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

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Abdominal Radiology Group Australia and New Zealand

Clinical Oncology Society of Australia

MOGA
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AUSTRALIA

TSANZ
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Disclaimer

The recommendations in this consensus statement represent the best available evidence at the time of compilation and are intended to be used as a guide only. The compilers of these recommendations shall not be liable for any loss, direct, indirect or consequential, on whatsoever account for any omission or negligent mis-statement contained herein, or by reason of, arising from or in relation to any such user, by any other person, company or body relying or acting upon or purporting to rely or act upon any matter contained therein or arising thereout.

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Contact

Gastroenterological Society of Australia
Level 3, 517 Flinders Lane
Melbourne VIC 3000
Australia
Phone: 1300 766 176
Website: www.gesa.org.au
Email: gesa@gesa.org.au

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Abstract

Introduction

In Australia, primary liver cancer — hepatocellular carcinoma (HCC) — is a leading cause of cancer morbidity and mortality. Due to recognised variation in the management of HCC in Australia, this consensus statement has been developed. It outlines 31 evidence-based practice recommendations and the detailed evidence underlying them. The recommendations are applicable to a range of health professionals involved in the care of adult patients with HCC, including specialists, general medical practitioners, nurses, health coordinators and hospital administrators.

Methods and recommendations

This consensus statement has been developed by specialists in hepatology, radiology, surgery, oncology, palliative care and primary care, including both medical practitioners and nurses. The statement addresses four main areas relevant to HCC management: (1) epidemiology and incidence; (2) diagnosis; (3) treatment; and (4) patient management. A modified Delphi process was used to reach consensus on the 31 recommendations. Recommendations cover the use of surveillance strategies, the importance of multidisciplinary meetings, diagnosis, current treatment options and supportive management of patients.

Change in management as a result of this statement

Adoption of and adherence to the evidence-based recommendations in this consensus statement will simplify HCC patient management and reduce clinical variation. Ultimately, this should result in better outcomes for patients with HCC in Australia.

1 Introduction

1.1 Scope and purpose

This consensus statement has been developed for health professionals involved in the care of adult patients with hepatocellular carcinoma (HCC). It is applicable to specialists, general medical practitioners, nurses, health coordinators and hospital administrators. This is an extensive audience, and this document is accordingly comprehensive. It is intended to be a *living* online document, with ongoing revisions as developments occur in this area.

The consensus statement begins by covering epidemiology and surveillance, followed by diagnosis and staging of HCC. The management section then covers surgery, liver transplantation, locoregional treatments and systemic therapies. Finally, the supportive care section provides a practical guide to the supportive management of patients with advanced liver disease and HCC.

The primary objective is to provide a consensus statement to inform clinical decisions and to set a standard of care, with particular reference to the Australian health care setting, thus providing a local context for management recommendations. The expected health benefits of this consensus statement include a standardised approach to the management of HCC across varied health care settings in Australia. At a community level, the benefits of producing locally relevant guidelines are ultimately to improve patient care, experience and outcomes.

A summary version of this consensus statement and its recommendations has been published elsewhere.[1]

1.2 Steering committee and working groups

A chair and co-chair were selected from among Executive members of the Liver Faculty (formerly the Australian Liver Association) of the Gastroenterological Society of Australia (GESA). A steering committee, comprising leading experts in the management of HCC in Australia, provided governance. The proposed consensus statement was divided into sections, with section chairs responsible for each working group. In total, 52 individuals contributed to writing the document. Patient advocacy groups were consulted and invited to provide advice on this document from a patient perspective. Their suggestions were relayed through the working group chairs to the steering committee. A complete list of contributors, with their roles, disciplines and institutions, is provided in the Acknowledgement of participation section.

1.3 Declaration of funding

Unrestricted grant funding was provided to GESA for completion of this consensus statement. Details of GESA's funding sources are available on the website (www.gesa.org.au). Sponsoring organisations are listed in the Acknowledgement of funding section.

1.4 Editorial independence

The decision to produce this consensus statement arose from interest among the Liver Faculty membership, which was expressed to the Liver Faculty Executive. The Liver Faculty Executive voted unanimously to proceed with preparation of the document. Two Executive members, Prof Nicholas Shackel and A/Prof John Lubel, were elected by the Executive to lead the development of this consensus statement. The steering committee oversaw and endorsed the draft document. Funding was from unrestricted grants provided by GESA, with editorial independence maintained throughout manuscript development. Consensus was ensured by use of the modified Delphi process, discussed in section 2.2.

1.5 Competing interests

A complete list of participants' potential conflicts of interest is given in the Author disclosures section.

1.6 Disclaimer

The recommendations outlined in this document should not be read or interpreted in isolation. The accompanying text and technical remarks

provide additional background and context for each recommendation, including the definition of terms used in the recommendations. Likewise, many of the recommendations complement each other and can be open to misinterpretation if taken in isolation. The authors have endeavoured to produce a contemporary document; however, the HCC landscape is evolving rapidly, and this document will inevitably contain outdated material between revisions. The online version of this document is scheduled for frequent updates to stay abreast with the developing therapeutic options for HCC.

1.7 Endorsements

This consensus statement has been endorsed by the following organisations:

- Abdominal Radiology Group Australia and New Zealand (ARGANZ)
- Australasian Hepatology Association (AHA)
- Australia and New Zealand Hepatic, Pancreatic and Biliary Association (ANZHPBA)
- Australian and New Zealand Society of Palliative Medicine (ANZSPM)
- Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM)
- Clinical Oncology Society of Australia (COSA)
- Interventional Radiology Society of Australasia (IRSA)
- Medical Oncology Group of Australia (MOGA)
- Palliative Care Australia (PCA)
- The Royal Australian and New Zealand College of Radiologists (RANZCR)
- The Transplantation Society of Australia and New Zealand (TSANZ)

1.8 What's new?

The use of magnetic resonance imaging (MRI) for diagnostic or staging purposes has been restricted in Australia because, until recently, it has not been a rebated item on the Medicare Benefits Schedule (MBS). This has undoubtedly shaped the choice of investigation of individual clinicians and multidisciplinary teams (MDTs). On 1 May 2019, a Medicare rebate became available for contrast-enhanced MRI liver scans (including with hepatobiliary-specific contrast agents). This Medicare item (no. 63546) is restricted to patients with known or suspected HCC for the purpose of diagnosis or staging. Other conditions for the use of this item number include: (i) the presence of pre-existing liver disease as confirmed by a specialist; (ii) an identified hepatic lesion of at least 10 mm in diameter; and (iii) Child–Pugh class A or B disease. This is a welcome change for most clinicians managing HCC and is likely to change the diagnostic and staging approach in many centres throughout Australia.[2]

From November 2020, atezolizumab in combination with bevacizumab became available through the Pharmaceutical Benefits Scheme (PBS) for patients with advanced unresectable or metastatic hepatocellular carcinoma. This occurred as a result of an accelerated pathway to funding and within a year of published data supporting the role of this combination therapy in the management of HCC.[3]

2 Methodology

2.1 Grading of evidence and strength of recommendation

The recommendations in this document have been graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.[4,5] The quality of the evidence was classified as one of four levels — high (A), moderate (B), low (C) or very low (D) — and the strength of recommendation as either strong (1) or weak (2) (Table 1).

This consensus statement was developed in accordance with the principles outlined by the Appraisal of Guidelines for Research & Evaluation (AGREE) instrument. This tool assesses the methodological rigour and transparency with which guidelines are developed and was first published in 2003.[6] The original AGREE instrument was refined in 2010, with the current AGREE II instrument being the preferred tool.[7]

2.2 Methodology for reaching consensus

The process by which consensus would be reached was defined from the outset and employed a modified Delphi approach.[8-10] This method was chosen as it allows for expert interaction in the final round and facilitates further clarification and debate of contentious issues in a face-to-face meeting. There is evidence to support use of the modified technique over the original Delphi method.[11] In brief, this process involved the following steps:

1. the steering committee generated clinically relevant questions;
2. working groups of members with relevant expertise were formed and asked to prepare a comprehensive appraisal of the medical literature on each topic and to address the questions raised, using the GRADE system to determine quality of evidence and strength of recommendations; and
3. working group chairs and the steering committee reviewed the recommendations and returned draft manuscripts to the working group members for further clarification or comment.

Table 1. Quality of evidence and strength of recommendation according to the GRADE system

Evidence quality	Definition	Grade
High	We are very confident that the true effect lies close to that of the estimate of the effect.	A
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.	B
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.	C
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.	D

Recommendation	Notes	Grade
Strong	Recommendation is made with strong certainty. Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes and cost.	1
Weak	There is variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or higher resource consumption.	2

GRADE = Grading of Recommendations Assessment, Development and Evaluation.

The modified Delphi method used an initial two-round online questionnaire that canvassed all document contributors and asked (when the topic was in their field of expertise) for (a) their level of agreement with each recommendation using a five-point Likert scale (see below)[12] and (b) any additional comments regarding the recommendation. There were 57 respondents (100%) to the first-round questionnaire. In the second-round questionnaire, participants (*n* = 51, 89.5%) were given access to the median, mode and interquartile range of the group score, their own individual previous score and any comments made by other participants and were asked to repeat their individual evaluation of the recommendation statements.

A five-point Likert scale (strongly disagree, disagree, neutral, agree, strongly agree) was used to determine level of agreement or disagreement. A *decision rule* with a supermajority of >80% (summative *agree* and *strongly agree* responses) was used as the determinant for consensus, as previously described.[11,13,14] A response period of 14 days was given for each round of questionnaires. All recommendations were then reviewed at a face-to-face workshop with 34 attendees in May 2019, and voting on agreement was conducted using a de-identified electronic voting system. Focused discussions were directed at six recommendations that had not reached consensus after the first two rounds. It was agreed through a voting process (with an 80% majority necessary) that four recommendations required rewording and were to be submitted to a third and final online questionnaire. Two of the recommendations (listed in the Supplementary data) were voted to be excluded. The third-round questionnaire was sent to all participants, with 48 experts (84.2%) responding. All four modified recommendations fulfilled the decision rule to be included. A table summarising the results of all the Delphi rounds is shown in the Supplementary data.

3 Summary of recommendations

The final recommendations are listed in Table 2. However, readers should refer to the relevant sections of this document for additional information and not interpret the recommendations in isolation.

Table 2. Recommendations

No.	Consensus recommendation	GRADE classification*	Percentage agreement†, *n*‡
1	HCC surveillance should be offered to all patients with cirrhosis if they are suitable and willing to receive treatment.	C1	100%, 48
2	HCC surveillance should be undertaken in non-cirrhotic individuals with chronic hepatitis B infection who are at increased risk of HCC.	C1	97.8%, 46
3	Surveillance for HCC should be undertaken using liver ultrasound every 6 months.	B1	98.0%, 49
4	Combining alpha-fetoprotein testing with liver ultrasound may be considered for surveillance of HCC.	C2	88.9%, 45
5	Antiviral therapy for HCV may be offered to patients with HCC who have undergone surgical or locoregional treatment with curative intent.	B2	92.5%, 40
6	Patients with HCV-related cirrhosis who achieve sustained virological response and undergo curative therapy for their HCC require ongoing surveillance.	B1	95.7%, 46
7	HCC surveillance in non-cirrhotic patients can be considered in select patient populations.	C2	90.7%, 43
8	In the setting of cirrhosis, imaging diagnosis of HCC should rely on standardised criteria, based on evidence and validated in clinical practice.	B1	98.0%, 50
9	Multiphase CT or MRI is the recommended investigation for lesions suspicious for HCC.	A1	98.0%, 50
10	For indeterminate lesions greater than 10 mm diameter in cirrhotic livers, either targeted liver biopsy or repeat interval imaging or an alternative imaging modality is required for diagnosis.	B1	97.8%, 45
11	It is recommended that the BCLC staging system is used as the framework for HCC management in Australia.	B1	94.0%, 50
12	The management choice for a patient with HCC should take into account the individual patient's wishes and medical and psychosocial circumstances.	C1	100%, 50
13	The management of HCC should be determined by a multidisciplinary team to optimise patient care.	B1	100%, 50
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	95.8%, 48
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	100%, 48

No.	Consensus recommendation	GRADE classification*	Percentage agreement†, *n*‡
16	University of California San Francisco (UCSF) criteria should inform patient selection for liver transplantation in patients with HCC.	B1	100%, 47
17	Patients with HCC initially beyond transplant criteria may be considered for liver transplantation after successful downstaging to within standard transplant criteria.	C1	97.6%, 41
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	94.9%, 39
19	Patients with early-stage (BCLC stage A and early stage B) disease, who are not candidates for surgery or liver transplantation, should be treated with locoregional therapy.	A1	100%, 48
20	In patients with BCLC-B HCC, TACE is recommended as first-line therapy.	B1	97.9%, 47
21	SIRT may be considered in select patients with intermediate or locally advanced HCC.	C2	88.6%, 44
22	Stereotactic external-beam radiation therapy may be considered for local tumour control in suitable patients with HCC.	C2	81.0%, 42
23	Patients with advanced (BCLC-C) or multifocal HCC that is not amenable to curative or locoregional therapy (BCLC-B) should be offered systemic therapy.	A1	93.9%, 49
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	100%, 48
25	The use of multikinase inhibitors as adjuvant therapy after hepatic resection or locoregional therapy is not recommended.	A1	100%, 44
26	In patients with HCC, regular assessment for clinical and radiological response to first-line therapy is recommended to monitor for disease progression.	A1	100%, 50
27	In patients with HCC, sorafenib or lenvatinib should be discontinued when there is unequivocal clinical and/or radiological progression.	A1	100%, 45
28	In patients with HCC, a second-line systemic therapy is recommended for suitable patients who have radiological progression while being treated with multikinase inhibitors but have preserved liver function and good performance status.	A1	92.7%, 41
29	HCC treatment response should be assessed by multiphase CT or MRI using standardised criteria, such as the mRECIST criteria.	B1	81.3%, 48
30	Patients with incurable HCC should be introduced to supportive care services early in their management.	B1	100%, 50
31	Patients with BCLC-D HCC should be managed symptomatically in conjunction with supportive care services.	B1	100%, 50

BCLC=Barcelona Clinic Liver Cancer; CT=computed tomography; GRADE=Grading of Recommendations Assessment, Development and Evaluation; HCC=hepatocellular carcinoma; HCV=hepatitis C virus; mRECIST=modified Response Evaluation Criteria in Solid Tumors; MRI=magnetic resonance imaging; SIRT=selective internal radiation therapy; TACE=transarterial chemoembolisation.

* GRADE quality of evidence: A=high; B=moderate; C=low; D=very low. GRADE strength of recommendation: 1=strong; 2=weak.

† Percentage of expert advisors who either agreed or strongly agreed (based on five-point Likert scale, comprising strongly disagree, disagree, neutral, agree and strongly agree).[4]

‡ Number of experts who participated in the final modified Delphi vote for each recommendation.

4 Epidemiology and surveillance

4.1 Global incidence of HCC

Liver cancer is the second leading cause of cancer death after lung cancer, has the same mortality rate as stomach cancer and is the seventh most common cancer globally.[15-17] Its incidence varies greatly around the world. East and South-East Asia and sub-Saharan Africa are the regions with the highest incidence, and half of all liver cancer deaths globally occur in China alone.[15,17] In the United States, the incidence increased from 4.4 to 6.7/100,000 between 2000 and 2012, with the increase mainly occurring in men aged 55–59 years, consistent with a birth cohort effect of the hepatitis C virus (HCV) epidemic.[18]

4.2 Incidence of HCC in Australia

Australia is also experiencing an increasing burden of liver cancer.[19] The age-standardised incidence of HCC in Australia increased markedly between 1982 (1.8/100,000) and 2019 (8.6/100,000).[20,21] This increase of 378% is only surpassed by the increase in thyroid cancer of 392%, which may be related to an increase in medical surveillance and new diagnostic approaches, such as neck ultrasound. Between 1982 and 2015, a total of 18,575 cases of HCC were reported to the Australian Cancer Registry. About 80% of these cases were in men, who had a considerably higher age-adjusted incidence than women (8.55 vs 1.65/100,000).

Within Australia, there is considerable variation in incidence, which shows a distribution associated with geographical region and socioeconomic status (Figure 1). The highest incidence is seen in the Northern Territory (12.607/100,000), Victoria (8.229/100,000) and New South Wales (7.798/100,000).[19] The variation in HCC incidence is linked to remoteness, with very remote areas having the highest incidence of HCC (11/100,000). A notable proportion of cases occur among people born overseas, including Europe (27%) and Asia (18%).[21] In 2016, the age-standardised mortality rate for liver cancer in Australia was 6.6/100,000.[19,20]

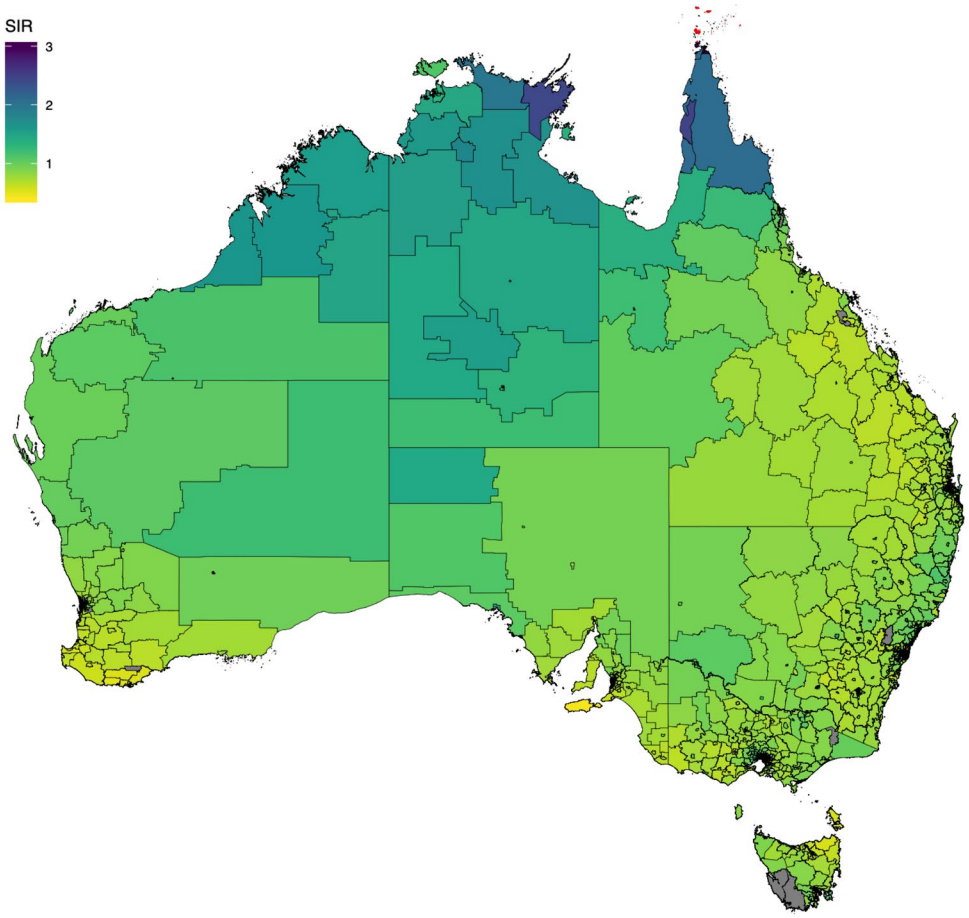
4.3 Incidence of HCC in Australian Indigenous populations

Indigenous Australians account for 3.3% of the population, yet are disproportionately affected by HCC compared with non-Indigenous Australians. Inequalities in health service access, risk factors for liver disease, socioeconomic disadvantage and geographical remoteness of Indigenous communities in many parts of Australia contribute to a greater burden of HCC incidence and mortality.[22] Prevalence of chronic hepatitis B virus (HBV) infection is estimated at 6% among Indigenous Australians in the Northern Territory,[23] where genotype C4 predominates. This genotype is associated with rapid liver fibrosis progression and greater risk of HCC.[24] Prevalence of HCV infection is also higher among Indigenous Australians (2.9%) than non-Indigenous Australians (1%).[23]

There are limited data on HCC incidence, mortality and age at onset among Indigenous Australians. A cancer registry-based cohort study conducted in the Northern Territory between 1991 and 2010 showed the relative risk of HCC among Indigenous Australians was six times higher than in non-Indigenous Australians (23/100,000 vs 4/100,000).[25] Only 14% of HCC in Indigenous Australians was detected through surveillance, and median survival was lower in Indigenous than non-Indigenous Australians (64 vs 172 days).

A further cancer registry-based cohort study in northern Queensland found that 4.5% of all HCC cases occurred in Indigenous Australians.[26] Mortality was higher among Indigenous Australians, although this was significantly confounded by lower socioeconomic index. Due to low surveillance rates among Indigenous Australians, it is impossible to characterise the median age of onset of HCC. However, high rates of vertical and early horizontal HBV transmission and early age of exposure to other risk factors for liver disease support beginning HCC surveillance at the age of 40–50 years in Indigenous Australians with chronic hepatitis B infection and no cirrhosis. As Indigenous Australians with liver disease are at greater risk of cirrhosis than non-Indigenous Australians, liver fibrosis stage should be regularly assessed.

Figure 1. Standardised incidence of HCC in Australia, 2005–2014



HCC = hepatocellular carcinoma. The standardised incidence ratio (SIR) is the ratio of the observed number of cases to the expected number of cases for age-specific rates in 5-year age bands, starting at 15 years (i.e. 15–19, 20–24, … 85+ years). The SIR for HCC is shown using the colour key. Map data sourced with permission from: Australian Cancer Atlas (https://atlas.cancer.org.au). Cancer Council Queensland, Queensland University of Technology, Cooperative Research Centre for Spatial Information. Version 09-2018.

Engagement of Indigenous Australians in HCC surveillance programs can be challenging because of population remoteness and inequitable access to health care. However, every effort should be made to engage Indigenous communities to find solutions to the problems associated with providing timely, culturally acceptable and effective HCC surveillance.

4.4 Aetiology of underlying liver disease

In most cases, HCC develops in the setting of chronic liver disease, and cirrhosis is present in 85%–90% of affected individuals. National data on the aetiology of underlying liver disease are not available, but evidence from New South Wales indicates an escalating incidence of HCV-related HCC, with a threefold increase from 2001 to 2013.[27] In contrast, the incidence of HBV-related HCC was stable during this period. Victorian data show that the major aetiologies for HCC in 2012–2013 were HCV (41%), alcoholic liver disease (39%), HBV (22%) and fatty liver disease (14%).[28] Given stable or declining rates of alcohol-related liver disease in Australia, HCV and fatty liver disease are the likely contributors to the increased incidence of HCC seen over the past decade.

The available Australian data are compatible with global statistics, which estimate that HCV and HBV are the aetiological factors responsible for 75% of HCC.[15,17,29] The prevalence of HCC correlates with the prevalence of viral hepatitis in a region. More than 80% of all HCC occurs in areas of sub-Saharan Africa and East Asia where HBV-related liver disease predominates. A notable exception is Japan, where the predominant factor is HCV.[15,17] In Australia, hepatitis B is more common in culturally and linguistically diverse populations and more than 50% of patients with HCC were born overseas.[28]

4.5 Mortality of HCC in Australia

Although mortality rates of many cancers have plateaued, death due to HCC has become the fastest rising cause of cancer death in Australia,[30] and, despite improvements in HCC treatment, overall 5-year survival in Australia is about 20%.[19,20] Studies from Queensland using population-based data from 1996 to 2011 showed an overall 5-year survival of 14.8%. Poorer survival was associated with older age, less recent periods of diagnosis, lower HBV prevalence in country of origin and greater area-level social disadvantage, which illustrates the important contribution of social determinants to HCC epidemiology in Australia.[19,31] The age-standardised mortality rate for HCC increased 304% between 1982 and 2019 (from 2.3/100,000 to 7.0/100,000).[20]

Epidemiological data should be interpreted with caution because primary liver cancer consists of several clinically different subtypes, with the two major types being HCC (75%–90%) and intrahepatic cholangiocarcinoma (10%–25%). Combined hepatocellular-cholangiocarcinoma is a rare variant with histological features of HCC and biliary components and accounts for less than 1% of primary liver tumours.[32,33]

4.6 Who should undergo HCC surveillance in Australia?

The single most significant risk factor for developing HCC is cirrhosis, which confers a hazard ratio (HR) of 6.69.[34] Age greater than 55 years confers an HR of 2.00, and diabetes confers an HR of 1.88. In people with HCV, genotype 3 infection (compared with genotype 1 infection) confers an HR of 1.60.[34]

Recommendation 1

HCC surveillance should be offered to all patients with cirrhosis if they are suitable and willing to receive treatment. *(Evidence quality: Low; Grade of recommendation: Strong)*

Recommendation 2

HCC surveillance should be undertaken in non-cirrhotic individuals with chronic hepatitis B infection who are at increased risk of HCC. *(Evidence quality: Low; Grade of recommendation: Strong)*

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 (Table 3).[35,36] In patients with cirrhosis, this threshold is an annual HCC incidence of 1.5%,[37] which is exceeded in people with cirrhosis secondary to viral hepatitis B and C, non-alcoholic steatohepatitis (NASH), primary biliary cholangitis and likely other aetiologies.[38,39] Further, it has been shown that 6-monthly surveillance correlates with earlier Barcelona Clinic Liver Cancer (BCLC) stage of HCC and portends better treatment options.[40,41] It is therefore recommended that surveillance be considered for all patients with cirrhosis.

Technical remarks

1. HCC occurs most commonly in the setting of cirrhosis (85%–90%).
2. The proportional contribution of liver disease risk factors to HCC is changing and in coming years will reflect the changing prevalence of disease and immigration to Australia.
    a. HBV-associated HCC occurs mainly in migrants, with subpopulation incidence approaching that of the migrant's country of origin.
    b. The effect of HBV national vaccination programs should reduce HCC incidence in future immigrants.
3. HCV-associated HCC will also decline with the availability of effective antiviral treatment and cure, a phenomenon that has been seen in countries with predominantly HCV-associated HCC.
4. In contrast, non-alcoholic fatty liver disease (NAFLD)-associated HCC is expected to rise with the increasing prevalence of obesity and metabolic syndrome in Western countries and the Asia–Pacific region.

Table 3. Populations in whom surveillance for HCC should be performed

Population	Estimated annual incidence of HCC
People with cirrhosis (any aetiology)*	2%–7%
People with chronic hepatitis B infection *without* cirrhosis	
• Asian men older than 40 years	0.4%–0.6%
• Asian women older than 50 years	0.3%–0.6%
• Sub-Saharan Africans older than 20 years	Variable†
• Indigenous and Torres Strait Islander people older than 50 years‡	0.36-0.9%

HCC=hepatocellular carcinoma.
*If patients are suitable for, and willing to receive, treatment.
†Reliable data not available but incidence likely to be increased.
‡Based on Northern Territory linkage data.[25]

Technical remarks

1. In the context of suppressive HBV treatment, evidence for the benefit of pre-cirrhosis HCC surveillance is limited.
2. Sub-Saharan Africans with HBV, especially men, have a greater rate of early-onset HCC, often in the absence of cirrhosis. A range of viral and host factors are thought to be important in this. Evidence of the role of specific surveillance strategies in these populations is limited.[42-44]
3. Viral load, genotype and duration of viral hepatitis infection change the observed incidence rate of HCC. Evidence of the role of specific screening surveillance accounting specifically for these viral factors is limited.[43,44]

4.7 Surveillance modalities available for detecting HCC in Australia

Liver ultrasound is the primary tool recommended for HCC surveillance. It is widely available, non-invasive, comparatively inexpensive and has Australian MBS reimbursement.

Although MRI is not presently considered a routine surveillance modality for HCC, there is emerging evidence that it can be considered as an alternative surveillance modality for selected patients, such as those with limited sonographic visualisation, preferably after MDT discussion. Computed tomography (CT) is not considered a suitable HCC surveillance modality.[45,46]

4.7.1 Ultrasound

Recommendation 3

Surveillance for HCC should be undertaken using liver ultrasound every 6 months. *(Evidence quality: Moderate; Grade of recommendation: Strong)*

Randomised trials have shown that surveillance improves HCC detection and reduces HCC-related cancer mortality. A randomised controlled trial (RCT) comparing 6-monthly HCC surveillance using ultrasound and alpha-fetoprotein (AFP) testing with no surveillance in a large cohort showed a 37% reduction in HCC-related mortality in patients with chronic HBV infection.[47] Patients enrolled in the surveillance arm had a significant improvement in 1-year, 3-year and 5-year survival. Thirty-two patients in the surveillance group died from HCC, compared with 54 in the control group. Importantly, the surveillance group completed just 58.2% of surveillance tests offered, suggesting that the benefits shown in this trial are the minimum that would be expected from surveillance.[47] A recent meta-analysis of patients with cirrhosis of mixed aetiologies showed an overall survival (OS) of 51% for patients under HCC surveillance, compared with 28% for patients not under surveillance.[48] HCC surveillance was associated with improved survival (odds ratio [OR], 1.9).

Ultrasound has developed a central role as the primary surveillance tool for HCC. The sensitivity of ultrasound

when used for HCC surveillance varies between 60% and 90%, with specificity generally agreed to be above 90%. Several recognisable factors may affect the diagnostic performance of ultrasound in the setting of HCC surveillance. In a large retrospective study of 941 patients with cirrhosis, more than 20% of ultrasounds were considered of inadequate quality for HCC surveillance. Obesity, male sex, fatty liver and advanced liver disease were all associated with ultrasound inadequacy.[49] The management approach for patients in whom ultrasound is inadequate for HCC surveillance should ideally be individualised and discussed in a multidisciplinary team meeting.

The optimal surveillance interval depends on tumour doubling time, which is about 4–8 months for HCC. Several international cohort studies have shown that 6-monthly HCC surveillance is cost-effective and improves survival.[37,41,50] Numerous relatively small RCTs have compared different ultrasound surveillance intervals, with most of these studies showing no difference in detection of curable lesions between various intervals. Similar studies comparing 6-monthly and annual surveillance have also been performed. However, cost-effectiveness studies found that 6-monthly surveillance improves quality-adjusted life-years at a reasonable cost.

Contrast-enhanced ultrasound (CEUS) allows the reliable detection of arterial neo-angiogenesis. As with ultrasound, it is relatively inexpensive, safe and widely available. CEUS is reported to have similar accuracy to CT and MRI scans in the diagnosis of HCC. However, ultrasound with contrast cannot be used for surveillance because the scan cannot screen the whole liver during the short duration of the arterial phase of the injection. Therefore, CEUS plays no role in surveillance for HCC. It does play a role as a second-line imaging modality for diagnosis of HCC once the lesion has been detected by ultrasound (see section 5.3.3).

4.7.2 Serum marker: alpha-fetoprotein

Recommendation 4

Combining alpha-fetoprotein testing with liver ultrasound may be considered for surveillance of HCC. (Evidence quality: Low; Grade of recommendation: Weak)

Pooled cohort studies[48,51] have shown that, compared with ultrasound alone, the surveillance strategy of combining liver ultrasound with serum AFP measurement improves earlier detection of HCC[52] but not survival. Furthermore, a recent meta-analysis that included data from 32 studies and more than 13,000 patients showed that ultrasound alone detected any-stage HCC at a lower rate than ultrasound in combination with AFP levels (relative risk, 0.88; 95% confidence interval [CI], 0.83–0.93).[53] Early-stage HCC was also detected at a lower sensitivity with ultrasound alone when compared with ultrasound with AFP levels (relative risk, 0.81; 95% CI, 0.71–0.93). In non-viral-associated HCC, there is a 25% increased detection rate in programs that use both ultrasound and AFP testing.[52]

4.8 Who should not undergo surveillance?

HCC surveillance is offered to those at risk, with the expectation 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 another comorbid condition before receiving treatment as a result of cancer surveillance, or if they are not able to receive curative therapy. Studies have now shown that the survival benefit of HCC surveillance is restricted to patients with cirrhosis whose disease is classified as Child–Pugh class A[54] or early class B. There is no survival benefit of surveillance in patients with Child–Pugh class C disease who are not candidates for liver transplant.[55]

Surveillance should not be performed in patients who have been identified as being at low risk of HCC or where surveillance is considered not cost-effective. This includes non-cirrhotic patients with NAFLD or other causes of chronic liver disease (hepatitis B being an exception). Surveillance may also be inappropriate in some Asian patients with HBV who are included in current surveillance programs based on age alone. In this patient group, the risk of HCC can be quantified using online published nomograms.[56] Using these nomograms to exclude patients from HCC surveillance where the annual risk of HCC is less than 0.2% is appropriate.

As high-risk patients progress to advanced ages, the potential survival benefit from HCC surveillance diminishes. Surveillance in patients older than 70

years with poor functional status or significant comorbidities would appear to be inappropriate. Outcomes due to comorbidities can be estimated using online calculators, such as the Charlson Comorbidity Index (https://www.mdcalc.com/charlson-comorbidity-index-cci).

Technical remarks

1. HCC surveillance has not been shown to benefit individuals with Child–Pugh class C cirrhosis, but this needs to take into account:
   a. suitability for transplantation;
   b. likelihood of hepatic recompensation;
   c. size and likely treatment of the HCC; and
   d. modifiable risk factors.
2. HCC surveillance has not been shown to benefit individuals with major comorbidity or those aged >70 years *with* poor performance status (Eastern Cooperative Oncology Group [ECOG] grade 2 or above), but this needs to take into account:
   a. quality of life and life expectancy;
   b. likelihood of improvement in performance status;
   c. the patient's wishes; and
   d. size and likely treatment of the HCC.

4.9 HCC surveillance in altered-risk populations

4.9.1 HBV and its association with HCC incidence

Patients with chronic hepatitis B infection without cirrhosis are more likely to qualify for curative surgery and achieve greater quality-adjusted life-years of benefit. Hence, the cost-effectiveness threshold is lower in this group, with an annual HCC incidence of only 0.2% required for surveillance.[57,58] As the incidence of HCC is influenced by age, sex, racial group and family history, surveillance is recommended for non-cirrhotic patients with hepatitis B and with risks exceeding the incidence threshold.[59] Although additional viral and immune risk factors, such as viral load, e-antigen status and alanine aminotransferase concentration, may increase risk further, these target populations meet the minimum risk required to achieve surveillance cost-effectiveness.

HCC can develop in non-cirrhotic patients with hepatitis B even after surface antigen seroconversion. Independent predictors include being male or aged 50 years or older at the time of surface antigen seroconversion. A recent retrospective analysis of Korean patients who achieved HBV surface antigen seroconversion estimated the annual HCC incidence to be 2.85% in patients with cirrhosis and 0.29% in those without cirrhosis.[60] A cohort study of 1271 Alaskan natives with hepatitis B showed an annual incidence of 37/100,000 after hepatitis B surface antigen clearance, compared with 196/100,000 per annum without surface antigen clearance.[61]

Technical remarks

1. The annual incidence of HCC in hepatitis B surface antigen carriers aged below 40 years for men and 50 years for women is <0.2%.[57,58]
2. Active viral replication confers a greater risk of HCC in those with HBV infection.[62]
3. HBV genotype and mutations affect HCC risk, but their overall contribution to risk is not known.[63]
4. Vaccination and antiviral therapy against HBV significantly decrease HCC risk.[62]

4.9.2 HCC incidence and risk of recurrence in people receiving HCV treatment with direct-acting antivirals

Recommendation 5

Antiviral therapy for HCV may be offered to patients with HCC who have undergone surgical or locoregional treatment with curative intent. *(Evidence quality: Moderate; Grade of recommendation: Weak)*

Recommendation 6

Patients with HCV-related cirrhosis who achieve sustained virological response and undergo curative therapy for their HCC require ongoing surveillance. *(Evidence quality: Moderate; Grade of recommendation: Strong)*

Early case series of high rates of HCC recurrence after curative therapy, and more aggressive tumour phenotypes in patients with chronic hepatitis C infection treated with direct-acting antiviral (DAA)

therapy, caused significant alarm.[64,65] However, it is now recognised that, compared with historical cohorts of patients with chronic HCV infection who were treated with pegylated interferon-based therapy, the cohort of patients who are undergoing treatment with DAAs have a greater risk of HCC recurrence because they are older, have a longer duration of HCV infection and have a higher prevalence of other risk factors for liver carcinogenesis, such as alcoholic liver disease and NAFLD, and more advanced liver disease.[57,66,67] These first case series also included patients who received non-curative therapy (i.e. transarterial chemoembolisation [TACE]), which carries an inherently high risk of recurrence.[57]

There are three clinical scenarios in which DAA treatment may affect HCC behaviour: the development of de novo HCC; recurrent HCC after curative treatment; and "aggressiveness" of tumour behaviour.

Several large studies have shown that sustained virological response (SVR) achieved by DAA therapy is associated with a significant reduction in de novo HCC. In one such report, SVR was associated with a reduced risk of HCC, with an adjusted HR of 0.28.[68] Similar results were reported in an Italian study of 2249 patients with cirrhosis.[69]

With regard to HCC recurrence, several centres have published data drawn from cohorts of patients treated with DAA-based regimens and have concluded that there is no increased risk of HCC recurrence, nor of a more aggressive tumour phenotype, among patients with hepatitis C treated with DAAs compared with those treated with interferon-based regimens.[67,70-73] However, major study design limitations included highly heterogeneous populations, retrospective or retrospective–prospective study designs, short follow-up periods, high loss to follow-up and the inclusion of patients who were not enrolled in HCC surveillance programs before initiation of therapy or who did not have convincing evidence of HCC exclusion before commencing DAA treatment. Despite these shortcomings, a recent meta-analysis and meta-regression that included 17 trials with an outcome measure of HCC recurrence after curative therapy (total of 2352 patients; 1485 received interferon-based therapies and 867 received DAAs) found no significant difference in HCC recurrence rates after curative therapy between those treated with interferon-based regimens or DAAs, when adjusted for age and duration of follow-up (rate ratio, 0.62; 95% CI, 0.11–3.45; $P = 0.56$).[66] Moreover, a 70% reduction in risk of de novo HCC was shown after DAA-induced SVR in patients with a previous history of HCC. Limitations in the meta-analysis included the low quality and marked heterogeneity of included studies, geographical collinearity with study type and the lack of key data (e.g. BCLC stage) in many studies, precluding the authors from being able to address more nuanced associations, such as tumour phenotype after SVR.

It has been suggested that tumour behaviour is more aggressive in the context of DAA therapy, with a higher frequency of multifocal and advanced cancers, perhaps due to downregulation of immune cancer surveillance.[64] However, a large US Veterans Health Administration study of 22,500 patients treated with DAAs found no difference in tumour size or stage between patients

Technical remarks

1. HCV treatment improves quality of life and helps prevent hepatic decompensation in patients with cirrhosis.
2. When deciding whether to commence DAA therapy in patients with HCV-related HCC, the lack of high-quality evidence of potential adverse risks of DAA therapy for HCC outcomes must be weighed against the positive impact of HCV cure on liver disease stage and progression.
3. Typically, 6 months is the accepted period to establish efficacy of curative therapy.
4. Patients who have curative therapy for HCC still carry a high risk of HCC recurrence and incident tumours irrespective of hepatitis C treatment, due to the carcinogenic field effect within the liver, and require frequent surveillance for at least 2 years after curative treatment.
5. The risk of HCC recurrence after curative therapy varies over time, based on achieving remission and changes in modifiable risk factors.

who developed HCC during antiviral therapy and those in whom it occurred after treatment.[68] These results await replication in other cohorts.

There is currently insufficient high-quality evidence to support the statement that DAA treatment increases the risk of HCC recurrence. High-quality, large, prospective studies in diverse populations with high HCC surveillance program attendance and longer follow-up times are needed to adequately refute reports of altered aggressiveness of HCC recurrence after DAA therapy. Any clinical decision to delay DAA therapy should be balanced by the growing body of evidence that, compared with no HCV treatment, DAA-induced SVR results in a significant reduction in risk of HCC recurrence.[74]

4.9.3 Fatty liver disease and its association with HCC incidence

Recommendation 7

HCC surveillance in non-cirrhotic patients can be considered in select patient populations. *(Evidence quality: Low; Grade of recommendation: Weak)*

Patients with NAFLD with or without the metabolic syndrome have a fivefold increased risk of developing HCC compared with patients with HCV-related HCC.[75] Meta-analyses have shown that obesity may increase the relative risk of HCC by 1.5- to fourfold.[76,77] Overweight patients have a relative risk of 1.17, whereas obese patients have a relative risk of 1.89.

There are increasing data showing that diabetes is an independent risk factor for developing HCC. Diabetes increases the relative risk of developing HCC by two- to 2.5-fold and increases HCC-associated mortality by 1.6-fold.[78-80] Emerging evidence suggests that patients with NAFLD or NASH may even develop HCC in the absence of cirrhosis. A retrospective analysis showed that 13% of patients with NASH-related HCC did not have cirrhosis.[75] Smaller cohort studies have found that 12%–56% of patients with NASH and HCC do not have cirrhosis.[75,81]

In a large retrospective cohort study that compared 296,707 patients with NAFLD with 296,707 age- and sex-matched controls, the relative risk of developing HCC was seven times higher in the NAFLD cohort. Most cases of HCC occurred in individuals with cirrhosis, with the relative incidence in non-cirrhotic participants not reaching the accepted threshold to justify surveillance.[82]

Thus, numerous cohort studies report an increased risk of HCC in patients with NAFLD, obesity or diabetes. Most of these studies include cirrhotic and non-cirrhotic patients. Some data suggest an increased risk of developing HCC in patients with NAFLD, obesity or diabetes independent of liver cirrhosis. However, most of these conclusions are based on retrospective cohorts.

The implication for future surveillance strategies in non-cirrhotic patients with NAFLD or NASH is not known, and further studies are required to elucidate their HCC risk.

Technical remarks

1. Surveillance for HCC in non-cirrhotic patients with NAFLD is not supported by current evidence.
2. Concurrent multiple causes of liver injury, in addition to NAFLD (such as HBV or HCV), significantly increase HCC risk in an individual.[83,84]
3. Most patients with NAFLD have features of the metabolic syndrome. Treatment of the metabolic syndrome in patients with NAFLD lowers their risk of HCC.[83,85] However, the minimum level of improvement in insulin resistance, lipid control, increased exercise and weight loss that is required to lower this risk cannot be accurately determined in an individual.
4. Treatment of patients with NAFLD and the metabolic syndrome with agents such as metformin, aspirin and statins can lower their risk of HCC.[86-88] However, it is unclear if this is due to treatment of the metabolic syndrome, anti-inflammatory actions and/or intrinsic anti-tumour effects of these agents.[86-88]
5. Patients with NAFLD and advanced-stage fibrosis (F3) have an increased risk of HCC, and surveillance can be considered.

5 Diagnosis and staging

In oncological practice, malignant neoplasms are generally diagnosed after histological examination of biopsied or excised tissue. HCC is an exception, as diagnosis and subsequent treatment can be implemented on the basis of non-invasive radiological diagnosis (Figure 2).

In part, the reliance on radiological diagnosis relates to the unique dual blood supply of the liver. This anatomical peculiarity, together with the predisposition for HCC to receive an arterial supply from the hepatic artery (arterial angiogenesis), leads to distinctive imaging characteristics of arterial phase hyperenhancement (APHE) and portal venous or delayed phase "washout". When these imaging characteristics are observed in individuals with a high pre-test probability for HCC (e.g. adult patients with cirrhosis, chronic hepatitis B infection or past HCC), the diagnosis of HCC can be confidently made. This non-invasive diagnostic approach was initially agreed in 2001[55] and subsequently updated in 2005 by the American Association for the Study of Liver Diseases (AASLD).[89]

In people with a lower risk of HCC (e.g. non-cirrhotic patients and those without hepatitis B), where imaging characteristics are not typical for HCC and a malignancy is suspected, targeted biopsy with histological confirmation is still required. Notwithstanding the role biopsy plays in confirming the diagnosis, obtaining histological material may also assist in determining the biology of HCC and thus inform the prognosis, as well as providing invaluable material for scientific research. Arguably, an over-reliance on imaging-based diagnosis has contributed to the occasional misdiagnosis and hampered research into understanding the natural history of HCC. Until histology comes to have a significant influence on the management of HCC, diagnosis in patients with cirrhosis will continue to rely on imaging characteristics in most patients.

5.1 Imaging criteria for diagnosis of HCC

Recommendation 8

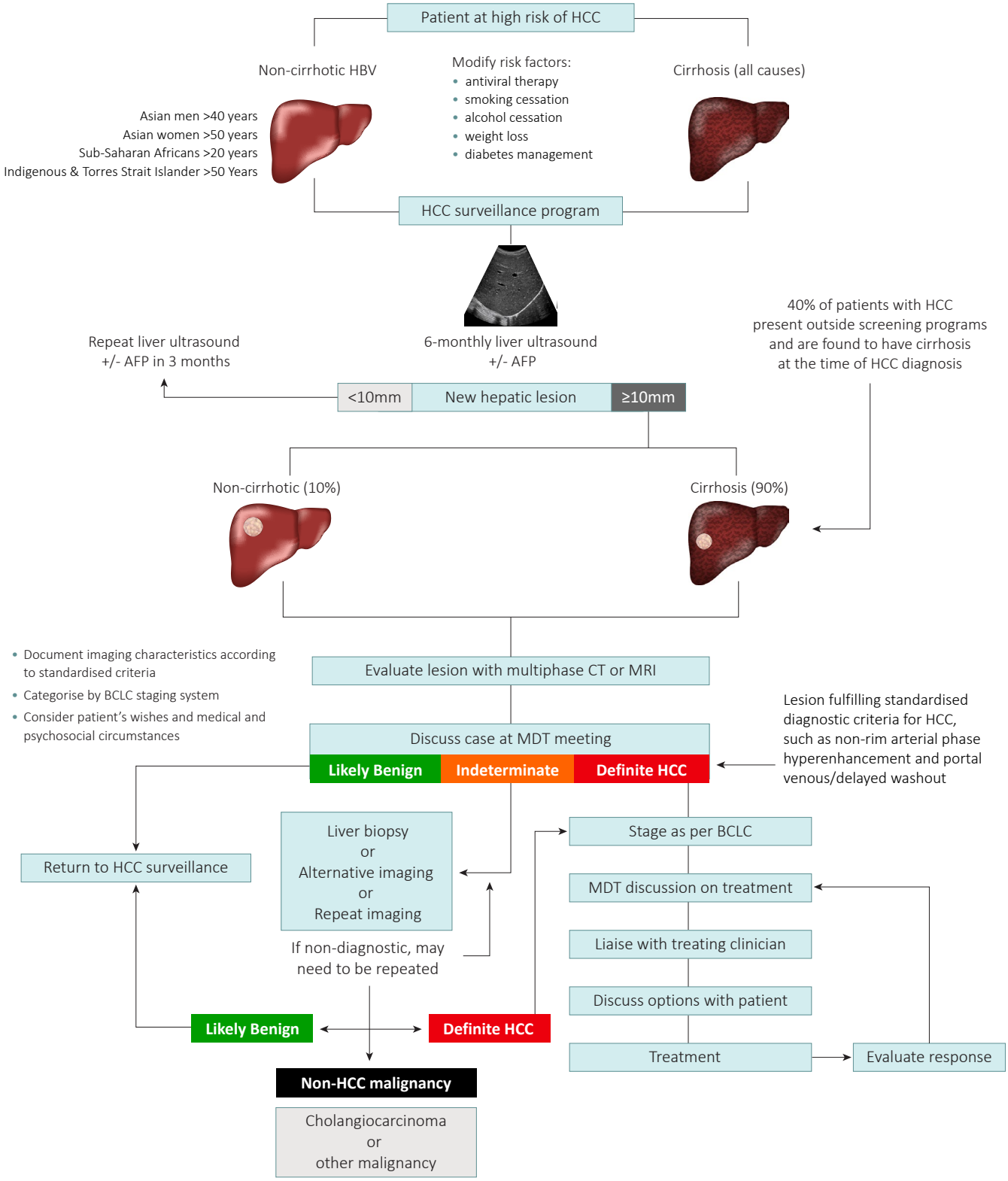
In the setting of cirrhosis, imaging diagnosis of HCC should rely on standardised criteria, based on evidence and validated in clinical practice. (Evidence quality: Moderate; Grade of recommendation: Strong)

For CT and MRI, APHE and washout are key imaging criteria. APHE occurs in HCC lesions because of the increased number of unpaired hepatic arteries (i.e. not paired with portal vein branches) that are present in typical HCCs as a result of tumour angiogenesis. Washout is less well understood, and its mechanisms are likely to be multifactorial. Probable factors include a decreased density of portal vein and hepatic vein branches in HCC lesions, compared with the background liver, as well as increased cellular density, with reduced extracellular spaces within HCCs.[90] Assessment of APHE and washout is typically based on subjective visual analysis.

Although the terms APHE and washout have been used often in medical literature, they were not well defined until the advent of the Liver Imaging Reporting and Data System (LI-RADS), a quality improvement tool developed by the American College of Radiology in 2011.[91] There have since been several iterations of LI-RADS, most recently in 2018, when diagnostic criteria for HCC from LI-RADS, the Organ Procurement and Transplantation Network (OPTN) and the AASLD 2018 guidelines became aligned.

Several factors determine the diagnostic accuracy of a particular imaging modality in detecting HCC. These include the pre-test probability (i.e. cirrhosis vs non-cirrhosis, presence of hepatitis B infection, prior HCC), together with tumour size and growth on interval imaging.

Figure 2. Surveillance and diagnosis of HCC



AFP=alpha-fetoprotein; BCLC=Barcelona Clinic Liver Cancer; CT=computed tomography; HBV=hepatitis B virus; HCC=hepatocellular carcinoma; 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 6-monthly liver ultrasound ± serum AFP. 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 to optimise patient care.

Technical remarks

1. Few studies have examined the role of subtraction imaging in HCC, which may be a useful technique for detecting subtle APHE.[92,93] Emerging technologies, such as dual-energy CT with iodine mapping, CT perfusion and high temporal resolution MRI sequences, offer opportunities for future research and potentially advances in diagnostic performance.[94-97]
2. An enhancing capsule appearance in the portal or late venous phases on CT or MRI is another useful feature and is included in OPTN and LI-RADS criteria. This appearance is typical of expansile progressed HCCs but is not seen in early HCCs or dysplastic nodules, nor in poorly defined diffusely infiltrating HCCs.[98] The presence of a capsule is not sensitive but is highly specific, with a specificity of 96% for HCC in a prospective study of 159 patients.[99]
3. In a recent multicentre prospective study analysing 544 nodules in 381 patients with cirrhosis using European Association for the Study of the Liver (EASL) and AASLD criteria, the sensitivity and specificity for the diagnosis of HCC were, respectively, 70.6% and 83.2% for MRI, 67.9% and 76.8% for CT, and 39.6% and 92.9% for CEUS in 10–20 mm nodules (n=342). For 20–30 mm nodules (n=202), the sensitivity and specificity were, respectively, 72.3% and 89.4% for MRI, 71.6% and 93.6% for CT, and 52.9% and 91.5% for CEUS.[100] Importantly, the reference standard employed in studies comparing different modalities can affect the observed diagnostic accuracy, with sensitivities and specificities significantly lower in studies using explant correlation. Sensitivities for lesions smaller than 20 mm in a meta-analysis of explant studies were significantly lower for both MRI (55% vs 95%; P=0.02) and CT (42% vs 87%; P=0.01).[101]

5.2 Diagnostic imaging systems: LI-RADS

The American College of Radiology has supported and endorsed the LI-RADS to aid consistent reporting and classification of lesions in patients at risk of HCC. This system is intended for use in those at risk of HCC, including patients with confirmed cirrhosis, hepatitis B infection and current or past HCC. The latest update of this system was published in 2018 and presents four algorithms designed for different clinical contexts, including ultrasound (in surveillance and diagnosis) and CEUS, CT and MRI for diagnosis and treatment response.[102] The AASLD has incorporated the latest LI-RADS version into its 2018 clinical practice guidelines.[45,103]

According to imaging characteristics, lesions can be classified into five LI-RADS categories: LR-1 (definitely benign), LR-2 (probably benign), LR-3 (intermediate probability of malignancy), LR-4 (probably HCC) and LR-5 (definitely HCC). Three further categories are described: LR-NC (non-categorisable due to image degradation or omission), LR-TIV (definite tumour in vein) and LR-M (probably or definitely malignant but not HCC-specific). Although lesions classified as LR-5 are intended to have nearly 100% certainty of being HCC, in some studies the diagnostic accuracy of this classification has fallen short of this value.[104] In the most recent LI-RADS version, the diagnostic accuracy for LI-RADS (version 2014 or 2017) was presented, which showed that the diagnosis of HCC was confirmed in 95% of patients with LR-5 and only 74% of patients with LR-4 lesions.[102] Clearly, lesions with imaging characteristics that fall short of LR-5 cannot be confidently diagnosed as HCC, and these lesions often require targeted biopsy and histological assessment to confirm the diagnosis.

LI-RADS version 2018 has made some important advances, with several changes and refinements. Threshold growth is now defined as a 50% increase in a lesion within 6 months of prior imaging, whereas both interval growth of >100% on imaging examinations more than 6 months apart and new >10 mm observations occurring within 24 months are now classed as subthreshold growth.

5.3 Imaging modalities for the diagnosis of HCC

Recommendation 9

Multiphase CT or MRI is the recommended investigation for lesions suspicious for HCC.
(Evidence quality: High; Grade of recommendation: Strong)

5.3.1 Computed tomography

Multiphase CT examinations can comprehensively assess suspicious hepatic lesions. Images are acquired before administration of a contrast agent (pre-contrast) and during three enhanced phases (after intravenous administration of iodine-based contrast). The three enhanced phases are the late hepatic arterial phase, portal venous phase and delayed phase. In the late arterial phase, full enhancement of the hepatic artery and its branches, together with enhancement of the portal vein, predicts maximal arterial perfusion and optimises identification of hypervascular HCCs.[105]

The hallmark diagnostic characteristics of HCC on multiphase CT imaging are APHE *together* with washout during the portal or delayed phase. Washout is defined as a temporal reduction in enhancement relative to the surrounding liver parenchyma, resulting in portal or delayed phase lesion hypoenhancement. The combined radiological features of APHE and washout in patients at risk of HCC confer a specificity approaching 100%. However, sensitivity is highly dependent on the size of the HCC, with excellent sensitivity for lesions greater than 20 mm, modest sensitivity for lesions 10–20 mm and poor sensitivity for lesions less than 10 mm in diameter.[90]

According to LI-RADS version 2018, a *definite* radiological diagnosis of HCC requires arterial phase hepatic enhancement (but not in a rim pattern) in a lesion larger than 10 mm, with at least one major feature in lesions ≥20 mm and at least two major features in lesions of 10–19 mm in diameter. Major features include washout, an enhancing capsule or threshold growth (defined as 50% or greater increase in size within a 6-month interval). The arterial enhancement excludes rim enhancement, which suggests malignancy other than HCC. The diagnostic accuracy using LI-RADS version 2018 has not yet been reported, but accuracy for versions 2014 and 2017 is shown in Figure 3.[106]

5.3.2 Magnetic resonance imaging

The principles of HCC diagnosis are similar for MRI and CT. With the use of extracellular contrast agents, the features of APHE and washout are highly suggestive of HCC in individuals who are at risk. Compared with multiphase CT, MRI offers additional imaging sequences that may provide supportive information for the diagnosis of HCC. These include T2-weighted sequences, as well as diffusion-weighted imaging (DWI) and hepatobiliary phase imaging using hepatocyte-specific contrast agents, such as gadoxetic acid (Primovist; Bayer Australia) and gadobenate dimeglumine (Multihance; Bracco).

5.3.2.1 Hepatocyte-specific contrast agents

Gadoxetate disodium and gadobenate are gadolinium-based contrast agents that are taken up by the bile transporter OATP1B3 (an organic anionic transporting polypeptide). These hepatocyte-specific contrast agents (HSCAs) have had a significant impact on MRI for HCC. After intravenous injection, the contrast agent is taken up by normally functioning hepatocytes, before being excreted in nearly equal proportions into the kidneys and bile duct canaliculi. During the arterial and portal phases, gadoxetic acid produces comparable images to those of extracellular contrast agents. However, in the delayed phase (about 20 minutes after administration), functional hepatocytes are enhanced, whereas non-functioning lesions, including most neoplastic lesions, appear hypointense.

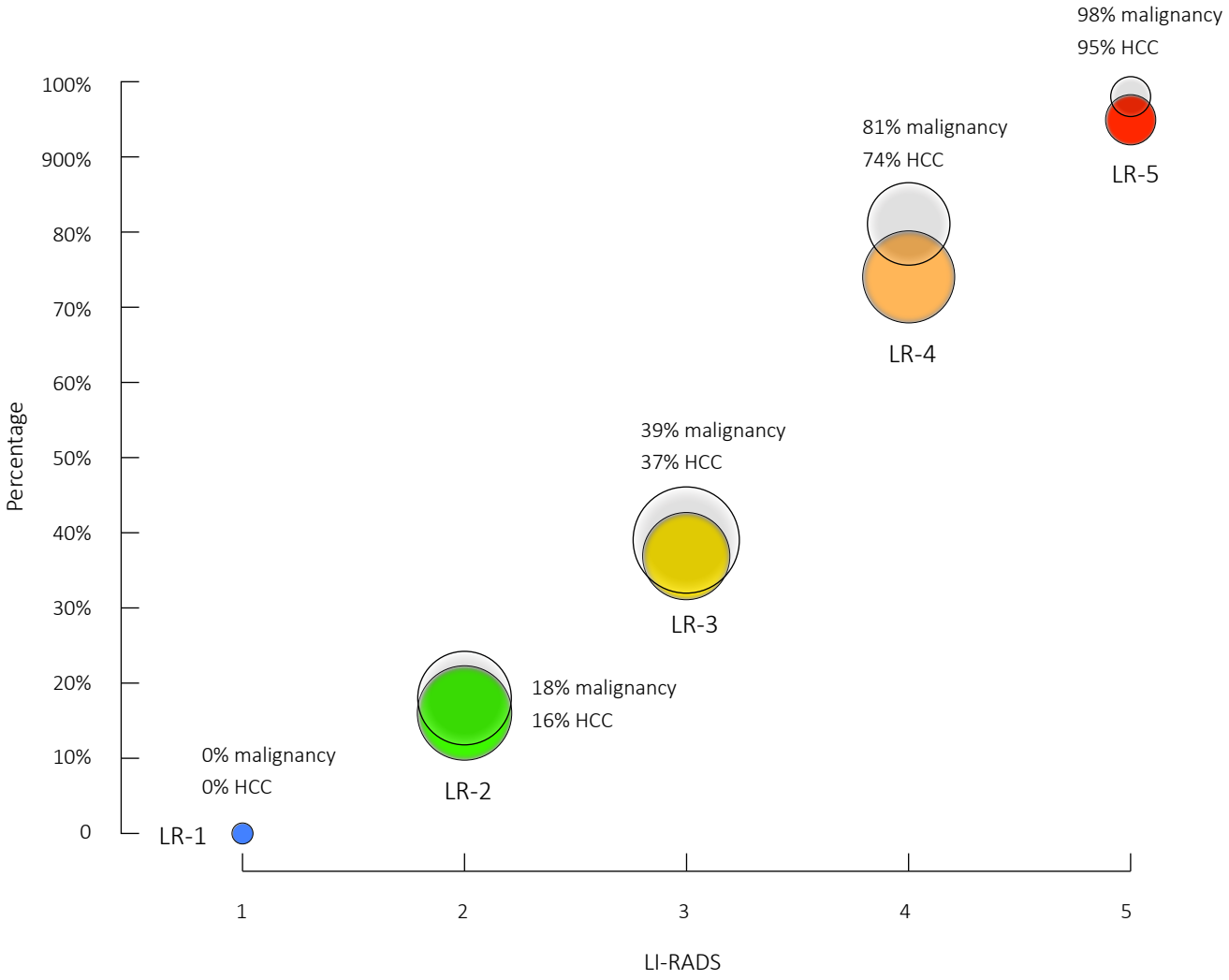
The expression of OATP1B3 is generally impaired in HCC, and most lesions appear dark on hepatobiliary phase images. In comparison, OATP1B3 expression remains high in cirrhotic nodules (regenerative nodules) and low-grade dysplastic nodules.[105] One issue with gadoxetic acid MRI is the presence of the transitional phase of enhancing at 2–5 minutes that precludes use of the term washout after the portal venous phase. This can result in a lower specificity for HCC than with conventional extracellular contrast agents.[107]

MRI with HSCAs has been shown to increase the sensitivity of HCC detection compared with multiphase CT, particularly for small lesions.[108,109] Retrospective meta-analyses comparing HSCA MRI with MRI performed with conventional extracellular agents also show improved sensitivity of HSCAs for detecting small HCCs.[101,110]

5.3.3 Contrast-enhanced ultrasound

CEUS can be used to interrogate a lesion identified through a surveillance program but, for technical reasons, does not allow for complete evaluation of the

Figure 3. Diagnostic accuracy of LI-RADS (versions 2014 and 2017)* in diagnosing malignant lesions and HCC



HCC = hepatocellular carcinoma; LI-RADS = Liver Imaging Reporting and Data System.
* Percentage with 95% confidence interval for LI-RADS categories LR-1–5. Based on data on LI-RADS versions 2014 and 2017.[106]

Technical remarks

1. In one study, CEUS for larger nodules in patients with cirrhosis performed well, with a positive predictive value (PPV) of 97.1% for lesions 21–30 mm in diameter and 100% for lesions 31–50 mm in diameter. Importantly, in lesions 20 mm or smaller, the PPV reduced to 69.2%.[111] Although this value seems low, the diagnostic performance of CEUS in patients with small (≤20 mm) hepatic nodules may be comparable to that of multiphase CT (PPV ranging from 67% to 100%).[112]
2. As with cross-sectional imaging modalities, such as CT and MRI, the imaging features of APHE and washout pertain to CEUS. However, important refinements to the definition of washout with CEUS have recently been made, in recognition that, first, early washout at less than 60 seconds can occur in cholangiocarcinoma and, second, the degree of washout that occurs with cholangiocarcinoma is greater than that seen in HCC.[113-116] Therefore, the typical pattern of enhancement with CEUS is non-rim APHE with late (greater than 60 seconds) and mild washout. LI-RADS for CEUS is available and is a highly useful reference for reporting CEUS examinations.[117]

entire liver and is problematic when multiple lesions are present in the same patient. It has the advantage of avoiding nephrotoxic contrast agents and the need for ionising radiation, and it can be performed relatively quickly by skilled operators. CEUS is not widely practised in Australia and is mainly limited to academic centres with personnel experienced in the technique.

5.4 Choice of imaging modality

The size of the lesion in question clearly influences the diagnostic performance of the imaging modality in detecting HCC and thus influences the choice of imaging. In one meta-analysis comparing multiphase CT with MRI (extracellular contrast-enhanced or gadoxetate-enhanced) in patients with cirrhosis, when all lesion sizes were considered, MRI had greater sensitivity (82% vs 66%) and a lower negative likelihood ratio (0.22 vs 0.37) than CT. Specificity and positive likelihood ratios were similar for MRI and CT (91% vs 92% and 8.8 vs 8.1, respectively). The summary area under the receiver operating characteristic curve for MRI was greater than that for CT (0.91 vs 0.80). However, both MRI and CT performed poorly with lesions smaller than 10 mm (0.69 vs 0.49).[118]

Several practical factors determine the choice between CT and MRI. Patients who experience claustrophobia, who are unable to hold their breath sufficiently long or who have ascites (which may result in image artefact) may be better imaged with CT, rather than MRI. However, CT has the inherent issues of ionising radiation exposure and potential nephrotoxicity of intravenous contrast agents.[118] In Australia, the choice between MRI and CT has been influenced by accessibility of the imaging techniques (CT is generally widely available) and MBS reimbursement. In May 2019, contrast-enhanced MRI liver scans (including the use of hepatobiliary-specific contrast agents) for the purpose of diagnosis or staging of known or suspected HCC became available on the MBS (item number 63546). This item is restricted to reimbursement for one scan within a 12-month period.

The recommended imaging algorithm for patients found to have a new liver lesion in an HCC surveillance program is shown in Figure 2.

5.5 Role of liver biopsy in diagnosing HCC

Recommendation 10

For indeterminate lesions of greater than 10 mm diameter in cirrhotic livers, either targeted liver biopsy or repeat interval imaging or an alternative imaging modality is required for diagnosis. *(Evidence quality: Moderate; Grade of recommendation: Strong)*

The frequent use of radiological criteria to diagnose HCC in people with cirrhosis has led to a decline in the routine use of liver biopsy for diagnosis. In addition, concerns about complications associated with liver biopsy are relevant; these include mild bleeding (in 3%–4%), major bleeding (0.5%) and needle-track seeding (up to 2.7%).[119,120] Although substantial progress has been made in the molecular understanding of HCC, the clinical usefulness of gene expression signatures for subtyping and prognosis of HCC has not yet been established, and these cannot therefore be recommended in routine clinical practice.

Despite the above limitations, there are several circumstances in which biopsy can be helpful in routine clinical care and for which its use is suggested by major society guidelines.[45,57,121] The major indication is for an indeterminate nodule 10 mm or larger in a cirrhotic liver. Indeterminate nodules smaller than 10 mm are not recommended for biopsy as they rarely contain malignancy and are often technically difficult to sample. Lesions of this size can be monitored with ultrasound or cross-sectional imaging until a clear change in size or growth pattern occurs. However, there is a higher rate of malignancy in nodules 10 mm or larger in cirrhotic livers that are indeterminate on at least two contrast-enhanced multiphase imaging techniques (CT or MRI). Typically, lesions >10 mm that are suspicious for malignancy (LR-4, LR-M) are good candidates for biopsy, and those with less convincing radiological features (LR-3) can be followed closely with imaging. For liver lesions appearing in people at lower risk of HCC (individuals with non-cirrhotic livers and patients without chronic hepatitis B), liver biopsy is required to establish the diagnosis.

Technical remarks

1. Factors that can affect technical feasibility of biopsy include location of the tumour (especially if high under the diaphragm), the presence of ascites and significant thrombocytopenia. Biopsy of nodules should be performed by an experienced radiologist and reviewed by an expert liver pathologist.
2. Needle core liver biopsy is preferred over fine needle aspiration because the specimen obtained is suitable for architectural and cytological assessment.[122] Tumour biopsy has a sensitivity of 67%–100% and specificity of 80%–100%. False negative results are largely due to sampling error (tumour size <10 mm and location in the upper and posterior liver segments) and challenges in distinguishing between high-grade dysplastic nodules and well differentiated HCC. If suspicion remains high for HCC, the nodule should be resampled for biopsy or closely followed with imaging.[123]
3. Once biopsy specimens are obtained, several histological markers may be useful to help distinguish dysplastic lesions from HCC in difficult biopsies. The markers include glypican-3 (GPC3), heat shock protein 70 (Hsp70) and glutamine synthetase (GS). When at least two markers are positive, sensitivity of 60% and specificity of 100% have been reported in a prospective validation study.[124]

5.5.1 Risk of seeding after biopsy

Liver biopsy of HCC can result in needle-track seeding of the tumour. Historically, reported seeding rates for HCC biopsy were high, but rates have fallen dramatically in modern series. For cutting needle techniques, the rate of seeding is estimated to be between 0.76% and 3.4%.[125-128] In a meta-analysis of eight studies involving 1340 patients, the estimated incidence of needle-track tumour seeding was 2.7% overall, with a risk of 0.9% per year.[120] Only one of the studies included in this analysis was prospective, and follow-up duration varied between 14 and 44 months. Fine needle biopsy may offer a lower risk of seeding but at the expense of reduced tissue for analysis.[129,130] The biopsy technique employed is likely an important determinant, as the risk of seeding may be substantially reduced by using a coaxial core biopsy technique. In one retrospective study of 128 patients with biopsy specimens taken using a 17-gauge introducer and 18-gauge biopsy needle during a 6-year period, there was not a single case of needle-track seeding.[131] In this study, the follow-up period was set as a minimum of 30 days — significantly shorter than in other similar studies.

5.6 Diagnostic work-up of nodules not fulfilling HCC criteria

An indeterminate nodule in the setting of chronic liver disease is defined as a nodule that cannot be definitively non-invasively characterised as benign or HCC. These nodules are typically small, usually under 30 mm in diameter. The role of imaging in these cases is to identify nodules that are likely to represent atypical HCC or cholangiocarcinoma and to differentiate them from benign nodules, which are further categorised as having high or low risk of progression.

Hypovascular nodules with hypointensity in the hepatobiliary phase of imaging have been found to have a rate of transformation into classic HCC of 7.1% at 12 months and 12.7% at 24 months,[132] although other studies suggest higher rates of progression, of more than 40% at 2 years.[133-135] Multiple studies have examined hypovascular hepatobiliary hypointense nodules (HHHNs) to determine risk factors for progression, and a consistent factor identified is increased signal on DWI scans.[134-137] DWI has a high sensitivity for diagnosis of HCC, which demonstrates increased signal, while low-grade dysplastic nodules are typically iso- to hypointense, and about a third of high-grade dysplastic nodules have elevated signal.[136] An HHHN that develops new DWI signal elevation after the baseline scan is also more likely to progress, as are nodules that develop elevated T2 signal or hypoenhancement in the portal venous phase.[134]

Multiple other factors have been examined to help predict which HHHNs will progress. Potential risk factors include elevated T1 signal,[137,138] history of HCC[134,137-140] and lesion size at baseline.[138,140,141] In practice, lesion size at baseline is challenging because the studies used various sizes between 8 mm and 12 mm, in part relating to selection criteria, and lesion size was also more heavily influential in studies with short follow-up.[141] In these studies, the HR of baseline lesion size was relatively small compared with that for other factors, especially DWI signal intensity. Lesion growth rate and volume doubling time are more likely to be accurate and useful in practice when dealing with diminutive indeterminate nodules,[138-140,142] illustrating the importance of follow-up examinations. Follow-up examinations are safe and do not result in upstaging of tumours when performed at 3–6-month intervals;[143] the caveat is that it is vital not to lose contact with patients during follow-up.

An alternative approach to follow-up is to perform CEUS for indeterminate nodules. CEUS is exquisitely sensitive for detecting arterialisation and is accurate in differentiating HCC from cholangiocarcinoma and benign nodules.[144] HHHNs with homogeneous arterial hyperenhancement and mild late (after 60 seconds) washout on CEUS can be diagnosed as HCC.

Another commonly encountered lesion in the cirrhotic liver is the hypervascular lesion, which is only seen in the arterial dominant phase. These transient hepatic attenuation differences are most often benign pseudolesions representing arterioportal venous shunts, although occasionally they may be associated with hepatic tumours.[145,146] Transient hepatic attenuation differences are often located in the subcapsular region of the liver, with a relatively wedge-shaped morphology. With more central lesions, MRI is reassuring when the lesions are occult on T2, DWI and hepatobiliary phase imaging.

5.7 Staging systems

Recommendation 11

It is recommended that the BCLC staging system is used as the framework for HCC management in Australia. (Evidence quality: Moderate; Grade of recommendation: Strong)

Recommendation 12

The management choice for a patient with HCC should take into account the individual patient's wishes and medical and psychosocial circumstances. (Evidence quality: Low; Grade of recommendation: Strong)

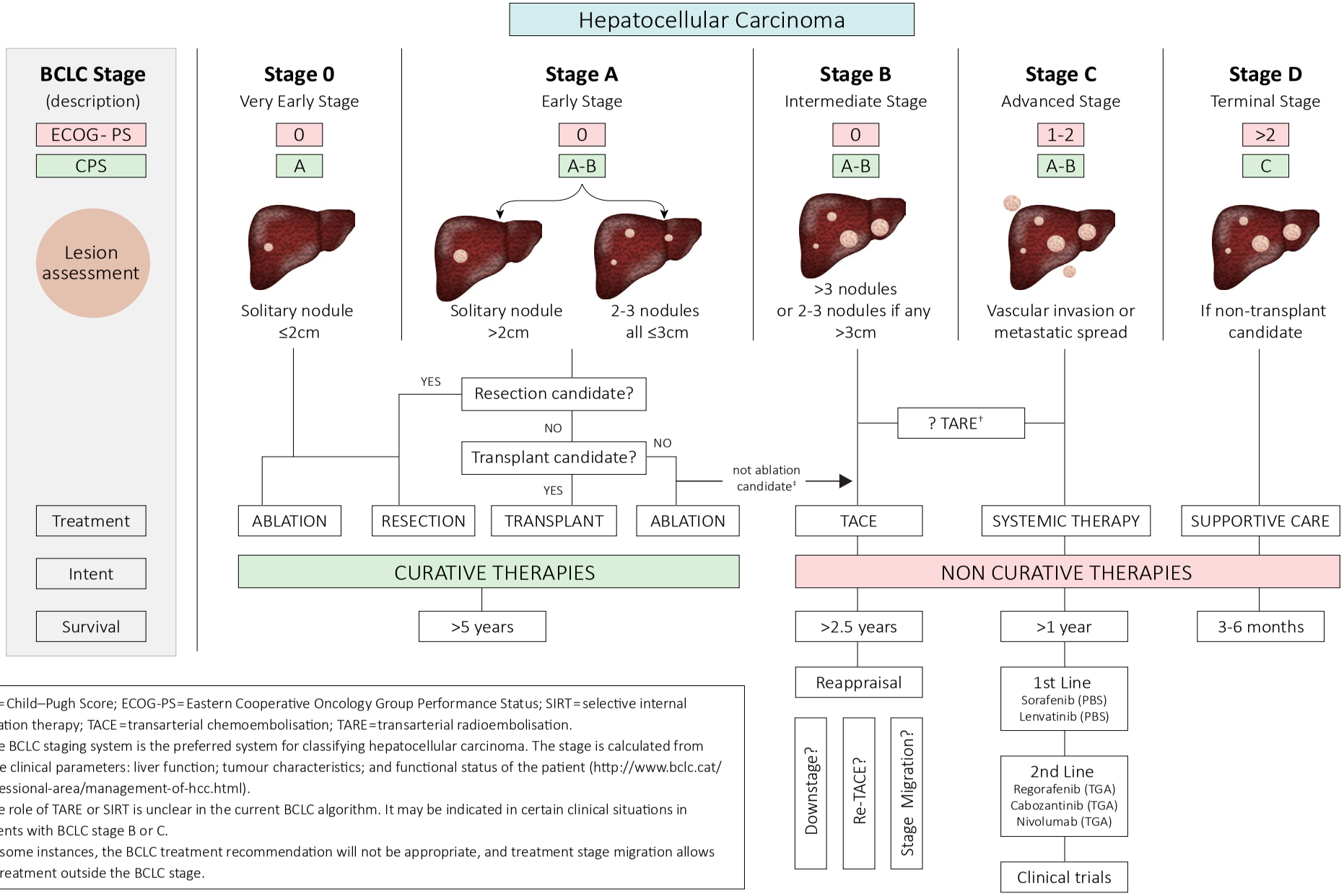
There is no universally accepted staging system for HCC because of the clinical heterogeneity and geographical differences in underlying aetiology and management practices. Of the many proposed staging systems, four have been identified as having potential applicability in an Australian context: the BCLC classification, the Model to Estimate Survival in Ambulatory HCC Patients (MESIAH),[147] the Hong Kong Liver Cancer (HKLC) system[148] and the Italian Liver Cancer (ITA.LI.CA) system.[149]

5.7.1 BCLC staging system

The BCLC classification is widely used and endorsed by the EASL and AASLD[57,58,150] (Figure 4). It was developed from experience at a single institution but has been validated in other cohorts. It incorporates three clinical parameters — liver function, tumour biology and performance status — and offers treatment recommendations based on stage (http://www.bclc.cat/professional-area/management-of-hcc.html). It performs well compared with other staging systems. The BCLC staging system is the most commonly used system in MDT meetings in Australia and is likely to remain the system of preference because of physician familiarity and ease of use.

The BCLC system has been criticised for the heterogeneity of patients in stage B, and it has also been suggested that the indication for some therapeutic options could be expanded. Additionally, it does not offer a recommendation for liver transplant for patients with decompensated cirrhosis but with

Figure 4. Barcelona Clinic Liver Cancer (BCLC) staging system*



CPS=Child–Pugh Score; ECOG-PS=Eastern Cooperative Oncology Group Performance Status; SIRT=selective internal radiation therapy; TACE=transarterial chemoembolisation; TARE=transarterial radioembolisation.
*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 (http://www.bclc.cat/professional-area/management-of-hcc.html).
†The role of TARE or SIRT is unclear in the current BCLC algorithm. It may be indicated in certain clinical situations in patients with BCLC stage B or C.
‡ In some instances, the BCLC treatment recommendation will not be appropriate, and treatment stage migration allows for treatment outside the BCLC stage.

HCC within transplant criteria, although this has recently been qualified with a footnote. It also does not consider retreatment or combination therapies.

5.7.2 MESIAH, HKLC and ITA.LI.CA systems

The MESIAH,[147] HKLC[148] and ITA.LI.CA[149] systems each have advantages over the BCLC classification; however, further validation of each is needed, particularly in Western cohorts.

In contrast to the BCLC system, the HKLC system extends the indications for resection, TACE and liver transplant. Furthermore, the stratification of intermediate disease in the HKLC system is more refined than in the BCLC system.[151-153]

A potential limitation of the HKLC system is that it was predominantly developed from a population with hepatitis B at a single Asian institution and therefore requires further prospective validation in Western cohorts to determine whether it can be robustly applied in other populations.

Similarly, the MESIAH and ITA.LI.CA systems warrant further validation and have not yet been widely adopted.

5.7.3 Treatment stage migration

A limitation common to any staging system dogma is applicability to the individual patient, including relevant medical history, as well as the patient's health beliefs and wishes. Based on these factors, a patient may be ineligible or inappropriate for the treatment option suggested by the tumour stage. Additionally, the staging systems generally do not provide direction on treatment failure and which second-line therapies or repeat first-line therapies are warranted. In these cases, the patient should be offered the next treatment option, which is usually applicable to the next prognostic stage.[57,154] This so-called treatment stage migration allows tailoring of therapy to the individual needs of a patient.

6 Management

6.1 Overview of HCC management in Australia

Management of HCC in Australia follows the broadly accepted principles of offering curative intent, when available, and exposing individuals to minimal risk with treatment. Staging of disease is necessary to determine the best treatment, and this should involve an MDT approach. A patient's understanding of his or her disease and the clinician's respect for his or her choices are essential parts of HCC management. Managing clinicians are expected to offer evidence-based treatment options.

6.1.1 The multidisciplinary team approach

Recommendation 13

The management of HCC should be determined by a multidisciplinary team to optimise patient care. (Evidence quality: Moderate; Grade of recommendation: Strong)

MDT care is being increasingly practised in cancer care services in Australia, the US and Europe.[155] In oncology, MDT 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.[156] There is conflicting evidence about MDT care, with some studies suggesting it does not improve patient survival,[156-159] while several retrospective cohort studies have reported an improvement in the OS of patients with HCC.[160-162] For patients with HCC, several studies have reported underutilisation and inappropriate administration of potentially curative and non-curative surgical and locoregional treatments,[163-166] with lack of access to MDT care noted as being a major contributor to suboptimal management.[163] Thus, all major societies recommend HCC MDT care in their latest clinical practice guidelines.[57,58,121] Most of the evidence supporting MDT care is derived from comparative retrospective cohort studies showing that MDTs improve surveillance and management, including:

- standardisation of surveillance procedures[160,167,168] and increases in the number of patients with an early diagnosis[160,161,168,169] and the proportion amenable to curative and palliative treatment;[160]
- an increase in the number of referrals for management;[160]
- an increased likelihood of providing the most appropriate treatment according to standard of care;[160,169] and
- an increase in the proportion of patients receiving active treatment, including curative and palliative therapy.[160,161]

Multiple specialists performing different roles are required to deliver optimal care and improve the clinical outcomes and quality of life for patients with HCC.[168,170] These include hepatologists/gastroenterologists, diagnostic and interventional radiologists, hepatobiliary and transplant surgeons, medical and radiation oncologists, palliative care physicians and HCC nurses.[168,170] However, the availability of treatment modalities and levels of expertise and experience of health care professionals within each specialty vary considerably across health care facilities that manage patients with HCC.[161] Hence, it is generally recommended that a liver cancer MDT should consist of at least one representative from each specialty of providers who care for patients with HCC at a particular institution, and the group should meet regularly to make consensus diagnostic and management recommendations.[160-162,168-170] The evidence in support of the composition of an MDT at institutions managing patients with HCC is mostly derived from expert opinion[168,170] and multiple societal clinical practice guidelines.[57,58,121] There is no general consensus in the literature about who should lead an HCC MDT. However, expert opinion recommends that, 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 an individual case.[171]

Technical remarks

1. Due to Australia's geographical size and population distribution, telemedicine approaches are increasingly being adopted for MDT patient management.
2. In establishing an MDT, it is important to identify the core health care professionals who have the necessary expertise, skills and availability to be regular key contributors, as well as a leader of the MDT to guide members and meetings.
3. MDT meeting frequency should be in accordance with institution size and patient numbers.
4. The MDT should endeavour to agree on a staging system and MDT treatment algorithm; document MDT meeting attendance; decide on case selection, presentation format and summary; and formally document the MDT decisions.
5. Health care institutions managing patients with HCC should provide the resources and infrastructure support needed to establish and maintain the HCC MDT.

6.2 Treatment goals

Treatment of HCC is based on staging of disease and considers curative intent before disease control and subsequent palliation. The great heterogeneity of HCC presentations is recognised, along with the need for individualised treatment plans. Treatment offered needs to be based on evidence, ideally that derived from RCTs. However, high-level evidence is not always available to support HCC management, and this is reflected in the recommendations presented here. An overview of current therapies by BCLC stage is shown in Figure 4.

6.3 Pre-treatment assessment of patients with HCC

Pre-treatment assessment of HCC requires, at a minimum: a detailed history; clinical examination; multiphase imaging of the liver and lesion(s); and determination of liver function, renal function, blood counts and ECOG patient performance status.[172] Gastroscopy is often required for surveillance and treatment of varices in the presence of known or suspected portal hypertension. The indications for, and frequency of, gastroscopy and management of varices are outlined in guidelines of chronic liver disease management and should take into consideration the expected benefit in and survival of patients with HCC.[173,174] Measurement of AFP level can add additional prognostic information in select cases and may have been undertaken as part of surveillance.

Determination of viral hepatitis B and C status is typically undertaken to determine the cause of HCC. Management of HBV infection is as per guidelines,[175] and HCV infection is discussed in section 4.9.2.

A pre-treatment assessment is needed to stage both the HCC and underlying liver disease by Child–Pugh classification and identification of portal hypertension. Adequate performance status (ECOG grade 0 or 1) is required for most treatment options. It is important to exclude extrahepatic metastatic disease at the initial assessment in patients being offered treatment with curative intent. However, the preferred routine screening investigations for metastatic disease in asymptomatic individuals are unproven, and individualised investigations should be undertaken based on treatment options.

6.4 Surgical therapies

6.4.1 Surgical resection

Recommendation 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. *(Evidence quality: Moderate; Grade of recommendation: Strong)*

6.4.1.1 Indications and contraindications

Liver resection (LR) is indicated for HCC in patients where 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, along with adequate inflow and outflow to preserve life. Assessment of patients for potential LR for HCC therefore requires evaluation of the patient, liver function, portal hypertension and tumour characteristics.[57,121,176] OS after LR for HCC depends on the risk of developing liver failure, succumbing to non-liver-related complications of surgery or developing recurrent HCC.

6.4.1.2 Outcomes after surgery

Perioperative outcomes for resection of HCC continue to improve, due to better surgical selection, operative techniques and perioperative management.[177] Although large-volume centres are achieving mortality rates <2%,[178] analysis of the American College of Surgeons National Surgical Quality Improvement Program database showed a mortality rate of 5% across North America,[179] with mortality usually related to postoperative hepatic failure.

The use of laparoscopic techniques has seen a reduction in complications (notably blood loss, ascites and liver dysfunction), while achieving similar long-term oncological outcomes.[180] Despite this, morbidity remains high, with overall morbidity of 32%–45%.[178,179] Although most complications are mild,[181] about 10% of patients experience more severe complications.[178] There is emerging evidence that postoperative complications are associated with lower long-term disease-free survival (DFS) and OS, possibly due to immunosuppressive effects of the inflammatory process.[178]

6.4.1.3 Post-resection complications

Increased complications are seen in patients with reduced hepatic functional reserve and obese patients. Large operative blood losses of >1000 mL are also associated with increased postoperative complications and inferior long-term outcomes.[178] Common complications of LR for HCC include pleural effusions (15%), ascites (6%–7%), liver failure (8%), pneumonia (2%–5%), superficial or deep surgical site infection (5%–11%), deep organ space infection (6%–11%), bile leak (3%–13%), deep venous thrombosis or pulmonary embolism (1%), sepsis (1%), postoperative haemorrhage (1%–9%) and blood transfusion (38%) (Table 4).[178-180,182,183]

Post-hepatectomy liver failure (PHLF) is a devastating complication, and a high risk of its occurrence precludes surgery. Predicting PHLF depends on pre-existing liver function, the presence or absence of portal hypertension and the size of the resection (segmental vs major). A functional liver remnant of 40%–50% is recommended in patients with underlying cirrhosis.[194] Liver function assessment has traditionally been performed using Child–Pugh status, with resection limited to patients with Child–Pugh class A status. Alternative measures of liver function that avoid the categorical and subjective nature of Child–Pugh assessment include the Model for End-Stage Liver Disease (MELD) score and liver stiffness measurement. A meta-analysis of six studies found transient elastography to be accurate in predicting post-hepatectomy complications, with a summary area under the curve of 0.87.[195] Similarly, a MELD score >9 is associated with a significantly higher rate of postoperative mortality.[196,197] However, it remains unclear how to best integrate liver stiffness measurement and MELD score into algorithms to optimise patient selection for surgery.

Among patients with cirrhosis, preserved liver function (defined by a normal bilirubin level) and absence of clinically significant portal hypertension (defined by platelet count <100,000/mm^3, oesophageal varices or hepatic venous portal gradient ≥10 mmHg) predict a 75% 5-year survival after resection for HCC and thus define optimal resection candidates.[198] Less easily defined factors, such as surgical technique and expertise, intensive care and postoperative management, influence the likelihood of PHLF and, where favourable, may also allow equivalent outcomes in patients with cirrhosis who do not fulfil these criteria.[57]

6.4.1.4 Outcomes of resection compared with ablation therapies

A meta-analysis of 15 studies involving 3627 patients compared the outcomes of LR and radiofrequency ablation (RFA) for HCC in patients with Child–Pugh class A cirrhosis.[200] Only two of the included studies

Table 4. Postoperative complications of liver resection for HCC

Complication	Comments
Liver failure	• Post-hepatectomy liver failure (PHLF) may be defined by the "50–50" rule (serum bilirubin level >50 µmol/L and prothrombin time <50% of normal on postoperative day 5). This rule is predictive of 60-day mortality.[184] • The International Study Group of Liver Surgery (ISGLS) defines PHLF as "the impaired ability of the liver to maintain its synthetic, excretory, and detoxifying functions, which are characterized by an increased international normalized ratio and concomitant hyperbilirubinemia… on or after postoperative day 5".[185] The ISGLS definition is sensitive for predicting mortality.[186] • Notably, both the above definitions were developed primarily in patients without cirrhosis and not specifically for hepatocellular carcinoma (HCC)-related surgery.
Ascites	• The development of postoperative ascites is not fully understood but includes impairment of hepatic functional reserve and increased portal pressures. • Risk factors include cirrhosis, extent of resection, low serum albumin level, low platelet count, operative blood loss and long duration of operation.[182,187,188] • Large losses of ascitic fluid with water and electrolyte disturbances can lead to hepatic failure.
Biliary leak	• Reported rates of biliary leak vary due to the lack of a standard definition, until one was recently proposed by the ISGLS.[189] • Risk factors include repeat resections and long operations. Intraoperative biliary injuries and biliary strictures from previous HCC treatments (transarterial chemoembolisation, surgery) may lead to intractable postoperative biliary leak, requiring biliary drainage procedures (endoscopic retrograde or percutaneous transhepatic biliary drainage).[183] • Methods proposed to reduce biliary leaks include preoperative biliary anatomy assessment, intrahepatic cholangiography, intraoperative bile leakage tests and intraparenchymal biliary division.[183]
Haemorrhage	• Median blood loss with resection varies from 100 mL to more than 1 L.[180] • There is conflicting evidence regarding the possible negative impact of perioperative blood transfusion on disease recurrence and overall survival.[190-192] • Various methods of vascular exclusion (Pringle manoeuvre, selective hepatic vascular exclusion, hanging manoeuvre) and the use of energy devices and staplers for parenchymal transection have been suggested for reducing blood loss. • There is good evidence that laparoscopic techniques result in lower blood loss.[180]
Pleural effusion	• Pleural effusion is a common complication of liver resection for HCC. • Causes include diaphragmatic injury, dissection of the hepatic coronary ligament and disruption of lymphatic channels. • It is seen more often in patients with longer operative times and greater intraoperative blood loss[193] and in those who develop ascites, possibly due to the presence of peritoneal pleural channels in patients with cirrhosis.[182,193]

were RCTs and, of the 13 retrospective observational studies, patients were eligible for both LR and RFA in only two studies. LR was superior to RFA when only the RCTs were considered (5-year mortality for RFA vs LR: OR, 2.863; 95% CI, 2.196–3.732; $P < 0.001$).[200] However, considering the studies where patients were eligible for both therapies and studies limited to patients with solitary tumours or tumours <30 mm,

Technical remarks

1. Either laparoscopic or open LR can be performed for patients with HCC.
2. Anatomical resection is preferred over non-anatomical resection where feasible, to minimise the risk of recurrence caused by occult segmental metastases.
3. An anterior approach with hanging manoeuvre is recommended for right hemi-hepatectomy, to minimise manipulation of the tumour and reduce the risk of recurrence.
4. There should be a surgical margin of at least 10 mm, where possible, to reduce the chance of recurrence.[199]
5. Postoperative liver decompensation is determined by the extent of hepatectomy, clinically significant portal hypertension and MELD score >9 (in descending order of importance).[197] Child–Pugh class and indocyanine green retention testing are not as reliable in predicting outcomes.[197]
6. Suitability for resection needs to be considered relative to other treatment options, such as ablative therapies, in terms of likelihood of success and patient tolerability.

there was no difference in OS and DFS between patients treated with LR or RFA.[200]

Comparing RFA with LR for HCC, another meta-analysis found there was no significant difference in 1-year OS (RFA vs LR: relative risk, 1.39; 95% CI, 0.36–5.33) or 3-year OS (RFA vs LR: relative risk, 1.40; 95% CI, 0.75–2.62).[201] There were only two included studies that assessed 5-year OS.[201] One of these found that 5-year OS (55% vs 76%; *P* = 0.001) and recurrence-free survival (RFS) (29% vs 51%; *P* = 0.017) were reduced in the RFA group.[202] However, almost a quarter of the patients had a tumour >30 mm in diameter, and a single RFA needle was used. An increased risk of recurrence would be expected in this situation. The other study found no difference in 5-year OS (RFA, 86% vs LR, 83%; *P* = 0.812) but a reduced 5-year DFS for RFA (31% vs 44%; *P* = 0.042).[203] This study did not include BCLC stage 0 patients (inclusion criteria included a solitary tumour ≥20 mm but ≤40 mm in diameter).

In a meta-analysis comparing the outcomes of microwave ablation (MWA) with those of LR for HCC for tumours <30 mm in diameter, there was no significant difference in OS or DFS.[204] However, MWA was associated with shorter operating time, less blood loss and reduced risk of morbidity.[204]

LR is probably preferable to ablation for treatment of superficial HCC and tumours adjacent to hepatic ducts, although there is little evidence regarding this.[205]

6.4.2 Liver transplantation

Recommendation 15

Liver transplantation should be considered for patients with HCC within transplant criteria who are not suitable for curative hepatic resection or ablative therapy. *(Evidence quality: High; Grade of recommendation: Strong)*

Liver transplantation (LT) is a definitive treatment option for patients with early-stage HCC, as it eliminates both the tumour and the associated liver disease.[206] In Australia and New Zealand, the 5-year OS among liver transplant recipients where HCC was the indication is excellent, at 75%, and similar to that in published series from overseas.[207,208] There are no randomised studies that have directly compared LT with surgery or other curative therapies for early-stage HCC, and such studies are unfeasible because of the large patient population required. Retrospective studies that include adjustment for disease severity suggest that OS after LT is as good as that after other forms of treatment.[198,209] Intention-to-treat analyses of LT for HCC have shown that OS and RFS rates are both higher at 5 years when compared with hepatic resection.[198,209]

Technical remarks

1. LT is limited to HCC that is confined to the liver.
2. A meta-analysis comparing LT and resection in patients with early-stage disease and well-compensated cirrhosis suggested a significant 5-year survival advantage for LT over resection (HR, 0.52; 95% CI, 0.298–0.911).[210]
3. A meta-analysis of patients comparing survival outcomes after curative locoregional therapy (LRT) with those after LT (stratified by the stage of liver disease, extent of cancer and whether salvage LT was offered) has shown that 5-year OS and DFS were both worse for all categories of curative LRT combined, compared with primary LT (OR, 0.59; 95% CI, 0.48–0.71). However, 5-year OS was not different for those with compensated (Child–Pugh class A) cirrhosis and a single HCC, although DFS was worse.[211]

6.4.2.1 Patient selection criteria for liver transplantation

Recommendation 16

University of California San Francisco (UCSF) criteria should inform patient selection for liver transplantation in patients with HCC. (Evidence quality: Moderate; Grade of recommendation: Strong)

Selection of the best candidates for LT is critical to both achieving optimal results and not misusing a valuable resource. Liver transplant units across Australia and New Zealand agree in principle that eligibility for entry to the LT waiting list should be based on an expected 5-year survival of greater than 50%; this aligns with international benchmarks.

In 2001, the UCSF criteria (a single tumour of up to 65 mm; or up to three tumour nodules, each not exceeding 45 mm in diameter and with a total tumour diameter up to 80 mm; no vascular invasion or extrahepatic disease; Table 5) were introduced.[212] Patients with HCC meeting the UCSF criteria had survival rates of 90% and 75.2% at 1 year and 5 years, respectively, after LT, compared with a 50% 1-year survival for patients with tumours exceeding these limits ($P = 0.0005$).[212] In the past decade in Australia and New Zealand, after the expanded UCSF criteria based on preoperative imaging were adopted, the 5-year OS when HCC was the indication for LT has been 80%. This cohort includes cases that were downstaged.

6.4.2.2 Metroticket 2.0: developments in transplant selection criteria

Expansion of the original Milan criteria — as proposed by the UCSF group[212] or in the extended Milan Up-to-seven rule,[213] among others — has shown that less restrictive criteria can be used without having an impact on survival. Despite the existence of such criteria, optimal patient selection for LT remains complex.

Table 5. Comparison of liver transplantation criteria for patients with HCC (listed in chronological order)

	Milan[207]	UCSF[212]	Up-to-seven[213]	Metroticket 2.0[214]
Criteria	Single lesion ≤50 mm ***or*** 2 or 3 tumours each ≤30 mm	Single lesion ≤65 mm ***or*** 2 or 3 tumours each ≤45 mm and total tumour diameter is ≤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 = alpha-fetoprotein; HCC = hepatocellular carcinoma; UCSF = University of California San Francisco.
* Online calculator available at http://www.hcc-olt-metroticket.org.

The prognostic value of AFP level as a surrogate of microvascular invasion and as a predictor of poor post-transplant outcomes in patients with HCC has also been established.[215-217] An AFP cut-off of >1000 ng/mL has been recommended in Australia and New Zealand as an exclusion for LT, in line with current US guidelines,[218] but more restrictive cut-offs have been used in other countries.[219] By adding AFP cut-offs to waitlisting and/or downstaging models, improvements in predicting post-transplant outcomes have been demonstrated.[214,216,220,221]

A novel tool called the Metroticket Calculator estimates 5-year post-LT survival based on post-LT explant findings (Calculator 1.0) or pre-LT morphology and AFP levels (Calculator 2.0). Predicted OS calculated by the Metroticket model in a single-centre liver transplant cohort (n = 82), based on pre-transplant radiological data, was 76.3% and 69.7% at 3 and 5 years, respectively, compared with observed survival of 83% (49/59) and 74% (35/47), respectively.[222] On an intention-to-treat analysis, OS after listing was 73.8% (95% CI, 62.7–82.1) at 3 years and 69.1% (95% CI, 53.7–78.2%) at 5 years.

The newer Metroticket 2.0 model pragmatically uses pre-transplant radiology (sum of tumour size and number of nodules) and AFP level to predict 5-year survival after transplantation.[214] Metroticket 2.0 uses a competing risks analysis to differentiate between death due to HCC recurrence and the competing risk of death due to other causes. Based on AFP level, HCC number and size, this model outperformed the UCSF, Up-to-seven, Milan and Shanghai-Fudan criteria ($P < 0.001$) and the AFP French model ($P = 0.044$) to predict 5-year survival after LT. There is, however, no analysis of the impact of LRT as bridging or downstaging therapy in this model, and to date there has been limited external validation. The Metroticket 2.0 model is under consideration by the Transplantation Society of Australia and New Zealand.

6.4.2.3 Bridging therapy

Patients on the waiting list for LT are at risk of tumour progression beyond UCSF criteria and hence of becoming ineligible for transplantation, resulting in waiting list dropout. To minimise waiting list dropout, "bridging" therapy — the use of LRT to deter tumour progression beyond transplant criteria — has been used. As bridging LRT is not without risk, careful patient selection is required to reduce the risk of exacerbating the underlying liver disease or worsening liver synthetic function and portal hypertension.[223]

Several bridging LRTs, including TACE, transarterial radioembolisation, ablative therapy and stereotactic ablative body radiotherapy, have been used, either alone or in combination.[223] Of these, TACE is the most commonly used, but it only offers complete pathological response in about 30% of cases.[223]

6.4.2.4 Risk of HCC recurrence after liver transplantation

Aggressive tumour biology is an important predictor of HCC recurrence risk and is indicated by poor histological differentiation and microvascular invasion, both of which have long been known to be strong predictors of HCC recurrence. In one study, microvascular invasion doubled mortality, with a post-LT 5-year OS rate of 64% and 33% in those without and with microvascular invasion, respectively, in patients outside the Up-to-seven criteria.[213] Conversely, the absence of these risk factors may justify LT in patients with large tumours, as shown by the Toronto experience. The extended Toronto criteria allow LT for patients with any number and any size of HCC lesions, as long as no evidence of vascular invasion or extrahepatic disease exists, no cancer-related constitutional symptoms are observed and a targeted biopsy of the largest lesion does not show poor differentiation.[224]

Histology to assess tumour grading and microvascular invasion is not readily available. If a biopsy is performed, microvascular invasion can be missed, and tumour grading may not be uniform across all lesions in patients with HCC. AFP level is a well-established surrogate of tumour biology, as it can correlate with histological grading and vascular invasion. Many studies have highlighted the importance of increased AFP values in the recurrence risk after LT.[225]

The following factors are surrogates for aggressive tumour biology and considerations for LT:

- HCC that progresses to beyond UCSF criteria despite LRT;
- microvascular invasion seen on histological analysis;

Technical remarks

1. There are no RCTs to confirm either the efficacy of LRT at reducing dropout or the superiority of one bridging LRT over another.
2. A recent systematic review and meta-analysis concluded that in patients with T1 and T2 HCC who were listed for LT, bridging LRT was associated with a non-significant trend towards improved waiting list and post-transplant outcomes, although the overall quality of evidence was poor and risk of selection bias high.[223]
3. Patients referred for LT should be carefully assessed over time to identify rapidly progressing tumours with aggressive biology that may adversely affect patient outcomes. Patients referred for LT for HCC should have baseline assessment to stage their HCC, along with AFP level, a bone scan and CT chest scan to exclude metastasis.
4. For patients on the waiting list for LT for HCC, continued documentation of tumour status is required every 3 months, using CT or MRI and AFP level, to ensure ongoing eligibility for LT.
5. When salvage LT is offered after curative LRT, there is no difference in 5-year OS (OR, 1.0; 95% CI, 0.6–1.7).[211]
6. In a study of patients who had undergone previous HCC resection and had recurrence within Milan criteria, 79% were eligible for salvage LT.[227]
7. Outcomes in patients undergoing primary LT or salvage LT after resection showed no difference in recurrence rates or OS between the two groups (5-year OS, 59% vs 61%).[228]

- poorly differentiated HCC seen on histological analysis, if available before transplantation; and
- high or rising AFP levels: increased AFP values are a risk factor for patients both within and outside of HCC LT criteria (a study including more than 200 patients with HCC within the Milan criteria showed a 5-year RFS of 53% for those with an AFP level >1000 ng/mL and 80% for those with an AFP level ≤1000 ng/mL).[217]

Absolute contraindications to LT include the presence of macrovascular invasion and extrahepatic metastases.[226]

6.4.2.5 Downstaging before liver transplantation

Recommendation 17

Patients with HCC initially beyond transplant criteria may be considered for liver transplantation after successful downstaging to within standard transplant criteria. (Evidence quality: Low; Grade of recommendation: Strong)

Factors that predict successful downstaging from LRT are largely unidentified, and the optimal form of liver-directed therapy for the purposes of downstaging remains unclear. Further, there is no standard accepted waiting period after downstaging to determine its efficacy and subsequent optimal timing for LT. Many studies define downstaging as a reduction in tumour burden to within UCSF criteria based on radiographic findings, although some studies define it as a complete absence of tumour on radiographic findings. This variability in the definition of successful downstaging is largely because of differences in tumour burden before LRT and type of LRT used, as well as differing methods to assess radiographic response and lack of a standardised period at which response to therapy is reviewed.[176] Prospective trials have shown that selected patients with a tumour burden exceeding the Milan criteria can undergo LT if they are successfully downstaged, with a recurrence risk and 5-year survival comparable to those for patients initially presenting with HCC within the Milan criteria.[229,230]

6.5 Locoregional therapies

Ablative therapies are generally restricted to a small number of lesions (up to three), while non-ablative therapies may be used when multiple lesions are present.

Technical remarks

1. A retrospective multicentre study of 187 patients in a downstaging protocol reported favourable results.[220] LT was performed after successful downstaging in 109 patients (58%). Explant tumour from one patient had poorly differentiated grade, and seven (6.4%) had vascular invasion. Based on Kaplan–Meier analysis of data collected a median of 4.3 years after LT, 95% of patients would survive 1 year and 80% would survive 5 years; probabilities of RFS were 95% and 87%, respectively. Patients were removed from the LT waiting list because of tumour progression (n=59; 32%) or liver-related death without LT (n=9; 5%). Based on multivariable analysis, factors associated with treatment failure were pre-treatment levels of AFP >1000 ng/mL (HR, 3.3; P<0.001) and Child–Pugh class B or C (HR, 1.6; P<0.001).
2. The probability of treatment failure at 2 years from the first downstaging procedure has previously been found to be 100% for patients with levels of AFP >1000 ng/mL and Child–Pugh class B or C, compared with 29.4% for patients with neither risk factor (P<0.001).[229]
3. A 6-month period of liver imaging stability is required before transplant list activation.

6.5.1 Ablative therapies

Recommendation 18

Ablative therapy is recommended as a curative locoregional therapy in suitable patients with very early or early (BCLC stage 0 or A) HCC. (Evidence quality: Moderate; Grade of recommendation: Strong)

Ablative therapies for HCC involve treatment of a lesion with the intent of local disease elimination. This can involve invasive therapies with direct manipulation of the tumour. Lesions do not typically recur with ablative therapies. Ablative therapies may involve multiple treatments to achieve local tumour ablation.

Recommendation 19

Patients with early-stage (BCLC stage A and early stage B) disease, who are not candidates for surgery or liver transplantation, should be treated with locoregional therapy. (Evidence quality: High; Grade of recommendation: Strong)

More than 75% of patients with early-stage (BCLC-A) HCC are not suitable for either surgical resection or LT because of age, underlying severity of liver disease, clinically significant portal hypertension or significant comorbidity.[231,232] For these patients, LRT — with image-guided percutaneous tumour ablation and/or image-guided transcatheter tumour therapy — should be considered. Image-guided tumour ablation techniques for which there is good evidence include thermal ablation with RFA and chemical ablation with percutaneous ethanol injection (PEI).[231] In addition, there is emerging evidence for use of MWA and, in select cases, the new image-guided ablative techniques of irreversible electroporation and stereotactic ablative body radiotherapy.

Technical remarks

1. Early-stage BCLC-A disease is typically defined as falling within criteria for the number of lesions considered suitable for transplantation.
2. Up to 40% of these patients may not be suitable for surgical or ablative techniques.
3. Uncontrolled studies suggest that treatment stage migration to LRT with TACE, either alone or in combination with local ablative techniques, should be considered.[232-235]

6.5.1.1 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 (RFA, MWA, laser, cryoablation) and chemical injection (PEI, acetic acid injection). Of these, RFA is the most widely recommended first-line ablation technique for patients not suitable for surgery.[231] This recommendation is based on evidence from five RCTs[236-239] and three meta-analyses[240-242] showing that it provides better

local disease control and survival outcomes than percutaneous ablation. The beneficial effects of RFA over PEI are most evident in HCC nodules >20 mm in size.[241] However, PEI does have a role in select situations where RFA is not possible because of the proximity of nodules to the gall bladder, stomach, colon or other viscera, where it may cause injury, or to large blood vessels, where it may cause a heat-sink effect.[231] For very early-stage (BCLC-0) HCC involving a solitary small nodule (≤20 mm), ablation is very effective, achieving near 100% complete necrosis and OS similar to that after surgery.[240] However, results from three RCTs comparing resection and RFA have produced conflicting results,[202,243,244] while a meta-analysis of these studies suggested the longer-term 5-year OS and RFS rates were better with surgery than with local ablation.[245]

MWA is a relatively recent and increasingly popular thermal ablative technique because of its ability to produce more rapid heating and a higher maximum tissue temperature.[246] In addition, MWA 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[231,246] and potentially treat larger lesions more effectively.

6.5.1.2 Percutaneous ablative therapy combined with TACE

Several studies and RCTs have compared the outcomes of TACE combined with RFA with outcomes from RFA alone in patients with early-stage HCC within the Milan criteria, the majority of which involved tumour sizes ≤50 mm.[113,254-259] An initial network meta-analysis of two of these studies concluded that the combination of TACE plus RFA was the most effective treatment for early-stage HCC.[260] However, a more recent Cochrane review that included an additional study[256] was unable to demonstrate a benefit of TACE plus RFA in the treatment of patients with early-stage HCC.[261] Only two small trials at high risk of bias,[254,256] including one presented only in abstract format,[254] were included in the Cochrane analysis, and only one of these studies reported mortality at maximal follow-up.[254]

6.5.2 Non-ablative therapies

Non-ablative therapies for HCC involve treatment of a lesion with the intent of local disease control. Lesions typically recur with non-ablative therapies and often require further treatment. TACE is the most common non-ablative therapy for HCC.

Technical remarks

1. MWA requires less procedural time than RFA and is not subject to a heat-sink effect, which is a known potential shortcoming of RFA.[247]
2. Studies to date comparing outcomes of RFA with those of MWA have yielded conflicting results, with no clear superiority of one technique over the other.[248-250] A Cochrane review reported that there were insufficient data in this area to recommend RFA over other thermal ablation techniques in the management of HCC,[251] with the authors emphasising that only a single small RCT comparing RFA with MWA, with a total of 72 patients, had been performed.[249]
3. A meta-analysis of seven studies, including the above RCT and six retrospective case–control studies, involving a total of 774 patients predominantly from Asia, concluded that there was similar efficacy between the two percutaneous techniques in terms of local recurrence rate (OR, 1.01; 95% CI, 0.53–1.87; P=0.98), complete response (P=0.67) and OS at 3 years (P=0.85).[252]
4. Rates of complications are low with both RFA (4.1%) and MWA (4.6%).[250,253]
5. Uptake of MWA is on the increase in preference to RFA in many large academic centres because of its ability to achieve a more rapid ablation, thereby providing a workflow advantage, particularly when performing multiple ablations.
6. Other percutaneous ablation methods, including cryotherapy and electroporation, are not proven in routine HCC management.

Technical remarks

1. There is significant heterogeneity between studies of TACE plus RFA compared with RFA alone in terms of tumour size and number.[256] On meta-analysis, subgroup analysis indicated that there were no significant differences between TACE plus RFA and RFA alone in the treatment of small HCC tumours (<30 mm), with the benefit confined to intermediate (30–50 mm) and larger (>50 mm) HCCs.[256]
2. A single-centre RCT compared TACE plus RFA with RFA alone in 189 patients with HCC measuring up to 70 mm. Patients in the TACE plus RFA group had better OS (HR, 0.525; 95% CI, 0.335–0.822; *P*=0.002) and RFS (HR, 0.575; 95% CI, 0.374–0.897; *P*=0.009) than patients in the RFA group.[113] On logistic regression analyses, treatment allocation, tumour size and tumour number were significant prognostic factors for OS, whereas treatment allocation and tumour number were significant prognostic factors for RFS. In contrast, another meta-analysis comparing RFA plus TACE with RFA alone reported a significant improvement in RFS (HR, 0.58; 95% CI, 0.42–0.80; *P*=0.001; *P*=0.094 for heterogeneity) and OS (HR, 0.60; 95% CI, 0.47–0.76; *P*<0.001; *P*=0.414 for heterogeneity).[262]

6.5.2.1 Transarterial chemoembolisation

Recommendation 20

In patients with BCLC-B HCC, TACE is recommended as first-line therapy.
(Evidence quality: Moderate; Grade of recommendation: Strong)

TACE, a procedure that involves the injection of both chemotherapy and embolic material into the arteries supplying a tumour, is considered the first-line standard of care for patients with BCLC-B HCC.[57,176] TACE is most often performed in these patients as a palliative procedure because tumour burden is considered too extensive for curative therapies. In addition, TACE may be used to downstage patients, to ultimately allow for treatment with curative intent (see section 6.4.2.5). The rationale of TACE is that the intra-arterial infusion of a cytotoxic agent, followed by embolisation of a tumour-feeding arterial vessel, induces cytotoxicity and necrosis. Multiple cytotoxic agents in varying doses have been employed for TACE, with no good evidence that one is superior over the others.[232]

TACE can be classified according to the mode of chemotherapy delivery as: i) conventional TACE (cTACE), where the chemotherapeutic agent(s) are typically mixed with iodised oil (Lipiodol; Aspen); or ii) drug-eluting bead TACE (DEB-TACE), where the chemotherapy

Technical remarks

1. When iodised oil can also be used to enhance visualisation of HCC lesions on CT, to facilitate curative ablations, then in this context TACE may be used in patients with BCLC-A disease.
2. Careful selection of patients with BCLC-B HCC for LRT with TACE is necessary.
3. Patients with poor performance status (ECOG grade >2) or significantly decompensated liver disease (Child–Pugh class >B8) are unlikely to benefit from TACE.
4. As superselective TACE has enabled highly accurate targeting of lesions, very carefully selected patients, even those with decompensated liver disease, can be treated successfully, albeit with caution.
5. Factors indicating poor prognosis include significantly elevated serum bilirubin level, large-volume tumour burden and angioinvasive HCC involving the main portal vein or its large branches.
6. Portal venous flow away from the liver is also considered a relative contraindication. In addition, patients who have had previous surgical or endoscopic biliary enteric interventions are at higher risk of liver abscesses after the procedure, although this is not considered a contraindication.
7. HCC scoring systems that predict survival outcomes before and after TACE should be considered in the management of the patient.

agent is absorbed onto the surface of microspheres, allowing increased local delivery of chemotherapy, with prolongation of action and reduced systemic exposure.

RCTs in the early 2000s showed a significant improvement in OS in well selected patients treated with TACE, compared with those treated with both bland embolisation and best supportive care.

Subsequent meta-analyses have also indicated a significant improvement in OS.[263] Data from recent series indicate an overall response rate of about 50% and a disease control rate of 75%–80% for TACE.[264]

Several scoring systems have been developed to facilitate the process of selecting patients for initial and repeat TACE (Table 6). To date, the formulation

Table 6. Scoring systems for predicting outcomes of TACE

Scoring system	Discussion
Hepatic arterial embolisation prognostic (HAP) score	The HAP score is a validated scoring system used to predict OS in patients undergoing TACE or transarterial embolisation. Points are allocated based on dominant tumour size and baseline serum albumin, bilirubin and AFP levels. A total point score of 0, 1, 2 or >2 points corresponds to a HAP risk group of A, B, C or D, respectively,[265,266] with low-risk groups (i.e. HAP A and B) having a significantly better median survival than high-risk groups (i.e. HAP C and D). The HAP score[265,266] performs better than Child–Pugh class, MELD score, CLIP score and BCLC stage in predicting OS in patients undergoing TACE, but it is limited by the failure to include baseline performance status and other tumour parameters.[267]
The Assessment for Retreatment with TACE (ART) score	The ART score is used to predict OS before performing a second and any subsequent TACE procedures.[268,269] The score integrates the three parameters of an increase in serum aspartate aminotransferase level by >25%, increase in Child–Pugh score from baseline and radiological tumour response after the first TACE. Validated in an independent external cohort, the ART score identifies two distinct patient groups with significantly different outcomes. Those with a score of ≥2.5 after the first TACE have a poor prognosis and may be better served by alternative treatment options. In contrast, those with a score of ≤1.5 points have a significantly better prognosis and are suitable for further TACE.[270] However, the ART score is yet to be validated prospectively and may be less than optimal in a real-world setting where there is heterogeneity in patient populations, TACE technique and frequency and chemotherapy agent used.[271-273]
AFP, BCLC, Child–Pugh and response (ABCR) score	The ABCR scoring system comprises baseline AFP level, BCLC stage, change in Child–Pugh score from baseline and radiological tumour response.[274] Derived from a retrospective single-centre study of 139 consecutive patients treated with TACE, three prognostic groups, with progressively worsening survival, were identified. Comparative studies have shown variable results, with one reporting that ABCR score correlated better with survival than did ART score in patients undergoing at least two TACE sessions,[274] while another showed that both ABCR and ART had insufficient predictive value to support clinical decisions.[275]
Albumin–bilirubin (ALBI) score	The ALBI score uses serum albumin and bilirubin levels to risk-stratify patients undergoing TACE into three separate prognostic grades.[276] The ALBI score correlates well with Child–Pugh and MELD scores in patients with HCC and performs better in patients with advanced liver disease. In addition, validation studies conducted in Asian, European and American cohorts have, in some cases, shown superiority in survival prognostication compared with the Child–Pugh and BCLC staging systems.[277-279] Other investigators continue to explore modifications to the ALBI score by adding radiological response (ABRAS score).[280] The ABRAS score stratifies patients into low-risk (score of 0–2) and high-risk (score of 3–8). The performance of the ABRAS model was shown to be better than BCLC stage, ALBI grade or TACE response alone. However, there is potential weakness in the ALBI scoring system, as it can be influenced by albumin replacement therapy or cholestasis, resulting in inaccurate estimation of liver reserve.

AFP = alpha-fetoprotein; BCLC = Barcelona Clinic Liver Cancer; CLIP = Cancer of the Liver Italian Program; MELD = Model for End-Stage Liver Disease; OS = overall survival; TACE = transarterial chemoembolisation.

of these scoring systems has relied on retrospective data collection in cohorts that show significant heterogeneity in patient and tumour characteristics. Furthermore, there is significant variation in TACE technique, chemotherapy agents used, treatment intervals and post-TACE treatments. Larger, externally validated prospective cohort studies are therefore required to determine if these scores can further improve clinical assessment and guidance in determining when and how to use TACE most effectively.

The methods used in chemoembolisation procedures are highly variable, particularly in relation to the choice of chemotherapeutic and embolic agents. Worldwide, the most common form of TACE uses doxorubicin mixed with iodised oil, with an absorbable gelatin sponge (Gelfoam; Pfizer) used as the embolic agent. Other drugs used either as solitary agents or in combination include cisplatin, mitomycin C and epirubicin.[232] Initial cohort studies in patients administered DEB-TACE suggested the possibility of improved survival when compared with cTACE. The slower elution time of the drug from drug-eluting beads was hypothesised to result in more sustained and higher intratumoural cytotoxic levels, producing an enhanced response. However, a randomised prospective trial of DEB-TACE and cTACE failed to reach its primary endpoint, although post-hoc analyses indicated better performance of DEB-TACE in subgroups such as patients with Child–Pugh class B HCC.[281] Subsequent studies, including an RCT,[282] and meta-analyses[283,284] have failed to show convincing superiority of DEB-TACE over cTACE, with equivalent OS and tumour response rates and very similar adverse event profiles. However, a more recent meta-analysis found significantly improved OS and RFS rates in patients treated with DEB-TACE compared with cTACE.[285] Still, concerns have been raised that DEB-TACE may predispose to higher rates of biliary complications than cTACE, particularly in patients with more decompensated disease.[286]

6.5.2.2 Selective internal radiation therapy

Recommendation 21

SIRT may be considered in select patients with intermediate or locally advanced HCC (Evidence quality: Low; Grade of recommendation: Weak)

Selective internal radiation therapy (SIRT) (also known as transarterial radioembolisation [TARE]) with Y-90 microspheres involves the injection of yttrium-90-loaded microspheres (comprised of resin or glass) into the hepatic arteries supplying the tumour, resulting in intratumoural brachytherapy. In practice, radioembolisation has been used as an equivalent treatment to 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 LT. However, the evidence base justifying the use of SIRT is much less advanced than that for other therapies. The publication of three RCTs that failed to demonstrate superiority of SIRT over sorafenib has further added to the uncertainty around its precise role in HCC management.[288-290] Therefore, SIRT cannot currently be recommended as routine therapy for HCC.

SIRT has also been used successfully in patients with locally advanced HCC and portal vein invasion. Several retrospective and prospective studies have

Technical remarks

1. Increasing numbers of drug-eluting bead preparations are now available, many of which have significant differences in their properties, including drug-binding and elution characteristics, further increasing the already extensive heterogeneity of TACE.[287]
2. Limited high-quality evidence, the heterogeneity of the patient population and variations in the TACE protocols used result in uncertainty regarding the superiority of one TACE preparation over another. Therefore, the choice of treatment can be individualised based on patient factors, local experience and proceduralist preference, preferably via an MDT.

Technical remarks

1. The Sorafenib versus Radioembolisation in Advanced Hepatocellular Carcinoma (SARAH) study compared SIRT with sorafenib in patients with locally advanced HCC, without portal vein thrombosis or metastases, who were either ineligible for other treatments or in whom TACE had failed twice.[291] Median survival after SIRT was 8 months, compared with 9.9 months for sorafenib, on an intention-to-treat basis (P=0.18).[288,292]
2. The SIRveNIB (SIRT vs sorafenib) study was very similar to the SARAH trial but also included patients with portal vein thrombosis. In both studies, SIRT did not reach the primary objective of superior survival compared with sorafenib. In the SIRveNIB trial, median survival after SIRT was 8.8 months compared with 10 months for sorafenib on an intention-to-treat basis (P=0.36).[289]
3. Limited data suggest that SIRT may be a more effective treatment than TACE for segmental disease, based on significantly higher response rates and superior progression-free survival with SIRT.[293]
4. Uncontrolled real-world studies involving large cohorts have reported good survival with SIRT for patients with BCLC-A and-B disease.[294,295]
5. A randomised controlled superiority trial of SIRT versus TACE in patients with BCLC-A or-B disease found similar response rates and OS (SIRT, 18.6 months vs TACE, 17.7 months) but with longer time to progression (SIRT, 26 months vs TACE, 6.8 months; P=0.001) and fewer significant side effects with SIRT than with TACE.[296]
6. Considerable uncertainty also surrounds the use of SIRT as bridging therapy or downstaging before LT, as most data on outcomes stem from small retrospective studies. Some downstaging studies have indicated longer time to progression with SIRT,[297] while others have suggested that SIRT is as effective as TACE for these indications.[223,298]
7. SIRT can be considered for select patients with intermediate and locally advanced HCC that is not suitable for initial or repeat TACE.
8. The Sorafenib and Micro-therapy Guided by Primovist Enhanced MRI in Patients With Inoperable Liver Cancer (SORAMIC) study examined treatment of intermediate and advanced HCC with SIRT followed by sorafenib. There was no OS advantage in the SIRT plus sorafenib group.[290] Subgroup analysis suggested a survival benefit with SIRT plus sorafenib in certain groups, including those without cirrhosis (HR, 0.46; 95% CI, 0.25–0.86; P=0.02).

confirmed the safety of SIRT in such patients,[299,300] although the survival benefit remains uncertain, with heterogeneous results reported in the literature.[301,302]

Although the SARAH study did not show a survival benefit of SIRT compared with sorafenib, secondary analysis of the data showed that higher tumour radiation dose was associated with improved overall survival and disease control.

A scoring system developed from a single centre in Australia using retrospective data from 113 patients with intermediate or advanced HCC identified patients in whom SIRT was safe and effective. The MAAPE score uses MELD score, AFP and albumin levels, absence of portal vein tumour thrombus and ECOG grade to characterise patients into three survival prognostic groups (good, average and poor). This scoring system is yet to be externally validated, and uncertainty over its applicability and reliability as a clinical decision tool therefore remains.[303]

Hence, the role of SIRT remains controversial and, for this reason, it has not been incorporated in several major HCC management algorithms. The results of further randomised trials of SIRT, such as the TheraSphere in the Treatment of Patients with Unresectable Hepatocellular Carcinoma (STOP-HCC) study, are eagerly awaited. Similarly, the results of trials of SIRT in combination with immunotherapy (such as ClinicalTrials.gov identifiers NCT03380130 and NCT03033446) are also awaited, given this combination could offer significant synergy.

6.5.3 Other locoregional therapies

6.5.3.1 Stereotactic external-beam radiation therapy

Historically, radiotherapy was seen to have a limited role in the management of HCC, likely due to fears of radiation-induced liver injury and uncertainty about its clinical efficacy. However, it is now recognised that HCC is a radiosensitive tumour,[304] and previous technical problems with delivery are being overcome with advances in technology and improved quality assurance. The possible place of radiotherapy in the management of HCC is in both local control and treatment with palliative intent.[305]

Stereotactic external-beam radiation therapy (SBRT) may theoretically be used as a curative treatment, but there are few data to support this use at present.[305] SBRT is a potentially ablative treatment, with potent doses delivered precisely with motion management and image guidance by many external beams or arcs. This treatment is typically delivered in fewer fractions than conventional radiotherapy (delivered in 25 to 30 fractions).[306-308]

Technical remarks

1. SBRT and external-beam radiotherapy (EBRT) have the equivalent meaning for the purposes of this discussion. Stereotactic ablative body radiotherapy (SABR) is an ablative form of SBRT.
2. HCC is a radiosensitive tumour.[304]
3. In patients with HCC, radiotherapy can be useful to treat main branch vascular invasion by a tumour thrombus.[309]
4. A pooled analysis of SBRT, consisting of five studies involving 431 patients, showed a 3-year local control rate of 86%.[307,310] Retrospective studies comparing RFA and SBRT, and TACE and SBRT, suggest similar local control outcomes for comparable patients.[306,308,311-313] However, there was considerable selection bias, and the results are therefore difficult to interpret.
5. A recent meta-analysis that focused on trials of TACE with or without SBRT included 25 trials (11 RCTs) and concluded that individuals receiving both therapies had a better survival and response time. However, SBRT led to higher rates of complications, and a subsequent systematic review rated all included trials as low quality.[312,314]
6. Additional data on the efficacy of SBRT are anticipated soon. Attention needs to be paid to which tumour and patient characteristics predict outcome, and whether combination therapy (with other LRTs) is of benefit.
7. A recent Canadian study compared SBRT with TACE and RFA as bridging therapy in people awaiting LT. SBRT was shown to have a similar safety profile and waiting list dropout rate as TACE and RFA.[315]

Recommendation 22

Stereotactic external-beam radiation therapy may be considered for local tumour control in suitable patients with HCC. *(Evidence quality: Low; Strength of recommendation: Weak)*

6.6 Systemic therapies

Recommendation 23

Patients with advanced (BCLC-C) or multifocal HCC that is not amenable to curative or locoregional therapy (BCLC-B) should be offered systemic therapy. *(Evidence quality: High; Grade of recommendation: Strong)*

Systemic therapies are indicated in patients with advanced HCC (where there is vascular invasion and/or extrahepatic disease) or in patients with unresectable HCC where LRTs have failed to control disease or cannot be delivered (Table 7). In general, liver function should be preserved in patients being considered for systemic therapy, and the concepts of TACE failure[316] and stage migration[317] should be recognised to allow appropriate transition to systemic therapy. Currently, there are three first-line therapies for HCC: sorafenib, lenvatinib and combination atezolizumab and bevacizumab. Additional first-line and second-line therapies have either shown positive results in Phase III clinical trials (Figure 5), or clinical trial results are still forthcoming. Results of a large Phase III clinical trial evaluating sorafenib versus nivolumab as first-line therapy are awaited. Combination studies of multikinase inhibitors plus immuno-oncology agents or

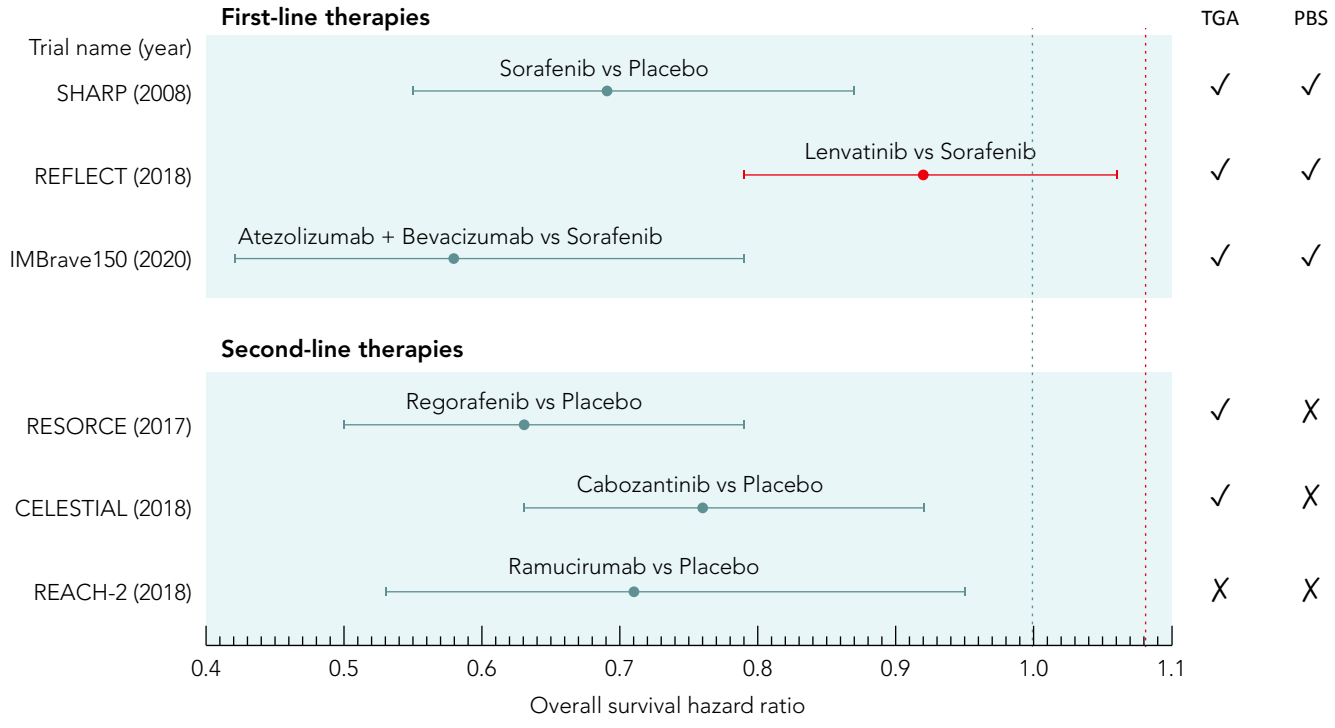
Table 7. Systemic therapies available for HCC

Feature	Stage	Comments	Level of evidence
Staging	Advanced BCLC-B (>3 nodules) or BCLC-C	BCLC-0 to BCLC-B should be considered for curative therapy first (PS ≤2) BCLC-D should be offered best supportive care	A1
Agent	**Indication**	**Comments**	**Level of evidence**
Sorafenib	Initial systemic therapy	PBS-listed: Initial HCC systemic therapy, Child–Pugh A, PS ≤2*	A1
Lenvatinib	Initial systemic therapy	PBS-listed: Initial HCC systemic therapy, Child–Pugh A, PS ≤2*	A1
Atezolizumab – bevacizumab	Initial systemic therapy	PBS-listed: Initial HCC systemic therapy, Child–Pugh A, PS ≤2*	A1
Regorafenib	Second-line therapy, after sorafenib	TGA-approved, not PBS-listed RESORCE study: 573 patients with Child–Pugh A, PS ≤2, progressive disease on sorafenib, who tolerated sorafenib (≥400 mg/day) for ≥20 of past 28 days of treatment[319]	A1
Cabozantinib	Second-line therapy	TGA-approved, not PBS-listed CELESTIAL study: 707 patients with Child–Pugh A, PS ≤2, progressive disease on sorafenib[320]	A1

BCLC = Barcelona Clinic Liver Cancer; HCC = hepatocellular carcinoma; PBS = Pharmaceutical Benefits Scheme; PS = performance status; RESORCE = Regorafenib after Sorafenib in Patients with Hepatocellular Carcinoma; TGA = Therapeutic Goods Administration.

* Patient must not have received prior treatment with a vascular endothelial growth factor (VEGF) tyrosine kinase inhibitor (TKI) for this condition; **or** patient must have developed intolerance to a VEGF TKI of a severity necessitating permanent treatment withdrawal.

Figure 5. Summary of Phase III clinical trials for HCC therapies



HCC = hepatocellular carcinoma; PBS = Pharmaceutical Benefits Scheme; TGA = Therapeutic Goods Administration.

Circles depict overall survival hazard ratio and bars represent 95% confidence intervals. Red bar indicates a non-inferiority study, whereas blue bars depict superiority studies. The right-hand columns indicate whether the investigational drug is TGA-approved or PBS-listed (✓ = yes, ✗ = no). The red dotted line indicates the threshold for the non-inferiority study (1.08), and the blue dotted line the threshold for superiority studies.

Technical remarks

1. Decisions to initiate systemic therapies should be undertaken within an MDT (see section 6.1.1).
2. Systemic therapy is offered based on Child–Pugh class A and ECOG performance status of 0 or 1.
3. Treatment of advanced HCC should be supervised by a clinician experienced in the use of systemic therapies.
4. A toxicity management plan should be in place before commencing systemic therapies.
5. First-line systemic therapy should be discontinued when there is radiological progression (section 6.7) and if the patient is eligible to proceed to second-line systemic therapy.
6. In patients who are not suitable for second-line systemic therapy, first-line treatment is suggested to be continued until clinical progression of the disease.
7. Therapy with checkpoint inhibitors is associated with a unique toxicity profile. Such agents should be commenced by physicians experienced in managing immuno-oncology agents and immune-mediated toxicities, as per international guidelines.[318]

combination immuno-oncology agents are underway. The decision about which agent to start, and when to transition therapy, will become increasingly complex and should be determined within an MDT with appropriate expertise (see section 6.1.1).

6.6.1 Multikinase inhibitors

Recommendation 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. *(Evidence quality: High; Grade of recommendation: Strong)*

The use of sorafenib as initial systemic therapy in patients with HCC is supported by two pivotal randomised placebo-controlled Phase III studies that showed a 30% reduction in the risk of death in patients randomly assigned to receive sorafenib.[321,322] In the global Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) study, an increase in median OS from 7.9 to 10.7 months (HR, 0.70; 95% CI, 0.55–0.87; $P < 0.001$) was observed.[322] In a similar study conducted in the Asia–Pacific region, where HBV was the most common cause of HCC and disease was more advanced, sorafenib was associated with an increase in median OS from 4.2 to 6.5 months (HR, 0.68; 95% CI, 0.50–0.93; $P = 0.014$).[321] Both studies involved patients with unresectable HCC and Child–Pugh class A cirrhosis who had predominantly advanced BCLC-C disease. Real-world studies have supported the efficacy and safety of sorafenib in patients with advanced HCC and Child–Pugh class A cirrhosis.[323,324]

In the open-label Phase III clinical REFLECT trial comparing lenvatinib with sorafenib in patients with unresectable HCC, lenvatinib was non-inferior to sorafenib.[325] This trial, which was powered to demonstrate non-inferiority, randomly assigned 954 patients to receive lenvatinib or sorafenib in a 1:1 ratio. The median OS 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). Progression-free survival (a secondary endpoint) was significantly higher in patients receiving lenvatinib (7.4 months; 95% CI, 6.9–8.8) compared with sorafenib (3.7 months; 95% CI, 3.6–4.6) (HR, 0.66; 95% CI, 0.57–0.77; $P < 0.0001$). Similarly, the median time to progression in patients receiving lenvatinib was significantly higher than in those receiving sorafenib (8.9 months [95% CI, 7.4–9.2] vs 3.7 months [95% CI, 3.6–5.4]; $P < 0.0001$). Furthermore, the objective response rate (complete plus partial response) was higher with lenvatinib (40.6%; 95% CI, 36.2%–45.0%) than sorafenib (12.4%; 95% CI, 9.4%–15.4%) (OR, 5.01; $P < 0.0001$), as determined by masked independent imaging review. Disease control was observed in 73.8% (95% CI, 69.9%–77.8%) of patients treated with lenvatinib compared with 58.4% (95% CI, 54.0%–62.8%) of those treated with sorafenib.

Technical remarks

1. The list of systemic therapies given here is considered current at the time of preparation of this consensus statement.
2. Sorafenib is an oral multikinase inhibitor that targets the Raf/MEK/ERK pathway and reduces cell proliferation and angiogenesis. Lenvatinib is a multikinase inhibitor of vascular endothelial growth factor (VEGF) receptors 1–3, fibroblast growth factor receptors 1–4, platelet-derived growth factor receptor α, RET and KIT.
3. The most appropriate patients for treatment with sorafenib or lenvatinib have compensated liver disease (Child–Pugh class A) and good performance status (ECOG grade 0–1).
4. Patients with Child–Pugh class B cirrhosis who are treated with multikinase inhibitors have reduced survival compared with those with Child–Pugh class A cirrhosis.
5. Patients with Child–Pugh class C or poor performance status (ECOG grade ≥2) have no survival advantage from multikinase inhibitors, and their use in these patients is not recommended.
6. The recommended starting dose of sorafenib is 400 mg twice daily. However, a lower starting dose may be considered for some patients, with an aim of increasing the dose as tolerated.
7. The recommended starting dose of lenvatinib is 12 mg (for patients weighing ≥60 kg) or 8 mg (for patients weighing <60 kg) once daily.
8. Sorafenib is associated with a range of side effects, most commonly diarrhoea, decreased appetite, weight loss, hand–foot skin reaction, skin rash and fatigue.[321,322,326,327]
9. Lenvatinib is associated with a range of side effects, most commonly hypertension (42%), diarrhoea (39%), decreased appetite (34%) and decreased weight (31%).[325]
10. Hand–foot skin reaction occurred in fewer patients receiving lenvatinib (27%, 3% grade ≥3) than those receiving sorafenib (54%, 11% grade ≥3).[325]
11. Reduction of the dose of sorafenib or lenvatinib may be indicated when side effects cannot be managed by alternative means. Dose reduction for side effect management does not affect response rates.
12. Pre-emptive and proactive side effect management may improve tolerability.

Recommendation 25

The use of multikinase inhibitors as adjuvant therapy after hepatic resection or locoregional therapy is not recommended. *(Evidence quality: High; Grade of recommendation: Strong)*

Sorafenib has been studied as adjuvant therapy in patients undergoing resection and TACE, with no reported benefit.[328-330] The Sorafenib as Adjuvant Treatment in the Prevention of Recurrence of Hepatocellular Carcinoma (STORM) trial was a Phase III RCT that evaluated sorafenib versus placebo in 1114 patients with complete radiological response after surgical resection or local ablation.[328] Neither the primary endpoint of RFS, nor the secondary endpoints of time to recurrence and OS, were reached. The SPACE[329] and TACE 2 trials[264] were Phase III RCTs of sorafenib plus TACE versus TACE alone. No difference in time to progression[329] or progression-free survival[264] was demonstrated. Other studies of TACE followed by treatment with sorafenib (POST-TACE),[331] brivanib (BRISK-TA)[332] or orantinib (ORIENTAL)[333] were also negative.

Technical remarks

1. Once a patient has had surgical resection, ablation or chemoembolisation, and radiological complete response has been shown, there is no role for adjuvant therapy with multikinase inhibitors.
2. If there is ongoing disease after surgery or LRT that cannot be controlled, then sorafenib or lenvatinib may be considered in the context of stage migration.

Recommendation 26

In patients with HCC, regular assessment for clinical and radiological response to first-line therapy is recommended to monitor for disease progression. *(Evidence quality: High; Grade of recommendation: Strong)*

In Phase III clinical trials of HCC, time to progression and progression-free survival have been key secondary endpoints[334] that have traditionally been regarded as surrogate endpoints for OS. However, recent

evidence from a Phase III study of regorafenib has questioned the reliability of these as surrogate prognostic determinants.[319] The benefit of ongoing use of sorafenib in patients with clinical progression of disease has not been established. With increasing availability of second-line agents, the presence of radiological progression is recognised as the indication for a change of therapy.[319,320]

Technical remarks

1. The determination of clinical response or progression requires regular assessment for features of hepatic decompensation, nutritional status, drug toxicity and serum tumour markers. This includes blood tests (urea, electrolytes and creatinine, liver function tests, full blood count, international normalised ratio, AFP) and physical examination (checking for ascites and hepatic encephalopathy plus nutritional assessment). Patients should be reviewed at least 4–12-weekly, according to their status.
2. Radiological response or progression should be assessed by multiphase CT or MRI scans using modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria on at least a 3-monthly basis.[335,336]

Recommendation 27

In patients with HCC, sorafenib or lenvatinib should be discontinued when there is unequivocal clinical and/or radiological progression. *(Evidence quality: High; Grade of recommendation: Strong)*

There are no clear benefits to continuing first-line therapy with multikinase inhibitors in patients with radiological or clinical disease progression. Second-line treatments approved by the Therapeutic Goods Administration (TGA) include two oral targeted therapies, regorafenib and cabozantinib, and a 2-weekly intravenous infusion of the immune checkpoint inhibitor nivolumab. A 4-weekly infusion schedule has also been approved. These drugs have been formally studied in patients with radiological progression while receiving treatment with either sorafenib alone or other first-line systemic therapies. There is no evidence to recommend one agent over the other in patients with disease progression while taking multikinase inhibitors. However, in patients with intolerance to sorafenib, regorafenib is not indicated

Technical remarks

1. Regorafenib is an oral multikinase inhibitor that blocks the activity of protein kinases involved in angiogenesis, oncogenesis, metastasis and tumour immunity (RAF, KIT, RET and platelet-derived growth factor receptors, VEGF receptor 1 and TIE2).
2. Regorafenib was TGA-approved on 18 December 2017 (and is awaiting PBS listing) for second-line treatment of advanced HCC that has progressed during treatment with sorafenib.
3. Second-line treatment with regorafenib is not appropriate for patients who are intolerant to sorafenib.
4. Before commencing regorafenib, patients should have been treated with sorafenib at a daily dose of at least 400 mg for at least 20 of the past 28 days of treatment (as studied in the RESORCE trial).
5. Regorafenib is administered as 160 mg once daily, in cycles of 3 weeks on and 1 week off.
6. Regorafenib has a similar safety profile to sorafenib. Dose reduction may be required for management of side effects.
7. In the RESORCE trial, hand–foot skin reaction (53%), diarrhoea (41%), fatigue (40%), hypertension (31%) and anorexia (31%) were the most often reported treatment-emergent adverse effects in patients taking regorafenib.[341]
8. Regorafenib should be continued until clinical progression.
9. A post-hoc analysis of the REFLECT study of first-line treatment with sorafenib versus lenvatinib showed that some patients in both arms of the trial were treated with a range of second-line therapies after radiological progression of HCC. Patients receiving second-line therapies achieved longer median OS than those receiving no second-line therapy. This applied to patients who received any post-study anticancer therapy after initial treatment with sorafenib (median OS, 22 months) or lenvatinib (median OS, 26 months).[342]

Technical remarks

1. Cabozantinib inhibits multiple receptor tyrosine kinases, including MET (hepatocyte growth factor receptor protein), VEGF, the Gas6 receptor (Axl), RET, Tyro3 and Mer.
2. Cabozantinib was approved by the TGA for HCC on 28 May 2019. It is indicated as monotherapy in adults with HCC who have previously been treated with sorafenib.
3. Cabozantinib is administered as an oral tablet with a recommended dose of 60 mg daily.
4. The safety and efficacy of cabozantinib was assessed in a randomised, double-blind, Phase III clinical study (CELESTIAL). A total of 707 patients were randomly assigned in a 2:1 ratio to receive 60 mg cabozantinib daily or placebo. Compared with those receiving placebo, the cabozantinib group had a significantly longer OS of 10.2 months (95% CI, 9.1–12.0) versus 8.0 months (95% CI, 6.8–9.4), extended median progression-free survival of 5.2 months (95% CI, 4.0–5.5) versus 1.9 months (95% CI, 1.9–1.9) and an HR for disease progression or death of 0.44 (95% CI, 0.36–0.52; P < 0.001).[320]
5. The most common grade 3 or 4 adverse events in the CELESTIAL study were hand–foot skin reaction in 17% (none in placebo), hypertension in 16% (placebo, 2%), elevations in aspartate aminotransferase level in 12% (placebo, 7%), fatigue in 10% (placebo, 4%) and diarrhoea in 10% (placebo, 2%). Serious adverse events were reported in 50% of cabozantinib-treated patients and 37% of placebo-treated patients.[320]

and nivolumab may be considered. None of these agents have yet been listed on the PBS for HCC.

Another agent with Phase III clinical trial evidence for improved survival in patients whose disease has progressed while taking, or who are intolerant to, sorafenib is ramucirumab (in patients with AFP level >400 ng/mL).[320,337,338] Pembrolizumab was granted accelerated approval by the US Food and Drug Administration in November 2018, based on a non-randomised, multicentre, open-label, Phase II trial in 104 patients with disease progression while or after taking sorafenib or with intolerance to sorafenib,[339] but it is not approved in Australia. Recently, a Phase III placebo-controlled trial of pembrolizumab plus best supportive care in patients with documented disease progression on or after treatment with sorafenib or with intolerance to sorafenib failed to meet the co-primary endpoints of OS and progression-free survival, compared with placebo plus best supportive care.[340]

Recommendation 28

In patients with HCC, a second-line systemic therapy is recommended for suitable patients who have radiological progression while being treated with multikinase inhibitors but have preserved liver function and good performance status. *(Evidence quality: High; Grade of recommendation: Strong)*

Until recently, multiple clinical trials in patients with advanced HCC with progression during sorafenib treatment were negative. In the placebo-controlled Phase III Study of Regorafenib after Sorafenib in Patients with Hepatocellular Carcinoma (RESORCE), treatment with regorafenib was associated with a 37% reduction in death compared with placebo (HR, 0.63; 95% CI, 0.50–0.79).[319] The median OS was 10.6 months for regorafenib versus 7.8 months for placebo. Sequential therapy with sorafenib followed by regorafenib was associated with a median OS of 26 months (95% CI, 22.6–28.1), compared with 19.2 months (95% CI, 16.3–22.8) for sorafenib–placebo.[341] This benefit was observed regardless of the speed of HCC disease progression during prior sorafenib treatment and regardless of the last sorafenib dose.

6.6.2 Immunotherapy

An important hallmark of HCC is that it develops in the context of chronic inflammation and infection. Immunogenicity of HCC has been evidenced by HCC immune profiles predicting clinical outcomes, documented presence of HCC-specific dysfunctional T cells and the immunogenic effects of ablative therapy.[343] Hence, HCC has been considered a prime target for immunotherapy.

Immunotherapeutic approaches include antibody-based therapies, cytokine-induced killer cells, vaccines

and chimeric antigen receptor (CAR) T cells, as well as immune checkpoint inhibitors against programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4).[343]

Nivolumab, a PD-1-targeting monoclonal antibody, has been approved by the TGA for the treatment of patients with HCC after prior sorafenib therapy. Nivolumab is not yet listed on the PBS for the treatment of HCC. The TGA approval is based on objective response rate and duration of response in a single-arm study (CheckMate 040).[344] This was a Phase I/II, open-label, non-comparative, dose escalation and expansion trial in 262 patients. Contrary to other studies with nivolumab in non-HCC cancers, a significant number of patients with chronic viral hepatitis B and C infection were included.[344] The dose escalation phase showed good safety and tolerability of nivolumab (grade 3–4 toxicity in 12/48 patients; discontinuation due to toxicity in 4/48 patients, compared with discontinuation due to disease progression in 42/48 patients). In the dose expansion arm, with 214 patients receiving nivolumab 3 mg/kg, the objective response rate was 20%. The disease control rate was 64%, and OS was 83% at 6 months. Notably, levels of the ligand of PD-1 did not predict response in this study.[344] Phase III studies are ongoing in this dynamic area.

An improvement in survival or reduction in disease-related symptoms has not been established with the use of nivolumab in patients with advanced HCC. A role for nivolumab in combination with other systemic therapies is under evaluation but is not yet established.

6.6.3 Combination immunotherapy

In a Phase III clinical trial (IMBrave150), first-line combination therapy with intravenous atezolizumab (anti-programmed death-ligand 1) and bevacizumab

Technical remarks

1. Immunotherapeutic treatment must be initiated and supervised by specialist physicians experienced in the treatment of HCC.
2. Clinical trials of nivolumab for HCC management have included patients with both Child–Pugh A and Child–Pugh B cirrhosis. Recent data from the CheckMate 040 trial showed that nivolumab produced durable responses and had a manageable safety profile in patients with Child–Pugh B disease, including a similar rate of drug-related serious adverse events to that in patients with Child–Pugh A disease.[344] Similarly, reported real-world experience suggests that nivolumab is safe in patients with Child–Pugh B cirrhosis. Treatment with nivolumab is not recommended in patients with Child–Pugh C cirrhosis.
3. Nivolumab 3 mg/kg is administered as an intravenous infusion over 30 minutes every 2 weeks. Alternative dosing schedules for nivolumab include 240 mg every 2 weeks or 480 mg every 4 weeks, although there are currently no published studies of these schedules in patients with HCC.
4. As with other immune checkpoint inhibitors, multiple immune-related adverse effects have been reported with nivolumab. These include pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies and skin reactions. The American Society of Clinical Oncology has published a clinical practice guideline to support clinicians in the care of patients with immune-related adverse effects.[345]
5. Nivolumab should be administered with extreme caution in patients with pre-existing autoimmune disease and only after a considered risk–benefit analysis. Severe allograft rejection has been reported in solid organ transplant recipients treated with immune checkpoint inhibitors, and nivolumab should not be administered after transplantation. Viral hepatitis is not a contraindication but should be well controlled with antiviral therapy.
6. Patients should be monitored for adverse events and efficacy with regular blood tests and clinical review. Immune-related adverse events may occur at any time during or after discontinuation of therapy.
7. Regular tumour assessments with imaging and measurement of AFP levels should be undertaken, and nivolumab should be ceased when there is radiological progression, as determined by RECIST 1.1.

(anti-VEGF) showed significant improvement in OS (HR, 0.58; 95% CI, 0.42–0.79; $P = 0.0006$) and progression-free survival (HR, 0.59; 95% CI, 0.47–0.76; $P < 0.0001$), as well as quality of life, when compared with sorafenib.[3] This regimen is now TGA-approved and PBS-listed.

6.7 Assessing response to therapy

6.7.1 mRECIST

Recommendation 29

HCC treatment response should be assessed by multiphase CT or MRI using standardised criteria, such as the mRECIST criteria.
(Evidence quality: Moderate; Grade of recommendation: Strong)

Treatment response in clinical trials has been assessed by OS; however, surrogate measures are necessary in clinical practice to determine the need for treatment continuation or interruption.[346,347] In oncological clinical practice, treatment response has traditionally been assessed according to a measurable reduction in tumour size on imaging, and although World Health Organization (WHO) guidelines were established to classify this response, the relevance of these guidelines has been challenged in the setting of molecular, immunological and locoregional therapies.[348] WHO criteria have now been replaced in oncology with the Response Evaluation Criteria in Solid Tumors (RECIST).[349] In turn, the mRECIST were developed by an AASLD working group and have been adopted in recent society guidelines.[57,176,335] These criteria measure the largest area of unidimensional arterial enhancement of the primary tumour and compare changes in this measurement on serial imaging to determine treatment response.[335] Treatment response can be assessed using dynamic contrast CT or MRI, as there is no conclusive evidence of superiority of either technique in this context.[346,347]

Treatment response to LRT should be assessed using mRECIST, as objective response has been shown to correlate with OS.[57,348] A recent meta-analysis of seven clinical trials evaluating survival outcomes after LRT found that objective response, as measured by mRECIST, was associated with improved OS after TACE (HR, 0.39; 95% CI, 0.26–0.61; $P < 0.0001$).[350] This finding has been replicated in clinical trials for systemic therapy in patients with HCC.[347] In clinical practice, AFP level may be used to complement imaging findings in assessing treatment response, as reduction in AFP level after TACE or sorafenib was associated with improved survival in single-centre studies.[351] More recently, iRECIST has been proposed to assess response in clinical trials of cancer immunotherapies to account for early pseudoprogression with these therapies.[352]

Technical remarks

1. "Standardised criteria" typically refer to mRECIST, but this is not universally adopted.
2. The decision to use CT or MRI should be based on local expertise, availability and individual patient considerations.
3. There is no requirement for liver-specific contrast agent (e.g. gadoxetate disodium) to be used for routine follow-up imaging.[353]
4. MRI with image subtraction may be advantageous for assessing tumour response after TACE with iodised oil because of CT image degradation from the iodised oil.[354]
5. The initial follow-up scan should be performed at least 4 weeks and less than 12 weeks after LRT or the initiation of systemic therapy.
6. Follow-up imaging should then be performed 3-monthly for the first 2 years after treatment.
7. Progression is well defined by mRECIST, but response is not as readily determined.
8. The LI-RADS treatment response algorithm is an alternative that allows washout to be considered residual disease.

7 Supportive care

7.1 Advance care planning and palliative care referrals

Recommendation 30

Patients with incurable HCC should be introduced to supportive care services early in their management. (Evidence quality: Moderate; Grade of recommendation: Strong)

Recommendation 31

Patients with BCLC-D HCC should be managed symptomatically in conjunction with supportive care services. (Evidence quality: Moderate; Grade of recommendation: Strong)

Patients with HCC present with advanced disease in 15%–20% of cases and have a median survival of less than 3–4 months.[355] The estimated 1-year survival rate of patients with BCLC stage D disease is <11%.[356] Dominant symptoms in patients with advanced disease include fatigue, oedema, cachexia, ascites, dyspnoea, anorexia and vomiting.[355] HCC usually occurs in the context of liver disease, a condition that presents its own unique clinical challenges. In addition to cancer-related complications, a patient's ultimate deterioration is often attributable to hepatic failure and its multiple manifestations. The management of liver decompensation is well known to hepatologists and will not be specifically discussed here.[174,357-361] Patients with HCC often have an established relationship with a hepatologist before their diagnosis of cancer because of their known liver disease.

Psychological stress in this group is significant, and patients with HCC have the third highest reported levels of stress among people with the 14 leading cancers.[362] Symptom relief and psychosocial support may be most effectively achieved through the co-management of patients by hepatologists and supportive care services (i.e. palliative care).[363] Palliative care can be delivered concurrently with active therapy, with the focus being on quality of life, management of symptoms, discussion of treatment preferences, provision of psychosocial support (including religious and spiritual needs) and the coordination of care. Models of care in individual services can be tailored to available or local resources. Creation of HCC-specific supportive care plans may assist with more effective interdisciplinary and multidisciplinary communication, facilitating continuity of care and reducing patients' anxiety in their trajectory (Table 8).

Non-tumour-related guidelines on the management of chronic liver disease describe the detailed management of many issues that patients with HCC and chronic liver disease have in common.[174,357-361] The management of portal vein tumour thrombosis (section 7.3.1), spontaneous tumour rupture (section 7.3.2), biliary obstruction (section 7.3.3), metastatic disease (section 7.3.4) and massive tumours (section 7.3.5) is discussed in this consensus statement.

Patients should have the opportunity to understand and plan for a variety of potential outcomes. The surgeon and author Atul Gawande suggests that conversations with a patient with advanced illness should include specific questions to elicit their knowledge and values on:

- their understanding of the illness;
- their specific fears or worries for the future;
- their goals and priorities;
- what they consider to be unacceptable outcomes (including what they are willing to sacrifice and the importance of survival to them in relation to unacceptable outcomes); and
- what a good day would look like to them.[364]

Such discussions take time, expertise and an appropriate physical environment and may be facilitated by referring the patient to palliative care services.[365,366] Advance care planning can explore trials of appropriate therapy but should incorporate shared decision-making principles. Burden and benefit of therapies need to be weighed against patient goals, with sensitive discussions about why futile treatments may not be offered.

Table 8. Supportive care, hepatology and medical goals in patients with 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 patient's expectations and maintain realistic goals • Develop coordination-of-care framework and symptom monitoring plan	• Manage symptoms of HCC and chemotherapy • Provide decision-making support, with focus on quality of life • Consider early referral to palliative care for ongoing support and counselling	• Manage severe cancer-related symptoms • Discuss referral to hospice for end-of-life care • Engage palliative care services for supportive measures
	Discuss and consider advance care directives			
Hepatology-focused goals	• Preserve and potentially restore hepatic function to prevent stage migration (e.g. alcohol abstinence, avoidance of hepatotoxins, consideration of 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 those with protein malnutrition • In patients with advanced HCC, investigate for possibility of metastatic disease or vascular invasion			• Manage symptoms associated with liver failure (e.g. ascites, hepatic encephalopathy) • Determine limits of care (e.g. in event of catastrophic events, such as variceal haemorrhage)
General medical issues	• Treat medical comorbidities that will affect survival or symptoms • Optimise patient medically for surgery/procedures/chemotherapy • Support cessation of smoking and alcohol • Provide psychological or psychiatric supports			• Provide 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; HCC = hepatocellular carcinoma; TACE = transarterial chemoembolisation.

In view of the poor prognosis of advanced HCC, advance care directives and not-for-resuscitation orders should be considered and discussed. Conversations with the patient, in conjunction with family members and important others, are useful to facilitate decisions about future health care, should the patient become incapable of participating in medical treatment decisions about themselves.

High-quality evidence in the setting of other malignancies supports the role of early palliative care interventions in improving quality of life and symptom control and increasing survival, with fewer aggressive end-of-life care treatments.[367] The same quality of evidence is not directly available in the setting of HCC; nevertheless, it is likely that the same principles apply.[367,368] Evidence shows incremental advantages according to timing of palliative care (e.g. palliative care provided more than 2 weeks before death is associated with reduced hospital use [$P < 0.001$]; care provided 4 or more weeks before death is associated with fewer emergency department presentations [$P < 0.001$]).[369] To achieve optimal patient outcomes, expert consensus and RCT data[370-374] suggest referral at least 3 months before death.[375] There is evidence that early palliative care interventions in patients with decompensated cirrhosis are useful and may be associated with decreased health care resource utilisation and reduced symptom burden, as well as improvements in end-of-life care parameters, such as the location of care and death (with patients being more likely to die at home) and a lower likelihood of undergoing resuscitation attempts at the time of death.[368,376-379]

7.2 Symptomatic relief and quality of life

Patients with advanced liver cancer have unique requirements with regard to analgesia use (section 7.2.1), nausea (section 7.2.2), pruritus (section 7.2.3), muscle cramps (section 7.2.4), anxiety and depression (section 7.2.5), fatigue, malnutrition and sarcopaenia (section 7.2.6) and corticosteroid use (section 7.2.7). In addition to symptom control, quality of life is correlated negatively with depression and with uncertainty (chance-held locus of control) and positively with satisfaction with medical services. Psychosocial interventions may reduce negative feelings and thus enhance quality of life.[380-382]

7.2.1 Analgesia

Pain is a common feature of HCC and can result from both the disease and its treatment.[355] The choice of analgesic agent must take into consideration many factors, including the severity of liver disease (impaired hepatic metabolism); portosystemic shunting; low circulating albumin level (potential for reduced drug binding and increased bioavailability); past history of, and risk of return to, opioid dependence; current medications (including opioid substitution therapy); and clinical features, such as hepatic encephalopathy and hepatorenal syndrome.[383] Table 9 summarises the commonly used analgesic medications and their role for patients with liver disease. In conjunction with this, the WHO analgesic ladder provides a well-accepted treatment algorithm for analgesia use in all cancers, including HCC (Figure 6).[355]

7.2.1.1 Paracetamol

Paracetamol is the preferred analgesic for mild to moderate pain.[355] However, many primary care physicians remain reluctant to prescribe paracetamol because of its reputation for hepatotoxicity at supratherapeutic doses. At a maximum daily dose of 2 g, paracetamol is well tolerated, with an absence of sedation, hepatotoxicity or nephrotoxicity and risk of dependence.[355,389] Two studies have shown that daily doses of 4 g are safe and, in a single study of 20 patients, only one patient developed abnormal liver function test results, which was considered unlikely to be caused by drug toxicity.[390,391] Toxicity is more likely to occur after prolonged starvation because of glutathione depletion. Glutathione is important, as it facilitates hepatic detoxification of paracetamol metabolites that cause liver injury if allowed to accumulate.[392]

7.2.1.2 Non-steroidal anti-inflammatory drugs and cyclo-oxygenase-2 inhibitors

Non-steroidal anti-inflammatory drugs (NSAIDS) are not recommended in patients with liver disease because of the risks of renal impairment, gastrointestinal bleeding and exacerbating peripheral oedema and ascites.[355] Cyclo-oxygenase-2 (COX-2) inhibitors are well tolerated, without the renal or gastrointestinal side effects of NSAIDS. However, COX-2 inhibitor efficacy and safety have not been rigorously

Table 9. Analgesia in patients with liver disease

Medicine	Use in liver disease	Prescribing tips
Paracetamol	• Underused (possibly related to perceived hepatotoxicity) • Use with caution in patients with chronic alcohol consumption >60 g/day and those with prolonged starvation	• Generally safe • In patients with liver disease, daily doses of 2–3 g are well tolerated
NSAIDs	• Can exacerbate or precipitate hepatorenal syndrome, gastrointestinal bleeding and fluid retention	• Avoid, except in well-compensated patients (but consider risk–benefit)
Oxycodone and naloxone	• First-pass metabolism reduced • Systemic absorption of naloxone might occur, with antagonism of the analgesia	• Avoid, except in very well-compensated patients without renal impairment
Codeine	• Requires metabolic conversion to active form, thus therapeutic levels are variable	• Unpredictable effect; requires monitoring
Tramadol	• Requires metabolic conversion to its active form, thus therapeutic levels are variable	• Unpredictable and low ceiling for toxicity; requires monitoring • Consider starting dose of 50 mg twice daily and titrate
Morphine	• Prolonged half-life, so increase dose intervals and reduce dose	• Consider low starting dose • Ordine (Mundipharma) 200 mL liquid in 1, 2, 5 and 10 mg/mL packs: start at 1–2 mg dose and monitor
Oxycodone	• Unpredictable metabolite levels • Increased bioavailability • Reduce dose or increase interval	• Consider low starting dose • Endone (Alphapharm) 5 mg or Oxynorm (Mundipharma) 1 mg/mL (250 mL): start at 1–2 mg dose and monitor
Hydromorphone	• For those with high morphine requirements	• Consider low starting dose • Dilaudid (Mundipharma) 1 mg/mL: start at 0.25–0.5 mg dose and monitor
Fentanyl	• Pharmacokinetics unaffected by liver failure or renal disease • Heavily protein-bound; may require reduced dose in patients with hypoalbuminaemia	• Consider low starting dose • Fentanyl patch: start at 12 mcg/h (lasts for three days); wait a week before increasing dose (12, 25, 75, 100 mcg/h packs available)
Pregabalin	• Not metabolised in the liver, renal excretion • No anticholinergic side effects	• Consider low starting dose: 25 mg at night, increase after 3 days
Nortriptyline	• Less sedating than amitriptyline	• Consider low starting dose: 10 mg at night, increase after 3 days to 25 mg

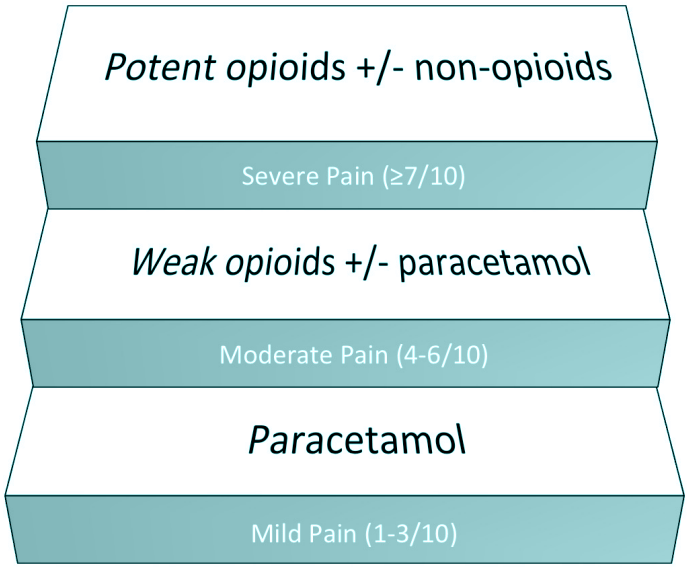
Adapted from various references.[384-388] NSAID = non-steroidal anti-inflammatory drug.

tested in this patient population, limiting their use due to a lack of reliable data on outcomes.

7.2.1.3 Opioids

Opioids are useful in providing effective analgesia in patients with moderate to severe pain. Expertise and familiarity with the use of opioids are required because of the risk of their sedative effects, as well as constipation that can precipitate hepatic encephalopathy.[355] Opioid prescription should take into account the opioid metabolism, the nature of metabolites (active and inactive) and the potential

Figure 6. WHO analgesic ladder, modified for HCC



HCC = hepatocellular carcinoma; WHO = World Health Organization. Adapted from J Clin Exp Hepatol 2014; 4 Suppl 3: S130-S139.[355]

for drug interactions. As drug metabolism of some opioids may be significantly impaired by reduced plasma clearance, prolonged half-life and increased oral bioavailability, starting at a lower dose or with an increased dose interval is recommended for many patients. Some opioids, such as codeine and oxycodone, require conversion to the active metabolite, which may be impaired in patients with advanced liver disease, resulting in unpredictable analgesia. Clearance of active metabolites, such as with morphine and its metabolites, may be affected by concurrent renal impairment. Monitoring with gradual titration to balance efficacy and toxicity is required. Newer agents, such as oxycodone with naloxone, reduce the risk of opioid-induced constipation; however, reduced first-pass metabolism, which may occur in patients with liver disease, can result in systemic naloxone absorption and inhibit the analgesic effect. These agents are therefore best avoided.

Tramadol is a centrally acting synthetic analgesic structurally related to codeine. Tramadol must be metabolised to achieve its opioid effect, and thus its effect may be unpredictable.[355,383] As tramadol is less constipating than other opioids, it may reduce the risk of hepatic encephalopathy. However, this benefit is variable, and it has a low ceiling for toxicity and many drug interactions.

Fentanyl is a potent analgesic with an elimination that is unaltered by liver disease. It thus may be a good choice once a stable opioid dose is established. However, fentanyl is significantly protein-bound and may require dose reduction in the presence of hypoalbuminaemia. Methadone, frequently used by patients with HCC, can be used safely because its pharmacokinetics are largely unchanged in patients with cirrhosis compared with healthy individuals.[393] Both methadone and fentanyl are potentiated by drugs that block the cytochrome P450 3A4 (CYP3A4) enzyme pathway, such as fluconazole and diltiazem. Methadone also has reduced bioavailability in the presence of protease inhibitors. It should be used with caution or avoided in combination with other drugs that use the glucuronidation pathway for their metabolism (e.g. naloxone and buprenorphine).[394] Methadone's variable half-life may result in drug accumulation. Close monitoring is required when changing dose, and advice should be sought from a pain or palliative specialist.

For all patients receiving opioids, lactulose should be prescribed pre-emptively to prevent constipation.

7.2.1.4 Other analgesic measures

Neuropathic pain may be better treated with gabapentin or pregabalin. Pain from bony

metastasis may be better treated by site-specific palliative radiotherapy, which is effective and well tolerated.[395,396]

7.2.2 Nausea

Nausea is an uncommon but significant symptom in patients with end-stage HCC. As concomitant medications may contribute, it is worthwhile to reduce tablet burden and use the lowest possible dose. Treating constipation, reflux and anxiety can help. If pharmacological management of nausea is required, 5-HT_3 receptor antagonists, such as ondansetron, may be useful[355] but can lead to constipation and exacerbate encephalopathy risk. Oral domperidone 10 mg taken three times daily 30 minutes before meals does not cross the blood–brain barrier, although in patients with severe hepatic impairment, dose reduction may be required. Oral metoclopramide 10 mg may be helpful, also before meals, but because of its effect on the central nervous system, extrapyramidal side effects can be significant, and sedation and encephalopathy may be precipitated. In a patient with concurrent agitation, oral haloperidol 0.5–1 mg twice daily, up to 4 mg daily, may be useful. Monitoring for constipation, as well as assessment for QT interval prolongation, is advised. For refractory nausea, the sedating antihistamine oral cyclizine 25–50 mg when necessary (up to 50 mg three times daily) may help; however, it can cause anticholinergic side effects. Adjuvants to antiemetics include proton pump inhibitor therapy, especially in patients with reflux or possible gastro-oesophageal reflux disease, and benzodiazepines for anxiety-induced nausea (e.g. oral lorazepam 0.5–1 mg when necessary). However, benzodiazepines should be used with caution, as they may precipitate hepatic encephalopathy and exacerbate risk of falls; both serious consequences of this strategy.

7.2.3 Pruritus

Although pruritus is not common in patients with HCC, it is a debilitating symptom. Optimising skin care — including minimising exposure to hot water and over-heating, using mild unscented soap and avoiding irritating, coarse-textured clothing — is worthwhile.[397] In the setting of biliary obstruction, biliary intervention is sometimes considered (section 7.3.3). However, failing this, bile acid binding resins, such as cholestyramine (4–16 g orally, daily in divided doses), may assist, if they are tolerated by the patient. Concomitant medications must be taken at least 1 hour before or 4–6 hours after cholestyramine to prevent inadvertent drug binding and reduced bioavailability. Side effects include constipation, for which lactulose may be a helpful adjunct.

Serotonergic agents, including oral sertraline 25–100 mg daily or oral mirtazapine 15 mg daily, may be useful. Sertraline is particularly helpful when there is concurrent depression or anxiety, but it can cause nausea. Mirtazapine is more useful for improving sleep and appetite and reducing anxiety. Mirtazapine and some of its pharmacologically active metabolites are metabolised by CYP3A4 enzymes in the liver and excreted by the kidney. The clearance of mirtazapine has been shown to decrease in patients with moderate to severe renal or hepatic impairment. Therapy with mirtazapine should be administered cautiously in such patients, and dosage adjustments may be necessary.[398,399] Although useful in anxious patients with pruritus, mirtazapine can be sedating and exacerbate encephalopathy, so it should be introduced and monitored with caution.

Antihistamines are generally not useful for cholestatic itch and should be ceased unless there is an alternative indication.[397,400]

7.2.4 Muscle cramps

Muscle cramps can be a significant problem for patients with advanced liver disease and are not solely attributable to diuretic therapy, as they occur far less often in patients with congestive heart failure receiving similar diuretic regimens. If magnesium deficiency is present, magnesium supplementation (500 mg to 1 g orally up to three times daily as needed to normalise levels) can be helpful. Proton pump inhibitors may occasionally be responsible for low magnesium levels, and the indication for using them should be reviewed.

Other therapeutic options include:

- oral vitamin E (500 international units twice daily), which may be effective although large controlled studies are lacking;[401]
- oral taurine 2 g daily, with small studies showing impressive results;[402]

- branch chain amino acids (oral leucine, isoleucine and valine 4 g three times daily), which aim to replace taurine and increase albumin concentrations;[403]
- oral zinc 220 mg twice daily after meals (not recommended on an empty stomach), which has been shown to be useful by limited but supportive data, although it may cause diarrhoea; and
- oral baclofen 5 mg three times daily (with meals) for 1 week (if tolerated, dose can be increased to 10 mg three times daily).

Baclofen can cause drowsiness, anxiety, urinary retention and confusional states on abrupt discontinuation, and it should therefore be gradually withdrawn over 1 to 2 weeks. It is safe in patients with cirrhosis, although it reduces seizure threshold and should be avoided in at-risk patients.[401,402,404-407]

7.2.5 Anxiety and depression

Anxiety and depression can contribute negatively to overall health-related quality of life but can be hard to distinguish from somatic symptoms directly attributable to HCC, such as fatigue, lethargy and insomnia.[355] Control of somatic symptoms is a priority, as these can directly affect the patient's mood and level of anxiety.[355]

Nevertheless, anxiety and depression are more common in the setting of HCC than other cancers, perhaps because of the degree of uncertainty and poor prognosis for many patients.[362] Referral to psycho-oncology services should be considered. Specific pharmacological treatment of depression, including citalopram, sertraline or mirtazapine, should be chosen with consideration of the patient's other symptoms and tolerability. Citalopram and sertraline may be helpful for patients who are lethargic because of its activating effects, whereas mirtazapine can be useful in those with poor appetite and sleep disturbance. Combining fentanyl with mirtazapine may increase the risk of serotonin syndrome.

Selective serotonin reuptake inhibitors and selective noradrenaline reuptake inhibitors are generally safe in patients with liver disease. As there has been some concern about selective serotonin reuptake inhibitors increasing the risk of gastrointestinal bleeding, co-administered antiplatelet medication or non-steroidal medication should be taken into consideration. For both classes of drugs, reduced clearance and increased half-life are expected in patients with cirrhosis, particularly in its advanced stages. Initial and maintenance doses should be reduced to about 50% and titrated.[377,380,381,408-411]

Exercise is known to improve mood and quality of life in cancer patients, as can meditation and mindfulness activities. Exercise may also assist patients through their treatment by providing a sense of physical and mental wellbeing. The Cancer Council of Australia recommends exercise for all cancer patients as part of routine cancer care.

7.2.6 Fatigue, malnutrition and sarcopenia

Malnutrition can be an obvious and distressing aspect of end-stage HCC and may result from both tumour burden and coexisting advanced liver disease. Fatigue is multifactorial and may be the most debilitating symptom affecting overall quality of life. Modifiers can include medications, as well as nutritional deficiencies that can be optimised by the use of frequent, small, high-protein meals. Malnutrition can be associated with worse functional status and quality of life in patients with HCC, and modification of malnutrition in the setting of cirrhosis (not specifically HCC) is associated with improved clinical outcomes.[412] Given the lack of evidence for the effect of aggressive nutritional supplementation on maintaining muscle mass in patients with advanced liver cancer, the patient's wishes and food preferences should be prioritised when recommending nutritional supplements designed to meet estimated energy and protein needs.[355] Expert dietitian advice is worth considering at an early stage, to prevent the development of malnutrition.

Although evidence regarding exercise in patients with cancer cachexia is not strong,[413] a systematic review has shown that it can be regarded as beneficial for patients with cancer-related fatigue, but recommendations on optimal type of exercise are still lacking.[414]

Symptom control in patients with liver disease is summarised in Table 10.

Table 10. Symptom control in patients with liver disease

Symptom	Liver disease nuance	Prescribing tips
Nausea	Exclude reflux, constipation, anxiety and concomitant medication	• Domperidone 10 mg three times daily • Metoclopramide 10 mg three times daily (sedation) • Cyclizine 12.5–25 mg three times daily
Pruritus	Exclude and/or treat biliary obstruction	• Cholestyramine 4–16 mg daily (be aware of constipation) • Sertraline 25–100 mg orally
Muscle cramps	Not always caused by diuretics, check magnesium level	• Magnesium • Vitamin E • Taurine 3 g orally • Zinc 220 mg • Baclofen 5 mg three times daily (use caution on abrupt withdrawal)
Anxiety and depression	Ensure other uncontrolled symptoms are not the cause	• Communication and helpful emotional practitioner responses are crucial • Supportive psychotherapy • Citalopram or sertraline for lethargy • Mirtazapine for sleep disturbance • Benzodiazepine has a risk of falls and encephalopathy; use with caution • Consider exercise and mindfulness activities
Fatigue and sarcopenia	Fatigue may be the most debilitating of all symptoms	• Exclude medications responsible • Nutritional support • Consider exercise (with caution)

7.2.7 Corticosteroids

Corticosteroids are often used in supportive care to assist with pain, quality of life, nausea and fatigue.[355] Their contribution to pain management is thought to be through multiple mechanisms, including the reduction of inflammation, tissue oedema, bone pain, neuropathic pain and headache.[355] For patients with advanced HCC, with or without liver disease, there is no specific evidence. Prednisolone is the active metabolic product of hepatic metabolism and may be preferred over the prodrug prednisone in patients with advanced liver disease.[415] Although dexamethasone is metabolised by the liver, the choice between dexamethasone, prednisone or prednisolone is often based on clinician experience and preference and options for route of administration.

7.3 Special considerations in management of advanced HCC

7.3.1 Portal vein tumour thrombosis

Portal vein thrombosis occurs in 7%–17 % of patients with cirrhosis (without HCC), with the risk depending on severity of liver disease, prior portal vein thrombosis and age.[416,417] In the presence of HCC, the risk of portal vein thrombosis increases significantly.[418] Distinguishing between portal vein tumour thrombosis (PVTT) and non-neoplastic portal vein thrombosis is clinically important, as the two conditions are managed differently, with important implications for prognosis and the potential for curative therapies such as LT.

Features to suggest PVTT rather than non-neoplastic portal vein thrombosis include the presence of APHE within the thrombus, expansion of the portal vein, neovascularity and proximity of the thrombus to the HCC or prior treatment site. Together with elevated AFP level, these characteristics have formed the basis

of non-invasive criteria (the A-VENA criteria) that accurately predict the presence of PVTT.[419]

The OS of patients with PVTT is between 2 and 4 months with best supportive care.[418,420,421] This is partly attributable to the associated advanced tumour stage, aggressive tumour biology and deterioration in hepatic function, as well as consequences of raised portal pressure. Patient survival correlates well with the extent of PVTT, with segmental portal vein involvement carrying a 1-year OS of 55%, whereas PVTT involving the superior mesenteric vein has a 1-year survival rate of 11%.[422]

Several classification systems have been developed to better define the extent of PVTT and to provide some nuance to management.[420-423] The BCLC staging system simply classifies patients with portal vein involvement as having advanced HCC (BCLC stage C) and suggests systemic therapy as the most appropriate treatment. Similarly, the presence of PVTT has been cited as a contraindication to both transarterial embolisation (TAE) and surgical resection. Yet, surgical treatment, comprising either en bloc resection of the thrombus and portal vein followed by reconstruction, or tumour thrombectomy, is offered in some centres. TACE can also be performed safely in the presence of PVTT with the use of superselective cannulation. TACE has been compared with conservative management in two prospective studies,[424,425] a meta-analysis[426] and a large retrospective series,[427] all of which suggested improved outcomes with TACE. TARE is less likely to cause an embolic syndrome and is considered an appealing modality for use in those with PVTT who are likely to be at higher risk. This theoretical benefit has not been proven, and it should also be remembered that those with proximal PVTT have poor survival and response to TARE.[428]

Finally, direct treatment of PVTT by portal vein stenting and/or stereotactic deep x-ray therapy has been described, but there is no quality evidence to support a clinical benefit of these techniques, even though patency can be achieved.[418,429-431]

7.3.2 Spontaneous tumour rupture

Spontaneous tumour rupture is a potentially catastrophic complication of HCC. Most of the data have come from Asian populations, where the incidence ranges between 2.3% and 26%.[432] In contrast, the incidence in Western populations is reported to be between 2% and 3%.[433,434] Spontaneous rupture of HCC represents the third most common cause of HCC-related death, after tumour progression and hepatic failure. It carries a grave prognosis,[435,436] with in-hospital mortality ranging from 30% to 70% and overall median survival between 7 and 24 weeks.[436-438] Factors associated with early mortality include severity of initial presentation, stage of cancer and baseline hepatic reserve.[437,439]

In a large multicentre European study, management of spontaneous tumour rupture after initial resuscitation and stabilisation included TAE to control ongoing and subsequent haemorrhage.[433] A minority of patients (18%) required surgery to control bleeding, and recurrent bleeding occurred in 22%. Elevated creatinine level and initial intensive care unit admission were independently related to bleeding recurrence on multivariate analysis, although univariate analysis had suggested BCLC and Child–Pugh stage, younger age and elevated bilirubin and bicarbonate concentrations also predicted a poor prognosis.[433,438,440] Chance of cure with surgery after spontaneous rupture is diminished because of the high likelihood of peritoneal contamination; accordingly, transplantation would not ordinarily be considered.[441-444]

7.3.3 Biliary obstruction

Bile duct involvement in primary liver cancer is usually due to cholangiocarcinoma but can occur in association with advanced and bulky HCC.[445] Involvement of the common bile duct is rare, with only 22 cases specifically described in the literature.[445] However, the true incidence may be underestimated, and biliary obstruction by HCC should be considered in any case of new biliary obstruction in a patient with cirrhosis.[445] HCC-induced biliary obstruction is associated with haemobilia[445] and biliary colic.[446] Initial treatment is typically with percutaneous or nasobiliary drainage.[447] Endoscopic prosthesis insertion resulted in successful or partial relief of biliary obstruction in a small series (nine of 13 patients).[447] However, mean survival after presentation was 60 days, with 12 of 13 patients dying of liver failure. It appears in this study that biliary endoprosthesis had a limited role in the palliation of bile duct obstruction, with prognosis dictated by other factors.[447] Although the

routine use of biliary drainage procedures cannot be recommended, there are reported longer-term survivors with this presentation who have had successful treatment.[447,448]

7.3.4 Metastatic disease

Extrahepatic metastases are found in 13.4% of people with HCC, with the most common sites being the lungs (53.8%), bone (38.5%) and lymph nodes (33.8%).[449] The presence of extrahepatic metastases was associated with advanced T3 or T4 intrahepatic HCC (73.8% vs 28.5%), and 24.9% of these patients were likely to have Child–Pugh B or C cirrhosis.[449,450] Documented vascular invasion is also more frequently seen in patients with extrahepatic metastases.[445] Unsurprisingly, in one study, the median survival time was reduced, yet a minority (11%) died as a consequence of the extrahepatic metastases, with most patients dying of intrahepatic disease or liver failure (median survival, 4.9 months).[451] In patients without advanced intrahepatic HCC (T0–T2), survival is significantly better and treatment can improve outcomes.[449,451] Intrahepatic lesion size also influences the likelihood of extrahepatic metastases, with lesions larger than 50 mm having a greater rate of metastatic disease.[452] The diagnosis of suspected metastatic disease is by CT or MRI,[453] with positron emission tomography having a potential role in detection of metastases larger than 10 mm in the lung or bone.[452]

7.3.5 Massive tumours

Massive HCC is a not infrequent presentation, with 58 of 361 individuals in a single institution (16%) having lesions in excess of 130 mm in diameter.[454] In univariate and multivariate analysis, massive HCC was associated with age younger than 40 years, hepatitis B infection, Asian ethnicity, absence of cirrhosis and a platelet count greater than 100×10^9/L.[454] These investigators concluded that massive HCC appears not to be identical to locally advanced TNM T3 or T4 HCC,[455] and treatment options can include surgical resection in the absence of vascular invasion or metastases.[454] In uncontrolled studies, TACE and radiotherapy appear to confer better OS than in untreated controls; however, selection bias may confound this interpretation, and complication rates are higher with TACE in this setting.[425,456] However, most treatment guidelines neither mention massive HCC nor discuss treatment individualisation based on medical and individual preference.

7.3.6 Palliative debulking

The size of a tumour is not the driving force in decision making in an MDT; rather, the location, liver function, estimated functional liver remnant, performance status and presence of portal vein invasion are the main factors to be considered. If there is no chance of cure, surgery should not be attempted and is generally not supported by guidelines or evidence. Radiotherapy can offer options for palliation in patients with HCC, particularly using highly conformational techniques (e.g. stereotactic radiotherapy for intrahepatic disease). Uses of radiotherapy include control of pain from disease within the liver and extrahepatic disease and for inferior vena cava tumour infiltration. Other therapies, such as TAE, SIRT and systemic therapy, have also been attempted in patients with end-stage disease, but best supportive care is usually the preferred management option.

8 Future therapies and management

Development of effective and well-tolerated systemic therapies for HCC is a priority in clinical drug development. Multiple clinical trials exploring the role of adjuvant immunotherapies and anti-angiogenic agents in monotherapy or in combination are underway. Initial studies focused on advanced HCC, but these therapies are increasingly being investigated in adjuvant settings after surgical resection, percutaneous ablation, TACE or SIRT in patients with intermediate or high risk of recurrence or progression.

As more is understood about the molecular basis of HCC, the utilisation of molecular biomarkers in liver biopsy or liquid biopsy, in conjunction with clinical biomarkers, may direct the most appropriate therapy for a particular patient. However, the significant phenotypic and molecular heterogeneity of HCC between individuals, and even within a specific tumour, poses a significant challenge to personalised treatment.

9 Conclusion

This consensus statement is intended to be a useful resource for health professionals managing patients with HCC. It stands out from other international guidelines with its broad and comprehensive approach. In addition, it addresses often neglected areas, including the management of patients with advanced disease, for whom the focus should be on preserving quality of life and planning for disease progression.

We value any feedback from the reader, as this is intended to be a living document and will be subject to ongoing revision as developments in this area occur.

Abbreviations

AASLD	American Association for the Study of Liver Diseases
AFP	alpha-fetoprotein
AGREE	Appraisal of Guidelines for Research & Evaluation
ALA	Australian Liver Association
APHE	arterial phase hyperenhancement
BCLC	Barcelona Clinic Liver Cancer
CEUS	contrast-enhanced ultrasound
CI	confidence interval
COX-2	cyclo-oxygenase-2
CT	computed tomography
cTACE	conventional transarterial chemoembolisation
DAA	direct-acting antiviral
DEB-TACE	drug-eluting bead transarterial chemoembolisation
DFS	disease-free survival
DWI	diffusion-weighted imaging
EASL	European Association for the Study of the Liver
ECOG	Eastern Cooperative Oncology Group
GESA	Gastroenterological Society of Australia
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HHHN	hypovascular hepatobiliary hypointense nodule
HKLC	Hong Kong Liver Cancer
HR	hazard ratio
HSCA	hepatocyte-specific contrast agent
ISGLS	International Study Group of Liver Surgery
ITA.LI.CA	Italian Liver Cancer
LI-RADS	Liver Imaging Reporting and Data System
LR	liver resection
LRT	locoregional therapy
LT	liver transplantation
MBS	Medicare Benefits Schedule

MDT	multidisciplinary team
MELD	Model for End-Stage Liver Disease
MESIAH	Model to Estimate Survival in Ambulatory HCC Patients
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
MRI	magnetic resonance imaging
MWA	microwave ablation
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NSAID	non-steroidal anti-inflammatory drug
OPTN	Organ Procurement and Transplantation Network
OR	odds ratio
OS	overall survival
PBS	Pharmaceutical Benefits Scheme
PD-1	programmed cell death protein 1
PEI	percutaneous ethanol injection
PHLF	post-hepatectomy liver failure
PPV	positive predictive value
PS	performance status
PVTT	portal vein tumour thrombosis
RCT	randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
RFA	radiofrequency ablation
RFS	recurrence-free survival
SBRT	stereotactic external-beam radiation therapy
SIRT	selective internal radiation therapy
SVR	sustained virological response
TACE	transarterial chemoembolisation
TAE	transarterial embolisation
TARE	transarterial radioembolisation
TGA	Therapeutic Goods Administration
UCSF	University of California San Francisco
VEGF	vascular endothelial growth factor
WHO	World Health Organization

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Table 11. Participants involved in manuscript development

Name	State	Organisation	Section (subsection)
Dr Leon Adams	WA	GESA	Treatment (Surgery)
Prof Golo Ahlenstiel	NSW	GESA	Treatment (Systemic)
Prof Peter Angus	Vic	GESA	Treatment (Locoregional)
Dr Sally Bell	Vic	GESA	Burden of Disease
Dr Kaye Bowers	Vic	ANZHPBA	Treatment (Surgery)
Dr James Burnes	Vic	IRSA	Treatment (Locoregional)
Dr Sarat Chander	Vic	RANZCR	Treatment (Radiotherapy, Systemic)
Dr Robert Cheng	NSW	GESA	Burden of Disease
Dr Asif Chinnaratha	SA	GESA	Burden of Disease
Dr Tim Churches	NSW	UNSW	Epidemiology (Figure 1)
A/Prof Maria Cigolini	NSW	ANZSPM	Patient Care
Dr Paul Clark	Qld	GESA	Burden of Disease
Prof Stephen Clarke	NSW	COSA	Treatment (Systemic) – SC member
Prof Darrell Crawford	Qld	GESA	Burden of Disease – **WG Chair**
Dr Olivia Cullen	Qld	AHA	Patient Care
A/Prof Anouk Dev	Vic	GESA	Treatment (Multidisciplinary teams)
Dr Greg Dore	NSW	GESA	Burden of Disease
Mr Michael Fink	Vic	ANZHPBA	Treatment (Surgery)
Prof Jacob George	NSW	GESA	Burden of Disease
Dr Mark Goodwin	Vic	Radiologist	Treatment (Locoregional) – **SC**, Diagnosis (feedback)
A/Prof Paul Gow	Vic	GESA	Burden of Disease
Dr Ingrid Hickman	Qld	Nutritionist	Patient Care
Dr Thai Hong	Vic	GESA	Burden of Disease
Dr Jessica Howell	Vic	GESA	Burden of Disease
Dr David Iser	Vic	ASHM	Diagnosis
Dr Ashu Jhamb	Vic	IRSA/RANZCR	Treatment (Locoregional)
Dr William Kemp	Vic	GESA	Treatment (Locoregional)
Dr Miriam Levy	NSW	GESA	Patient Care – **WG Chair** Patient Care, Diagnosis (feedback)
A/Prof Lara Lipton	Vic	Palliative Care	Patient Care, Treatment (Systemic)
A/Prof John Lubel	Vic	GESA	Diagnosis – **WG Chair, SC, Co-Chair**

Name	State	Organisation	Section (subsection)
Prof Gerry MacQuillan	WA	GESA	Treatment (Liver Transplant)
Dr Suzanne Mahady	NSW	GESA	Burden of Disease
Prof Geoff McCaughan	NSW	GESA	Treatment (Liver Transplant)
Ms Barbara Moore	NSW	AHA	Patient Care
Dr Kate Muller	SA	GESA	Diagnosis
Dr Michael Ng	Vic	RANZCR	Treatment (Radiotherapy, Systemic)
A/Prof Amanda Nicoll	Vic	GESA	Patient Care
Prof John Olynyk	WA	GESA	Treatment (Multidisciplinary teams)
Prof Jennifer Philip	Vic	Palliative Care	Patient Care – **SC**
Dr David Pryor	Qld	RANZCR	Treatment (Radiotherapy)
Dr Kate Reed-Cox	NSW	PCA	Patient Care
Prof Stuart Roberts	Vic	GESA	Treatment – **WG Chair**, Treatment (Multidisciplinary teams), **SC**
Dr Chris Rogan	NSW	IRSA	Treatment (Locoregional)
Dr Marno Ryan	Vic	GESA	Treatment (Radiotherapy, Systemic)
Dr Glen Schlapoff	NSW	IRSA/RANZCR	Treatment (Locoregional)
Prof Nick Shackel	NSW	GESA	Treatment (Systemic) – **SC**, **Co-Chair**
Dr James Seow	WA	ARGANZ	Burden of Disease
Prof William Sievert	Vic	GESA	Patient Care
Dr Manfred Spanger	Vic	IRSA/RANZCR	Diagnosis
Ms Sally Spruce	NSW	AHA	Patient Care
A/Prof Simone Strasser	NSW	GESA	Treatment (Systemic, Locoregional), **SC**, Patient Care (feedback)
Dr Katherine Stuart	Qld	GESA	Treatment (Locoregional), Patient Care
Dr Tom Sutherland	Vic	RANZCR	Diagnosis
Dr Caroline Tallis	Qld	GESA	Treatment (Liver Transplant)
A/Prof Niall Tebbutt	Vic	Non-GESA	Treatment (Systemic)
Prof Alex Thompson	Vic	GESA	Treatment (Systemic) – **SC**
Dr Michael Wallace	WA	IRSA	Treatment (Locoregional), Burden of Disease (feedback)
A/Prof Martin Weltman	NSW	GESA	Diagnosis
A/Prof Allan Wigg	SA	GESA	Diagnosis
A/Prof Amany Zekry	NSW	GESA	Diagnosis

AHA=Australasian Hepatology Association; ANZHPBA=Australia and New Zealand Hepatic, Pancreatic and Biliary Association; ANZSPM=Australian and New Zealand Society of Palliative Medicine; ARGANZ=Abdominal Radiology Group Australia and New Zealand; ASHM=Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine; COSA=Clinical Oncology Society of Australia; GESA=Gastroenterological Society of Australia; IRSA=Interventional Radiology Society of Australasia; PCA=Palliative Care Australia; RANZCR=Royal Australian and New Zealand College of Radiologists; SC=steering committee; UNSW=University of New South Wales; WG=working group.

Author disclosures

Leon Adams has been a member of the Metavention Advisory Board since 2019 and was a member of the Pfizer Advisory Board in July 2018. He is a holder of Australian and US patents for Hepascore.

Paul Clark is a member of the Board of the Australian Liver Foundation and has received grants for overseas travel or conference expenses from Gilead, AbbVie and Bristol-Myers Squibb.

Stephen Clark has received significant hospitality from the Bayer Board.

Darrell Crawford is Chair of the Eisai Advisory Board.

Olivia Cullen received accommodation expenses from Bayer for the ILCA Conference 2017.

Greg Dore is a member of the Hepatitis C Advisory Board. He is a member of the Board, has performed paid employment or contracting work and has received international conference travel support and research grants from Gilead Sciences, AbbVie and Merck Sharp & Dohme. He has supported PBS listing of all major DAA regimens, including in public statements and the media.

Jacob George holds Board membership or another office and has performed paid employment or contracting work with Bristol-Myers Squibb, Gilead, Eisai, Bayer, Pfizer, AbbVie and Merck Sharp & Dohme. Members of his immediate family hold Board memberships or other offices; have performed paid employment or contracting work with Bayer, Novartis, Pfizer, Sanofi, Genzyme and Shire Actelion; and have received grants for overseas travel or conference expenses from Genzyme, Bayer and Actelion.

Mark Goodwin has received payments as a consultant for Bayer and Sirtex Medical (Proctor).

Ingrid Hickman has received speaker fees from Gilead Sciences for a professional education series.

David Iser is a member of the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM) Board of Directors (2016–2020) and has received speaker fees from AbbVie (2017–2020), Gilead (2017) and Merck Sharp & Dohme (2017–2018).

Lara Lipton is a member of the Bayer Advisory Board.

John Lubel holds Board membership or another office and has performed paid employment or contracting work with Bayer, Gilead and AbbVie.

Suzanne Mahady is a member of the PICO Advisory Sub-committee of the Medical Services Advisory Committee (MSAC) in the Department of Health.

Michael Ng has been employed by or done contracting work with the MSAC.

Amanda Nicoll is a member of the AbbVie Advisory Board and has received a research grant from Merck Sharp & Dohme, speaker fees from Bayer and grants for overseas travel or conference expenses from AbbVie (EASL 2015 conference).

John Olynyk has been employed by or done contracting work with the WA Department of Health and is the recipient of an NHMRC Project Grant (2019–2022).

Jennifer Phillip has been a member of the Eastern Palliative Care Committee of Management and has been employed by or done contracting work with the Peter MacCallum Cancer Centre, St Vincent's Health Australia, the University of Melbourne and Royal Melbourne Hospital.

David Pryor has received speaker fees from Janssen and Mundipharma.

Kate Reed-Cox is a member of the Australian College of Nurse Practitioners Board (unpaid position) and has been employed or done contracting work as a PCA National Clinical Advisor.

Stuart Roberts is a member of the Gilead, AbbVie and MSD Advisory Boards and the Bristol-Myers Squibb HCC Advisory Board.

Chris Rogan previously held shares in Sirtex Medical, is an AllVascular Advisory Board member and has received grants for overseas travel or conference expenses from Terumo Medical Corporation (Japan physician education, May 2019, microcatheters and

wires) and BET Medical (Korea physician education, TACE masterclass, April 2018).

Nick Shackel has been an Advisory Board member and speaker for Roche, Bristol-Myers Squibb, Gilead, Bayer, Astellas and Novartis.

James Seow has, since 2013, been an unpaid executive member of the Abdominal Radiology Group of Australia and New Zealand (ARGANZ) and the WA Branch of the Royal Australian and New Zealand College of Radiologists. He has received speaker fees for the Siemens Liver Imaging Workshops (Sydney and Perth) and had his expenses paid for the Bayer International Liver Forum in Basel. He is a member of the American College of Radiology Ultrasound LI-RADS Working Group.

Sally Spruce is President of the Australasian Hepatology Association (unpaid position); has performed paid employment or contracting work with the Advanced Hepatitis B Nursing Workshop: ASHM (November 2019) and as a member of the expert group Liver Disorders: Therapeutic Guidelines; and has received travel and accommodation expenses from Bayer for the HCC Project (2019).

Simone Strasser is President of GESA, a member of the Board of the Australian Liver Foundation and an Associate Editor for *Transplantation*. She is employed by the Sydney Local Health District (SLHD) and in the past 3 years has received honoraria for consulting, participation on advisory boards or speaker fees from Bayer, Eisai, AbbVie, Gilead, Bristol-Myers Squibb, Merck Sharp & Dohme, Norgine, Astellas, Novartis, WL Gore, Ipsen, Pfizer, NPS and the TGA. She has received significant hospitality at (mandatory) national and international investigator meetings for clinical trials.

Katherine Stuart is a member of the Advisory Boards of, and has received honoraria from, MSD, Bristol-Myers Squibb, Bayer and AbbVie.

Tom Sutherland is an unpaid executive member of ARGANZ, is affiliated with the University of Melbourne Faculty of Medicine and the Medical Imaging Department of St Vincent's Hospital Melbourne, and has received speaker fees from Siemens and Bayer.

Caroline Tallis is a member of the Gilead Hepatitis C Advisory Board and has made public statements about the Hepatitis C Consensus Statement.

Michael Wallace has received grants for overseas travel or conference expenses from Bayer (ILCA Conference).

Martin Weltman is a member of the Advisory Boards of Gilead, AbbVie and Janssen-Cilag and has received travel grants for educational conferences from Gilead and AbbVie.

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Amany Zekry is a member of the Bayer Advisory Board.

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Supplementary data

Framework questions

A list of clinically relevant questions was devised by the steering committee and working group leads, in consultation with the working group members. These questions provided a framework only and were not intended to cover all areas of the consensus statement, which aimed to provide a comprehensive review of the topic.

A. Burden of Disease

1. Is the true incidence of HCC increasing in Australia? Why?
2. Has improved surveillance uptake resulted in increased incidence?
3. With an improved approach to management, has the mortality from HCC decreased over the past decade?
4. What is the impact of HCV treatment with DAAs on:
    a. de novo HCC?
    b. recurrent HCC?
5. Should DAAs be avoided/delayed after an initial diagnosis of HCC in a patient with HCV?
6. What is the impact of obesity/NAFLD on the development of HCC?
7. Which patients should be screened for HCC?
8. Should patients without cirrhosis and either NAFLD or hereditary haemochromatosis be screened for HCC?
9. Is liver ultrasound an appropriate screening modality? Should AFP testing be used in conjunction in Australia?
10. When should screening not be performed?

B. Diagnosis and Staging

1. How precise are the imaging criteria?
2. What are the key imaging criteria for the different imaging modalities?
3. What is the recommended imaging algorithm?
4. How does the diagnosis of cirrhosis impact on the diagnostic algorithm for HCC?
5. How should cirrhotic patients with new lesions not fulfilling HCC criteria (indeterminate hepatic nodules) best be managed?
6. What is the role of liver biopsy in making the diagnosis of HCC?
7. What are the differential diagnoses?
8. What are the risks of tumour seeding and tumour rupture?
9. What are the best staging systems? What are their shortcomings? What is stage migration?

C. Treatment

Surgery

1. What are the contraindications/limitations of surgery?
2. What factors predict surgical success/failure?
3. How to predict and manage post-resection liver failure? Is the 50:50 rule useful?
4. What are the common complications following resection?
5. When is surgery preferable to ablative therapies for small HCC?

Liver Transplant

1. Which criteria are used for liver transplantation in Australia in patients with HCC?
2. What is the overall survival following liver transplantation for HCC in Australia?
3. What is the role of downstaging in Australia?
4. What are the expanded criteria? Are these used in Australia?

Locoregional Therapy

1. Which locoregional therapy is appropriate?
2. What are the contraindications for TACE?
3. Is there any advantage of DEB-TACE over cTACE?
4. Is MWA better than RFA?
5. When should locoregional therapies be abandoned?
6. How does SIRT fit into the treatment algorithm?
7. What are the complications of SIRT? When should repeat SIRT be performed?

Radiotherapy

1. What is the role of RT in HCC?
2. What are the contraindications to RT?

Systemic Therapies

1. What are the first- and second-line therapies?
2. What are the important contraindications and complications of these therapies?
3. When should these therapies be abandoned?
4. What new therapies are likely to be available for the treatment of HCC?

D. Multidisciplinary Management and Response Assessment

1. What evidence is there that MDTs are beneficial to patients with HCC?
2. Which clinicians should be included in the MDT? Who should lead the MDT?
3. How do we assess treatment response? What are the scoring systems used for TACE?

E. Patient Care

1. When should a patient be referred to palliative care? When should locoregional or systemic therapies be abandoned?
2. What strategies can improve quality of life at the end of life?
3. How should PE and PVT be managed in patients with advanced HCC?
4. Should palliative debulking therapies such as resection or SIRT ever be employed?

Summary of modified Delphi results

		mDELPHI 1								mDELPHI 2								mDELPHI 3				
Final number*	Initial number	*n*	Mode	Mean	Median	25th Percentile	75th Percentile	IQR	% Agreement	*n*	Mode	Mean	Median	25th Percentile	75th Percentile	IQR	% Swing D1–D2†	% Agreement	*n*	Mode	Mean	Median	% Agreement
1	1	54	5	4.8	5	5	5	0	96.3	48	5	4.9	5	5	5	0	3.7	100.0					
2	2	50	5	4.5	5	4	5	1	90.0	46	5	4.6	5	4	5	1	7.8	97.8					
3	3	53	5	4.7	5	5	5	0	94.3	49	5	4.9	5	5	5	0	3.7	98.0					
4	4	47	4	4.0	4	4	5	1	78.7	45	4	4.2	4	4	5	1	10.2	88.9					
-	5	50	4	3.6	4	2.75	4	1.25	68.0	46	4	3.5	4	3	4	1	-13.7	54.3					
-	6	53	4	3.5	4	3	4	1	54.7	48	3	3.2	3	2.25	4	1.75	-19.3	35.4					
5	7	44	4	4.0	4	4	5	1	79.5	42	4	4.0	4	4	5	1	-0.9	78.6	40	5.0	4.4	4.5	92.5
6	8	49	5	4.7	5	5	5	0	95.9	46	5	4.8	5	5	5	0	-0.2	95.7					
7	9	45	4	4.1	4	4	5	1	84.4	44	4	4.0	4	4	4	0	2.0	86.4	43	4.0	4.1	4.0	90.7
8	10	55	5	4.7	5	4	5	1	100.0	50	5	4.9	5	5	5	0	-2.0	98.0					
9	11	55	5	4.9	5	5	5	0	98.2	50	5	4.9	5	5	5	0	-0.2	98.0					
10	12	52	4	3.9	4	4	4.75	0.75	80.8	47	4	3.9	4	3	4	1	-6.3	74.5	45	5.0	4.6	5.0	97.8
11	13	55	5	4.4	5	4	5	1	87.3	50	4	4.4	4	4	5	1	6.7	94.0					
12	14	54	5	4.6	5	4	5	1	100.0	50	5	4.7	5	4	5	1	0.0	100.0					
13	15	53	5	4.9	5	5	5	0	100.0	50	5	5.0	5	5	5	0	0.0	100.0					
14	16	51	5	4.5	5	4	5	1	92.2	48	5	4.5	5	4	5	1	3.6	95.8					
15	17	51	5	4.6	5	4	5	1	98.0	48	5	4.7	5	4	5	1	2.0	100.0					
16	18	50	5	4.6	5	4	5	1	98.0	47	5	4.7	5	4	5	1	2.0	100.0					

mDELPHI 1										mDELPHI 2									mDELPHI 3				
Final number*	Initial number	*n*	Mode	Mean	Median	25th Percentile	75th Percentile	IQR	% Agreement	*n*	Mode	Mean	Median	25th Percentile	75th Percentile	IQR	% Swing D1–D2†	% Agreement	*n*	Mode	Mean	Median	% Agreement
17	19	40	4	4.3	4	4	5	1	92.5	41	4	4.4	4	4	5	1	5.1	97.6					
18	20	40	4	4.2	4	4	5	1	87.5	39	4	4.2	4	4	4	0	7.4	94.9					
19	21	51	5	4.7	5	4	5	1	98.0	48	5	4.8	5	5	5	0	2.0	100.0					
20	22	49	5	4.5	5	4	5	1	91.8	47	5	4.5	5	4	5	1	6.1	97.9					
21	23	48	4	3.5	4	3	4	1	66.7	44	4	3.5	4	3	4	1	-3.1	63.6	44	4.0	4.1	4.0	88.6
22	24	45	4	4.0	4	4	4	0	84.4	42	4	3.9	4	4	4	0	-3.4	81.0					
23	25	52	5	4.5	5	4	5	1	94.2	49	5	4.5	5	4	5	1	-0.3	93.9					
24	26	51	5	4.7	5	4	5	1	100.0	48	5	4.8	5	5	5	0	0.0	100.0					
25	27	46	5	4.5	5	4	5	1	93.5	44	5	4.6	5	4	5	1	6.5	100.0					
26	28	52	5	4.7	5	4.25	5	0.75	98.1	50	5	4.8	5	4.75	5	0.25	1.9	100.0					
27	29	49	5	4.6	5	4	5	1	98.0	45	5	4.5	5	4	5	1	2.0	100.0					
28	30	42	5	4.4	5	4	5	1	92.9	41	4	4.4	4	4	5	1	-0.2	92.7					
29	31	51	4	4.3	4	4	5	1	90.2	48	4	4.0	4	4	5	1	-9.0	81.3					
30	32	52	5	4.6	5	4	5	1	98.1	50	5	4.8	5	5	5	0	1.9	100.0					
31	33	52	5	4.8	5	5	5	0	100.0	50	5	4.9	5	5	5	0	0.0	100.0					

mDELPHI=modified DELPHI; *n*=number of participants voting; IQR=interquartile range.
*Final number refers to the recommendation number (31 recommendations). The initial recommendations 5 and 6 were rejected at the face-to-face meeting.
†% swing D1–D2=percentage swing between modified DELPHI 1 and modified DELPHI 2 rounds.

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Recommendations not reaching consensus agreement for inclusion

Recommendation (formerly) 5: HCC screening should not be offered to patients with Child–Pugh C cirrhosis (who are not suitable for liver transplantation) (Evidence quality: Low, Grade of recommendation: Weak)
Number of voting members, 46; median score, 4; 25th percentile, 3; 75th percentile, 4; percentage reaching consensus agreement, 54.3%

Recommendation (formerly) 6: HCC screening should not be offered to patients with major comorbidity and/or patients aged >70 years with poor performance status (Evidence quality: Low, Grade of recommendation: Weak)
Number of voting members, 48; median score, 3; 25th percentile, 2.25; 75th percentile, 4; percentage reaching consensus agreement, 35.4%

GESA
Gastroenterological Society of Australia

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The Gastroenterological Society of Australia (GESA) is the peak membership organisation for health care professionals and researchers working in the fields of gastroenterology and hepatology.

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Gastroenterological Society of Australia (GESA)
Level 3, 517 Flinders Lane, Melbourne Victoria 3000
Phone: 1300 766 176
www.gesa.org.au
ABN: 44 001 171 115

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