to diagnose HCC is now being challenged with biopsy likely to become increasingly necessary with the increased uptake of personalised medicine management. Managing HCC is complex involving many disciplines with the multidisciplinary team approach being the current accepted standard of care for patients. New immunotherapy combinations promise to offer patients with advanced HCC promising novel management options. However, the Australian inequities in prevalence, diagnosis and service provision, especially in Aboriginal people, need to be redressed concurrently with the adoption of new HCC management options.

Introduction
Primary liver cancer, also known as hepatocellular carcinoma (HCC), is the sixth most commonly encountered malignancy and fourth leading cause of cancer deaths globally.1 Management of HCC in Australia is outlined in a recent consensus document with evidence-based recommendations.2 Several important HCC specific issues within Australia will be addressed in this article: (i) the disease epidemiology and effect of both remoteness and socioeconomic status on HCC incidence and outcomes; (ii) the disease prevalence and outcomes in Aboriginal and Torres Strait Islander peoples (hereafter respectfully referred to as Aboriginal peoples); (iii) early detection of HCC, use of biopsy and the importance of multidisciplinary care team meetings; and (iv) advanced HCC management with immunotherapy.

Epidemiology of HCC in Australia
The incidence and mortality of HCC from 1982 to 2019 has increased markedly compared to all other commonly encountered cancers.2,3 Between 1982 and 2014, HCC incidence increased Australia wide from 1.38 to 4.96 per 100 000, and over the same period this was associated with an improvement in survival from a median of 2.1 to 12.1 months.3

International outcome predictions for HCC incidence until 2030 show that marked regional differences within
Australia predicted to have a 68% increase in incidence rate compared to 2005. Across the Asia-Pacific region, there is a changing burden of liver disease, but the increase in metabolic diseases and associated non-alcoholic fatty liver disease (NAFLD) in Australia is of concern that will have a long-term negative impact on HCC diagnosis and management in this country.

The Australian Institute of Health and Welfare (AIHW) Cancer in Australia report lists HCC as the 10th most commonly diagnosed cancer in Australian men (n = 1907) and for women 19th (n = 692). However, reflecting the poor outcomes seen with HCC, deaths in 2019 were elevated to the fifth (n = 1436) and eighth (n = 725) most common causes for men and women respectively.

Age is a significant contributor to both incidence and mortality related to HCC with diagnoses being the highest in men aged 75–79 years (incidence 24.3/100 000). Disparities have been noted in HCC incidence between men and women across all age groups with highest in the age group 50–59 years where the gap is 28 times higher among men than women. In this age group and lower age groups, a hepatitis C virus (HCV) incidence cohort effect is evident and it will be of great interest to monitor the impact of curative HCV treatments on HCC prevalence and outcomes. However, the increasing prevalence of NAFLD with the well-documented increase in associated obesity and diabetes will likely offset some or all of these gains.

Place of residence and socioeconomic status significantly impact HCC diagnosis and outcomes in Australia. The AIHW reports the HCC age standardised incidence rate is double in very remote regions compared to urban centres. Early diagnosis of HCC is essential for the best outcomes. However, people who live in very remote areas are 50% less likely to be diagnosed with HCC. Deaths are also reflected in these regional differences with the age-standardised death rates rising from 5.7 in urban areas to 11 per 100 000 in very remote regions.

The prevalence of HCC in Australian urban centres is greater than that previously predicted. In Melbourne, a detailed analysis based on cases reviewed showed that the true incidence of HCC per 100 000 was 10.3 in men and 2.3 in women. In contrast, the Victorian Cancer Council reported rates of 5.3 and 0.7/100 000 respectively. Similarly, a Queensland-based study concluded that there was a higher incidence in major cities, among Aboriginal peoples, and also confirmed that social disadvantage is associated with worse survival.

Socioeconomic status similarly impacts appropriate diagnosis with HCC, with people living in highest socioeconomic areas being 58% more likely to be diagnosed compared to the residents in lowest socioeconomic status areas. Similarly, mortality rates attributable to HCC increase with disadvantaged socioeconomic status, with the age standardised rates per 100 000 increasing from 4.9 to 7.9 in lowest socioeconomic status areas with an overall 61% increase. Thus, both remoteness and lower socioeconomic status negatively impact HCC diagnosis and outcomes to an extent that is significantly worse than that seen for virtually any other common malignancy encountered in Australia.

**HCC among Aboriginal peoples of Australia**

Aboriginal peoples are disproportionately affected by liver disease and HCC compared to the rest of the Australian population. In Aboriginal peoples, HCC is much more common than the rest of the Australian population. HCC is diagnosed as the 5th and 11th most common malignancy in Aboriginal men and women respectively, and the 3rd and 5th cause of cancer death in men and women respectively. Five-year survival from HCC is <20% placing it among the lowest long-term survival rates for any common malignancy, with even worse outcomes in Aboriginal peoples. A Northern Territory study conducted between 1991 and 2011 identified 145 incident HCC, and in Aboriginal peoples showed age-adjusted incidence was 5.9 times higher, only 15% of HCC were detected through a surveillance programme, presentation is at a later disease stage with larger tumours and the median survival was only 64 days after diagnosis compared with 172 days in the rest of the Australian population.

Importantly, the risk for HCC in Aboriginal peoples is compounded by increased prevalence of several synergistic risks for liver carcinogenesis. Alcohol misuse and smoking are common among Australians, including Aboriginal peoples, and contribute to liver fibrosis progression and carcinogenesis. Prevalence rates of viral hepatitis are higher among Aboriginal peoples than the rest of the Australian population. Hepatitis B virus (HBV) infection is reported at four times the rate among Aboriginal peoples (4%) compared with the rest of the Australian population (1%) and is the primary aetiology in 40.5% of HCC patients. Moreover, Aboriginal peoples have a more aggressive HBV genotype (C4) associated with rapid progression of liver disease and HCC risk. High vaccination coverage including birth dose immunisation among Aboriginal communities has led to impressive reductions in chronic HBV prevalence among children under 5 years of age. However, despite this, the future risk of HBV-related HCC among Aboriginal peoples will remain for several generations. Additionally, HCV prevalence is higher among Aboriginal peoples at 3% compared with 1% in the Australian
population. Furthermore, in Aboriginal peoples, the prevalence of obesity is estimated to be between 30% and 40% and Type 2 diabetes ranging 15–25%, both being key risks for NAFLD development and independently associated with HCC. Finally, alcohol misuse and smoking are common among Aboriginal peoples and contribute to liver fibrosis progression and carcinogenesis. Therefore, every common major liver disease risk factor associated with HCC development is increased in Aboriginal peoples.

Multiple health system barriers exist for Aboriginal peoples that impede timely healthcare access and therefore adversely impact liver disease diagnosis, management and HCC prevention. Around 20% of Aboriginal peoples live in remote or very remote areas compared with 2% of non-indigenous Australians. Healthcare service utilisation and health literacy among Aboriginal peoples, in both metropolitan and rural areas, are adversely affected by other social determinants of health such as socioeconomic inequality, homelessness, disproportionate rates of incarceration, reduced education opportunities, stigmatisation and distrust in hospital-based services. Other barriers to Aboriginal peoples in Australia accessing healthcare services include stigmatisation, lack of trust in healthcare services, lack of continuity of care in health services, inadequate culturally appropriate and native language resources and a lack of community consultation with meaningful engagement.

Ongoing efforts to redress the social determinants of health that drive health inequity are required. The renewed Close the Gap National Agreement (2020) aims to redress many of the persistent drivers of health inequity by 2030. To address the poor outcomes of HCC in Aboriginal peoples in Australia aside from ongoing efforts to address upstream drivers of health inequity, an investment in a public health approach to reduce liver disease is imperative. Strategies proposed include the implementation of universal HBV vaccination for adults, greater availability of harm minimisation strategies particularly in regional and remote areas as well as optimised management of obesity and the metabolic syndrome.

Funded models of care delivered in the community by appropriately trained non-specialists as well as the use of point-of-care diagnostics and telemedicine innovations may improve diagnosis, linkage to care and treatment uptake for people living in regional and remote areas. Programmes developed in collaboration with Aboriginal communities have greatest efficacy and have been shown to be feasible, acceptable and effective for improving liver disease diagnosis and linkage to care.

**Diagnosis of HCC and use of biopsy**

The identification of early HCC requires effective surveillance. The diagnosis of HCC is unusual in oncological practice as it is widely accepted that it can be made without liver biopsy. However, there is renewed interest in histological and molecular analysis of tissue samples for the purpose of diagnosis, prognosis and therapeutic targeting of HCC.

**Surveillance and imaging diagnosis of HCC**

Surveillance results in detecting significantly earlier stage HCC with improved rates of curative therapy. The mainstream of surveillance is imaging with liver ultrasound. Patients with cirrhosis or those at increased risk of HCC (e.g. certain non-cirrhotic patients with hepatitis B) should undergo surveillance for HCC with 6-month liver ultrasound and serum alpha-fetoprotein (AFP). In cirrhotic patients undergoing ultrasound surveillance for HCC, >60% of new lesions will be HCC. AFP has been widely adopted with its addition leading to an increase in detection of early HCC detection although an improvement in overall survival (OS) has not been demonstrated. The new Australian-specific recommendations recommended ultrasound surveillance every 6 months, which can be combined with AFP. Recognition of the importance and use of the correct modality of surveillance are clear determinants of efficacy. However, in an Australian setting, the effect of these issues combined with remoteness and socioeconomic status impact on surveillance efficacy is unknown and this will be important to understand.

If a suspicious lesion greater than 10 mm is identified, patients should proceed to cross-sectional imaging with either multiphase computed tomography or magnetic resonance imaging to further characterise the lesion. The diagnostic accuracy of imaging criteria to identify HCC correctly increases in parallel with lesion size. HCC less than 10 mm in diameter may not display the characteristic imaging features and depending on location may be technically difficult to biopsy, requiring an alternative imaging modality or repeat imaging after a short interval being the recommended approach.

The non-histological approach to HCC diagnosis is beginning to be challenged. In the era of personalised medicine, understanding individual tumour biology with molecular testing and the use of targeted therapy is being adopted. Previous reluctance for histopathological confirmation of HCC related to the limited systemic therapeutic options available, as there was only one systemic therapy approved up until 2019. The reliance on imaging rather than tissue diagnosis and paucity of molecular research may have impeded the development of the
therapeutic and prognostic opportunities enjoyed by other tumour streams, such as colorectal and breast cancer, where a personalised medicine approach is being adopted. Subclassification of HCC based on morphomolecular and clinical characteristics is important for appreciating the heterogeneity of HCC and has been updated in 2019. It is estimated that 20–30% of HCC can be defined as distinct subtypes of HCC. Prognostic information from tissue sampling is still not mainstream but can already provide clinically relevant prognostic information.

Changing the current diagnostic approach of HCC with its dependency on imaging criteria must be reconciled by the likelihood of clinically relevant information provided by histopathology and molecular markers and the additional risk to the patient from an invasive test such as liver biopsy. Potential complications such as mild and severe bleeding (3–4% and 0.5% respectively) and needle-track tumour seeding (up to 2.7%) need to be considered in settings outside that of clinical research.

In the future, routine biopsy of HCC may predict response to new novel therapies such as immunotherapy-based regimens. However, to date there are few data demonstrating clinical relevance of biopsy findings to predict HCC response to immunotherapies. Expression of PD-1 on tumours can predict response in other malignancies such as melanoma and lung cancer. Furthermore, a quarter of all liver cancer have an immunophenotype with expression of markers consistent with an inflammatory response. Finally, the nature of biopsy specimens may change with liquid biopsies, particularly cell-free DNA, being used in other malignancies to predict the tumour mutational profile and thus classify and individualise therapy.

**Multidisciplinary team management in HCC**

HCC is recognised to be a complex disease from diagnosis to management. Furthermore, up to 20% of patients presenting have advanced decompensated liver disease and greater than 40% have significant hepatic decompensation during their illness. Therefore, multidisciplinary team (MDT) care is now widely recommended in the management of HCC to optimise patient care. MDT care appears to improve several aspects of HCC management including: (i) screening procedures; (ii) early diagnosis rates; and (iii) treatment including a higher likelihood of receiving curative and palliative therapy and treatment deemed the most appropriate according to standard of care. Importantly, MDT care also improves the OS of HCC patients. Implementation of an MDT at a single centre improved OS of patients from 21% to 65% while the median patient follow up improved from 4.5 months to 9.5 months with the odds ratio for survival being 7.1. Similarly, in a large cohort study an MDT tumour board was independently associated with reduced patient mortality. Furthermore, the introduction of an MDT was associated with a significant improvement in survival of patients with the median survival being 13.2 months post-MDT initiation compared to 4.8 months prior to MDT formation.

**MDT composition for HCC management**

Multiple specialists performing different roles are required to deliver optimal care and improve the clinical outcomes and quality of life in patients with HCC. These include: (i) hepatologists/gastroenterologists; (ii) diagnostic and interventional radiologist(s); (iii) hepatobiliary and transplant surgeons; (iv) medical oncologists; (v) radiation oncologists; (vi) palliative care physicians; and (vii) HCC nurses. However, the availability of treatment modalities and level of expertise and experience that manage HCC within each specialty varies considerably across healthcare facilities. Hence, when establishing a HCC MDT, it is recommended that at least one representative from each specialty of providers who care for patients with HCC at a particular institution be included. Interestingly, the relationship between MDT speciality and OS showed that specialist care by a hepatologist, medical oncologist, or surgeon were all individually associated with reduced patient mortality. MDT meetings should be held regularly to make consensus diagnostic and management recommendations with the frequency of these being in accordance with institution size and patient numbers. There is no consensus in the literature about who should lead the MDT. For effective MDT functioning, leadership should be based on the principles of cohesiveness and consensus, whereby clinical decision-making is devoid of collective and individual bias and appropriate weighting is placed on features specific to individual cases. Where deficiencies have been identified within an institution’s HCC management programme (e.g. absence of liver transplantation), relationships should be established with external healthcare providers to address these. Furthermore, if healthcare professionals diagnosing and managing HCC cases are not in a position to establish an MDT within their own centre such as in regional and rural communities, relationships should be developed with larger centres who have access to MDT care to facilitate patient management.

In Australia, MDT offer potential access to the best standard of care particularly using telehealth facilities, teleconferencing or Internet-based technologies. Although many patients who are not near major urban
Table 1 Phase III clinical studies using immunotherapy agents alone or in combination for HCC

| Agent | Class | Number | Comparator | Survival | Progression-free survival | ORR | DCR | Grade 3 and 4 TRAE | Study/identifier | Reference |
|-------|-------|--------|------------|----------|---------------------------|-----|-----|-------------------|----------------|-----------|
|       |       |        |            |          |                           |     |     |                   |                 |           |
| Nivolumab (240 mg IV Q2W) | Anti PD-1 | n = 743 | Sorafenib | 16.4 (13.9–18.6) months vs 14.7 months (11.9–17.2) | NS (HR = 0.85 (95% CI: 0.72–1.02); P = 0.0752) | 15% vs 7% | NR = not reported | 22% vs 49% | 15% vs 7% | Discontinue 4% vs 8% | CheckMate 459 | NCT02576509 |
| Atezolizumab + bevacizumab | Anti PD-L1 + anti-VEGF | n = 501 | Sorafenib | 6- and 12-month survivals | 84.8% (95% CI, 80.9–88.7) vs 72.2% (95% CI, 65.1–79.6) | 54.6% (95% CI, 45.2–64.0) | 27.3% (95% CI, 22.5–32.5) vs 17.9% (95% CI, 14.0–21.8); P < 0.001 | 73.6% vs 55.3% | 56.5% vs 55.1% | Withdrawal 15.5 vs 10.3% | IMBrave150 | NCT03434379 |
| Pembrolizumab dual end-point of OS and PFS did not reach statistical significance | Anti PD-1 | n = 413 | Placebo | 13.9 months (95% CI, 11.6–16.0 months) for pembrolizumab vs 10.6 months (95% CI, 8.3–13.5 months) for placebo | Not reached (HR, 0.781; 95% CI, 0.611–0.986; P = 0.0238) | 18.3% (95% CI, 14.0–23.4%) for pembrolizumab and 4.4% (95% CI, 1.6–9.4%) for placebo one-sided P = 0.00007 | 62.2% (95% CI, 56.2–68.0%) and 53.3% (95% CI, 44.6–62.0%), respectively; nominal one-sided P = 0.03807 | 18.6 vs 7.5% | 14.3% vs 5.2 (adj 3–4 leading to discontinue) | KEYNOTE-240 | NCT02702401 |
| Nivolumab + carbozantinib ± ipilimumab | Anti PD-1 + MKI ± Anti CTLA4 | n = 71 | Sorafenib naive or experienced | Not reached | (1) 5.5 months vs (2) 6.8 months | (1) 1.7% vs (2) 26% | (1) 81% vs (2) 83% | (1) 42% vs (2) 71% | Discontinue for SAE in (1) 3% vs (2) 20% | CheckMate 040 | NCT01658878 |

Negative studies are shaded grey. DCR, disease control rate (objective response plus stable disease according to RECIST 1.1); ORR, objective response rate (complete response plus partial response according to RECIST 1.1); TRAE, treatment-related adverse events.
centres are being managed in MDT, it is unknown to what extent these services are used and what are the barriers to further uptake. Further initiatives should be explored to understand how regional approaches of MDT can be implemented across vast tracts of land where Aboriginal peoples reside and who are at a greater risk of HCC and its consequences.

The role of immunotherapy in the treatment of advanced HCC

Systemic therapy is the standard of care for patients with advanced HCC or multifocal HCC that is not amenable to curative therapy. The past decade has seen the multikinase inhibitor therapy with sorafenib and lenvatinib, being the only approved initial systemic therapy for HCC in patients. However, survival outcomes with these therapies have been modest and the side effects can be significant leading to poor quality of life and high treatment discontinuation rates.

In comparison, immunotherapies (i.e. checkpoint inhibitors) have shown promising clinical efficacy and safety in the treatment of HCC (Table 1). Following the early failures of immunotherapeutic monotherapy regimens as first-line therapy in advanced HCC, these agents have been combined with vascular endothelial growth factor (VEGF) inhibitors, multikinase inhibitors or other immunotherapies to improve clinical efficacy (Table 1).

The combination of atezolizumab with the VEGF inhibitor, bevacizumab, is the most promising new immunotherapy regimen now approved for advanced HCC treatment. In Phase III trials, this combination demonstrated superior efficacy as well as good tolerability and safety when compared with sorafenib in the treatment of unresectable HCC. Treatment improved OS by 42% and progression-free survival (PFS) by 41% compared to sorafenib. The safety profile was acceptable with Grade 3 or Grade 4 adverse events similar in frequency to that seen with sorafenib (56.5 vs 55.1%), while only 7% withdrew from combination therapy. Based on these data, the regimen has been approved for the treatment of advanced HCC by both the Food and Drug Administration (FDA) in the United States and the Pharmaceutical Benefits Scheme (PBS) in Australia. The PBS recommendations are for the treatment of patients with unresectable locally advanced or metastatic Barcelona Clinic Liver Cancer (BCLC) Stage B or Stage C HCC who have not received prior systemic therapy, are Childs Pugh class A cirrhosis and are unsuitable for transarterial chemoembolisation. Patients intolerant of VEGF tyrosine kinase inhibitors requiring permanent treatment withdrawal are also eligible for this therapy. This is a significant advance in systemic HCC management showing an overall marked improvement in outcome with more tolerable side effects.

Looking to the future, there is cause for optimism in improving survival outcomes of patients with advanced HCC, given the new combination immunotherapies in Phase III clinical trials as first-line therapy. These include the dual immunotherapy regimen of durvalumab plus tremelimumab that demonstrated promising clinical activity in an ongoing Phase II study in which it achieved an objective response rate (ORR) of 24% and median OS of 18.7 months in a predominantly second-line population. Similarly, the combined immunotherapy regimen of nivolumab plus ipilimumab data showed promising results in a Phase II study as second-line therapy with an ORR of 32% and median duration of response of 17.5 months. Other promising regimens in advanced clinical trial development include the combination of immunotherapies with multikinase inhibitors including pembrolizumab plus lenvatinib, atezolizumab plus cabozantinib and camrelizumab plus apatinib.

However, several challenges remain particularly in determining the appropriate choice of initial treatment for patients, the optimal sequencing of treatments in those who progress or are intolerant of first-line therapy. Further resources are required to provide appropriate and timely intravenous-based immunotherapy particularly to remote and regional communities. These complicated treatment options require careful consideration of the benefit to safety risk profile of the therapy in the context of the individual patient profile including liver disease severity and tumour characteristics.

Conclusion

In Australia, HCC incidence is rising and predicted to continue to rise. This is associated with poorer rates of diagnosis and increased deaths in remote regions, socioeconomic disadvantaged groups and Aboriginal peoples in Australia. This must be addressed by tackling key socioeconomic and health system barriers, public health and clinical strategies that drive inequity in liver disease outcomes. More work and urgent resource allocation are required to both better understand and redress the discrepancies in care in remote regions, socially disadvantaged individuals and Aboriginal peoples. Key areas that need to be addressed include the barriers to uptake better HCC surveillance, as well as ensuring the widespread adoption of MDT in HCC management. However, there is cause for optimism as there are new treatment options for managing advanced HCC using immunotherapies that offer fresh hope to patients.
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