The Diagnosis and Staging of Hepatocellular Carcinoma

A Review of Current Practices

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KEYWORDS

• Liver Imaging Reporting and Data System • Barcelona-Clinic Liver Cancer • Biomarkers • Prognosis • Liver cancer

KEY POINTS

- The early detection and diagnosis of hepatocellular carcinoma (HCC) is a critical strategy that allows for greater access to curative treatments.
- The majority of HCC is diagnosed through imaging-based examinations. The Liver Imaging Reporting and Data System (LI-RADS) aims to standardize the terminology and categorization of liver lesions seen on computed tomography, MRI, or contrast-enhanced ultrasound.
- Staging of HCC is essential for determining prognosis and appropriate treatment options. The Barcelona Clinic Liver Cancer system, most recently modified in 2022, is widely used and integrates tumor burden, the severity of liver dysfunction, and patient performance to help guide treatment options.

INTRODUCTION

Hepatocellular carcinoma (HCC), the leading cause of primary liver cancer, is the sixth most common cancer and the third leading cause of cancer-related deaths worldwide.[1] Despite advancements in the treatment of viral hepatitis, the incidence of HCC is projected to rise due to the increased prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD).[2] The prognosis after HCC diagnosis is

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generally poor with a 5-year survival rate of only 20%.[3] However, one of the strongest predictors of HCC-related mortality is the stage at diagnosis.[4,5] Early detection of HCC can result in greater access to curative treatments and better outcomes, with 5-year survival rates exceeding 55%.[4,6] Promoting the early detection and diagnosis of HCC is therefore a critical strategy to improve patient outcomes. This review aims to outline (1) the imaging and biomarker-based testing that is used to diagnose HCC and (2) HCC staging.

Ultrasound Liver Imaging Reporting and Data System Categories and Visualization Score

HCC surveillance is targeted toward patients who have elevated risks of HCC, that is, those with cirrhosis and chronic hepatitis B virus (HBV) infection.[7–9] Guidelines from major international societies, including the American Association for the Study of Liver Diseases (AASLD),[7] the European Association for the Study of the Liver[9] and the Asia-Pacific Association for the Study of the Liver[8] have all recommended the use of semi-annual abdominal ultrasound (US) testing for HCC surveillance.

The Liver Imaging Reporting and Data System (LI-RADS) US algorithm (**Table 1**)[10] most recently updated in 2024, includes both an evaluation and visualization score that can be used in patients at high risk for HCC. There are 3 possible evaluation scores: US-1, US-2, and US-3. The *US-1* category (Negative) is assigned when there are definitely benign observations and without any observations worrisome for HCC, and routine US surveillance in 6 mo is recommended. The *US-2* category (Subthreshold) is assigned when there is an observation that is less than 10 mm and not definitively benign; in such cases, short-interval surveillance in 3 to 6 mo to evaluate for interval growth or changes is recommended. If there are changes, further diagnostic imaging with computed tomography (CT) or MRI can be pursued. Finally, US-3 (Positive) is assigned when there are liver observations that are greater than 10 mm and not definitively benign, or if there is a new portal vein or hepatic vein thrombus. For *US-3* classification, prompt testing with multiphase contrast-enhanced abdominal CT or MRI is recommended.

However, as a surveillance test, US has the limitations of being highly operator dependent[11] and is susceptible to technical factors (ie, patients' body habitus, beam attenuation, and heterogeneous parenchymal echotexture)[12] that can impede liver visualization. Such technical barriers are more prevalent in patients with obesity, MASLD, and alcohol-associated liver disease (ALD).[13,14] According to a recent meta-analysis of 31 studies and 12,977 patients, the overall pooled sensitivity of US for HCC at any stage is 84% (95% confidence interval [CI] 76%-92%); however, the sensitivity in the primary studies ranged 28% to 100%, demonstrating severe heterogeneity in the analyzed data. Sensitivity for detecting early-stage HCC is lower at 47% (95%CI 33%–61%) for US alone and 63% (95%CI 48%–75%) when combined with measurement of alpha-fetoprotein (AFP).[15] Concurrent cross-sectional imaging studies such as CT or MRI were not done in most studies included in this meta-analysis, but actual sensitivity of US may even be lower if HCC diagnosis can be confirmed or ruled out with concurrent cross-sectional imaging studies such as CT or MRI at the same time as US. Indeed, a recent prospective phase 3 study comparing a novel HCC biomarker with US with concurrent multiphase MRI as the "clinical truth" among about 1900 patients with cirrhosis found that the sensitivity of US was only 28% overall (95% CI 16%–44%) and 0% for HCC tumors smaller than 2 cm.[16]

These limitations are also further characterized within the LI-RADS US visualization algorithm (see **Table 1**).[10,13,17] This algorithm consists of 3 ordinal categories that progressively indicate poorer visualization (A, B, and C): *A* indicates minimal or no

Table 1
Liver imaging reporting and data system ultrasound surveillance categories and visualization scores for patients at high risk for hepatocellular carcinoma (eg, cirrhosis of any etiology or chronic hepatitis B at risk for hepatocellular carcinoma)

Category	Description/Examples:	Follow-up Recommendations
US-1 (Negative)	• No observation or definitely benign observation	• Continue routine surveillance
US-2 (Subthreshold)	• Observations < 10 mm, not definitely benign	• Repeat US in 3–6 mo up to 2 times • If observation remains <10 mm or not visualized on follow-up twice, then the observation can be recategorized as US-1 with return to routine surveillance
US-3 (Positive)	• Solid Observations $\geq$10 mm including areas of parenchymal distortion • New hepatic or portal vein thrombus	• Evaluate with multi-phase and contrast-enhanced CT, MRI, or CEUS
US Visualization-A (No or minimal limitations)	• Liver homogeneous or mildly heterogeneous • Minimal beam attenuation or shadowing • Liver visualized in near entirety	• No special considerations
US Visualization-B (Moderate Limitations)	• Limitations that may obscure small (<10 mm) observations • Moderate beam attenuation or shadowing • Some portions of liver or diaphragm not visualized	• Repeated VIS-B scores may warrant an alternative study (multiphase CT or MRI)
US Visualization-C (Severe Limitations)	• Liver severely heterogeneous • Severe beam attenuation or shadowing • Majority (>50%) of right or left lobe not visualized • Majority (>50%) of diaphragm not visualized	If poor visualization risk factors present (MASLD- or alcohol-associated cirrhosis, CTP class B or C cirrhosis, BMI $\geq$35 kg/m^2) • Consider alternative surveillance modality (eg, CT or MRI) If poor visualization risk factors NOT present: • Repeat US within 3 mo in 1 time. If still VIS-C, consider other surveillance method (multiphase CT or MRI)

Abbreviations: BMI, body mass index; CTP, Child-Turcotte-Pugh; MASLD, Metabolic-dysfunction associated steatotic liver disease.

limitations in visualization; *B* indicates moderate limitations, which may obscure small masses; and *C* is consistent with severe limitations, which lowers the sensitivity of the study for focal liver lesions. A visualization score of A or B is typically considered acceptable for HCC surveillance. However, repeated studies (ie, with visualization score B) may warrant assessment with an alternative modality. A visualization score of C indicates that the quality of the US examination is insufficient for HCC surveillance. In this setting, follow-up options include either a short interval repeat US (if there are no patient-level risk factors for poor visualization, eg, obesity, MASH or ALD, Child-Pugh B or C cirrhosis) or short interval testing with another imaging modality (multiphase contrast-enhanced CT or MRI). In a study of 2053 patients with cirrhosis of various etiologies, Schoenberger and colleagues reported that the LI-RADS visualization score was B for 13% and C for 5% of patients.[14] Obesity, cirrhosis related to alcohol or MASLD, and Child–Pugh stage B or C were independent predictors of limited visualization. This finding is critical, as it indicates that visualization limitations will become gradually more problematic given the increasing prevalence of obesity, MASLD, and ALD.[18,19]

Novel Tests for Hepatocellular Carcinoma Screening: Biomarker and Biomarker Panel-Based Tests

Blood-based biomarkers have been used to address some of these US-based limitations and to enhance our overall ability to detect HCC. The most widely studied biomarker used in HCC surveillance and diagnosis is the AFP. A meta-analysis has shown that adding AFP to ultrasonography improves the sensitivity of early-stage HCC detection from 53% to 63% and with only a small decrease in specificity.[15] The AASLD therefore recommends the combination of US + AFP to be used for HCC surveillance, rather than US alone.[7] However, AFP, as an isolated test, has poor sensitivity and specificity for the detection of HCC as over 40% of HCC will have normal AFP levels and elevated AFP levels can be observed in other cancers such as intrahepatic cholangiocarcinoma, gastric cancer, and germ cell tumors.[20] Given insufficient accuracy, AFP alone is not routinely recommended for HCC diagnosis although elevated levels (ie, >20 ng/mL) and/or upward trending levels typically warrant diagnostic testing with multiphase contrast-enhanced CT or MRI.[7,10] Other serum biomarkers, such as des-carboxy-prothrombin (DCP) and AFP-L3% have been used in real-world clinical settings for HCC surveillance but their sensitivity for early HCC, similar to AFP, is also poor (<50%).[21,22]

Combinations of biomarkers have also been used and have shown promise; such combinations include the HCC early detection screening (HES) algorithm[23] (AFP, rate of AFP change, alanine aminotransferase, and platelet count) and GALAD[22,24] (gender, age, AFP, AFP-L3%, and DCP) scores. In a prospective phase 3 cohort study examining AFP, AFP-L3%, DCP, GALAD, and HES for early HCC detection, the HES and GALAD offered increased sensitivity, but with a notable increase in false positives compared to the other examined modalities.[22] The study of blood-based biomarkers and biomarker panels to detect early HCC remains an area of active investigation. As the data emerge, it will be important to weigh the benefits (ie, ease of implementation) and the costs of using these novel tests for HCC diagnosis. Special consideration should also be given to the potential for sequential application of biomarkers and imaging modalities to optimize the early detection of HCC.

Cell-free tumor DNA (cfDNA) biomarkers have also been developed in the recent years to aid in the diagnosis of HCC, with a recent phase 3 study reporting superior sensitivity of a novel multi-analyte cfDNA-based blood test compared to US alone, especially for HCC tumors smaller than 2 cm.[25]

Diagnostic Multiphase Contrast-Enhanced Computed Tomography and MRI and The Corresponding Liver Imaging Reporting and Data System Categories

If HCC is suspected based on US or serologic testing, diagnostic confirmation with multiphase contrast-enhanced CT or MRI is recommended. The CT/MRI LI-RADS (**Table 2**) is a standardized system for the imaging-based diagnosis of HCC in patients with cirrhosis or any etiology and in patients with chronic HBV without cirrhosis.[26] This algorithm was first released in 2011 and has since undergone multiple iterations and refinements, with the most recent (v2018) being incorporated into the AASLD clinical practice guidance.[7]

It is important to note that the LI-RADS algorithm does not apply to patients without cirrhosis or HBV, or vascular causes of cirrhosis such as Budd–Chiari syndrome given the association between these conditions and hypervascular benign liver lesions.[27] The LI-RADS algorithm applies a decision tree, diagnostic table, ancillary features, and tie-breaking rules to categorize observations on an ordinal scale according to the probability of HCC. This scale ranges from LR-1 (definitely benign) to LR-5 (definitely HCC).

- *LR-1* refers to liver lesions that are definitely benign, such as simple cysts, hemangiomas with characteristic imaging features, perfusion anomalies, and focal fat sparing or deposition, which have minimal risk of being malignant.
- *LR-2* includes lesions that are probably benign, with a very low probability of malignancy. Examples include atypical hemangiomas, focal nodular hyperplasia-like nodules, and small (<20 mm) arterially enhancing lesions without concerning features. These lesions might show arterial phase enhancement (increased enhancement during the arterial phase of imaging) but lack other suspicious features.
- *LR-3* categorizes lesions with an intermediate probability of being HCC (~38%).[28] These might include observations with some suggestive features but not definitively diagnostic, such as small (<10 mm) arterially enhancing nodules without washout (a reduction in enhancement from arterial to portal venous or delayed phase) or pseudocapsule (a rim of enhancement around the lesion indicating a fibrous capsule or compressed liver parenchyma). These nodules might have indeterminate imaging features that warrant close follow-up.
- *LR-4* encompasses observations that are probably HCC, and characterized by a high probability of malignancy (~74%).[28] These observations can include those modest in size (10–19 mm) with arterial phase hyperenhancement (APHE) and the presence of a pseudocapsule.
- *LR-5* defines lesions that meet criteria for HCC and are definitively malignant. These observations are all greater than or equal to 10 mm in size and have APHE. To meet LR-5 criteria, depending on the size, these observations need to also have washout in the portal venous or delayed phase, a pseudocapsule, substantial interval growth, or a combination of these features.

The other 3 categories in the algorithm are LR non-categorizable (LR-NC), LR Tumor in Vein (LR-TIV), and LR-Malignancy (LR-M).

- *LR-NC* is assigned when there is either imaging sequence omission (ie, lack of an arterial phase) or image degradation to the point where there is insufficient image quality to allow for adequate evaluation of an observation.
- *LR-TIV* is used when there is a tumor thrombus within the hepatic vasculature, particularly within branches of the portal and hepatic veins. Key imaging features of LR-TIV include APHE and washout appearance within the thrombus, reflecting

Table 2
Liver Imaging Reporting and Data System computed tomography/MRI categories for untreated observations without pathologic proof of hepatocellular carcinoma

Category (Description, % Risk HCC)	Description/Examples:	Follow-up Recommendations
LR-1 (Definitely benign, 0% HCC)	• Observations such as cysts, hemangiomas, arterioportal shunts, hepatic fat deposition, hypertrophic pseudomass, confluent fibrosis or focal scar	• Return to routine surveillance
LR-2 (Probably Benign, 16% HCC)	• Solid nodule <20 mm without major (APHE, washout, capsule, or threshold growth[a]) or ancillary features of HCC	• Continued routine surveillance, consider repeat diagnostic imaging in 6 mo or less
LR-3 (Intermediate probability of malignancy, 37% HCC)	<20 mm without APHE • No more than one of the following: ○ Washout ○ Capsule ○ Threshold growth <20 mm with APHE • No washout, capsule, or threshold growth	• Repeat or alternative diagnostic imaging in 3–6 mo
LR-4 (Probably HCC, 74% HCC)	<10 mm with APHE • One or more of the following: ○ Non-peripheral "washout" ○ Enhancing capsule ○ Threshold growth 10–19 mm with APHE • Enhancing capsule, but does not have washout or threshold growth ≥20 mm with APHE • No major suspicious features, such as washout, enhancing capsule, or threshold growth	• Multidisciplinary team discussion for tailored workup, may include biopsy
LR-5 (Definitely HCC, 95% HCC)	10–19 mm with APHE • Washout or meets threshold for growth ≥ 20 mm with APHE • One or more of the following: ○ Washout ○ Enhancing capsule ○ Threshold growth	• HCC confirmed, multidisciplinary team for consensus management
LR-NC (Not categorizable)	• Cannot be categorized due to image degradation or omission	• Repeat or alternative diagnostic imaging in 3 mo or less
LR-M (Probably or definitely malignant, not necessarily HCC)	• Targetoid mass • Nontargetoid mass with one or more of the following: ○ Infiltrative appearance ○ Marked diffuse restriction ○ Necrosis or severe ischemia	• Multidisciplinary team discussion for tailored workup, often includes biopsy

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Table 2
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Category (Description, % Risk HCC)	Description/Examples:	Follow-up Recommendations
	○ Other features per reviewing radiologist that would suggest non-HCC malignancy	
LR-TIV (Tumor in vein)	• Unequivocal enhancing soft tissue in vein, regardless of visualization of parenchymal mass	• Multidisciplinary team discussion for tailored workup, may include biopsy

Abbreviation: APHE, arterial phase hyperenhancement.
[a] Threshold growth is defined as a diameter increase ≥50% in ≤6 mo.

characteristics typical of HCC. The affected vein often appears expanded or distended due to the presence of the tumor thrombus, which may be contiguous with a primary liver mass showing similar HCC features. However, non-contiguous tumor thrombi can also be classified as LR-TIV; the presence of a parenchymal mass is not necessary to classify an observation as LR-TIV. In addition, LR-TIV is not specific for HCC. Prior meta-analysis has shown that nearly 30% of LR-TIV cases were due to non-HCC malignancies.[29] However, when found with HCC, LR-TIV signifies advanced disease with vascular invasion, which is associated with a higher risk of metastasis and a poorer prognosis.[30] This classification heavily influences treatment decisions, often steering management toward locoregional therapies (such as transarterial chemoembolization or radioembolization) or systemic therapies, rather than curative surgical resection or liver transplantation.

- Finally, *LR-M* used to identify liver lesions that are very likely malignant, but do not specifically meet the criteria for HCC. This category can include lesions related to other malignancies such as intrahepatic cholangiocarcinoma (ICC), combined HCC-ICC, or metastases.[31] Lesions classified as LR-M typically exhibit imaging features atypical for HCC, such as heterogeneous or rim-like enhancement in the arterial phase, progressive or persistent enhancement in the delayed phase, and the presence of necrotic areas or marked heterogeneity. They often lack the uniform APHE and capsule appearance typical of HCC. The identification of LR-M lesions requires careful consideration for further diagnostic testing, including sampling for histologic examination. In the LR-M category, 93% to 99% of observations are malignant, with 22% to 36% still being HCC.[28]

Diagnostic Contrast-Enhanced Ultrasound and The Corresponding Contrast-Enhanced Ultrasound Liver Imaging Reporting and Data System Categories

Most patients with concerning observations can undergo CT or MRI for further evaluation. However, in clinical scenarios where a patient is not a candidate for either of these imaging tests due to renal dysfunction, prior adverse reactions, or other technical concerns, contrast-enhanced ultrasound (CEUS) offers an additional modality that can confirm an HCC diagnosis.[32] CEUS is a specialized form of US performed with an intravenous, non-nephrotoxic injection of microbubble contrast agents. As a single injection generally focuses on a single observation with the maintenance of the transducer in a fixed location, CEUS is best suited to characterize a set number of observations and not to survey the entire liver parenchyma or many observations.

Thus, it is inherently not suited to be a surveillance or staging test. CEUS also has similar limitations as US, including operator dependency and patient/tumor factors on visualization. CEUS can be utilized for both the diagnosis of and imaging guidance for ablative treatment of HCC. After bolus intravenous injection, these contrast agents allow capillary blood flow to be imaged and contrast enhancement to be assessed with a temporal resolution (10 f/sec) even higher than those compared to CT or MRI. Therefore, CEUS can detect both early and late APHE that would have been missed on CT or MRI. CEUS can also detect rapidly changing arterial phase enhancement patterns, which are typically seen with many benign lesions including hemangiomas.

The hallmark of HCC on CEUS is a homogeneous and intense APHE with mild washout starting greater than 60 sec after injection. In contrast to the CT/MRI LI-RADS criteria, the timing and degree of washout are important for the characterization of HCC, which typically shows milder and more delayed (>60 seconds) washout compared to metastases and cholangiocarcinoma (both with more marked and early [<60 sec] washout). Pseudocapsules are also not seen on CEUS.

Moreover, a CEUS LI-RADS algorithm (**Table 3**)[33] has been introduced by the American College of Radiology to aid in the accurate characterization of nodules in patients with cirrhosis and at high risk for HCC. The major criteria are APHE, nodule size, and portal-late mild wash-out. A rim APHE and early (<60 second) or marked wash-out represents LI-RADS M criteria (LR-M) favoring the diagnosis of a non-hepatocellular malignancy. This algorithm divides liver observations into several categories, which are designed to be analogous to the CT/MRI LI-RADS categories.

- *CEUS LR-NC* is not categorizable due to image degradation or sequence omission.
- *CEUS LR-1* indicates a definitely benign lesion such as a cyst, hemangioma, or hepatic fat deposition/sparing.
- *CEUS LR-2* is for probably benign lesions, including distinct iso-enhancing solid nodules less than 10 mm or non-mass-like iso-enhancing observations not typical of hepatic fat deposition/sparing.
- *CEUS LR-3* indicates an intermediate probability of malignancy and includes nodules less than 20 mm without APHE or washout, or with late and mild washout.
- *CEUS LR-4* indicates probable HCC, which includes nodules greater than or equal to 20 mm without APHE but with late and mild washout, nodules less than 10 mm with APHE and late mild washout, and nodules greater than or equal to 10 mm with APHE and no washout.
- *CEUS LR-5* indicates definitely HCC, as characterized by nodules greater than or equal to 10 mm with APHE and late mild washout.
- *CEUS LR-M* suggests probable or definite malignancy, not specific to HCC, characterized by rim APHE, early washout, or marked washout. Finally,
- *CEUS LR-TIV* indicates a tumor in the vein, defined by unequivocally enhancing soft tissue in a vein or early visualization of intravenous contrast in the vein.

An Emerging Imaging Test That Could Allow for Both Surveillance and Diagnosis of Hepatocellular carcinoma: Abbreviated MRI

Abbreviated MRI (aMRI) protocols are emerging as a promising modality for both HCC surveillance and diagnosis.[34] Compared to the complete multiphase MRI protocol, aMRI is designed to have a much lower cost and time burden (<15 minutes), coupled with improved accuracy as compared to US. For example, in a retrospective, simulation study, an aMRI protocol demonstrated a per-patient sensitivity of 82.6%,[35] which

Table 3
Liver Imaging Reporting and Data System Contrast-enhanced Categories for untreated observations without pathologic proof of hepatocellular carcinoma

Category (Description, % Risk HCC[57])	Description/Examples:	Follow-up Recommendations
CEUS LR-1 (Definitely benign)	• Observations such as cysts, hemangiomas, arterioportal shunts, hepatic fat deposition, hypertrophic pseudomass, confluent fibrosis or focal scar	• Return to routine surveillance
CEUS LR-2 (Probably Benign)	• Distinct isoenhancing nodule <10 mm • Nonmasslike isoenhancing observation of any size, not typical hepatic fat deposition//sparing • CEUS LR-3 nodules with size stability for ≥2 y	• Continued routine surveillance, consider repeat CEUS in 6 mo or less
CEUS LR-3 (Intermediate probability of malignancy, 60% HCC)	<10 mm with APHE • No washout <20 mm without APHE • No washout or with late and mild washout ≥20 mm without APHE • No washout	• Repeat or alternative diagnostic imaging in 6 mo or less
CEUS LR-4 (Probably HCC, 88% HCC)	<10 mm with APHE • With washout ≥10 mm with APHE • No washout ≥20 mm without APHE • With late and mild washout	• Multidisciplinary team discussion for tailored workup, may include biopsy • If biopsy or treatment not planned, repeat assessment with CEUS or alternative diagnostic imaging in 3 mo or less
LR-5 (Definitely HCC, 98% HCC)	10–19 mm with APHE • With late and mild washout	• HCC confirmed, multidisciplinary team for consensus management
LR-NC (Not categorizable)	• Cannot be categorized due to image degradation or omission	• Repeat or alternative diagnostic imaging in 3 mo or less
LR-M (Probably or definitely malignant, not necessarily HCC)	Observation (any size) with any of the following: • Rim (non-peripheral discontinuous globular) APHE • Early (<60 s) washout • Marked washout	• Multidisciplinary team discussion for tailored workup, often includes biopsy
LR-TIV (Tumor in vein)	• Unequivocal enhancing soft tissue in vein, regardless of visualization of parenchymal mass. • If contiguous with CEUS LR-5, definitely due to HCC	• Multidisciplinary team discussion for tailored workup, may include biopsy

Threshold growth, defined as a diameter increase ≥50% in ≤6 mo, is considered an ancillary feature in the LI-RADS CEUS algorithm.
Abbreviation: APHE: arterial phase hyperenhancement.

was much higher than the sensitivity for US + AFP testing (~62%).[15] The sensitivity of the aMRI protocol for the detection of HCC was also similar to the sensitivity for the complete study with gadoxetic acid.[34] Additional prospective studies are needed to better characterize the diagnostic accuracy and cost-effectiveness of using aMRI in diverse patient populations.

Biopsy and Histopathologic Diagnosis of Hepatocellular Carcinoma

Although most HCCs have characteristic features on imaging, ~10% of liver lesions will lack the imaging hallmarks to be diagnosed as HCC (eg, LR-5). In selected patients, histologic diagnosis via biopsy of the liver tumor can be considered when imaging studies are inconclusive, but there is still high enough suspicion for HCC or another non-HCC malignancy (ie, LR-4 or LR-M). As the LI-RADS algorithm has only been studied in patients with an elevated risk of HCC (ie, cirrhosis and chronic HBV), a biopsy may also be warranted for patients with liver lesions who do not have underlying liver disease, cirrhosis, or chronic HBV infection.

There are substantial risks to tumor biopsies. In addition to bleeding, pain at the site of the biopsy, infection, and injury to other nearby organs,[36] the additional risk of needle track seeding needs to be considered. A meta-analysis of 8 studies reported a 2.7% risk of needle track seeding and reported a median of 17 mo that had elapsed from the time of biopsy to the discovery of needle track seeding.[37] The sensitivity of a tumor biopsy is ~70 to 80%, but is lower with smaller (<2 cm) observations due to the possibility of missing lesions, as well as the difficulty in distinguishing well-differentiated HCC from dysplastic nodules.[38] Some patients may therefore require multiple biopsies for a diagnosis, so patients with a negative biopsy but suspicion for HCC should continue to be followed with serial multiphase abdominal imaging. If the lesion enlarges but continues to lack imaging characteristics typical for HCC, a repeat biopsy can be considered.

Staging of Hepatocellular Carcinoma: Evaluating Liver Function and Tumor Burden to Help Inform Prognosis and Guide Treatment

All patients newly diagnosed with HCC should undergo multiphase contrast-enhanced abdominal CT or MRI and a non-contrast CT chest for assessment of tumor staging and metastatic disease. Technetium-99m methylene diphosphonate bone scintigraphy can be considered to assess for bone metastases in selected patients, including those with markedly elevated AFP values and imaging evidence for macrovascular invasion or multifocal and bilobar disease.[39] An assessment of the underlying liver function will also be critical to for providing prognostic and treatment information.

Several staging systems for HCC have been proposed, including but not limited to the Barcelona-Clinic Liver Cancer (BCLC),[40] Hong Kong Liver Cancer,[41] Okuda system,[42] China Liver cancer staging system,[43] Cancer of the Liver Italian Program system,[44] and the American Joint Commission on Cancer, which is based on the tumor, nodes, metastasis system.[45] Due to variability in treatment options and expertise, there is no universally accepted staging system, but the BCLC, most recently updated in 2022, is the widely used and has been well-validated in diverse populations.[46,47] We will focus the remainder of this review on the BCLC system for staging HCC. A brief review of treatment options for each stage is provided in this synopsis but more extensive discussion is reviewed in a separate article of this issue.

Barcelona Clinic Liver Cancer system

The BCLC classification system incorporates tumor status (size, number, vascular invasion, nodal involvement, and metastases), liver function (albumin, portal hypertension),

and functional status (Eastern Cooperative Oncology Group performance status) to categorize patients into 1 of 5 ordinal stages (0, A, B, C, and D) and to help guide prognosis and treatment options (**Fig. 1**).

Very early HCC (BCLC stage 0) is defined as a single tumor less than or equal to 2 cm without vascular invasion or extrahepatic metastases in a patient with well-preserved liver function and good functional status (ECOG-0). The main treatment options for BCLC stage 0 include radiofrequency ablation, microwave ablation, or resection, with the choice depending on tumor location, expertise, and the presence of clinically significant portal hypertension.[48] For patients who may be good candidates for orthotopic liver transplantation (OLT), another option is to "wait and not ablate" by surveying with serial cross-sectional imaging until the lesion reaches 2 cm (ie, within Milan criteria for liver transplantation).[49] An alternative approach is resection or ablation as first-line therapy, with OLT reserved for tumor recurrence or hepatic decompensation. The median 5-year survival following treatment with resection or ablation exceeds 70%.[50]

Early HCC (BCLC stage A) is defined as a single tumor greater than 2 cm or 3 nodules (all of which are less than or equal to 3 cm in diameter), ECOG-0, and preserved liver function. Median survival of patients with early HCC reaches 50% to 70% at 5 y after liver transplantation, local ablation, or resection in select candidates.[51] As OLT can potentially cure both the tumor and the underlying liver disease (including reducing the risk of HCC recurrence), this is an important option for patients who meet the Milan criteria (single tumor $\leq$5 cm or 3 nodules $\leq$3 cm). In the subset of patients with BCLC-A who have tumor burden outside of the Milan criteria but within

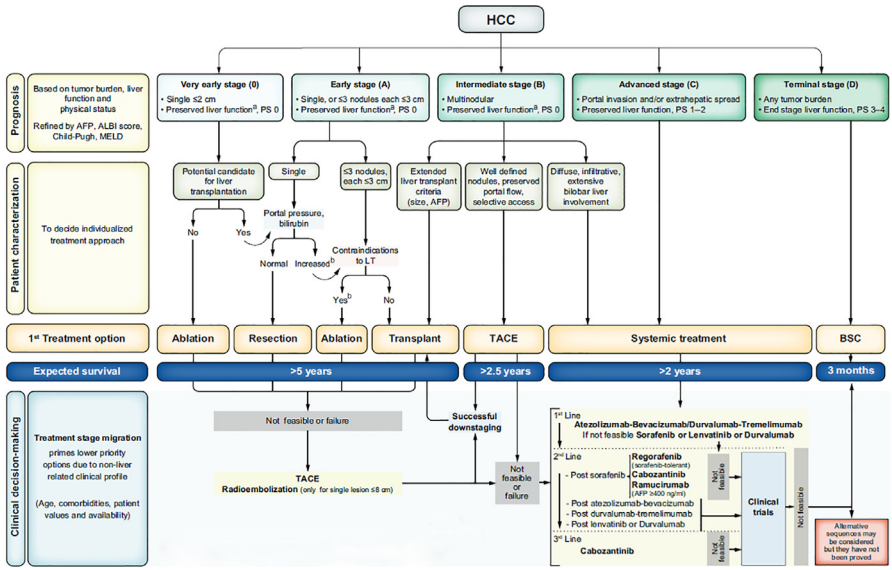

Fig. 1. Barcelona Clinic Liver Cancer (BCLC) hepatocellular carcinoma staging system, 2022 update. The BCLC system incorporates tumor status (size, number, vascular invasion, and metastases), liver function (albumin, portal hypertension), and functional status (Eastern Cooperative Oncology Group performance status) to categorize patients into 1 of 5 ordinal stages (0, A, B, C, and D) and to help guide discussions surrounding prognosis and treatment. [a]Except for those with tumor burden acceptable for transplant. [b]Resection may be considered for single peripheral HCC with adequate remnant liver volume. (Maria Reig et al., BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update, Journal of Hepatology, 76 (3), 2022, 681-693, https://doi.org/10.1016/j.jhep.2021.11.018.)

downstaging criteria, (ie, single lesion >5 cm and ≤8 cm; 2 or 3 lesions that meet all of the following: at least 1 lesion >3 cm, each lesion ≤5 cm, and a total diameter of all lesions ≤8 cm), effective downstaging (typically via transarterial chemoembolization [TACE] or radioembolization), to a tumor burden within Milan criteria may allow for liver transplantation.

Intermediate HCC (BCLC stage B) is defined as multifocal HCC (exceeding BCLC A), without vascular invasion or extrahepatic spread, ECOG-0, and preserved liver function. Untreated, the expected median survival is 16 mo.[52] The most recent 2022 revision has further divided those with BCLC-B into 3 subgroups. The first subgroup consists of those with well-defined nodules. These patients may be eligible for OLT if their total tumor burden is less than or equal to 8 cm and they undergo downstaging treatment to achieve a tumor burden within Milan criteria. The second subgroup is patients who have well-defined nodules but who would not be transplant candidates either due to HCC or non-HCC related factors. For these patients, TACE would be considered first-line therapy and systemic therapies as second-line. The third subgroup of patients consists of those with diffuse, infiltrative liver involvement. Systemic therapy should be considered as the first-line option as there may not be selective access to feeding tumor arteries for TACE or other catheter-based therapies.

Advanced HCC (BCLC stage C) is defined by macrovascular invasion, cancer-related symptoms (ECOG 1–2), or extrahepatic spread (lymph node involvement or metastases). In the past several years, major advancements have been made in the treatment of those with BCLC-C. For these patients, systemic therapy is first-line treatment. Atezolizumab (a PD-L1 immune checkpoint inhibitor) with bevacizumab (a VEGF targeting monoclonal antibody) is considered first-line therapy as it has been shown to provide a significant survival benefit (median overall survival rate of 19.2 mo) when compared to sorafenib.[53] An alternative first-line therapy is the immunotherapy combination of durvalumab (PD-L1 inhibitor) and tremelimumab (CTA4 inhibitor).[54] For patients who are not candidates for these first-line agents, sorafenib, lenvatinib, or durvalumab monotherapy has been recommended.

Terminal-stage HCC (BCLC stage D) includes patients with poor performance status (ECOG 3–4) that reflects a severe tumor-related disability and/or hepatic dysfunction. Their median survival is 3 to 4 mo.[55] This category captures patients who may have a tumor burden more characteristic of the earlier stages (ie, BCLC 0 B), but severe liver dysfunction and who are not candidates for OLT. For these patients, the best supportive care is recommended.

Limitations of the Barcelona Clinic Liver Cancer system. While the BCLC staging system is widely used and well-validated, it does have certain limitations. Notably, it does not incorporate external beam radiotherapy (EBRT) as a treatment option. This omission can be significant, as EBRT has shown to improve survival in patients with macrovascular invasion with TACE + EBRT compared to sorafenib alone.[56] Future updates to the BCLC system may benefit from including EBRT to provide a more comprehensive treatment framework.

SUMMARY

The early detection of HCC is crucial for improving patient outcomes. The US, CT/MRI, and CEUS LI-RADS algorithms allow for a standardized and systemic evaluation of liver observations, which can facilitate the diagnosis of HCC in a timely manner. Following a new diagnosis, the appropriate staging of HCC is essential for guiding treatment decisions and providing patient prognosis. Staging systems like the BCLC classification

system incorporate tumor characteristics, liver function, and performance status to provide a comprehensive framework for managing HCC.

CLINICS CARE POINTS

- Ultrasound (US) abdominal imaging, as a screening test for hepatocellular carcinoma (HCC), has the limitation of being highly operator dependent and is susceptible to technical factors that can impede liver visualization. These limitations are categorized within the Liver Imaging Reporting and Data System (LI-RADS) US visualization algorithm.
- The CT/MRI and contrast-enhanced ultrasound (CEUS) LI-RADS algorithms provide a standardized framework for evaluating liver lesions. The proper application of these algorithms can help clinicians distinguish between benign, probably malignant, and definitely malignant liver lesions.
- A comprehensive evaluation of liver function, performance status, and tumor burden is essential for determining the appropriate treatment options and for predicting patient prognosis. The Barcelona Clinic Liver Cancer (BCLC) staging system is a widely used framework for this purpose.

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