Australian recommendations for the management of hepatocellular carcinoma: a consensus statement

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Abstract

Introduction: Hepatocellular carcinoma (HCC) is a leading cause of cancer deaths both globally and in Australia. Surveillance for HCC in at-risk populations allows diagnosis at an early stage, when potentially curable. However, most Australians diagnosed with HCC die of the cancer or of liver disease. In the changing landscape of HCC management, unique challenges may lead to clinical practice variation. As a result, there is a need to identify best practice management of HCC in an Australian context. This consensus statement has been developed for health professionals involved in the care of adult patients with HCC in Australia. It is applicable to specialists, general medical practitioners, nurses, health coordinators and hospital administrators.

Methods and recommendations: This statement has been developed by specialists in hepatology, radiology, surgery, oncology, palliative care, and primary care, including medical practitioners and nurses. The statement addresses four main areas relevant to HCC management: epidemiology and incidence, diagnosis, treatment, and patient management.

A modified Delphi process was used to reach consensus on 31 recommendations. Principal recommendations include the adoption of surveillance strategies, use of multidisciplinary meetings, diagnosis, treatment options and patient management.

Changes in management as a result of this statement: This consensus statement will simplify HCC patient management and reduce clinical variation. Ultimately, this should result in better outcomes for patients with HCC.

This consensus statement is applicable to specialists, general medical practitioners, nurses, health coordinators and administrators involved in the care of adult patients with hepatocellular carcinoma (HCC).

These recommendations summarise the complete document, available at https://www.gesa.org.au/resources/hepatocellular-carcinoma-hcc-management-consensus/.

Methodology

Recommendations were graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE).[1] The quality of the evidence was classified as high, moderate, low, or very low, and the strength of recommendation was classified as either strong or weak.

This consensus statement was developed with the principles outlined by the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument.[2]

Consensus was defined as a greater than 80% agreement by experts. The modified Delphi process was used to determine consensus and comprised two face-to-face meetings and three rounds of online questionnaires.[3] The complete list of recommendations and the level of agreement are shown in Box 1.

Epidemiology and surveillance

Globally, hepatocellular carcinoma is a leading cause of cancer death and the seventh most common cancer.[4] In Australia, the incidence has increased markedly from 1982 (1.38/100 000) to 2014 (4.96/100 000)[5] and within Australia there is significant regional variation in incidence. Although mortality rates of many cancers have plateaued, cancer death due to HCC is rising,[6] and despite improvements in treatment, the overall 5-year survival in Australia is about 20%.[7]

HCC usually develops in the setting of chronic liver disease, and cirrhosis is present in 85–90% of affected individuals. Male incidence is three to four times that of females[7,8] and the major aetiologies for HCC are shared with the causes of cirrhosis (hepatitis C virus [HCV] infection, 41%; alcohol-related liver disease, 39%; hepatitis B virus [HBV] infection, 22%; and fatty liver disease, 14%).[8] HBV infection is more common in culturally and linguistically diverse populations, and in Australia, more than 50% of patients with HCC were born overseas.[8]

Incidence of HCC in Australian Indigenous populations

Indigenous Australians account for 3.3% of the population, yet are disproportionately affected by HCC, with 2.4-fold higher rates of diagnosis and mortality compared with non-Indigenous populations.[7] Inequalities in health service access with resulting late presentation, greater incidence of risk factors for liver disease, socio-economic disadvantage and geographical remoteness of Indigenous communities in many parts of Australia contribute to a greater burden of HCC incidence and mortality.[9] Chronic HBV and HCV infection prevalence is estimated at 6% and 2.9% respectively among Indigenous Australians in the Northern Territory.[10] Of concern, among Indigenous Australians, only 14% of HCC is detected through surveillance programs, and the median survival time is markedly lower in Indigenous compared with non-Indigenous Australians (64 *v* 172 days).[11]

Target populations for HCC surveillance in Australia

Several target populations for surveillance have been defined based on decision analyses that show surveillance becomes cost-effective when the incidence of HCC in these at-risk populations approaches certain thresholds.[12] The single most significant risk factor for developing HCC is cirrhosis.[13] However, HCC risk is sufficiently high in some non-cirrhotic patients with hepatitis B to justify surveillance[11] (Box 2).

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1 Recommendations of the hepatocellular carcinoma (HCC) consensus statement

No.	Consensus recommendation	GRADE quality of evidence*	Level of agreement *n*† (%)‡
1	HCC surveillance should be offered to all patients with cirrhosis if they are suitable and willing to receive treatment	C1	48 (100%)
2	HCC surveillance should be undertaken in non-cirrhotic individuals with chronic HBV infection who are at increased risk of HCC	C1	46 (97.8%)
3	Surveillance for HCC should be undertaken using liver ultrasound every 6 months	B1	49 (98.0%)
4	Combining α-fetoprotein testing with liver ultrasound may be considered for HCC surveillance	C2	45 (88.9%)
5	Antiviral therapy for HCV infection may be offered to patients with HCC who have undergone surgical or locoregional treatment with curative intent	B2	40 (92.5%)
6	Patients with HCV infection-related cirrhosis who achieve sustained virological response and undergo curative therapy for their HCC require ongoing surveillance	B1	46 (95.7%)
7	HCC surveillance in non-cirrhotic patients can be considered in select patient populations	C2	43 (90.7%)
8	In the setting of cirrhosis, imaging diagnosis of HCC should rely on standardised criteria, based on evidence and validated in clinical practice	B1	50 (98.0%)
9	Multiphase CT or MRI is the recommended investigation for lesions suspicious for HCC	A1	50 (98.0%)
10	For indeterminate lesions > 10 mm diameter in cirrhotic livers, either targeted liver biopsy or repeat interval imaging or an alternative imaging modality is required for diagnosis	B1	45 (97.8%)
11	It is recommended that the BCLC staging system is used as the framework for HCC management in Australia	B1	50 (94.0%)
12	The management choice for a patient with HCC should take into account the individual patient's wishes and medical and psychosocial circumstances	C1	50 (100%)
13	The management of HCC should be determined by a multidisciplinary team to optimise patient care	B1	50 (100%)
14	Liver resection is a first-line therapy option in suitable patients with HCC where there is preserved liver function, sufficient liver remnant, and absence of significant portal hypertension	B1	48 (95.8%)
15	Liver transplantation should be considered for patients with HCC within transplant criteria who are not suitable for curative hepatic resection or ablative therapy	A1	48 (100%)
16	UCSF criteria should inform patient selection for liver transplantation in patients with HCC	B1	47 (100%)
17	Patients with HCC initially beyond transplant criteria may be considered for liver transplantation after successful downstaging to within standard transplant criteria	C1	41 (97.6%)
18	Ablative therapy is recommended as a curative locoregional therapy in suitable patients with very early or early (BCLC stage 0 or A) HCC	B1	39 (94.9%)
19	Patients with early stage disease (BCLC stage A and early stage B), who are not candidates for surgery or liver transplantation, should be treated with locoregional therapy	A1	48 (100%)
20	In patients with BCLC-B HCC, TACE is recommended as first-line therapy	B1	47 (97.9%)
21	SIRT may be considered in select patients with intermediate or locally advanced HCC	C2	44 (88.6%)
22	Stereotactic external-beam radiation therapy may be considered for local tumour control in suitable patients with HCC	C2	42 (81.0%)
23	Patients with advanced HCC (BCLC-C) or multifocal HCC that is not amenable to curative or locoregional therapy (BCLC-B) should be offered systemic therapy	A1	49 (93.9%)
24	Sorafenib or lenvatinib§ is recommended as initial systemic therapy in patients with advanced (BCLC-C) or multifocal HCC that is not amenable to curative or locoregional therapy (BCLC-B) and who have preserved liver function and good performance status	A1	48 (100%)
25	The use of multikinase inhibitors as adjuvant therapy after hepatic resection or locoregional therapy is not recommended	A1	44 (100%)
26	In patients with HCC, regular assessment for clinical and radiological response to first-line therapy is recommended to monitor for disease progression	A1	50 (100%)
27	In patients with HCC, sorafenib or lenvatinib should be discontinued when there is unequivocal clinical and/or radiological progression	A1	45 (100%)
28	In patients with HCC, a second-line systemic therapy is recommended in suitable patients who have radiological progression while being treated with multikinase inhibitors but preserved liver function and good performance status	A1	41 (92.7%)
29	HCC treatment response should be assessed by multiphase CT or MRI using standardised criteria such as the mRECIST criteria	B1	48 (81.3%)
30	Patients with incurable HCC should be introduced to supportive care services early in their management	B1	50 (100%)
31	Patients with BCLC-D HCC should be managed symptomatically in conjunction with supportive care services	B1	50 (100%)

BCLC = Barcelona Clinic Liver Cancer; CT = computed tomography; GRADE = Grading of Recommendations Assessment, Development and Evaluation; HBV = hepatitis B virus; HCV = hepatitis C virus; mRECIST = modified Response Evaluation Criteria in Solid Tumors; MRI = magnetic resonance imaging; SIRT = selective internal radiation therapy; TACE = transarterial chemoembolisation; UCSF = University of California San Francisco. * GRADE quality of evidence classification: A = high, B = moderate, C = low, D = very low; strength of recommendation: 1 = strong, 2 = weak. † Number of experts who participated in the final modified Delphi process vote for this recommendation. ‡ Percentage of expert advisors who either strongly agreed or agreed (based on five-point Likert scale, comprising: strongly disagree, disagree, neutral, agree and strongly agree). § Or combination of atezolizumab and bevacizumab (listed in the Pharmaceutical Benefits Scheme on 1 November 2020). Source: Hepatocellular Carcinoma Consensus Statement Working Group. Australian recommendations for the management of hepatocellular carcinoma: a consensus statement. Melbourne: Gastroenterological Society of Australia, 2020. https://www.gesa.org.au/resources/hepatocellular-carcinoma-hcc-management-consensus/. [Corrections added on 12 May 2021 after first online publication: a footnote was added to recommendation 24 in Box 1.]

2 Populations that should undergo hepatocellular carcinoma surveillance

People with cirrhosis (any aetiology)

People with chronic hepatitis B virus infection without cirrhosis in:
- Asian men older than 40 years
- Asian women older than 50 years
- People born in sub-Saharan Africa older than 20 years
- Aboriginal and Torres Strait Islander people older than 50 years

Surveillance modalities available for detecting HCC in Australia

Liver ultrasound

Liver ultrasound, the primary tool recommended for HCC surveillance, is widely available, non-invasive, comparatively inexpensive, and has Australian Medicare Benefit Schedule (MBS) reimbursement. The sensitivity of ultrasound used for HCC surveillance varies between 60% and 90%, with specificity generally above 90%. Computed tomography (CT) and magnetic resonance imaging (MRI) are not suitable routine surveillance modalities for HCC.

The optimal HCC surveillance interval reflects the tumour doubling time of 4–8 months. Several international cohort studies have shown that HCC surveillance every 6 months is cost-effective and improves survival.[14]

Serum marker: α-fetoprotein

Serum α-fetoprotein may increase the sensitivity of surveillance but can be associated with false-positive results. As α-fetoprotein improves earlier detection of HCC compared with ultrasound alone, we recommend surveillance with a combination of ultrasound and serum α-fetoprotein levels every 6 months.

Populations not requiring HCC surveillance

The expectation with HCC surveillance is that it will reduce mortality by allowing patients to access curative therapy. Benefit is not seen if the patient is expected to die of progressive liver failure or other comorbid conditions before receiving treatment. The survival benefit of HCC surveillance appears to be restricted to patients with Child–Pugh class A and early class B cirrhosis and with Child–Pugh class C disease who are candidates for liver transplantation.[15]

Non-alcoholic fatty liver disease and its association with HCC incidence

Non-alcoholic fatty liver disease patients with cirrhosis should undergo surveillance. Meta-analyses have shown that obesity may increase the relative risk of HCC by 1.5- to four-fold.[16,17] Diabetes increases the relative risk of developing HCC by two- to 2.5-fold and increases HCC-associated mortality by 1.6-fold.[18,19] In a large retrospective study, the relative risk of developing HCC was seven-fold that of controls. Most cases occurred in cirrhotic individuals, with the relative incidence in non-cirrhotic subjects not reaching the accepted threshold to justify surveillance.[20] Therefore, surveillance for HCC in non-cirrhotic patients with non-alcoholic fatty liver disease is not supported by current evidence.

Diagnosis and staging

Unlike other malignant neoplasms, the diagnosis of HCC may be made principally on radiological criteria. The Liver Imaging Reporting and Data System (LI-RADS)[21] provides a framework for reporting and criteria for HCC diagnosis.

In individuals with high pre-test probability for HCC (ie, with cirrhosis or HBV infection) the diagnosis of HCC can be confidently made when non-rim arterial phase hyperenhancement (APHE) and portal venous or delayed phase washout is present.[22] In patients with a lower risk of HCC (eg, non-cirrhotic patients and those without hepatitis B) or when imaging characteristics are concerning but not typical for HCC and malignancy is suspected, targeted biopsy with histological confirmation is indicated (Box 3).

Imaging criteria for diagnosis of HCC

Computed tomography

Multiphase CT with pre-contrast and three post-contrast phases (late hepatic arterial, portal venous, and delayed) is the optimal imaging protocol for HCC diagnosis. The appearances of non-rim APHE together with washout during the portal or delayed phase confer a specificity approaching 100%. The sensitivity of these radiological findings is highly dependent on lesion size, with excellent sensitivity for lesions greater than 2 cm, modest sensitivity for lesions 1–2 cm, and poor sensitivity for lesions less than 1 cm in diameter.[23]

Magnetic resonance imaging

The principles of HCC diagnosis are similar for both MRI and CT. With the use of extracellular contrast agents, the features of non-rim APHE and washout are highly suggestive of HCC in individuals at risk. Compared with multiphase CT, MRI offers additional imaging sequences that may provide supportive information for the diagnosis of HCC, including T2-weighted sequences, diffusion-weighted imaging and hepatobiliary phase imaging (when liver-specific contrast agents are used).

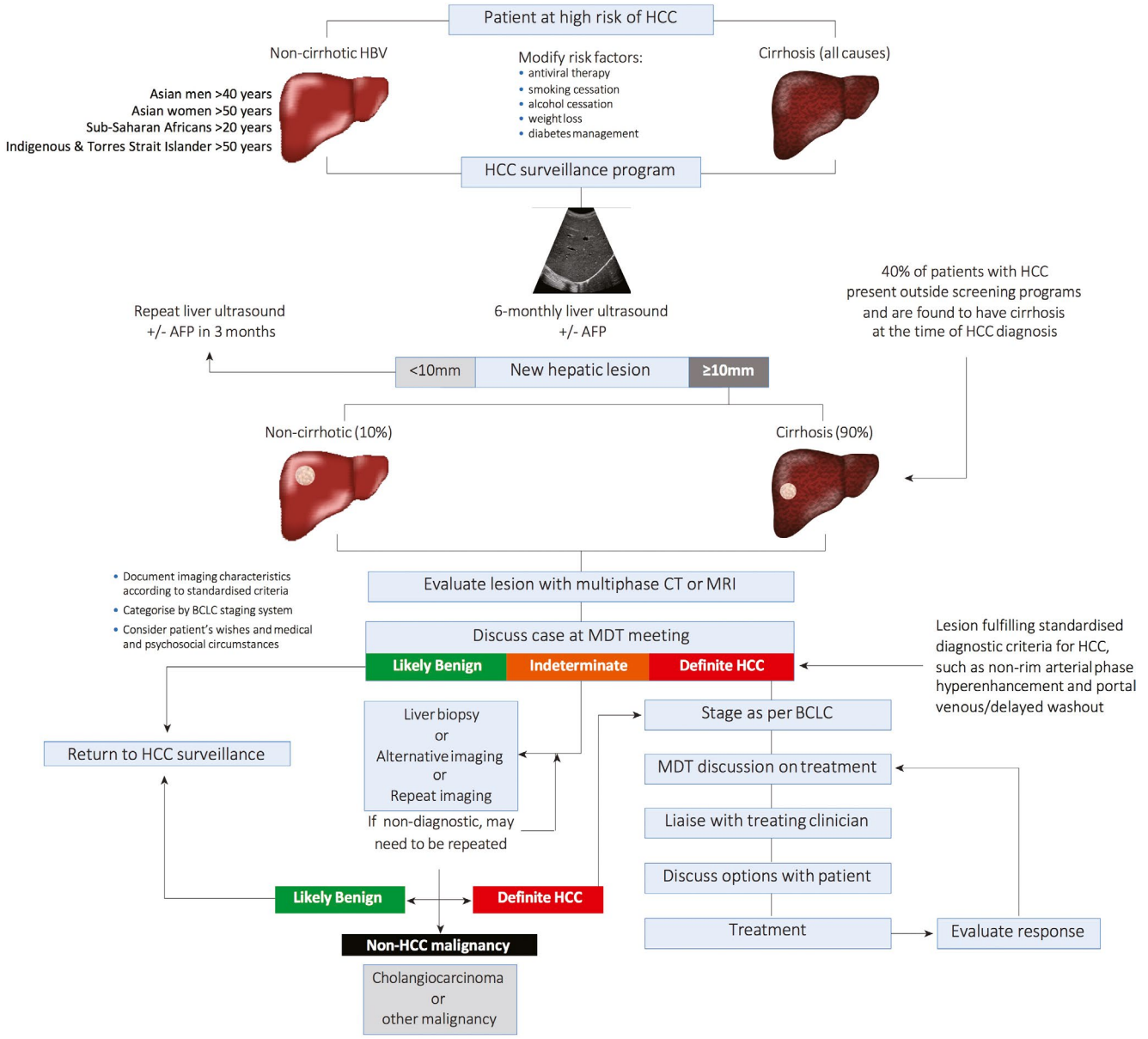
Contrast-enhanced ultrasound

Contrast-enhanced ultrasound is not widely practised in Australia and requires skilled operators, but can be used to interrogate a suspicious lesion and has the advantage of avoiding ionising radiation and nephrotoxic contrast agents. As with cross-sectional imaging modalities, such as CT and MRI, the imaging features of APHE and washout pertain to contrast-enhanced ultrasound.

Choice of imaging modality

Several practical factors determine the choice between CT, MRI and contrast-enhanced ultrasound. Patients who experience claustrophobia, who are unable to hold their breath sufficiently long or who have ascites (which may result in image artefacts) may be better imaged with CT. However, CT requires ionising radiation exposure and potential nephrotoxicity from intravenous contrast agents.[24] In Australia, the choice between MRI and CT has been influenced by accessibility of the imaging techniques and MBS reimbursement. Contrast-enhanced MRI liver scans (including the use of hepatobiliary-specific contrast agents) for the purpose of diagnosis or staging of known or

3 Surveillance and diagnosis of hepatocellular carcinoma (HCC)



AFP = α-fetoprotein; BCLC = Barcelona Clinic Liver Cancer; CT = computed tomography; HBV = hepatitis B virus; MDT = multidisciplinary team; MRI = magnetic resonance imaging. All cirrhotic and non-cirrhotic patients at increased risk of HCC should be offered surveillance (if willing to receive treatment). The preferred surveillance method is liver ultrasound ± serum AFP every 6 months. Once a lesion is identified on ultrasound, depending on size, further evaluation is required with either multiphase CT or MRI. Depending on the imaging characteristics, lesions may be classified as: likely benign, intermediate, or definite HCC. Discussion in an MDT meeting is recommended in order to optimise patient care. Source: Hepatocellular Carcinoma Consensus Statement Working Group. Australian recommendations for the management of hepatocellular carcinoma: a consensus statement. Melbourne: Gastroenterological Society of Australia, 2020. https://www.gesa.org.au/resources/hepatocellular-carcinoma-hcc-management-consensus/

suspected HCC is funded by the MBS in Australia (one scan per 12-month period).

Staging systems

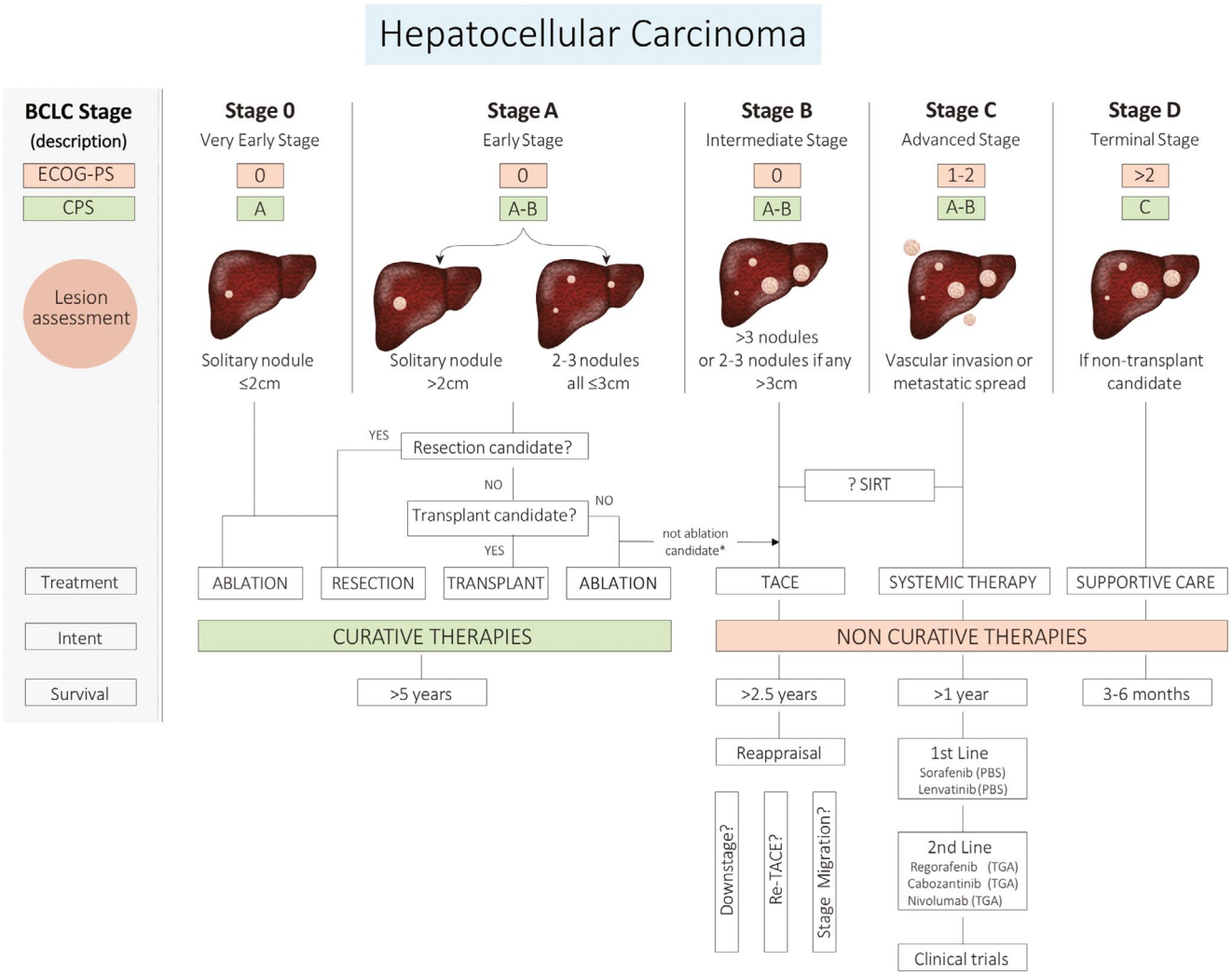
Barcelona Clinic Liver Cancer staging system

The Barcelona Clinic Liver Cancer (BCLC) staging system is used and endorsed by international guidelines.[22,25,26] It incorporates three clinical aspects: liver function, tumour biology and performance status, and offers treatment recommendations based on stage (Box 4). The BCLC staging system is the most commonly used system in multidisciplinary team meetings in Australia and is likely to remain the system of preference because of physician familiarity and ease of use.

Management

Management of HCC in Australia is to offer curative intent when possible while minimising exposure to risk with treatment. Staging of disease and determination of appropriate management through a multidisciplinary team are critical. A patient's understanding of their disease and the clinician's respect for patient choices are essential elements of HCC management. Managing clinicians are expected to offer evidence-based treatment options.

4 Barcelona Clinic Liver Cancer (BCLC) staging system



CPS = Child–Pugh Score; ECOG-PS = Eastern Cooperative Oncology Group Performance Status; PBS = Pharmaceutical Benefits Scheme; SIRT = selective internal radiation therapy; TACE = Transarterial chemoembolisation; TGA = Therapeutic Goods Administration. The BCLC staging system is the preferred system for classifying hepatocellular carcinoma; the stage is calculated from three clinical parameters: liver function, tumour characteristics, and functional status of the patient. Updated versions are available at http://www.bclc.cat/professional-area/management-of-hcc.html. Source: Hepatocellular Carcinoma Consensus Statement Working Group. Australian recommendations for the management of hepatocellular carcinoma: a consensus statement. Melbourne: Gastroenterological Society of Australia, 2020. https://www.gesa.org.au/resources/hepatocellular-carcinoma-hcc-management-consensus/

The multidisciplinary team approach

Multidisciplinary team discussion is recommended for every patient diagnosed and being managed with HCC. Multidisciplinary team care is being increasingly practised in cancer care services in Australia, the United States and Europe.[27] This type of care has several benefits, including improvement in staging and diagnosis accuracy, increased treatment rates, reduction in time to treatment after diagnosis, and increased adherence to clinical guidelines.[28] Several retrospective cohort studies show an improvement in the overall survival of patients with HCC managed through a multidisciplinary team.[29]

Surgical therapies

Surgical resection

Liver resection is indicated and recommended for HCC in patients in whom the tumour is confined to the liver and can be completely removed, while leaving a sufficient liver remnant in terms of both quantity and quality to preserve life. Therefore, assessment of patients for potential liver resection for HCC requires evaluation of the patient, liver function, portal hypertension and tumour characteristics.[25] Overall survival after liver resection for HCC depends on the risk of developing liver failure, succumbing to non-liver-related complications of surgery, or developing recurrent HCC.

Liver transplantation

Liver transplantation is a definitive treatment option for patients with early stage HCC, as it eliminates both the tumour and the associated liver disease.[30] In Australia and New Zealand, the 5-year overall survival among liver transplant recipients for HCC is 75%, similar to overseas experience.[31]

Appropriate patient selection for liver transplantation is critical to both achieving optimal outcomes and appropriate donor organ utilisation. Eligibility for entry to the liver transplantation waiting list should be based on an expected 5-year survival rate

greater than 50%. The University of California San Francisco (UCSF) criteria[32] provides the current framework for patient selection in Australia (Box 5).[31-34] Patients within UCSF criteria have survival rates after liver transplantation of 90% and 75.2% at 1 and 5 years respectively, compared with a 50% 1-year survival for patients with tumours exceeding these limits.[32] An alternative system, Metroticket 2.0, incorporating α-fetoprotein and tumour characteristics under review by the Australasian transplant societies may broaden patient selection without adverse impact on patient outcomes.[34]

Locoregional therapies

More than 75% of patients with early stage (BCLC-A) HCC are not suitable for either surgical resection or liver transplantation because of underlying severity of liver disease, clinically significant portal hypertension, significant comorbidity, or age.[35] For these patients, locoregional therapies, with image-guided percutaneous tumour ablation and/or image-guided transcatheter tumour therapy should be considered. Ablative therapies are generally restricted to small number of lesions (three or fewer), while non-ablative therapies may be used when multiple lesions are present.

Ablative therapies

Ablative therapies for HCC involve treatment of a lesion with the intent of local disease elimination.

Percutaneous tumour ablative therapies

Percutaneous tumour ablation under imaging guidance is an important and widely accepted treatment option for patients with early stage HCC. The two common methods used to induce tumour necrosis are temperature alteration (eg, radiofrequency ablation and microwave ablation) and chemical injection (most commonly percutaneous ethanol injection). Radiofrequency ablation is the most widely recommended first-line ablation technique for patients not suitable for surgery.[36] Microwave ablation is a relatively recent and increasingly popular thermal ablative therapy[37] that has the advantages of producing wider and more predictable ablation volumes, resulting in high complete ablation rates, and the ability to simultaneously treat multiple lesions[36,37] and potentially treat larger lesions more effectively. Ablation is effective in early stage (BCLC-0) HCC involving a solitary small nodule (< 2 cm), achieving near 100% complete necrosis and with overall survival similar to that of surgery.[38]

Non-ablative therapies

Non-ablative therapies for HCC involve treatment of a lesion with the intent of local disease control. Although small lesions may be cured, typically lesions recur, requiring further treatment. Transarterial chemoembolisation (TACE) is the most common non-ablative therapy for HCC.

Transarterial chemoembolisation

TACE involves injection of chemotherapy and embolic material into hepatic artery branches supplying a tumour and is considered first-line therapy for patients with BCLC-B HCC.[25,39] It is regarded as a non-curative procedure in this stage of cancer.

Meta-analyses have demonstrated that patients treated with TACE derive a significant improvement in overall survival compared with bland embolisation or best supportive care.[40] An overall response rate of about 50% and a disease control rate of 75–80% can be expected with TACE therapy.[41]

Selective internal radiation therapy

Selective internal radiation therapy (SIRT) involves Yttrium-90 microspheres injection into the hepatic arteries supplying the tumour. Radioembolisation has been used instead of TACE for patients with BCLC-B disease, as an alternative to sorafenib for patients with BCLC-C disease (including portal vein invasion), and for bridging or downstaging to liver transplantation. However, the evidence base justifying the use of SIRT is less advanced than that for other therapies. Three randomised controlled studies failed to demonstrate superiority of SIRT over sorafenib. This has contributed to the uncertainty around the precise role of SIRT in HCC management.[42-44] However, SIRT can be considered in select patients with intermediate or locally advanced HCC.

Other locoregional therapies

Stereotactic external-beam radiation therapy

Stereotactic external-beam radiation therapy (SBRT) is emerging as a potential option for early stage disease not amenable to surgical or percutaneous ablative therapies. A systematic review of SBRT for early stage HCC incorporating 16 studies (973 patients, 1034 lesions) reported a mean weighted local control of 94% and 93% at 1 and 3 years respectively.[45] For more advanced disease, a small randomised study reported improved overall survival with upfront TACE and SBRT compared with sorafenib in the setting of macrovascular invasion (median, 55 weeks *v* 43 weeks; $P = 0.04$).[46] Further prospective randomised studies are required before SBRT can be recommended for routine use.

Systemic therapies

Systemic therapies are indicated in patients with advanced HCC, with vascular invasion and/or extrahepatic disease, or in patients

5 Comparison of liver transplantation criteria for patients with hepatocellular carcinoma (in chronological order)

	Milan[31]	UCSF[32]	Up-to-7[33]	Metroticket 2.0[34]
Criteria for liver transplantation	Single lesion ≤ 50 mm *or* 2 or 3 tumours, all ≤ 30 mm	Single lesion ≤ 65 mm *or* 2 or 3 tumours all ≤ 45 mm and total tumour diameter ≤ 80 mm	Sum of the diameter of the largest tumour (in cm) and the total number of tumours ≤ 7	Predictive model based on HCC number, maximal size and Log_{10} of AFP*
Conditions	No macrovascular invasion, no regional nodal disease, no distant metastases			

AFP = α-fetoprotein; CT = computed tomography; HCC = hepatocellular carcinoma; UCSF = University of California San Francisco. * Online calculator available at: http://www.hcc-olt-metroticket.org. Source: Hepatocellular Carcinoma Consensus Statement Working Group. Australian recommendations for the management of hepatocellular carcinoma: a consensus statement. Melbourne: Gastroenterological Society of Australia, 2020. https://www.gesa.org.au/resources/hepatocellular-carcinoma-hcc-management-consensus/

with unresectable HCC when locoregional therapies have failed to control disease or cannot be delivered. Systemic therapy is restricted to patients with preserved liver function, non-cirrhotic patients, or those with Child–Pugh class A cirrhosis.

There are currently three first-line therapies for HCC: sorafenib, lenvatinib and combination atezolizumab and bevacizumab. Sorafenib was the first therapy to show an increase in median overall survival from 7.9 to 10.7 months (hazard ratio [HR], 0.70; 95% CI, 0.55–0.87).[47] In a subsequent trial comparing lenvatinib with sorafenib, lenvatinib was non-inferior to sorafenib The median overall survival was 13.6 months (95% CI, 12.1–14.9) with lenvatinib and 12.3 months (95% CI, 10.4–13.9) with sorafenib (HR, 0.92; 95% CI, 0.79–1.06).[48] Progression-free survival was significantly higher in patients receiving lenvatinib (median, 7.4 months; 95% CI, 6.9–8.8) compared with sorafenib (median, 3.7 months [95% CI, 3.6–4.6]; HR, 0.66 [95% CI, 0.57–0.77]). The combination of atezolizumab (programmed death-ligand 1 antibody) and bevacizumab (antivascular endothelial growth factor) has shown significant improvement in progression-free survival (median, 6.8 months; 95% CI, 5.7–8.3) compared with sorafenib (median, 4.3 months; 95% CI, 4.0–5.6) and is the most recently approved therapy in Australia.[49]

There are no clear benefits to continuing first-line therapies in patients with radiological or clinical disease progression. Second-line treatments approved by the Therapeutic Goods Administration include two oral targeted therapies (regorafenib and cabozantinib) and nivolumab (immune checkpoint inhibitor) administered by intravenous infusion.

6 Supportive care, hepatology and medical goals in hepatocellular carcinoma (HCC)

	BCLC-0/A	BCLC-B	BCLC-C	BCLC-D
Description	Very early/early stage	Intermediate	Advanced	Terminal
Overall aim	Curative intent	Non-curative, increased survival while considering trade-offs of treatment side effects	Non-curative, increased life expectancy while considering trade-offs of treatment side effects and symptom management	Palliative care, symptom control
HCC extent	Confined to liver and small volume of tumour	Confined to liver and large or multinodular	Vascular invasion or spread outside liver	Defined by poor liver function or cancer-related symptoms
Liver function	Preserved (no portal hypertension in stage 0)	Preserved	Preserved	Decompensated
Cancer-related symptoms	None (ECOG 0)	None (ECOG 0)	Mild (ECOG 1–2)	Marked (ECOG 3–4)
Type of therapy offered	Ablation/resection or transplantation	TACE	Systemic therapy	Best supportive care
Expected median survival (with treatment)	> 5 years	> 2.5 years	> 1 year	< 3 months
Supportive care aspects	• Explore with patient and family their understanding of the diagnosis of cancer and long term implications • Explore patient's cultural and religious beliefs	• Explore expectations of patient and maintain realistic goals • Develop coordination of care framework and symptom monitoring plan	• Symptom management of HCC and chemotherapy • Decision-making support with focus on quality of life • Consider early referral to palliative care for ongoing support and counselling	• Management of severe cancer-related symptoms • Discuss referral to hospice for end of life care • Engage palliative care services for supportive measures
	Discuss and consider advanced care directives			
Hepatology-focused goals	• Preserve and potentially restore hepatic function to prevent stage migration (eg, alcohol abstinence, avoidance of hepatotoxins, antiviral therapy, increased coffee consumption) and consider opportunities for downstaging • Screen for varices in cirrhotic patients with portal hypertension • Consider nutritional status especially before surgery and in patients with protein malnutrition • In advanced HCC, investigate for possibility of metastatic disease or vascular invasion			• Manage symptoms associated with liver failure (eg, ascites, hepatic encephalopathy etc) • Determine limits of care (eg, in event of catastrophic events such as variceal haemorrhage)
General medical issues	• Treat medical comorbidities that will have an impact on survival or symptoms • Optimise patients medically for surgery, procedures or chemotherapy • Support cessation of smoking and alcohol • Psychological or psychiatric support			• Pharmacological management of symptoms in the context of advanced liver disease and other medical comorbidities, including drug and alcohol dependency

BCLC = Barcelona Clinic Liver Cancer; ECOG = Eastern Cooperative Oncology Group. Integration of BCLC staging system with supportive care needs, hepatological goals, and medical issues at an early stage. Source: Hepatocellular Carcinoma Consensus Statement Working Group. Australian recommendations for the management of hepatocellular carcinoma: a consensus statement. Melbourne: Gastroenterological Society of Australia, 2020. https://www.gesa.org.au/resources/hepatocellular-carcinoma-hcc-management-consensus/

Systemic therapies for advanced HCC are evolving rapidly, and it is likely that the standard of care will change in the near future.

Supportive care

Many patients either present with incurable disease or progress after failed attempts at curative therapy. Patients with incurable HCC should be introduced to supportive care services early in their management (Box 6). Patients presenting with advanced disease (15–20% of cases) have a median survival of less than 3–4 months. The estimated 1-year survival rate of patients with BCLC-D disease is less than 11%.[50] In addition to cancer-related complications, clinical deterioration may also be related to the underlying liver disease, which has unique clinical challenges. Symptom relief and psychosocial support may be most effectively achieved through the co-management of patients by hepatologists and supportive or palliative care services.

For patients with BCLC-D disease, management should occur in conjunction with supportive care services and should focus on symptom relief. Pain is a common feature of HCC and can result from both the disease and its treatment. The analgesic choice must take into consideration the severity of liver disease, portosystemic shunting, low circulating albumin (changing bioavailability), risk of return to opioid dependence, current medications, and clinical features, including hepatic encephalopathy and hepatorenal syndrome.[51] The World Health Organization analgesic ladder provides an accepted treatment algorithm for analgesia use in all cancers, including HCC.

Conclusion

The management of HCC requires a team of experts delivering multiple therapeutic modalities while balancing the issues of pre-existent liver disease and risk of hepatic decompensation. Overall, mortality remains high despite all the recent advances in locoregional and systemic therapies. A priority for Australia, is to recognise patients at risk of HCC and to institute surveillance strategies at a time when the HCC is curable.

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