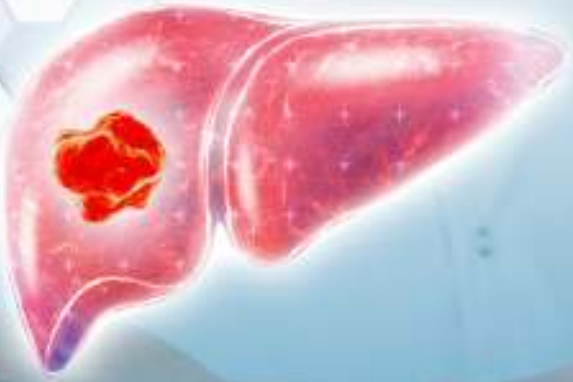
Clinical Practice Guidance for HCC GLF (Myanmar)



Diagnosis, Staging and Management of Hepatocellular Carcinoma: 2024 Clinical Practice Guidance Recommendations by GI and Liver Foundation (Myanmar)

Preamble

GI and Liver Foundation (Myanmar) has produced clinical practice guidelines on Hepatitis B, Hepatitis C and Cirrhosis of the Liver to assist all the practicing doctors in the treatment of Liver Diseases.

However, AASLD has recently adopted a policy to differentiate between guidelines and guidance. AASLD published guidelines on some topics and guidance on some other diseases.

And therefore, it's time for GLF (Myanmar) to review the policy whether it should be clinical practice guidelines or guidance in future publications. For that purpose, GLF (Myanmar) decided to follow the AASLD policy.

According to the AASLD, practice guidelines use clinically relevant questions, which are then answered by systematic reviews of the literature and followed by data-supported recommendations. The guidelines are developed by a multidisciplinary panel of experts who rate the quality (level) of the evidence and the strength of each recommendation using the Grading of Recommendations Assessment, Development, and Evaluation system ("GRADE"). (AASLD Family of Websites:AASLD.org)

AASLD also publishes guidance on aspects of some topics. Practice guidances are based on a comprehensive review and analysis of relevant published data and put forward guidance statements to help clinicians understand and implement the most recent evidence. (AASLD Family of Websites:AASLD.org)

By AASLD policy mentioned above what GLF (Myanmar) has published are not practice guidelines but practice guidance. Therefore, future GLF (Myanmar) clinical practice publications will be labelled as "GLF (Myanmar) Clinical Practice Guidance".

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ABBREVIATIONS

AASLD	American association for the study of liver diseases
AFP	Alpha fetoprotein
AFP-L3%	Lens culinaris-agglutinin-reactive fraction of AFP%
AFs	Aflatoxins
ALBI	Albumin-bilirubin grade
APHE	Arterial phase hyperenhancement
AJCC/UICC	American joint committee on cancer/International union against cancer
ASA	American society of Anesthesiologists
BCLC	Barcelona clinic liver cancer
CECT	Contrast enhanced computed tomography
CI	Confidence interval
CLIP	Cancer of the liver Italian program
CR	Complete responder
CSPH	Clinically significant portal hypertension
CTLA-4	Cytotoxic T lymphocyte-associated protein 4
CTP	Child-Turcotte-Pugh
CUPI	Chinese university prognostic index
DAAs	Direct-acting antivirals
DCP	Des-gamma-carboxy prothrombin
DEB-TACE	Drug-eluting bead-TACE
EBRT	External beam radiation therapy
ECOG	Eastern cooperative oncology group
F-FDG	18F-fluorodeoxyglucose
FGFR	Fibroblast growth factor receptor
FLR	Future liver remnant
GABA	Gamma aminobutyric acid
GLF	GI and liver foundation
HCC	Hepatocellular carcinoma
HBV	Hepatitis B virus
HCV	Hepatitis C virus

HFSR	Hand-foot skin reaction
HR	Hazard ratio
HVPG	Hepatic venous pressure gradient
ICIs	Immune checkpoint inhibitors
INR	International normalized ratio
irAEs	Immune related adverse effects
JCS	Japanese integrated staging
kPa	Kilopascal
LCSGJ	Liver cancer study group of Japan
JIS	Japan integrated staging
LAT	Local ablation therapy
LDLT	Living donor liver transplantation
LIRAD	Liver imaging reporting & data system
LR	Liver resection
LRT	Locoregional therapy
LSM	Liver stiffness measurement
LT	Liver transplantation
MASLD	Metabolic dysfunction-associated steatotic liver disease
MASH	Metabolic dysfunction-associated steatohepatitis
MELD	Model for End-Stage Liver Disease
MRI	Magnetic resonance imaging
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
MTAs	Molecular targeted agents
mTOR	Mammalian target of rapamycin
MWA	Microwave ablation
NAFLD	Non-alcoholic fatty liver disease
NLR	Neutrophil-lymphocyte ratio
NSAIDs	Non-steroidal anti-inflammatory drugs
OPTN	Organ procurement and transplantation network
ORR	Objective response rate
OS	Overall survival

PD	Progressive disease
PDI	GAogrammed death I
PD-LI	Programmed death-ligand I
PEI	Percutaneous ethanol injection
PET	Positron emission tomography
PFS	Progression free survival
PIVKA-II	Protein induced by vitamin K absence/antagonist-II
PR	Partial responder
PS	Performance status
PVTT	Portal vein tumor thrombus
RCT	Randomized controlled trial
RFA	Radiofrequency ablation
SBRT	Stereotactic body radiation therapy
SD	Stable disease
SHARP	Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol
SSRI	Serotonin reuptake inhibitors
SVR	Sustained viral response
TACE	Trans-arterial chemoembolization
TARE	Trans-arterial radioembolization
TE	Transient elastography
TKI	Tyrosine kinase inhibitors
TSH	Thyroid stimulating hormone
TTP	Time to progression
TTV	Total tumor volume
UCSF	University of California San Francisco
UNOS	United network for organ sharing
UNOS-DS	United network for organ sharing downstaging
USG	Ultrasound
VEGFR	Vascular endothelial growth factors
WHO	World Health Organization

CONTENTS Page

INTRODUCTION

Primary liver cancer is the sixth most common cancer and the third leading cause of cancer-related deaths worldwide. In South-Eastern Asia, it is the second most common cancer and leading cause of cancer-related death.[1] The Global Cancer Observatory's 2020 report revealed liver cancer prominence as one of the five most prevalent cancers and the third leading cause of cancer-related deaths in Myanmar. Global Cancer Observatory (The Globocan) estimated that 5,466 new liver cancer cases and 5,281 liver cancer death occurred in Myanmar in 2020.[2] Hepatocellular Carcinoma (HCC) is the most common type of primary liver cancer, accounting for 75% – 86% of cases. Rates of both incidence and mortality are 2 to 3 times higher among men than women in most regions.[3]

Various nations have published distinct guidelines for the effective management of HCC, each incorporating comparable yet distinct strategies. These discrepancies arise from factors like incidence and prevalence rates, primary etiology of HCC, diverse staging systems, governmental and medical insurance reimbursement policies, medical resource availability, compliance levels among healthcare professionals and patients. At present, Myanmar lacks a unified consensus on clinical practice guidelines for the management of HCC.

The primary objective of the HCC management guideline in Myanmar is to facilitate the early detection of HCC through heightened awareness of risk factors, implementation of an efficient screening system, and timely initiation of necessary management. In terms of therapeutic interventions for HCC, Myanmar offers a range of treatment options tailored to different clinical staging scenarios. These include liver resection (LR), radiofrequency ablation (RFA), trans-arterial chemoembolization (TACE), systemic therapy including oral tyrosine kinase inhibitors and immune checkpoint inhibitors. Additionally, living donor liver transplantation (LDLT) programs have been initiated, yielding good outcomes in Myanmar. Consequently, the guidelines are designed to assist in selecting the optimal and most suitable therapeutic interventions for individual patients with HCC.

Henceforth, the GI and Liver Foundation (Myanmar) has resolved to create clinical practice guidance for the effective management of HCC, aligning with the vision of the foundation. The development of this guidance serves the purpose of updating the knowledge of Myanmar doctors and striving to provide patients with the most current and optimal treatment options available.

1. RISK FACTORS AND PREVENTION

1.1 Risk Factors

The strongest risk factor for developing HCC is cirrhosis from any liver disease etiology, which is present in over 80% of patients with HCC. The main risk factors for HCC in Myanmar are chronic viral infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) followed by heavy alcohol intake, MASLD/MASH (Metabolic dysfunction-associated steatotic liver disease/ Metabolic dysfunction-associated steatohepatitis) and aflatoxin B1 contaminated foodstuffs.[4]

Hepatitis B virus (HBV) infection is the most prominent risk factor for HCC development, accounting for ~50% of cases.[5] Chronic hepatitis B increases the risk of HCC even in the absence of cirrhosis. Antiviral therapy for HBV and HCV also significantly reduces HCC risk, although patients with cirrhosis (and possibly those with advanced fibrosis) continue to have persistent risk of developing HCC. Several studies have reported that long-term therapy with entecavir and tenofovir significantly reduce the incidence of HCC compared with the untreated control group[8, 9] and more evident in patients with baseline cirrhosis.[10]

With the use of highly effective direct-acting antivirals (DAAs) therapy, increasing proportion of patients with HCV infection have been successfully treated to achieve a sustained viral response (SVR), resulting in a 50-80% reduction in the risk of HCC. However, patients with HCV-induced cirrhosis continue to have a persistent risk of developing HCC (>2% per year) even after SVR.[6, 7]

Alcohol-associated cirrhosis is a known risk factor for HCC development, and alcohol use as a cofactor with other etiologies increases HCC risk as much as 5-fold. A proportion of alcohol-attributable liver cancers could be the result of synergism with hepatitis B or hepatitis C virus infection or aflatoxin exposure or obesity, diabetes.[11] In a meta-analysis, HCC risk declined by approximately 6% per year with abstinence from alcohol.[12] Smoking more than 25 cigarettes per day is associated with a 55% increased risk of HCC, which can return nearly to baseline after 30 years of smoking cessation.[13]

The prevalence of MASLD and MASH is rising worldwide in parallel with increases in the prevalence of obesity and metabolic comorbid disease (insulin resistance, dyslipidemia, central obesity, and hypertension) in the past decades,[14, 15] which can lead to fibrosis and cirrhosis and, eventually, HCC.[16] HCC related to MASLD/MASH is probably underestimated and is expected to rise in the near future, possibly overtaking the other etiologies in some areas of the world.[17] A significant portion of patients with MASLD/MASH associated HCC do not have histological evidence of cirrhosis.[18, 19] Although the annual incidence of HCC is lower in MASH-related cirrhosis (1-2% per year) than in viral-mediated cirrhosis (3-5% per), the incidence is > 1.1 per 100 person-years, indicating that surveil

lance is cost-effective and should therefore be implemented.[20]

Aflatoxins (AFs) are toxic secondary fungal metabolites (mycotoxins) produced by Aspergillus flavus and Aspergillus parasiticus. Epidemiologic research has documented a significant risk for HCC development among individuals who consume highly AF-contaminated diets and HBV infection.[21-23]

1.2 Prevention

Primary prevention is the intervention to prevent disease before it occurs. Vaccination for HBV infection should be given in all newborns as well as adults who failed to receive vaccination at birth to reduce the risk of HCC. Antivirals should be given in all patients who meet criteria for treatment according to National treatment guidelines of viral hepatitis B and C infection. In patients with chronic viral hepatitis, suppression of HBV and eradication of HCV infection decreases the risk of HCC development. Patients with chronic liver disease should be counseled to maintain a healthy weight, have a balanced diet, avoid tobacco and alcohol, and achieve adequate control of comorbid conditions including components of the metabolic syndrome. A healthy lifestyle has multiple benefits and may decrease HCC risk. Coffee consumption may be recommended for patients with chronic liver disease, as it has associated with decreased risk of HCC development although there are insufficient data to recommend a specific dose.[24]

Secondary prevention is the interventions to reduce the impact of a disease by detecting it early. Patients at high risk of developing HCC should be entered into HCC surveillance programs.[24]

Recommendations (Risk Factors and Prevention)

1. Cirrhosis from any liver disease etiology is the strongest risk factor for HCC.
2. HBV and HCV are main viral causes of HCC in Myanmar.
3. Alcohol consumption have increased the risk of HCC in patients with preexisting chronic liver disease.
4. MASLD and MASH are associated with a significant risk of HCC development, which is higher in the presence of cirrhosis.
5. Chronic Aflatoxin exposure may also be one of the contributing factors for the development of HCC.
6. Primary and secondary preventive measures must be undertaken to patients with known risk factors.

2. SURVEILLANCE

HCC is a highly fatal tumor, with most cases detected at late stages and an incidence-to-mortality ratio that approaches.[25] HCC surveillance should be performed in at-risk individuals, including those with cirrhosis. HCC surveillance is a secondary prevention strategy associated with improved overall survival through detection of HCC at a very early or early stage. Patients detected at an early stage are eligible to receive potentially curative treatment and can achieve 5-year survival exceeding 70%.[26] Table 1 shows the population at risk for HCC that should undergo surveillance.[24]

2.1 Surveillance tests

HCC surveillance should be performed using ultrasound (USG) and alpha fetoprotein (AFP). A meta-analysis of available data showed the sensitivity and specificity of ultrasound alone for early-stage HCC detection is only 53% (95% CI, 35%–70%) and 91% (95%CI, 86%–94%), respectively, whereas ultrasound plus AFP achieves a sensitivity of 63% for early-stage HCC (95% CI, 48%–75%).[24] Although contrast enhanced computed tomography (CECT) and Magnetic resonance imaging (MRI) have superior sensitivity for early-stage HCC detection compared with USG-based surveillance, their uses are limited by concerns about cost-effectiveness, potential harm associated with radiation exposure, and contrast-related injuries. [27] In very obese cases with clinically suspicious of HCC (increase AFP) with difficult to examine for detection of HCC, CECT or MRI might be necessary to confirm diagnosis of HCC.

Although several biomarkers and biomarker panels (for example, GALAD score, [gender, age, Lens culinaris-agglutinin-reactive fraction of AFP (AFP-L3%), AFP, des-gamma-carboxy prothrombin (DCP)]) have shown promising results in early phases of evaluation, most still require validation in large Phase III and Phase IV biomarker cohort studies.[24] Two well-studied biomarkers include AFP-L3%, which measures a subfraction of AFP and des gammacarboxy prothrombin (DCP), also called protein induced by vitamin K absence/antagonist-II (PIVKA-II), a variant of prothrombin that is also specifically produced at high levels by a proportion of HCCs. DCP has insufficient sensitivity to detect early-stage HCC when used alone; however, this biomarker may be complimentary to AFP.[24]

2.2 Surveillance interval

Semiannual surveillance (approximately every 6 months) is associated with earlier tumor stage and improved survival compared with annual surveillance. This recommendation is based on HCC tumor doubling time. A subsequent multicenter RCT demonstrated quarterly surveillance did not improve early HCC detection or survival compared with semiannual surveillance.[24] If there are features of cirrhosis of the liver as manifested

by clinically or Fibroscan ≥ 14 kPa, the follow up should be done 4 monthly. However, the surveillance interval can be tailored to the individualized patients with low risk for HCC such as young age, advanced fibrosis but without cirrhotic in patients with post-SVR for HCV infection, MASH, alcoholic liver diseases, and family history of HCC present but no history of chronic viral infection.

Table I. At risk population for surveillance

Population at high risk
Patients with cirrhosis of liver regardless of any etiology
(1) All chronic HBsAg carrier
(2) HCV infection including treatment naïve and treated with or without SVR achieved
(3) Chronic alcoholic
(4) MASLD/MASH

Recommendations (Surveillance)
7. HCC surveillance should be performed in population at risk by using ultrasound and AFP at semiannual (approximately every 6 months) intervals or as required.

3. DIAGNOSIS

3.1 Imaging Diagnosis

Patients with an abnormal surveillance test; detection of a liver nodule in ultrasonography abdomen or high serum AFP level (>20 ng/ml) belong to at-risk population[28] and require timely diagnostic evaluation with either contrast enhanced CT or MRI. However, CECT (contrast enhanced computed tomography) plays a major role in the diagnostic imaging of HCC because of its capacity for assessing arterial vascularity in lesions through dynamic studies, as well as its widespread availability. Multiphasic contrast enhanced CT or MRI examination also must be performed according to technical standards. Administration of intravenous contrast and acquisition of a multiphase liver protocol (e.g., before contrast, late hepatic arterial phase, portal venous phase, and delayed phase images) is mandatory to allow for diagnosis of HCC.[29-32]

The classic radiological hallmarks with an HCC lesion are characterized by intense arterial phase hyperenhancement (APHE) followed by contrast washout or hypointensity in the portal venous or delayed phase since they drive most of their blood supply from the hepatic artery. This is unlike the surrounding liver, which receives its blood supply from both the portal vein and hepatic artery.[33-35] In fact, these radiological features are to be interpreted and reported by the radiologists. When these typical features are observed in CECT, the diagnosis is confirmed and no need to do further MRI examination. However, if these typical features of HCC are not seen in CECT especially in cases of < 2 cm lesions, MRI examination should be continued to confirm HCC. Liver biopsy is not necessary[36-39] and not recommended for the diagnosis of HCC.

GI and Liver Foundation (Myanmar) supports the Liver Imaging-Reporting and Data System (LI-RADS) diagnostic algorithm for HCC, which is based on imaging features including tumor size, APHE, delayed phase washout, and capsule appearance (Figure 1). LI-RADS criteria consider tumor size because accuracy for imaging techniques decreases in lesions <2 cm. APHE and delayed washout are the characteristics most strongly associated with HCC. LI-RADS categorizes liver nodules on a scale from LI-RADS -1 (benign) to LI-RADS -5 (HCC). The probability of HCC and recommended management strategies differ by LI-RADS category (Figure 2).
Multiple studies, including meta-analyses, demonstrate that LI-RADS -5 lesions have a 95%–99% probability of being HCC.[41, 42-44] Conversely, HCC probability is ~75% for LI-RADS -4 lesions, so these patients are advised to undergo biopsy or close-interval follow-up imaging at 3 months, depending on the clinical scenario.[44, 45] LR-3 observations have a ~30% probability of HCC, so need to continue surveillance with repeat CT or MRI in 3–6 months.[46, 47] LI-RADS -M observations have radiological features suggesting malignancy; 93%–100% of cases are malignant on tissue sampling, but only 29%–44% are HCC.[40, 41, 44, 47-49] Therefore, biopsy should be performed

for patients with LI-RADS -M observations. Similarly, the positive predictive value of LI-RADS -TIV (tumor in vein) for being HCC is lower, and biopsy is recommended in those patients.

Positron emission tomography (PET) using 18F-fluorodeoxyglucose (F-FDG) has poor sensitivity in the diagnostic evaluation of HCC.[50] Therefore, there is no significant role of F-FDG PET/CT (fluorodeoxyglucose (FDG)-positron emission tomography)/CT in diagnosis of HCC and not recommended for the diagnosis of HCC.

Arterial phase hyperenhancement (APHE)	No APHE	APHE (not rim)			
Observation size (mm)	<20	≥20	<10	10-19	≥20
Count major features: - "Washout" (not peripheral) - Enhancing "capsule" - Threshold growth	None	LR-3	LR-3	LR-3	LR-3	LR-4
	One	LR-3	LR-4	LR-4	LR-4 / LR-5	LR-5
	≥Two	LR-4	LR-4	LR-4	LR-5	LR-5

Observations in this cell are categorized LR-4, except:

- LR-5g, if ≥ 50% diameter increase in < 6 months (equivalent to OPTN 5A-g)
- LR-5us, if "washout" and visibility at screening ultrasound (per AASLD HCC criteria)

FIGURE 1. Liver Reporting and Data System (LI-RADS) classification of computed tomography (CT) or magnetic resonance imaging (MRI) liver observations in patients who are at risk.

LI-RADS	Description	Management
Negative	no observations detected	return to surveillance in 6 months
LR-NC	not categorizable due to image degradation or omission	repeat or alternative imaging in < 3 mo
LR-1	definitely benign observation	return to surveillance in 6 mo
LR-2	probably benign	consider repeat diagnostic imaging in 6 mo.
LR-3	intermediate probability of malignancy	repeat or alternative imaging in 3-6 mo
LR-4	probably HCC	multidisciplinary discussion for further work-up
LR-5	definitely HCC	multidisciplinary discussion for management consensus
LR-M	probably/definite malignancy not HCC specific	multidisciplinary discussion, consider biopsy
LR-TIV	definite tumor in vein	multidisciplinary discussion, may include biopsy

FIGURE 2. Risk of hepatocellular carcinoma (HCC) and recommended management strategy

3.2 Tumor Markers

There are 3 major tumor markers for HCC: AFP, Lens culinaris-agglutinin-reactive fraction of AFP (AFP-L3), and protein induced by vitamin K absence II/ des-gamma-carboxy prothrombin (PIVKA- II/DCP). The expected diagnostic value of tumor markers includes,

(I) Determining the presence/absence of disease (early diagnosis, degree of cancer progression.
(2) Qualitative diagnosis (differential diagnosis, degree of malignancy)
(3) Evaluating treatment response and detecting recurrence.

Since no single tumor marker can satisfy all criteria, combining the above 3 markers can increase their diagnostic performance. But serum AFP at a threshold of > 400 ng/mL was recommended as a diagnostic criterion for HCC (WHO). Although AFP and PIVKA- II/DCP testing is available in Myanmar, PIVKA-II/DCP testing is only available in a very limited centers and is very expensive. So PIVKA-II/DCP might not be necessary for the diagnosis of HCC if typical radiological features are seen in CECT. Knowing very well that over 40% of HCC have normal AFP levels, and elevated AFP can be observed in other cancers, including intrahepatic cholangiocarcinoma, gastric cancer, and germ cell tumors.[56] However, according to the real-world experience of Myanmar gastroenterologists and hepatologists, AFP is still regarded as a useful diagnostic test for diagnosis of HCC. If baseline AFP level is high, AFP level monitoring is also useful for detection of recurrence risk in patients with resected HCC[50, 51] or who received radiofrequency ablation (RFA).[52-54] Moreover, it is also useful for monitoring tumor treatment responses following transarterial chemoembolization (TACE)[55-58] and systemic therapies.[21-24]

Recommendation (Diagnosis)

8. Ultrasound finding suggested of HCC can also be regarded as a supportive factor.
9. AFP level of > 400 IU/L can be complimentary (WHO).
10. The diagnosis can be established by the multiphasic contrast enhanced CT or MRI finding of typical vascular hallmarks of HCC (hypervascularity in the arterial phase defined as arterial phase hyperenhancement (APHE) with washout in the portal venous or delayed phase.
11. When typical features of HCC are observed in CECT, the diagnosis is confirmed and not necessary to proceed further MRI examination. However, MRI may be helpful in clinical suspicious of HCC with increase AFP but no typical features of HCC are seen in CECT.
12. Liver biopsy is not recommended.
13. Positron emission tomography (PET) using 18F-fluorodeoxyglucose (^{18}F-FDG) scan is not recommended for diagnosis of HCC.

4. INITIAL WORKUP

Initial assessment for patients with suspected HCC including investigation of etiologic origin of liver disease, a detection of viral hepatitis B and C, an assessment of the presence of comorbidity, imaging studies to detect the presence of metastatic disease and an evaluation of the hepatic function, including a determination of whether portal hypertension is present.

The performance status scale developed by the Eastern Cooperative Oncology Group (ECOG), (Table 2) is recorded from 0 (fully active, able to carry on all pre disease performance without restriction) to 5 (dead). These criteria and scales are extensively used by physicians to evaluate the progression of diseases and how the daily living ability of patients is affected in patients with a variety of malignancies.[67] It also serves as an indicator of cancer therapy and predictor of patient survival. Performance status is included in the Barcelona Clinic Liver Cancer (BCLC) system for hepatocellular carcinoma (HCC) as an essential parameter for treatment guidance for HCC.[29, 30, 68, 69] In prospective studies showed that performance status is strongly associated with both tumoral and cirrhotic factors and accurately predicts long-term survival in HCC patients.[70, 71]

Multiphasic contrast-enhanced CT or MRI of the abdomen is used in the evaluation of the HCC tumor burden to detect the presence of metastatic disease, nodal disease, and vascular invasion; to assess whether evidence of portal hypertension is present; to provide an estimate of the size and location of HCC and the extent of chronic liver disease; and, in the case of patients being considered for resection, to provide an estimate of the future liver remnant (FLR).[35] Chest CT and Bone scan and/or additional bone imaging may be considered if clinically indicated for metastatic diseases.

An initial assessment of hepatic function involves liver function testing including measurement of serum levels of bilirubin, alanine transaminase, aspartate aminotransferase, alkaline phosphatase, measurement of prothrombin time expressed as international normalized ration (INR), albumin, and platelet count (surrogate for portal hypertension). Other recommended tests include complete blood count, blood urea nitrogen and creatinine to assess kidney function; creatinine is also an established prognostic marker in patients with liver disease.[36] Further assessment of hepatic functional reserve before hepatic resection in patient with cirrhosis may be performed with different tools such as ultrasound and non- invasive liver stiffness measurement by transient elastography (TE) *Fibroscan may provide and quantify the degree of cirrhosis.

The Child-Turcotte-Pugh classification (Table 3) has been traditionally used for the assessment of hepatic functional reserve in patients with cirrhosis.[74, 75] The Child-Turcotte-Pugh score incorporates laboratory measurements (i.e., serum albumin, bilirubin, prothrombin time) as well as

more subjective clinical assessment of hepatic encephalopathy and ascites. It provides a general estimate of the liver function by classifying patients as having compensated (class A) or decompensated (classes B and C) cirrhosis.[76] Advantages of the Child-Turcotte-Pugh score include ease of performance (i.e., can be done at the bedside) and the inclusion of clinical parameters.

The albumin-bilirubin (ALBI) grade model, which considers serum albumin and bilirubin levels, is another helpful tool to assess liver dysfunction.[77, 78] It has been shown to be especially helpful in predicting the survival outcome of patients with stable decompensated cirrhosis.[79, 80]

Model for End-Stage Liver Disease (MELD) is another system for the evaluation of hepatic reserve. MELD is a numerical scale ranging from 6 (less ill) to 40 (gravely ill) for individual 12 years or older. It is derived using 3 laboratory values (serum bilirubin, creatinine, and INR) and was originally devised to provide an assessment of mortality for patients undergoing transjugular intrahepatic portosystemic shunts.[81, 82] These scores can be calculated using online website https://www.mdcalc.com/.

An important additional assessment of liver function does not include in the Child-Pugh score is an evaluation of signs of clinically significant portal hypertension; CSPH (i.e., esophageal varices, splenomegaly, splenorenal shunts and recanalization of umbilical vein, thrombocytopenia). Although the clinically significant portal hypertension can be measured invasively by the transjugular route (hepatic-venous pressure gradient (HVPG) > 10 mmHg, non-invasive tests are sufficiently accurate to identify CSPH in clinical practice. A platelet counts $\geq$ 150 x 10^9/L and liver stiffness measurement (LSM) by transient elastography (TE) "Fibroscan $\leq$ 15 kPa rules out CSPH with sensitivity and negative predictive value > 90%.[83] A LSM value by TE of $\geq$ 25 kPa is sufficient to rule in CSPH with specificity and positive predictive value > 90%, defining the group of patients at risk of endoscopic signs of portal hypertension and at higher risk of decompensation.[73] If LSM by TE is $\geq$ 20 kPa or platelet counts $\leq$ 150 x 10^9/L should undergo an endoscopy for variceal screening.[46] Evidence of portal hypertension such as presence of collaterals and splenomegaly may be evident on CT or MRI.[72, 74, 75, 84,85]

Table (2) Eastern Cooperative Oncology Group (ECOG) Performance Status (PS)

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair
5	Dead

Table (3) Child-Turcotte-Pugh Classification

Parameter	1 point	2 points	3 points
Total Bilirubin mg/dL umol/L	 < 2 < 34	 2 – 3 34 – 50	 > 3 > 50
Albumin g/dL g/L	 > 3.5 > 35	 2.8 – 3.5 28 – 35	 < 2.8 < 28
PT time prolonged (sec) (or) **INR**	0 – 4 (or) < 1.7	4 – 6 (or) 1.71 – 2.30	> 6 (or) > 2.30
Ascites	None	Mild (or controlled by diuretics)	Moderate to severe (or refractory to diuretics)
Hepatic encephalopathy	None	I – II (or absent with medication)	III – IV (or recurrent)

Recommendation (Initial Workup)

Initial assessment for patients with HCC includes the following.

14. Investigation of the etiologic origin of liver diseases, detection of viral causes such as HBV, HCV and non-viral causes.
15. Assessment of the presence of comorbidity and performance status (ECOG PS).
16. To look for and investigate the presence of extrahepatic metastasis whenever suspected clinically or radiologically.
17. Evaluation of liver function will be assessed by Child-Turcotte-Pugh (CTP) grade.
18. Upper GI Endoscopy should be done for determination of portal hypertension and variceal band ligation if necessary. It is mandatory whenever the facility is available.

5. STAGING

Staging systems aim to stratify patients into groups with similar prognoses. As such, these staging systems may serve to guide choice of therapy, aid in patient counseling, allow comparisons of the end results of therapy, and facilitate patient selection and randomization for research protocols. Staging systems for hepatocellular carcinoma (HCC) are broadly divided into clinical and pathological staging system. The clinical staging systems can be particularly useful in guiding choice of therapy and include Okuda staging system,[86] Caner of the Liver Italian Program (CLIP) score,[87] and Barcelona Clinic Liver Cancer (BCLC) staging system.[88] The pathological staging systems are useful after resection or transplantation are include the Liver Cancer Study Group of Japan (LCSGJ) staging system,[89] Japanese Integrated Staging (JIS) score,[90] Chinese University Prognostic Index (CUPI),[91] and American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) staging system.[92] The key factors affecting prognosis in patients with HCC are the clinical stage, growth rate of the tumor, the general health of the patient, the liver function of the patient, and the treatments administered.[93]

Due to the unique characteristics of HCC that vary with geographic region, many of the existing staging systems are specific to the region in which they are developed and there is no universally accepted staging system that could be used across all institutions in different countries. Various staging systems have been proposed and evaluated for HCC and each has its merits.

Staging of HCC is necessary to provide clear guidelines for the practicing doctor at all levels. Among at all the staging system, Barcelona Clinic Liver Cancer (BCLC) staging system is time tested, widely accepted and repeatedly validated all over the world. For this reason, BCLC staging system is adopted for the GI and Liver Foundation (Myanmar) guidelines. This staging system defines five prognostic subclasses and allocates specific treatments for each stage. Five treatments can extend the life expectancy of patients with HCC: surgical resection, liver transplantation, radiofrequency ablation, trans-arterial chemoembolization, multikinase inhibitor: sorafenib, Lenvatinib and immunotherapy: combination of Atezolizumab and Bevacizumab.

igure (3) Barcelona Clinic Liver Cancer (BCLC) Staging System Diagram

Figure (4) Barcelona Clinic Liver Cancer (BCLC) Staging System: 2022

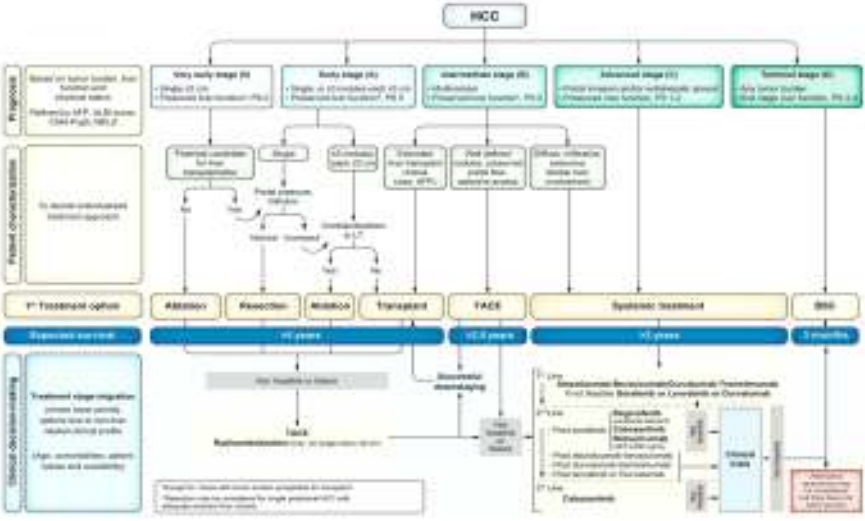

Table (4) Barcelona Clinic Liver Cancer (BCLC) Staging System

BCLC stage 0 (Very early)	• Single tumour < 2 cm • Preserved liver function • Performance status 0
BCLC stage A (Early)	• Single tumour, or ≤ 3 nodules each ≤ 3 cm • Preserved liver function • Performance status 0
BCLC stage B (Intermediate)	• Multiple tumors • Preserved liver function • Performance status 0
BCLC stage C (Advanced)	• Cancer has spread into the portal vein • Cancer has spread to lymph nodes or organs outside the liver • Preserved liver function • Performance status 1–2
BCLC stage D (Terminal)	• Any tumor burden • End-stage liver function • Performance status 3–4

Recommendation (Staging)

19. GLF (Myanmar) adopted BCLC as the framework for the HCC staging and management in Myanmar.
20. Treatment options can be considered basing upon the different BCLC stages.

6. MULTIDISCIPLINARY CARE

Treatment options for patients with HCC include surgical, locoregional, and systemic therapies, depending on tumor burden, degree of liver dysfunction, and patient performance status. Although decisions for some patients are well delineated by guidelines, with widespread consensus among providers, other patients are eligible for multiple therapies, with decisions requiring input from different specialties. A growing number of trials evaluating combination therapies and transitions between types of therapies during follow-up related to tumor progression or response also highlight the importance of close collaboration and communication between disciplines.

Accordingly, multidisciplinary care is critical for HCC management, with a goal to review clinical data to verify HCC diagnosis and staging, facilitate provider communication, determine optimal treatments, and thereby improve clinical outcomes. This process extends

beyond initial HCC presentation and continues over time as treatment strategies evolve based on changes in HCC tumor burden and patient status.

Multidisciplinary care most commonly occurs in the form of a tumor board, in which providers review imaging with radiology and discuss management among a broad base of consultants. Presentation at a multidisciplinary tumor board can change imaging and histological interpretation in 18.4% and 10.9% of patients, respectively, with management plans altered in 41.7% of all patients.[94] Core disciplines typically include but are not limited to hepatologists; radiologists; pathologists; interventional radiologists; transplant and hepatobiliary surgeons; and medical, radiation, and surgical oncologists.

Multidisciplinary care for patients with HCC significantly increases patient satisfaction, improves timely guideline concordant care, and increases overall survival (OS), highlighting this approach as a best practice that should be considered standard of care for the management of patients with HCC.[93] A single-center study showed a multidisciplinary co-located clinic paired with a multidisciplinary tumor board increased receipt of curative treatment, decreased time to treatment, and improved stage-by-stage survival.[96] Similarly, a multicenter study from the national Veterans Affairs health system found multispecialty evaluation was associated with higher likelihood of receiving HCC therapy, and review by a multidisciplinary tumor board was associated with reduced mortality.[97] Based on these data, patients with HCC should be discussed and managed in a multidisciplinary care setting.

7. SURGICAL RESECTION

Liver resection (LR) represent the first option in patients with early tumors, leading to the best outcomes in resectable cases (five-year survival of 60–80%). Surgical interventions can often be extended to other stages of HCC, once effective tumor downstaging is achieved by non-surgical means.

Surgical resection is the curative treatment of choice for patients with localized HCC in the absence of cirrhosis, where even major resections can be performed with low rates of life-threatening complications and acceptable outcome. Patients without cirrhosis have lower postoperative liver-related morbidity, lower cumulative HCC recurrence rates, and higher disease-specific survival compared with those with underlying cirrhosis who undergo resection.[98] However, surgical resection in non-alcoholic fatty liver disease (NAFLD), metabolic syndrome and other co-morbidities is a surgical procedure with a risk profile closer to cirrhotic rather than to truly normal livers. Although patients with a single HCC of any size can be offered LR with a definitive survival advantage over other treatments – especially for tumor >5 cm – surgical feasibility may vary according to the liver volume and function-preservation principles.

In patients with HCC and underlying liver cirrhosis, recommendations for surgical resection must consider a multidimensional assessment of tumor characteristics (tumor number, anatomic location, presence of vascular invasion and extrahepatic spread), non-tumor factors, such as degree of liver reserve and planned extent of hepatectomy.[99, 100] Of equal importance is an assessment of the anticipated future liver remnant (FLR) size (typically >30% in the absence of, cirrhosis and >40% in patients with cirrhosis),[101] patient performance status (ECOG status), and absence of clinically significant portal hypertension (CSPH). In these patients, surgical resection affords 5-year survival exceeding 70% and postoperative mortality of <3%.

Liver resection requires a detailed preoperative work-up with the assessment of liver function and future liver remnant volume. The combination of both variable determines the perioperative risk of liver failure and the associated complications. The most widely utilized assessment of liver reserve remains the Child-Turcotte-Pugh score, with surgical resection reserved to those with Child-Turcotte-Pugh class A cirrhosis. Other measures including the MELD score or MELD including sodium (MELD-Na), ALBI score,[102] indocyanine green kinetics,[103] and liver stiffness measurement by transient elastography[104] are associated with risk of post-resection hepatic decompensation and may also be used to refine patient selection.

The presence of CSPH, defined as a hepatic venous pressure gradient > 10 mmHg, is associated with post-hepatectomy liver failure[105] and can be directly measured by calculating the difference between the

free and wedged hepatic venous pressures. Because this may not routinely be measured, lack of ascites, portosystemic varices, splenomegaly and platelet count >150,000 per microliter are useful surrogates in clinical practice indicating the absence of CSPH.

An assessment of the FLR is easily made with contrast-enhanced CT or magnetic resonance volumetric imaging, allowing for precise measurements of the liver volume that is expected to remain behind. If there are concerns regarding the adequacy of the FLR, preoperative portal vein embolization can increase the size of the contralateral hepatic lobe to allow for safer resection.[105]

Child-Pugh A patients without significant portal hypertension are considered good candidates for minor/major liver resection. Child-Pugh C patients are not suitable for surgical therapy. A meta-analysis demonstrates that the presence of portal hypertension or Child-Pugh B status might not be an absolute contraindication and provide acceptable results for these carefully selected patients.[107, 108]
According to tumor size, number of detectable tumor satellites, intrahepatic tumor location at intraoperative ultrasound and the available surgical experience, anatomic LR (i.e. providing systematic removal of the tumor-bearing portal territories, with exposure of the landmark veins framing the segmental territory) should be preferred than non-anatomic LR.

The best candidate for liver resection is in HCC patient with single tumor located in superficial-peripheral positions of the liver with minor resection, no evidence of gross vascular invasion or extra-hepatic spread and well-preserved liver function (Child-Pugh A, MELD < 9) in the absence of clinically significant portal hypertension (platelet count >150, no splenomegaly, no ascites, no esophageal varices) and condition in anatomic resection (Figure 5 and 6).[109]

7.1 Indications for liver resection

(a) localized HCC in the absence of cirrhosis with future liver remnant volume > 30%
(b) single tumor < 5 cm or 2 lesions with each nodules ≤3 cm with minor resection (< 3 segment) and sufficient liver remnant volume > 40% after resection in well compensated cirrhosis (Child-Pugh A, MELD score < 9) without clinically significant portal hypertension (platelet count >150, no splenomegaly, no ascites, no esophageal varices)

7.2 Contraindications for liver resection

(a) diffuse infiltrative HCC or multifocal or bilobar HCC
(b) decompensated cirrhosis of liver (Child-Pugh B or C) and poor performance status (ECOG score ≥1)
(c) HCC-related macrovascular invasion
(d) extrahepatic metastasis

(e) any contraindications to open resection (advanced age > 70 years, cardiac or respiratory insufficiency, or ASA status > 3)
(f) any contraindications for surgical techniques

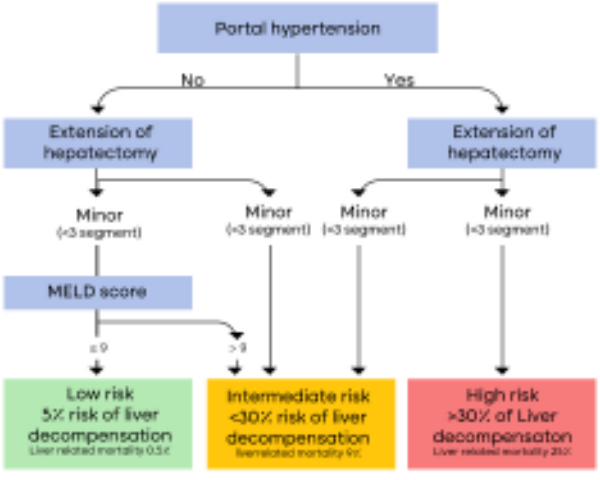

Figure (5) Multi-parametric assessment of the risk of liver decompensation after LR for HCC in cirrhosis. Simplified decisional algorithm identifying high (red), intermediate (yellow) and low (green) risk of liver decompensation, according to a hierarchic interaction of the three main determinants of liver insufficiency: portal hypertension, extent of resection and liver function. HCC, hepatocellular carcinoma; LR, liver resection. Adapted from[99] with permission.

7.3 Neoadjuvant or adjuvant therapies in liver resection

The risk of recurrence following liver resection remains high, approaching 50%–70% at 5 years, with the highest risk in the first year after resection.[10, 11] Tumor recurrence can be divided into either early (often within 2 years following surgery) resulting from micrometastases or late (occurring more often beyond 2 years) resulting from de novo: a new HCC arising in the remaining cirrhotic liver.[12] Factors associated with high tumor recurrence include older age; male sex; degree of liver dysfunction; and tumor size > 5 cm, more than 3 tumors, and poor tumor differentiation; microvascular or macrovascular invasion; presence of satellite lesions; and higher AFP level. Given the higher HCC risk than those without prior HCC, patients should undergo surveillance following surgical resection with cross-sectional imaging of the abdomen and chest plus serum AFP every 3–6 months.

Tumor recurrence complicates 70% of cases at five years, reflecting either intrahepatic metastases (true recurrences) or the development of de novo tumors. There is a need for effective (neo)adjuvant therapy to reduce risk of HCC recurrence after surgical resection. But current data do not support use of (neo)adjuvant therapy in patients with HCC undergoing surgical resection outside of a clinical trial. Neoadjuvant or adjuvant therapy tested, including chemotherapy, trans-arterial chemoembolization, internal radiation and retinoids, did not provide any benefit in terms of prevention of relapse.[83]

Preoperative TACE in patients with large resectable HCC does not improve recurrence-free survival and may increase risk of interval tumor progression, precluding surgical resectability.[84] Similarly, an RCT of adjuvant sorafenib in patients with HCC undergoing resection or thermal ablation did not improve recurrence-free survival in patients compared with placebo (HR, 0.94; 95% CI, 0.78–1.13)[85] Adoptive immunotherapy reduced HCC recurrence, whilst increasing recurrence-free survival[86] and overall survival after curative treatment.[87] The open-label phase III RCT comparing atezolizumab plus bevacizumab versus active surveillance (IMbrave 050) in the adjuvant setting for HCC patients at high-risk of recurrence after resection or local ablation was the first to demonstrate positive results.[88]

Follow-up after resection is recommended to detect tumor recurrence using USG or contrast-enhanced multiphasic CT or MRI every 3 months during the first 2 years and every 6 months thereafter and as required.

Recommendations (Resection)

21. Liver resection should be the treatment of choice for localized HCC in the absence of underlying cirrhosis with future liver remnant volume > 30%.
22. Liver resection should be considered for single tumor < 5 cm or 2 lesions with each nodules ≤3 cm with minor resection (< 3 segment) and sufficient liver remnant volume > 40% after resection in well compensated cirrhosis (Child-Pugh A, MELD score < 9) without clinically significant portal hypertension (platelet count >150, no splenomegaly, no ascites, no esophageal varices).
23. Diffuse infiltrative HCC or multifocal HCC, decompensated cirrhosis of liver, poor performance status (ECOG score ≥1), HCC-related macrovascular invasion, and extrahepatic metastasis are contraindications for liver resection.
24. Neoadjuvant therapy is not recommended for HCC patients undergoing liver resection but adjuvant therapy after liver resection may be helpful in patients with high risk of recurrence.
25. Follow-up after resection is recommended to detect tumor recurrence using USG or contrast-enhanced multiphasic CT or MRI every 3 months during the first 2 years and every 6 months thereafter and as required.

8. LIVER TRANSPLANTATION

8.1 Patient selection for liver transplantation

For patients with early-stage HCC who are ineligible for resection because of liver dysfunction or tumor multifocality, liver transplantation is an optimal treatment strategy because it provides a cure for both HCC and the underlying liver disease. Liver transplantation is also associated with a median survival of 10 years and a significantly lower risk of recurrent cancer compared with resection or ablation (5-year incidence: ~10% vs. 50%–60%).[120]

The expected five-year survival rates of liver transplantation (LT) for HCC meeting conventional Milan criteria (single tumor ≤5 cm or multiple tumors ≤3 nodules ≤3 cm in size, without vascular invasion)[121] are 65%–80%, and patients meeting the Milan criteria have a significant survival advantage (hazard ratio 1.68) over patients beyond the criteria.[122, 123]

Because of the ongoing critical organ shortage and recent allocation changes, Living Donor Liver Transplantation (LDLT) is increasing in worldwide, with a recent analysis of Organ Procurement and Transplantation Network (OPTN) data demonstrating excellent post-LT survival in the setting of LDLT for HCC.

The Milan criteria (one lesion < 5 cm; alternatively, up to three lesions, each < 3 cm; no extrahepatic manifestations; no evidence of macrovascular invasion) are currently the benchmark for the selection of patients with HCC for liver transplantation (Figure 4).[124] The outcomes have been excellent within the Milan criteria, with a 5 year-survival and a 10 years-survival of 70% and 50% respectively, and recurrence rates of 20 % at 10 years[125-127] Long-term outcomes of liver transplantation are considered superior than resection, which has a 70% recurrence rate and a 10-year survival of 7 – 15%.[118]

Extrahepatic tumor spread cannot be cured by an extreme loco-regional treatment such as LT and represents a clear contraindication for LT. Macrovascular tumor invasion – either at portal vein or hepatic veins level – is an absolute contraindication for LT, since it is the most important and independent risk factor for post-transplant HCC recurrence and for significant decrease in survival.[129]

8.2 Role of biomarkers for liver transplantation

Worldwide, nearly all LT selection criteria now include markers of tumor biology in addition to tumor size and number. Both the Metroticket 2.0 and French AFP models demonstrated that a combination of AFP and tumor burden predicts post-LT outcome better than tumor burden alone. Several AFP cut-offs have been proposed for incorporation into transplant criteria: 100 ng/ml,[130, 131] 200 ng/ml,[132] 400 ng/ml,[133, 134] 1,000 ng/ml.[135, 136] If a patient has an AFP > 1000 ng/ml at baseline, this level must fall below 500 ng/ml to be eligible for exception.[137, 138]

Additional serum biomarker cutoffs associated with high-risk explant pathology and worse post-LT outcome include AFP-L3 > 15%, des-γ carboxyprothrombin (DCP) or PIVKAII > 7.5 ng/ml, and neutrophil-to-lymphocyte ratio (NLR) > 5, although these thresholds have not yet been validated.

8.3 Indications for liver transplantation in patients with HCC

(a) Milan criteria (one lesion < 5 cm; alternatively, up to three lesions, each < 3 cm; no extrahepatic manifestations; no evidence of macrovascular invasion)
(b) very early stage HCC (one lesion < 2 cm with decompensated cirrhosis of liver; no extrahepatic manifestations; no evidence of macrovascular invasion)
(c) AFP < 500 ng/ml before liver transplantation

8.4 Contraindications for liver transplantation in patients with HCC

(a) diffuse infiltrative HCC or multifocal or bilobar HCC
(b) AFP > 1000 ng/ml before liver transplantation
(c) portal vein thrombosis suggested of tumor vascular invasion and extrahepatic metastasis
(c) any contraindications to open surgery (advanced age > 70 years, cardiac or respiratory insufficiency, or ASA status > 3)

8.5 Use of bridging therapy

Bridging therapy describes treatment of accepted transplant candidates within Milan criteria while on the waiting list. Given the mandatory 6-month wait time prior to the awarding of MELD exception, neoadjuvant locoregional therapy (LRT) such as with TACE, TARE, ablation, and external beam radiation therapy (EBRT) is typically used as a bridge to control tumor growth and reduce the risk of waitlist dropout.[139]

Because tumor progression despite LRT is associated with worse post-LT outcome[140-142] observing tumor behavior after LRT may allow for a more refined selection of candidates for LT.[143, 144] Although a recent United Network for Organ Sharing (UNOS) national analysis suggested ablation or TARE because initial LRT may be associated with reduced waitlist dropout compared with TACE,[145] currently no one type of LRT is recommended over another for bridging therapy. AASLD does not recommend the routine use of systemic therapies as bridging therapy for transplantation; however, their use does not preclude LT eligibility. Although immune checkpoint inhibitors (ICIs) can increase risk of rejection and graft loss, increasing case series suggest this practice is safe in some patients.

Patients with HCC meeting Milan criteria who undergo resection or LRT and develop recurrence within Milan criteria are eligible to bypass the 6-month observation period before receiving MELD exception.[146]

8.6 Downstaging to liver transplantation

Tumor downstaging is defined as a reduction in the size of viable tumor using locoregional therapy (LRT) to meet acceptable LT criteria. This process likely serves as a selection tool to identify a subgroup with favorable tumor biology. In patients with HCC

exceeding Milan criteria but meeting well- defined upper limits of tumor size and number, post-LT outcome in those successfully down-staged to Milan criteria do not significantly differ from those always within Milan criteria.[147-150]

Criteria beyond Milan that have claimed non-significant differences compared to the Milan criteria in terms of post-LT survival, and that have been externally validated are: UCSF criteria (i.e.: single nodule ≤6.5 cm or 2–3 nodules ≤4.5 cm and total tumor diameter ≤8 cm,[151, 152] Up-to-7 criteria (i.e.: those HCCs having the number 7 as the sum of the size (cm) of the largest tumor and the number of tumors,[153] Total tumor volume (TTV) criteria + alpha-fetoprotein (AFP) (i.e.: total tumor volume <115 cm3 and AFP <400 ng/ml,[154, 155] and the AFP-French model (i.e.: points system based on tumor size, number of tumors and AFP cut-off levels at 100 ng/ml and 1,000 ng/ml.[156]

Among several more liberal proposals for the use of extended criteria (up-to-seven criteria (71% 5-year survival), extended Toronto criteria (68% 5-year survival), Kyoto criteria (65% 5-year survival), University of California San Francisco (UCSF) criteria (81% 5-year survival) (Table 5), only the UCSF criteria were prospectively validated and show similar outcome and, as such may also be considered for liver transplant in patients with HCC beyond Milan criteria (Figure 6).[125, 157, 157]

The risk of hepatic decompensation because of LRT should be con-sidered when selecting patients for bridging/downstaging therapy. It has been proposed that only patients with adequate hepatic function (e.g., Child-Turcotte-Pugh class A or B and bilirubin <3 mg/dL) should undergo attempted downstaging.[158]

Criteria for successful downstaging, criteria for downstaging failure and exclusion from liver transplant, and timing of liver transplantation in relation to downstaging are shown in Table 6.

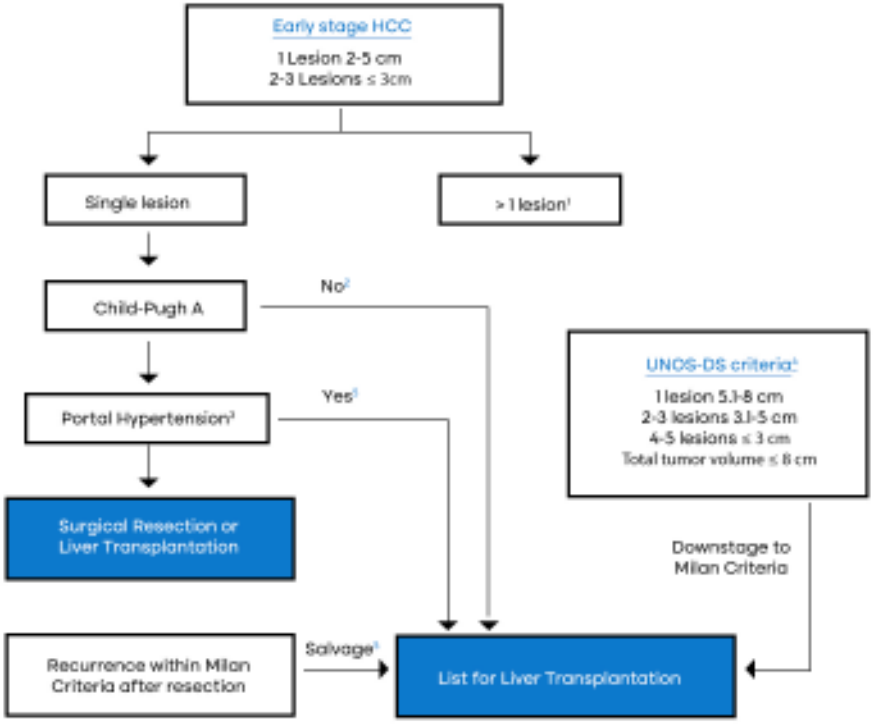

Figure (6) Algorithm for surgical treatment of BCLC stage early HCC. 1In non-liver transplant (LT) candidate, can consider surgical resection if >1 lesion in the same lobe. 2In non-LT candidate, can consider minor surgical resection if CTP score B7 and/or mild portal hypertension. 3E.g., varices, splenomegaly, platelets <100 × 109/L, hepatic venous pressure gradient >10 mmHg. 4Living donor liver transplant can be considered on a case-by-case basis for patients beyond UNOS-DS criteria. 5Eligible for Model for End-Stage Liver Disease exception without 6-month wait period.

TABLE (5) Proposed expanded criteria for liver transplantation and associated outcomes

Examples of expanded criteria (All criteria include absence of vascular invasion and metastatic spread)		Post-transplant survival
UCSF criteria	One tumor ≤6.5 cm **or** 2–3 tumors, each ≤4.5 cm, with total tumor volume ≤8 cm	81% 5-year survival
Total tumor volume <115 cm	Sum of volume for each tumor ≤115 cm	75% 4-year survival
Up-to-seven criteria	Diameter or largest tumor (cm) + number of tumors ≤7	71% 5-year survival
Extended Toronto criteria	Biopsy demonstrating well-to-moderate differentiation for patients beyond Milan criteria and ECOG performance status 0–1	68% 5-year survival
Kyoto criteria	Number or tumors ≤10, maximum diameter of each tumor ≤5 cm, and serum DCP ≤400 mAU/ml	65% 5-year survival

TABLE (6) Application of UNOS-DS criteria for liver transplantation

Criteria for successful downstaging
Residual tumor size and diameter within Milan criteria (1 lesion ≤5 cm, 2–3 lesions ≤3 cm) (a) Only viable tumor(s) are considered; tumor diameter measurements should not include the area of necrosis from tumor-directed therapy. (b) If there is more than one area of residual tumor enhancement, then the diameter of the entire lesion should be counted toward the overall tumor burden.
Criteria for downstaging failure and exclusion from liver transplant
1. Progression of tumor(s) to beyond inclusion/eligibility criteria for downstaging (as defined above) 2. Tumor invasion of a major hepatic vessel based on cross-sectional imaging 3. Lymph node involvement by tumor or extrahepatic spread of tumor 4. Infiltrative tumor growth pattern 5. Persistent AFP elevations >500 ng/ml in patients who had prior AFP ≥1000 ng/ml
Timing of liver transplantation in relation to downstaging
1. There should be a minimal observation period of 3 months of disease stability from successful downstaging to liver transplant 2. Per current UNOS policy, the patient must remain within Milan criteria for 6 months after successful downstaging before receiving MELD exception points

8.7 Post liver transplant follow up

Adjuvant therapy is not recommended for HCC patients after liver transplant. Mammalian target of rapamycin (mTOR) inhibitors are used as immunosuppressant to prevent graft rejection in liver transplantation (sirolimus/everolimus) because of its antineoplastic properties[159] but have failed to improve recurrence-free survival in a phase III SiLVER RCT trial,[160] the subgroup within Milan criteria had improved recurrence-free survival with mTOR inhibitor based immunosuppression.[161]

Even with adherence to the Milan criteria, HCC recurs post-LT in 10%–15%.[162-164] Because the two most common sites of post-transplant recurrence are the lung (~40%) followed by the liver (33%), surveillance using contrast-enhanced abdominal CT or MRI and chest CT scan is advised. In patients who present with significantly elevated AFP or other tumor markers but without overt recurrence on abdominal and chest imaging, repeat abdominal imaging with an alternative modality (e.g., MRI if the patient first underwent abdominal CT), pelvic CT, or PET scan may be considered. Although the optimal timing and duration of post-transplant surveillance is uncertain, risk stratification scores may assist in determining surveillance intervals, though this approach still requires validation.

8.8 Liver transplantation in Myanmar

First liver transplantation in Myanmar was successfully performed in August, 2004 at New Yangon General Hospital. Deceased Donor Liver Transplantation was done by Professor Norman Hla, Professor Khin Maung Aye, Professor Khin Maung Win and team. At that time, Myanmar surgeon's first successful liver transplant in Southeast Asia is a record for the state as well as an honor for the nation and the people. Second time liver transplantation was Living Donor Liver Transplantation which was continued in December, 2009 with the same team.

Liver transplant programme in Myanmar was continuously performed at Yangon Specialty Hospital but also in Mandalay General Hospital since 2017. This programme was collaborated with transplant surgeons from Seoul National University Hospital, Korea and Yashoda Hospital, Hyderabad, India.

Liver transplant programme in Myanmar Military Medical Corps was started in September, 2022 at No. (1) Defence Services General Hospital (1000-bedded), Yangon. This programme was collaborated with transplant surgeons from Apollo Hospital, New Delhi, India. Living Donor Liver transplantation cases were continuously performed as 3 cases per time and 4 to 5 times per year. Liver transplantation will be started in 2024 at No. (2) Defence Services General Hospital (1000-bedded), Nay Pyi Taw.

Donor for liver transplantation must be first degree relative, unsolicited volunteer, healthy, age between 18 to 50 years, blood group compatible (donor 'O' to recipient 'O', donor 'A' or 'O' to recipient 'A', donor 'B' or 'O' to recipient 'B', 'all' blood groups donor to recipient 'AB'), no history of previous

major surgery, negative serology tests, normal liver and appropriate size for donation.

Recommendations (Liver Transplantation)

26. Liver transplantation should be the treatment of choice for transplant-eligible patients with early stage HCC within Milan criteria with or without prior liver resection or local ablation therapies.
27. Patients who are otherwise transplant-eligible except with initial tumor burden exceeding the Milan criteria, especially those meeting UCSF downstaging criteria, should be considered for liver transplantation following successful downstaging to within Milan criteria.
28. HCC patients with AFP > 1000 ng/ml must be downstaged to AFP < 500 ng/ml to be considered downstaged prior to liver transplantation.
29. The use of pre-transplant locoregional bridging therapy (Ablation, TACE, TARE, and external beam radiation therapy (EBRT) for patients being evaluated or listed for living donor liver transplantation, if they have adequate hepatic reserve, to reduce the risk of waitlist dropout in the context of anticipated prolonged wait times for transplant and aims at lowering post-LT recurrence – particularly when complete or partial tumor response are achieved.
30. Positron emission tomography (PET) using 18F-fluorodeoxyglucose (^{18}F-FDG) (FDG-PET) scan is recommended to detect extrahepatic metastasis before liver transplantation.
31. Portal vein thrombosis suggested of tumor vascular invasion and extrahepatic metastasis in HCC patients are absolute contraindications for liver transplantation.
32. Surveillance for detection of post-transplant HCC recurrence is recommended using USG or multiphasic contrast-enhanced abdominal CT/MRI or PET scan and chest CT scan and as required.
33. Liver transplantation can be performed in Myanmar.

9. LOCAL ABLATIVE THERAPY

Local ablative therapies are percutaneous ethanol injection (PEI), thermal ablative therapies which are classified as either hyper-thermic treatments (heating of tissue at 60 °C - 100 °C) – including radiofrequency ablation (RFA), microwave ablation (MWA), and laser ablation – or cryoablation (freezing of tissue at -20 °C and -60 °C). Most procedures are performed using a percutaneous approach, although in some instances ablation with laparoscopy is recommended.

Patients with solitary HCC who are ineligible for or decline surgery should be considered for curative ablative therapies. An ablation-first strategy may be considered for patients with centrally located tumors requiring major hepatectomy or those with very-early-stage HCC because RCTs demonstrate ablation affords similar survival and is cost-effective compared with resection in patients with HCC <2 cm; however, resection has superior survival for those with larger tumors.[165-170]

Eligibility for local ablation therapy is determined by tumor size and location and the ability to achieve adequate ablation margins. HCC >3 cm and those located near critical structures (e.g., large vessels, diaphragm, heart, or central bile ducts) may be best treated with other locoregional modalities, including radiation segmentectomy or EBRT.

Local ablation therapy is associated with lower objective response rates (ORRs), higher recurrence rates, and worse OS in HCC >3 cm compared with smaller tumors,[171, 172] although some studies suggest efficacy may be improved by combining LAT with TACE in these cases.[173-175]

9.1 Percutaneous ethanol injection (PEI)

PEI induces coagulative necrosis of the lesion as a result of cellular dehydration, protein denaturation, and chemical occlusion of small tumor vessels. Percutaneous or Image-guided ablation therapies are usually performed by interventional radiologists and are accepted as potentially curative therapy for small, early-stage HCC tumors who are not candidate for surgery.[176] The first local ablative modality was percutaneous ethanol injection (especially if tumor ≤2 cm), although this has since been replaced by radiofrequency ablation, microwave ablation, and cryoablation – all of which induce superior objective responses with fewer sessions.[177-178] Percutaneous ethanol injection is a well-established technique for the treatment of nodular-type HCC that leads to complete necrosis in 90% of tumors <2 cm.[182, 183] Yet, PEI is associated with incomplete necrosis in most HCCs >2 cm and suffers a high local recurrence rate, which may reach 49% in lesions exceeding 2 cm.[184]

Percutaneous ethanol injection is nevertheless a valuable option for tumors located near the large hepatic vessels and bile duct, or in treatment centers with limited access to technology. Although local tumors progression or relapse is higher after percutaneous ablation than after

hepatic resection, the long-term outcomes as well as survival rate are similar in appropriately selected patients,[165-168] and ablation has been proposed as first-line therapy for tumors that are ≤ 2 cm in size.[176]

9.2 Radiofrequency or Microwave Ablation

Radiofrequency ablation (RFA) is widely performed for the treatment of small hepatocellular carcinoma (HCC) as a curative treatment owing to safety, reasonable cost, and applicability as a minimally invasive technique. Additionally, clinical management guidelines consider RFA as an effective treatment modality for early-stage HCC. As a result, radiofrequency is the standard ablative therapy at very early single lesion ≤ 2cm or early stage of HCC single lesion ≤ 3cm (Figure 7) as it provides better results than percutaneous ethanol injection.[190] Recently, with the advent of new devices, multipolar RFA, that can cause cauterization up to 6 cm in one session, and newer generation microwave ablation systems have been found to achieve treatment success for large HCC.[191]

The mechanisms of cell death in RFA are based on the frictional heat generated using high-frequency alternating current. Heat produces coagulative necrosis of the tumor and allows extension of the necrosis to a "safety ring" in the peri-tumoral tissue, which might eliminate small-undetected satellites. RFA has been evaluated as first-line therapy in early HCCs. Several RCTs have demonstrated a significant benefit of radiofrequency ablation compared to percutaneous ethanol injection in terms of completed response rate (absence of contrast uptake within the treated lesion in the arterial phase of CT or MRI) and time to recurrence.[189]

Five-year survival rates after radiofrequency ablation average at 60%.[192] The main predictor of treatment failure is tumor size. When RFA is used as first-line therapy for early-stage HCC, complete response rates by mRECIST range from 70% to 90%[193, 194] and is significantly associated with better overall survival.[194] In addition, studies have reported a median overall survival of 60 months and a 5-year recurrence rate of 50-70% with RFA.[166, 195]

Although there have been no randomized head-to-head studies showing superiority of one thermal ablative modality over another, microwave ablation may be less susceptible to heat sink effects near large vessels.[196] Similar efficacy between the radiofrequency and microwave ablation have been reported in meta-analyses.[197]

In patients with HCC larger than 3 cm in diameter, combination of TACE and RFA is associated with significantly higher overall survival (OS) and recurrence-free survival, than RFA monotherapy without significant difference in major complications.[198-200] However, the combination of the two techniques on the same occasion is quite demanding in term of resources.

Assessment of response in HCC should be based on mRECIST for local ablative therapies. Multiphasic contrast-enhanced abdominal CT or MRI are recommended for assessment of response after local ablative

therapies as every 3 months during the first 2 years and every 6 months thereafter or as required. The use of changes in serum biomarker levels for assessment of response (i.e. AFP levels) is under investigation but AFP levels changes can be considered for assessment of treatment response if AFP level is higher from baseline.

9.2.1 Indications for Radiofrequency Ablation

(a) very early stage HCC ≤ 2cm with no potential candidate for liver resection or liver transplantation
(b) early stage HCC (single tumor < 5 cm, or ≤ 3 nodules each ≤ 3 cm) with no potential candidate for liver resection or liver transplantation
(c) lesion able to detect by ultrasonography
(d) preserved liver function (Child-Pugh A or early B (score ≤ 8)
(e) correctable platelet count more than 50 × 103/mL and PT:INR <1.5

9.2.2 Contraindications for Radiofrequency Ablation

(a) intermediate stage HCC (tumor > 5cm or multifocal or bilobar HCC or diffuse infiltrative HCC
(b) decompensated cirrhosis of liver (Child-Pugh score > 8) and poor performance status (ECOG score ≥1)
(c) major vessels invasion or bile duct invasion
(d) HCC-related macrovascular invasion or extrahepatic metas tasis
(e) any contraindications for ablation techniques
(f) any contraindications to open surgery for ablation (advanced age > 70 years, cardiac or respiratory insufficiency, or ASA status > 3)

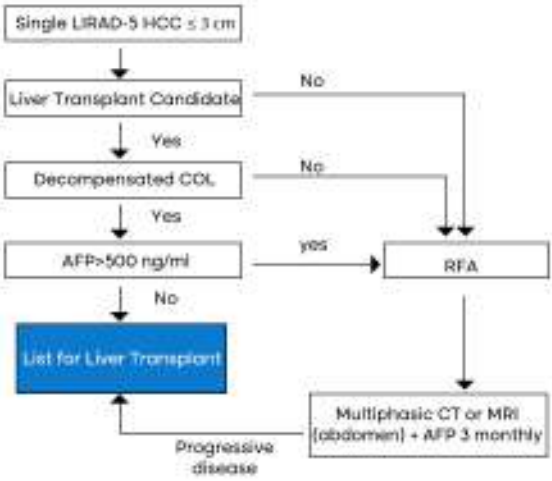

Figure (7) Management algorithm for unresectable very early or early BCLC HCC ≤ 3 cm lesion in patient with cirrhosis. If lesion not amenable to ablation, alternate options include transarterial chemoembolization (TACE), radiation segmentectomy, or stereotactic body radiation therapy (SBRT). Patient has higher risk of rapid tumor progression, defined as >0.3 cm per month increase in tumor diameter.

Recommendation (Local Ablative Therapy)

34. Patients with solitary tumors ≤5 cm should be treated with curative intent using local ablative therapies if ineligible for or they decline surgical therapy.
35. Radiofrequency ablation (RFA) is the treatment of choice for patients with very early stage HCC solitary tumor < 2 cm or early-stage HCC ≤3 lesions, ≤3 cm who are ineligible for or they decline surgery therapy.
36. Ethanol injection (PEI) is an option in some cases where thermal ablation is not technically feasible, especially in tumors < 2 cm.
37. The different forms of other ablation therapies are very scantly practice in Myanmar.
38. TACE followed by RFA should be done if the lesion is 3-5 cm.
39. Assessment of response in HCC should be based on mRECIST with multiphasic contrast-enhanced CT or MRI every 3 months during the first 2 years and every 6 months thereafter or as required.
40. AFP levels changes can be considered for assessment of treatment response if AFP level is higher from baseline.

10. TRANSARTERIAL CHEMOEMBOLIZATION (TACE)

Because of HCCs are uniquely supplied by the hepatic artery,[201,202] transarterial treatments have proven to be extremely effective in blocking the blood supply from both the artery and portal vein to the tumor delivering targeted embolic therapy while minimally damage the surrounding liver parenchyma.

TACE is the global standard of care therapy that has shown a consistent survival benefit in the intermediate stage HCC population of the BCLC staging system[203-205] The basic for TACE is the intra-arterial infusion of a chemotherapy agent such as doxorubicin or cisplatin, frequently embedded in lipiodol as a vehicle for increasing tumor exposure to the drug,[206] followed by embolization of the blood vessel with embolic agents such as gelatin sponge particles,[207] polyvinyl alcohol,[208] starch microspheres.[209] Subsequently, part of the agent passes through the tumor's drainage portal vessel and portal vein through the peribiliary plexus, which temporarily embolizes both the artery and portal branches around the tumor (temporal liver infarction).[210] This approach results in a strong cytotoxic effect that is combined with ischemia in tumor tissues.

TACE refractoriness can occur in some cases. TACE induces hypoxic and chemotherapeutic stress on HCC cells, and the surviving hypoxic tumors frequently change to sarcomatous or mixed hepatocholangiocellular phenotypes (more aggressive and TACE-resistant tumor tissue); in addition, it induces production of vascular endothelial growth factors (VGEF) from residual tumor cell, which further promote tumor progression.[211-213] Moreover, when the artery is impaired, some surviving tumor cells can be fed by the collateral arteries, and infrequently by the portal vein, which suggests that ineffective TACE can also produce uncontrollable tumor.[214] It is speculated that these factors underlie the development of TACE refractoriness.

10.1 Indication for TACE

Meta-analyses of RCTs comparing TACE and best supportive care demonstrate significant improvements in Overall survival among patients with BCLC Stage B HCC.[215] Therefore, TACE is the primary treatment option for patients with BCLC Stage B HCC.[216, 217]

The indication for TACE should be consider depending on tumor burden, underlying liver disease, and performance status (Eastern Cooperative Oncology Group [ECOG]).[218]

10.2 Selection for TACE

Patient selection and vascular selectivity are critical factors to optimize TACE outcomes. TACE should be performed using selective catheterization of segmental or distal branches, with c-arm CT when possible to ensure localization. This approach maximizes delivery of therapy to the tumor(s) to maximize chance of response and minimizes ischemic injury to

noncancerous background liver. Patient selection for TACE eligibility must carefully consider degree of liver dysfunction and tumor burden to minimize risk of toxicity. Patients with significant liver dysfunction, potal vein tumour thrombus (PVTT), or large intrahepatic tumor burden have a lower chance of achieving objective responses and have a higher risk of hepatic decompen-sation after TACE, so these patients may be considered TACE unsuitable (Table 5); however, established cutoffs for liver dysfunction or tumor burden have not been well defined.[219]

Table (7) Baseline factors that contribute to unsuitability for TACE

Proposed factors for TACE unsuitability	
Tumor size	• Beyond UNOS-DS criteria (beyond up-to-7 criteria)
Tumor appearance	• Multinodular, bilobar, with > 50% liver involvement • Infiltrative or nodular with poorly defined margins
Tumor marker	• Marked AFP elevations (No specific cutoff has been identified although marked elevations or increasing AFP may suggest increased risk of metastatic spread and/or poor response to locoregional therapy)
Potal vein tumour thrombus (PVTT)	• Large vessel vascular invasion, e.g., main PVTT or hepatic vein tumor thrombus
Liver function	• ALBI 2–3, especially if tumor exceeds segmental treatment zone • Deteriorating liver function over time

Several prognostic scoring systems have been proposed (e.g., beyond UNOS-DS, 6-and-12 model, or beyond up-to-7 criteria) based on factors including tumor number, tumor size, ALBI score, and AFP levels; however, further validation is needed to identify the subset of patients who are TACE unsuitable.[220-222] The Up-to-7 criteria, defined as HCC with seven as the sum of the diameter of the largest tumor (in cm) and the number of tumors, which were originally developed for transplantation, are used globally to describe tumor burden.[223]

The UNOS-DS criteria were defined as I lesion being > 5 cm and < 8 cm; 2 to 3 lesions each < 5 cm; and 4 to 5 lesions each < 3 cm with a total tumor diameter of < 8 cm. The 6 and 12 score determines 3 groups with different prognosis (G1, the sum ≤6; G2, the sum >6 but ≤12; G3, the sum >12). A survival benefit of more than 20 months can be expected for patients with HCC and an index ≤12, and more than 40 months for those with an index ≤ 6.

Patients considered unsuitable for TACE may be better treated with systemic therapy, particularly considering improved responses and survival reported in the advanced-stage setting.[224]

10.3 Contraindication for TACE

TACE is contraindicated in the following patients.

(a) Decompensated cirrhosis (the presence of ascites, encepha lopathy, jaundice or variceal bleeding)
(b) Hepatic encephalopathy
(c) Biliary obstruction or bilirubin greater than 3 mg/dL
(d) Poor performance status (ECOG) >2
(e) Uncorrectable coagulopathy
(f) Extra-hepatic metastases
(g) Hepatofugal blood flow
(h) Main portal vein thrombosis
(i) Patients with contraindications to contrast media
(j) Patients with impaired renal function (Creatinine ≥ 2 mg/dL or Creatinine Clearance <30 ml/min)

10.4 Technical factors for TACE

Generally, selective TACE is defined as TACE segmental hepatic artery, whereas superselective TACE is defined as TACE at the sub segmental hepatic artery. TACE at the most distal level of subsegmental hepatic artery is termed ultra-selective TACE.[225, 226]
Selective TACE can be performed in patients with small tumors in whom ablation is difficult to perform because of tumor location (or) medical comorbidities.[227]

10.5 TACE and Portal vein tumor invasion

Portal vein tumor invasion is found in approximately 50% of HCC patients at initial diagnosis in Myanmar. When TACE is performed for HCC patients with good hepatic function with portal vein tumor invasion, the risk of hepatic functional deterioration after TACE is reported to be acceptably low.[228-231] In patients with unresectable HCC with portal vein invasion, survival outcomes are more favorable in the TACE treated group than in the supportive treatment group.[232-235] Among HCC patients with portal vein invasion, patients with Child-Pugh A,[228] tumor localized within the liver, tumors showing nodular growth[230, 232] or portal vein invasion not involving the main portal vein[231] showed a better prognosis.

10.6 Complication after TACE

The most common complication after TACE is post-embolization syndrome, including fever, abdominal pain, nausea and vomiting. According to a systematic review, the common complications after TACE was fever (57.8%), followed by liver enzyme abnormalities (52.0%), Post Embolization Syndrome (47.7%), abdominal pain (42.5%), fatigue/ malaise (39.9%), anorexia (38.0%), vomiting (34.2%), nausea (32.4%) and hepatological/bone marrow toxicity (28.6%). Hepatic failure occurred in only 1% of patients and no new (or) unexpected safety concerned were identified. [236]

Recently, the use of anti-inflammatory drugs, such as dexamethasone (or) parecoxib, to reduce post-symptomatic syndrome before and after TACE has been reported in RCTs[237-240] and clinical application can be considered. However, caution need to be taken because of the risk of adverse effects, such as worsening of viral hepatitis or diabetes.

10.7 Response Assessment after TACE

Objective response to TACE is generally assessed according to mRECIST.[241, 242] Patients treated with TACE should undergo multiphase contrast enhanced CT (or) MRI approximately 6 weeks after treatment. Repeat treatment is provided on demand in those with continued viable disease, whereas repeats imaging every 3-6 monthly is recommended in those without viable disease.[243]

Patients who achieved objective responses to TACE for at least 6 months but then have local progression are likely to respond to additional locoregional therapy.[244] In contrast, patients who fail to have initial treatment response or have observed progression after one to two TACE sessions should be considered TACE is refractory and alternative treatments, including systemic therapy should be considered.[245, 246]

10.8 TACE refractory and treatment stage migration

Patients refractory to TACE should be considered for molecular targeted therapy. Repeated TACE in patient who has become refractory to TACE leads to impaired liver function and consequently poor prognosis.[248, 249] An international, prospective non-interventional, OPTIMIS reported that patients who switched to sorafenib immediately after developing refractoriness to TACE had a better prognosis than who continued TACE.[250] Another first-line agent, lenvatinib, is associated a markedly high response in BCLC stage B patients eligible for TACE.[250] Lenvatinib treatment also shows favorable results in TACE resistant tumors such as poorly differentiated, confluent multinodular type or infiltrative type HCC.[251-253]

Table (8) Factors suggesting TACE-refractory HCC

TACE refractoriness
Lack of objective response: >50% definite viable disease after 2 TACE treatments
Development of new HCC within treatment zone after 2 consecutive TACE
Lack of improvement for tumor markers (e.g., AFP) after 2 consecutive TACE
Stage migration to advanced HCC, including new vascular invasion or extrahepatic metastases

Combination Therapy

Usual practice of HCC treatment in Myanmar, Tyrosine Kinase Inhibitor is already started when the patient is arrived to Hepatologist. GLF (Myanmar) is favor to use combination of TACE and Tyrosine Kinase Inhibitor to reduce the tumor progression after TACE and prolonged the interval between TACE session.

TACE is technically possible with potentially curable disease in intermediate-stage HCC except very high tumor burden such as bilobular multifocal disease >10 nodules or beyond up-to-11 criteria. The treatment goal is always to achieve clinical/pathological complete response (CR) and drug-free status.

Immune checkpoint inhibitors using Atezolizumab plus Bevacizumab therapy is extremely effective in the treatment of intermediate-stage hepatocellular carcinoma (HCC), with a response rate of 44%, as reported in the IMbravel50 trial. When tumor shrinkage is obtained, achieving CR is possible in many cases using curative conversion with resection, ablation, or superselective transarterial chemoembolization (TACE) with curative intent. This concept, i.e., curative conversion by combining systemic therapy and locoregional therapy, has not been reported before. The multicenter proof-of-concept study was conducted by Kudo et al. to show the value of curative conversion in immunotherapy treated intermediate-stage HCC meeting TACE-unsuitable criteria.

The study concluded that among unresectable and TACE unsuitable intermediate-stage HCC cases, 35% achieved clinical CR, and 23% achieved drug-free status and by curative conversion therapy with Atezolizumab plus Bevacizumab as the preceding therapy. No recurrence was observed from this patient subgroup with CR and drug-free status. A drug-free status can be achieved when significant tumor shrinkage is obtained with Atezolizumab plus Bevacizumab therapy; at this stage, resection, ablation, and superselective TACE with curative intent are possible by actively performing curative conversion to achieve CR. In some cases, clinical CR and drug-free status could be achieved when the tumor shrinkage effect was not obtained even after 4–6 cycles of Atezolizumab plus Bevacizumab therapy or when PET-positive HCC was present. Clinical CR was achieved in five PET-positive patients by conducting selective TACE or LEN-TACE sequential therapy followed by Atezolizumab plus Bevacizumab, which does not decrease liver function during the whole treatment course.

Thus, achieving CR and/or drug free status should be a therapeutic goal for patients with intermediate-stage HCC without vascular invasion or extrahepatic spread. To that end, the timing of curative conversion during the Atezolizumab plus Bevacizumab combination therapy for intermediate-stage HCC needs to be determined with cautious intention.[254]

Recommendation (TACE)

41. Transarterial chemoembolization (TACE) is the most widely used therapeutic procedure in Myanmar.
42. TACE is recommended as first-line therapy in patient with two to seven nodules and each lesion ≤ 7 cm (within up to 7 criteria), well defined nodules, preserve portal flow, involved in one lobe, good performance status, (ECOG-PS 0), no extrahepatic spread or vascular invasion, compensated liver function.
43. TACE can be performed in patients with small tumors but the lesion should be > 2 cm in whom ablation or resection is difficult to perform because of tumor location or medical comorbidities and liver transplantation is not feasible to perform.
44. The conditions unlikely to respond to TACE or TACE resistance are simple nodular tumor with extranodular growth, confluent multinodular tumor, massive tumor (beyond up to 7 criteria), intrahepatic multifocal metastasis, poorly differentiated HCC and sarcomatous change caused by TACE.
45. Huge tumor burden (beyond up to 7 criteria, > 50% of liver volume and bilobar multifocal tumors) should be considered systemic therapy first and TACE should be started after successful down-staging or best response with systemic therapy.
46. TACE should not be used in patients with decompensated liver disease, advanced liver and/or kidney dysfunction, macroscopic vascular invasion or extrahepatic spread.
47. TACE is safe to use in patient with limited tumor invasion of portal vein but are contraindicated in patients with Child -Pugh class C disease.
48. TACE assessment should be done at 6-8 weeks after TACE and TACE failure should be considered after at least 2 consecutive TACE procedure.
49. TACE failure (remaining > 50% viable lesion, stage progression to BCLC 'C', continuous tumor marker elevation immediately following TACE should be switched to systemic therapy instead of further continuous TACE procedure.
50. The combination of TACE with molecular targeted agents (MTAs) is recommended to reduce the tumor progression after TACE and prolonged the interval between TACE session.
51. Immunotherapy using Atezolizumab plus Bevacizumab as the preceding therapy for unresectable and TACE-unsuitable intermediate-stage HCC is recommended to achieve complete response rate by curative conversion with TACE.

11. Other Radiological interventions

11.1 TRANSARTERIAL INFUSION OF CHEMOTHERAPY (TACI)

TACI can be considered in patients with ineligible for TACE such as intrahepatic multinodular lesions and major portal vascular thrombosis.

11.2. Drug-eluting bead-TACE (DEB-TACE), Transarterial Radioembolization (TARE), External Beam Radiation Therapy (EBRT)

In patients who are not amenable to thermal ablation, EBRT, including proton beam therapy (PBT) and stereotactic body radiation therapy (SBRT) delivered in five or fewer sessions, is another method of achieving durable local control. In contrast to ablation, EBRT can be used for central tumors and for tumors adjacent to vascular structures, with no age or absolute size limits (although most data are for HCC <8 cm). EBRT should be avoided in patients with significant liver dysfunction (e.g., Child-Turcotte-Pugh score ≥8, uncontrolled ascites, or uncontrolled hepatic encephalopathy) given the risk of radiation-induced liver injury. HCC adjacent to stomach or bowel is also not well suited for EBRT given risk of ulceration.[255] EBRT has also been used as a bridge to liver transplantation, with high observed response rates and comparable dropout rates with thermal ablation or TACE.[256] These treatment modalities are currently not available in Myanmar.

12. Systemic Therapy in HCC

Systemic therapies are mainly indicated for patients with advanced HCC or patients who progressed upon locoregional therapies. HCC is recognized as the most chemo insensitive tumour type and conventional chemotherapies did not demonstrate any survival benefits for patients with HCC in clinical trials.

Approved systemic therapies broadly fall into two groups: Antiangiogenic targeted therapies include the multi-tyrosine kinase inhibitors (mTKIs) (sorafenib, lenvatinib, cabozantinib, regorafenib) and monoclonal antiangiogenic antibodies (ramucirumab and bevacizumab). Immune checkpoint inhibitors (ICIs) currently include inhibitors of programmed death 1 (PDI) (pembrolizumab and nivolumab) or its ligand (PD-LI) (durvalumab and atezolizumab), and cytotoxic T lymphocyte–associated protein 4 (CTLA4) inhibitors (tremelimumab and ipilimumab). Some drugs are not available in Myanmar.[257]

Table (9) Antiangiogenic targeted therapies for TACE

Antiangiogenic targeted therapies		
Tyrosine Kinase Inhibitors	Sorafenib	SHARP Trial,[258] Asia-Pacific study[259]
	Lenvatinib	REFLECT Trial[260]
	Carbozantinib	CELESTIAL[261]
	Regorafenib	RESORCE[262]
Monoclonal anti-angiogenic Abs	Ramucirumab	REACH-2[263]
	Bevacizumab	IMbrave 150 trial[264]
Immune checkpoint inhibitors		
PD1 inhibitors	Pembrolizumab	KEYNOTE-240[265] KEYNOTE-394[266]
	Nivolumab	CheckMate 040[267]
PD-L1 inhibitors	Durvalumab	HIMALAYA[268]
	Atezolizumab	IMbrave150 trial[264]
CTLA4 inhibitors	Tremelimumab	HIMALAYA[268]
	Ipilimumab	CheckMate 040[267]

12.1 Tyrosine Kinase Inhibitors

12.1.1 Sorafenib

Sorafenib is a multikinase inhibitor targeting the vascular endothelial growth factor receptor intracellular kinase pathway and other kinases. Sorafenib was the first systemic therapy to demonstrate a survival advantage versus placebo for patients with advanced-stage HCC. The survival

benefits of sorafenib of approximately 3 months was demonstrated in phase 3, double blind, multicenter placebo controlled SHARP trial[256] and the Asian-Pacific study.[259]

Sorafenib is indicated in Child- Pugh A and B patients as the safety and efficacy of sorafenib are reported to be comparable between Child-Pugh A and B patients in real world practice.[269] However, it is contra-indicated in Child Pugh C patients as the presence of ascites and higher Child-Pugh score are significantly associated with the poor prognosis of sorafenib treated patients.[259]

The most common adverse event related to sorafenib treatment is hand-foot skin reaction (HFSR) and diarrhea which occurred in 8-16% and 8-9% of patients respectively. HFSR and hypertension have been reported as potential surrogate predictors of a good response to sorafenib.[272] In Myanmar, hand-foot skin reaction (HFSR) and diarrhea are the common side effects of Sorafenib and most of the patients are intolerance to take recommended dosage.

Table (10) Common side effects of Sorafenib and their management[270]

Common side effects of Sorafenib	Management
Hand-foot skin reaction (HFSR)	1. Patient education • Keeping hands and feet moisturized with a thick urea-based cream • Wearing comfortable shoes with minimal pressure points, and avoiding hot water 2. Follow-up at 2-week intervals for the first 2 months following sorafenib initiation to proactively manage HFSR. 3. If dose modification is needed, consider 50% dose reduction. 4. In severe cases, consider Clobetasol 0.05% ointment, bid, for erythematous areas and topical analgesic (eg, lidocaine 2%) for pain.
Dyspepsia	1. Low -fiber diet, sorafenib dosing before meals and use of supplements, such as probiotics and digestive enzymes. 2. If these approaches are ineffective, the addition of a proton pump inhibitor and sucralfate can be considered
Diarrhoea	1. Antimotility agents (eg Loperamide) 2. Loperamide at a dose of 4 mg, followed by 2 mg every 4 hours or after each loose stool 3. Sorafenib dose reduction for grade 3 or 4 diarrhoea
Fatigue	1. Weight bearing exercise 2. Night time taking of drug 3. Monitor and correct electrolyte imbalance, anaemia, hypophosphatemia, hypothyroidism

12.1.2 Lenvatinib

Lenvatinib is an oral multikinase inhibitor that targets VEGFR1–3 and fibroblast growth factor receptor (FGFR)1–4 and other kinases. In 2018, lenvatinib met its primary endpoints of noninferiority versus sorafenib in a global phase 3, randomized study, REFLECT.[256] Although there was no significant difference in overall survival (OS) between the group, Lenvatinib improved secondary endpoints versus sorafenib such as time to progression (TTP), progression free survival (PFS), quality of life and objective response rate (ORR).

Hypertension, proteinuria, dysphonia and hypothyroidism were more common with Lenvatinib, whereases HFSR, alopecia and diarrhea were more common with sorafenib.[265] Diarrhoea and hypertension are the common side effects of Lenvatinib in Myanmar. The recommended starting dose of lenvatinib for patients with HCC is 8 mg once daily for those with a body weight of < 60 kg and 12 mg once daily for patients with a body weight of ≥ 60 kg.

Both sorafenib and lenvatinib can be available in Myanmar. But Sorafenib is not widely used as first line treatment option for patients with advanced HCC because of its intolerable side effects. So Lenvatinib remain first line treatment options for patients with advanced HCC in Myanmar.

Table (11) Common side effects of Lenvatinib and their management[282, 283]

Common A/E of Lenvatinib	Management
Hypertension	1. SBP 140 to 159 mmHg or DBP 90 to 99 mmHg • Continue Lenvatinib, initiate antihypertensive therapy SBP ≥ 160 mmHg or DBP ≥ 100 mmHg despite optimal antihypertensive therapy • Withhold Lenvatinib until BP ≤ 150/95 mmHg and resume at a reduced dose 2. Life- threatening condition (Malignant hypertension, hypertensive crisis) • Discontinue Lenvatinib
Proteinuria	1. >1.0–3.5 g/24 h • Hold Lenvatinib until proteinuria resolves to ≤2.0 g/24 h 2. >3.5 g/24 h • Hold Lenvatinib until proteinuria resolves to ≤2.0 g/24 h • Refer patient to Nephrology 3. Nephrotic syndrome • Discontinue Lenvatinib permanently

Diarrhoea	1. Antimotility agents (eg Loperamide) 2. Loperamide at a dose of 4 mg, followed by 2 mg every 4 hours or after each loose stool 3. Sorafenib dose reduction for grade 3 or 4 diarrhoea
Hand-foot skin reaction (HFSR)	1. Patient education • Keeping hands and feet moisturized with a thick urea-based cream • Wearing comfortable shoes with minimal pressure points, and avoiding hot water 2. Follow-up at 2-week intervals for the first 2 months following sorafenib initiation to proactively manage HFSR. 3. If dose modification is needed, consider 50% dose reduction. 4. In severe cases, consider Clobetasol 0.05% ointment, bid, for erythematous areas and topical analgesic (eg, lidocaine 2%) for pain.
Decreased appetite and weight loss	• Regularly monitor appetite and body weight. Lenvatinib dose reduction or interruption may be required. Antiemetics, oral nutrition, or appetite stimulants may be helpful.
Fatigue/asthenia	1. Weight bearing exercise 2. Night time taking of drug 3. Monitor and correct electrolyte imbalance, anaemia, hypophosphatemia, hypothyroidism

12.2 Immune Checkpoint Inhibitors (ICIs)

In contrast with classical chemotherapy (or) molecular targeted therapies that target cancer cells directly, immunotherapies aim to block immune-escapes mechanism of tumors and consecutively, induce a strong and predominantly T-cell mediated immune response against cancer cells. To date, several clinical trials have evaluated the efficacy of antibodies against programmed death-1 (PD-1) (pembrolizumab and nivolumab) or its ligand (PD-LI) (durvalumab and atezolizumab) and cyto-toxic T lymphocyte associated protein 4 (CTLA-4) inhibitors (tremilimumab and ipilimumab), both as monotherapy as well as in combination therapies in patients with advanced HCC.

12.2.1 Atezolizumab-Bevacizumab

Combination of atezolizumab (1,200 mg, intravenously (IV) every 3 week), an immunotherapy targeted PD-L1, plus bevacizumab (15 mg/kg, intravenously (IV) every 3 week), a monoclonal antibody targeting VEGF, was established as the preferred standard of care for patients with advanced HCC in open-label, randomized phase 3, IMbrave 150 trial. The medial OS of 19.2 months with atezolizumab plus bevacizumab is the longest median OS of any first-line treatments for advanced stage HCC to date. Additionally, improved PFS, ORR and time to deterioration of quality of life all favored atezolizumab plus bevacizumab over sorafenib.[26,6]

Given bevacizumab increases the risk of GI bleeding, likely related to VEGF mediated endothelial disruption, patients were required to have endoscopic evaluation within 6 months before initiation of therapy. Patients with large varices should likely undergo at least one session of band ligation prior to atezolizumab plus bevacizumab, although carvedilol may also be effective. The optimal time to wait between band ligation and initiation of atezolizumab plus bevacizumab to minimize risk of bleeding from banding ulcer is unknown, although 2 weeks is likely reasonable given risk of post banding ulcer.[257]

12.2.2 Tremelimumab-Durvalumab

Data from the open-label, randomized phase III HIMALAYA trial demonstrated improved OS with the immunotherapy combination of durvalumab (a PD-L1 inhibitor) plus tremelimumab (a CTLA4 inhibitor) versus sorafenib (median OS 16.4 vs. 13.7 months, respectively) and noninferior OS with durvalumab monotherapy versus sorafenib* Durvalumab plus tremelimumab is another preferred option for patients in the first-line setting, particularly for patients who are not candidates for anti-VEGF therapy[266] (Currently the drugs are not available in Myanmar).

ICIs are often well tolerated but can be associated with immune related AEs (irAEs) that can involve any organ system. The risk of irAEs are higher when two ICIs are used together. ICIs are not recommended in patients with moderate to severe autoimmune disease and post-transplant patients given high risk of graft loss and mortality.[257]

12.3 Second-line therapy

Several multicenter randomized trials addressed systemic therapy options in the second-line setting following sorafenib therapy. Second-line therapy is advised in patients with preserved liver function (Child-Turcotte-Pugh A or well-selected Child-Turcotte-Pugh B cirrhosis), ECOG PS 0-1, who develop HCC progression or intolerance with first-line systemic therapy. Cabozantinib or regorafenib (or ramucirumab in patients with AFP ≥ 400 ng/ml) are preferred agents after sorafenib or Lenvatinib. Regorafenib should not be used in patients who do not tolerate sorafenib due to toxicity.[257]

Following first-line treatment with atezolizumab plus bevacizumab, treatment with a first-line mTKI (sorafenib or lenvatinib) is advised as preferred agents, although second-line mTKIs (cabozantinib or regorafenib) or ramucirumab (if AFP ≥400 ng/ml) may also be considered.[257]

Recommendation (Systemic Therapy)

51. Patients with advanced HCC (BCLC-C) or patients with BCLC B who are ineligible to locoregional therapy or in whom TACE failure cases should be offered systemic therapy (antiangiogenic targeted therapies) but the patient should have preserved liver function (Child Pugh– A/B) and ECOG PS 0-1.
52. Side effects of Tyrosine kinase inhibitors usually occur during the first few weeks of treatment, especially Hand-Foot Skin Reaction (HFSR) in Sorafenib and Hypertension or Diarrhoea in Lenvatinib therapy in Myanmar population.
53. Lenvatinib is recommended as first-line treatment of patients with advanced HCC (BCLC-C) or patients with BCLC B who are ineligible to locoregional therapy or in whom TACE failure cases.
54. Other Tyrosine kinase inhibitors (TKIs) such as Regorafenib (sorafenib tolerant but non responder), Cabozantinib (Sorafenib non tolerant and non-responder), Ramucirumab (Sorafenib non responder and AFP > 400) are second-line treatment of patients with advanced HCC (BCLC-C) but they are not available in Myanmar.
55. Immune checkpoint inhibitors (Atezolizumab + Bevacizumab) is recommended as first-line treatment of patients with advanced HCC (BCLC-C) with preserved liver function (Child-Pugh class A) and ECOG PS 0-1.
    a. Gastrointestinal bleeding is a known adverse effect of Bevacizumab and individuals should undergo endoscopic evaluation and treatment for esophageal varices within approximately 6 months before treatment or according to institutional practice and based on the assessment of bleeding risk.
    b. Immune checkpoint inhibitors are often well tolerated but can be associated with immune related AEs (irAEs) that can involve any organ system.

13. Treatment response assessment and follow up schedule

13.1 Radiological assessment of response

Patients treated with TACE should undergo multiphase contrast-enhanced CT or MRI approximately 6 weeks after treatment. Those treated with TARE or EBRT should undergo imaging to assess response approximately 12 weeks after treatment.[257] Repeat treatment is provided on demand in those with continued viable disease. Repeat imaging every 3–6 months is recommended in those without definite viable disease.[257]

Radiologically, response evaluation criteria in solid tumors (RECIST) version 1.1 is used to measure response and progression in oncology. In HCC patients, in order to provide Modifications of RECIST criteria (mRECIST) (measurement of the diameter of viable tumor component of target lesions) is used to adapt RECIST criteria for HCC patients.[273] Thus, mRECIST is the standard tool to assess radiological response after locoregional therapy for patients with early and intermediate stages of HCC.
The response should be categorized as CR (complete response), PR (partial response), SD (stable disease) or PD (progressive disease). CP and PR should be considered as responder and SD and PD patients as non-responder.[274]

AFP responses predict outcomes in patients treated with atezolizumab-bevacizumab, sorafenib, regorafenib, cabozantinib and ramucirumab. However, increased AFP levels in the absence of radiological confirmation should not be taken as an unequivocal sign of tumor progression and should not lead to treatment discontinuation.[275]

13.2 Follow up schedule

The timing of initial treatment response evaluation and subsequent follow-up should depend on treatment modality used. Follow-up of patients who underwent radical treatments (resection or RFA or transplantation) should consists of the clinical evaluation of liver decompensation and the early detection of recurrence. Recurrence usually develops within 2 years after potentially curative treatment. Follow-up with contrast enhanced CT or MRI is recommended every 3 months for the first 2 years after curative treatment. After 2 years without recurrence, follow-up can be performed at 6-month intervals.[276-279]

Follow-up patients who underwent TACE should be follow-up at 6-8 weeks after TACE procedure and patients with more advanced stages of HCC who are treated with systemic therapies are evaluated clinically for signs of liver decompensation and for tumor progression by dynamic CT or MRI every 3 months to guide therapy decisions.[279]
In addition, the monitoring interval should be individualized on the basic of patients-specific risk factors according to tumor biology and underlying liver diseases.[279]

Recommendation (Treatment response assessment and follow up schedule)

56. Post treatment follow-up with USG or contrast enhanced CT or MRI is necessary in patients with potentially curative therapy (ablation, liver resection and liver transplantation) because recurrent risk is present.
57. Contrast enhanced CT or MRI with mRECIST criteria is recommended for assessment of treatment response or progression after ablation and locoregional therapies.
58. Follow-up patients who underwent radical treatments (resection or RFA or transplantation) should consist of the clinical evaluation of liver decompensation and the early detection of recurrence by USG or contrast enhanced CT or MRI studies every 3 months during the first 2 years and every 6 months thereafter and as required.
59. Patients treated with TACE should undergo multiphasic contrast-enhanced CT or MRI approximately 6 weeks after treatment with continued viable disease and every 3–6 months for without definite viable disease and as required.
60. Patients with more advanced stages of HCC treated with systemic therapies are evaluated clinically for signs of liver decompensation and for tumor progression by contrast enhanced CT or MRI every 3–6 months to guide therapy decisions and as required.
61. AFP levels changes can be considered for assessment of treatment response if AFP level is higher from baseline.

14. Palliative care

Palliative care is an approach that improves the quality of life of patients and their families associated with life-threatening illness, through the prevention and relief of suffering by means of early identification, assessment and treatment of pain and other problems, physical, psychosocial, and spiritual.

Patients with advanced HCC (BCLC D) have dismal prognosis and life expectancy of about 3-4 months. Management of end-stage disease is only symptomatic, and no tumor directed treatment is indicated. These patients should receive palliative support including management of pain, nutrition and psychological support. Effective symptom management allows patients and their families to focus on maintaining hope, reaffirming important connections, and attaining a sense of completion. The clinical picture of patients with terminal HCC is particularly complex, resulting from a combination of symptoms deriving both from their end- stage cirrhotic liver disease and the effect of large tumor bulk.[281]

14.1 Pain management

WHO stepwise approach may be useful in management of pain in HCC. The choice of appropriate analgesic requires a thorough understanding of their pharmacokinetics and side-effect profile. Susceptibility to adverse effects increases with worsening of liver function due to altered pharmacokinetics and hemodynamic change.

14.1.1 Acetaminophen: 500 mg every 6 hours, up to maximum dose of 2 g/day is the preferred first line pharmacotherapy for the management of pain.

14.1.2 Non-steroidal anti-inflammatory drugs (NSAIDs): are associated with increased risk of gastrointestinal bleeding, decompensation of ascites and nephrotoxicity, particularly in patients with clinically significant portal hypertension and should be avoided.[283]

14.1.3 Gamma Aminobutyric Acid Inhibitors (GABA Inhibitors): Gabapentin 300 mg daily (starting dose) or Pregabalin 50 mg bd, (starting dose) are effective in treating neuropathic pain.

14.1.4 Opioid: In case of moderate-to-severe pain, which usually is insufficiently controlled by acetaminophen, opioids are the drugs of choice. However, opioid metabolism may be deeply affected by liver cirrhosis and opioid-treated patients are at increased risk of constipation and consequently of hepatic encephalopathy. pharmacologic treatments including osmotic laxatives may be helpful. Morphine and derivatives are the first choice and Fentanyl is an excellent option in patients with impaired liver

function. Cachexia is a relative contraindication to transdermal fentanyl, rendering it impractical to use in many patients with cirrhosis.[282, 283]

14.1.5 Glucocorticoids: are often used to alleviate symptoms such as pain, nausea, fatigue, anorexia and malaise and improved overall quality of life. Dexamethasone is usually preferred for the management of cancer-related pain, presumably because of its long half-life and relatively low mineralocorticoid effect. Prednisone and methylprednisolone are acceptable alternatives. A typical regimen for patients with cancer related pain is 1-2 mg of dexamethasone orally or parenterally twice daily.[270]

14.1.6 Palliative radiotherapy: is indicated when pain is generated by well identified bone metastasis or when a lytic bone metastasis is considered at high risk of spontaneous fracture. Radiotherapy can also be used to relieve pain from lung and lymph node metastasis.[282]

14.2 Nutritional management

Patients with decompensated cirrhosis commonly suffer weight loss and muscle wasting. Nutritional status, assessed through psoas muscles mass for example, has been found to be independently associated with overall survival in patients with advanced HCC.

Since patients with terminal HCC may also have fluid retention and ascites and are highly subject to infections, oral supplementation should be preferred over intravenous administration. If patients are not able to maintain adequate oral intake, tube feeding is recommended (even when oesophageal varices are present). At the very final time of life, at least every decision on therapeutic interventions should base on the individual situation and needs of the patients.[282]

14.2.1 Anorexia-Cachexia

Weight loss is a frequent problem in HCC patients. Anorexia is next leading symptom and therefore a common term for cancer wasting syndrome is anorexia-cachexia syndrome. Thorough assessment of potential contributors such as chronic nausea, constipation, early satiety, taste alteration, and depression should be done. Megestrol acetate (dose ranging from 160 to 1,600 mg/day) significantly improves appetite. Late evening snack of 200 kcal such as a rice bowl or liquid nutritional supplement is recommended to improve nocturnal fasting, nutritional status increasing body protein content and to diminish fat and protein oxidation. Individualized dietary counseling is effective in improving patient's food intake, nutritional status, and quality of life.[282]

14.2.2 Nausea and vomiting

For patients who suffer from nausea and/or vomiting, an evaluation should include assessment of electrolytes, adrenal insufficiency and pharmaceutical causes as well as assessment for the and treatment of gastroesophageal reflux disease. Ondansetron (maximum 8 mg/day) is the first-line pharmacotherapy for nausea and vomiting. Patients should be monitored for constipation and QTc prolongation.[283]

14.3 Pruritus

Initial treatment includes moisturizing creams, avoidance of hot baths and rubbing of the skin, minimizing use of harsh soaps and detergents, and using loose-fitting clothing and cool humidified air. Antihistamines, which are often used for pruritus, may have sedating effect or exacerbate encephalopathy. Cholestyramine (4 g/day with titration to 16 g/day) is first-line treatment for pruritus. Sertraline, an SSRI, has been shown to reduce cholestatic pruritus symptoms at 75 – to 100 mg doses. Sertraline is well tolerated but it is largely metabolized in the liver, it requires careful administration (e.g., a starting dose of 25 mg with titration) in patients with decompensated cirrhosis. Rifampicin and Naltrexone can be used in refractory cases.[283]

Recommendation (Palliative care)

62. Patients with BCLC-D HCC should be managed symptomatically in conjunction with best supportive care services including management of pain, nutritional management and psychosocial support.

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