RadioGraphics

# Hepatocellular Carcinoma: Illustrated Guide to Systematic Radiologic Diagnosis and Staging According to Guidelines of the American Association for the Study of Liver Diseases[1]

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**SA-CME**

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**LEARNING OBJECTIVES FOR TEST 6**

*After completing this journal-based SA-CME activity, participants will be able to:*

- Describe the appropriate steps for investigation of focal liver nodules identified during cirrhosis surveillance.
- Recognize the characteristic dynamic perfusion pattern of hepatocellular carcinoma.
- Assign a BCLC stage to a lesion that satisfies the noninvasive imaging criteria for hepatocellular carcinoma.

**INVITED COMMENTARY**

*See discussion on this article by Ros (pp 1668–1671).*

**TEACHING POINTS**

*See last page*

Hepatocellular carcinoma is a malignancy that predominantly occurs in the setting of cirrhosis. Its incidence is rising worldwide. Hepatocellular carcinoma differs from most malignancies because it is commonly diagnosed on the basis of imaging features alone, without histologic confirmation. The guidelines from the American Association for the Study of Liver Diseases (AASLD) are a leading statement for the diagnosis and staging of hepatocellular carcinoma, and they have recently been updated, incorporating several important changes. AASLD advocates the use of the Barcelona Clinic Liver Cancer (BCLC) staging system, which combines validated imaging and clinical predictors of survival to determine stage and which links staging with treatment options. Each stage of the BCLC system is outlined clearly, with emphasis on case examples. Focal liver lesions identified at ultrasonographic surveillance in patients with cirrhosis require further investigation. Lesions larger than 1 cm should be assessed with multiphasic computed tomography or magnetic resonance imaging. Use of proper equipment and protocols is essential. Lesions larger than 1 cm can be diagnosed as hepatocellular carcinoma from a single study if the characteristic dynamic perfusion pattern of arterial hyperenhancement and venous or delayed phase washout is demonstrated. If the imaging characteristics of hepatocellular carcinoma are not met, the alternate modality should be performed. Biopsy should be used if neither modality is diagnostic of hepatocellular carcinoma. Once the diagnosis has been made, the cancer should be assigned a BCLC stage, which will help determine suitable treatment options. Radiologists require a systematic approach to diagnose and stage hepatocellular carcinoma with appropriate accuracy and precision.



**Abbreviations:** AASLD = American Association for the Study of Liver Diseases, AFP = α-fetoprotein, BCLC = Barcelona Clinic Liver Cancer, CTP = Child-Turcotte-Pugh, EASL = European Association for the Study of the Liver, ECOG = Eastern Cooperative Oncology Group, LI-RADS = Liver Imaging Reporting and Data System, NCCN = National Comprehensive Cancer Network, TACE = transcatheter arterial chemoembolization

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## Introduction

Hepatocellular carcinoma is the fifth most common cancer worldwide, and its incidence is rising in many countries, including the United States (1). The major risk factor for development of hepatocellular carcinoma is cirrhosis, particularly cirrhosis related to chronic viral hepatitis, alcoholic cirrhosis, cirrhosis caused by hemochromatosis, and primary biliary cirrhosis (2). For patients with an established diagnosis of cirrhosis, surveillance by means of ultrasonography (US) and measuring serum α-fetoprotein (AFP) levels has been shown to reduce hepatocellular carcinoma–related mortality by 37% (3).

Unlike other tumors that develop within a background of normal tissue, hepatocellular carcinoma occurs as part of a hepatic field change, characterized by replacement of liver parenchyma with fibrosis, scarring, and nodular regeneration. Hepatocarcinogenesis is a sequence of dedifferentiation from regenerative nodule, through dysplastic nodule, to hepatocellular carcinoma. Hepatocarcinogenesis should be considered a continuum, rather than a series of discrete states. Changes to feeding vessels and neovascularization occur during the process (Fig 1). Overt hepatocellular carcinoma does not have a portal blood supply; it is supplied solely by abnormal, unpaired hepatic arteries. This results in a characteristic vascular enhancement pattern that can be used to make a definitive radiologic diagnosis.

Hepatocellular carcinoma differs from most malignancies because it is commonly diagnosed on the basis of imaging features alone, without histologic confirmation. Multiplicity of nodules, small size of nodules, and "nodules within nodules" each represent part of the disease spectrum and make routine biopsy of cirrhotic nodules impossible. Also, biopsy of hepatocellular carcinoma carries a theoretical risk of seeding cancer cells along the needle tract, which may lead to tumor recurrence after liver transplantation. This risk is small. Meta-analysis has shown that the prevalence of tumor seeding after biopsy is 2.7% (4). Use of trocars during biopsy has not been associated with tumor seeding (4,5). There is no reliable tumor marker for hepatocellular carcinoma. Measurement of the serum levels of AFP is used as an aid to diagnosis and in screening. A rise in the serum level of AFP in a patient with cirrhosis should raise concern that hepatocellular carcinoma has developed. However, an elevated level of AFP is not specific for hepatocellular carcinoma; in particular, AFP may be elevated in flares of viral hepatitis. Furthermore, when a cutoff value of 20 μg/L is used, measurement of serum AFP level has a sensitivity of only 60% (6,7).

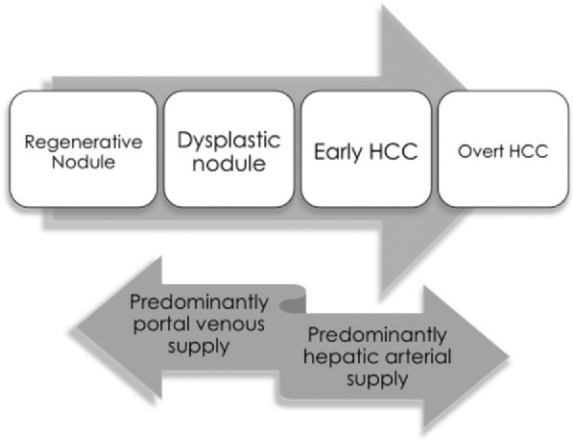



**Figure 1.** Diagram illustrates the sequence of hepatocarcinogenesis and neovascularization in cirrhosis. *HCC* = hepatocellular carcinoma.

In 2005, the American Association for the Study of Liver Diseases (AASLD) published practice guidelines for the diagnosis and management of hepatocellular carcinoma in *Hepatology* (8). In 2011, the guidelines were updated, with changes made to the diagnostic criteria on the basis of new evidence (9). AASLD advocates the use of the Barcelona Clinic Liver Cancer (BCLC) staging system, which links cancer staging with treatment options.

Because imaging is the primary means for diagnosis and staging of hepatocellular carcinoma, radiologists require a systematic approach to perform this task with appropriate accuracy and precision. The purpose of this article is to illustrate the use of the AASLD radiologic diagnostic criteria and BCLC staging system in the detection, diagnosis, and staging of hepatocellular carcinoma in patients with cirrhosis.

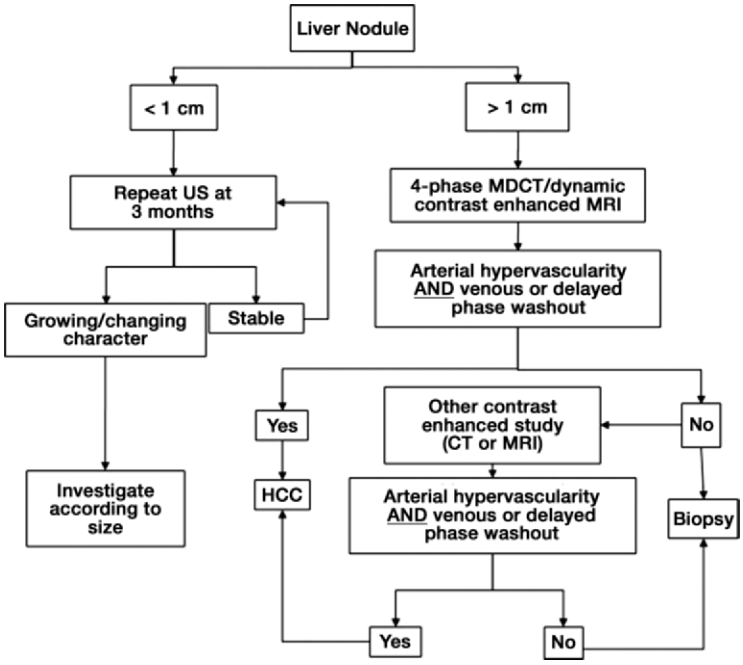



**Figure 2.** Algorithm for the investigation of liver nodules found at US surveillance of patients with cirrhosis. *HCC* = hepatocellular carcinoma, *MDCT* = multidetector CT. (Reprinted, with permission, from reference 9.)

## Detection of Focal Lesions in Cirrhosis with Surveillance US

The AASLD recommends that US surveillance be performed at 6-month intervals in patients with cirrhosis. The detection of a focal liver nodule during imaging surveillance should always suggest the possibility of hepatocellular carcinoma, although, practically speaking, many such nodules will be regenerative nodules. It is not possible to distinguish between these two entities with US alone.

Hepatocellular carcinoma does not have a characteristic appearance at US. The lesions are typically hypoechoic, but they can be hyperechoic or have mixed echogenicity. The majority of nodules that measure less than 1 cm are not hepatocellular carcinoma (8). Detected nodules that measure less than 1 cm should be rescanned at a 3-month interval with the modality by which the lesions were first identified. If the nodules remain stable for a 2-year period, regular 6-month follow-up examinations can be resumed for routine surveillance (Fig 2). The nodules that are suspicious for hepatocellular carcinoma are new nodules that measure more than 1 cm or nodules that enlarge over a time interval. These suspicious nodules require immediate further investigation with multiphasic computed tomography (CT) or magnetic resonance (MR) imaging.

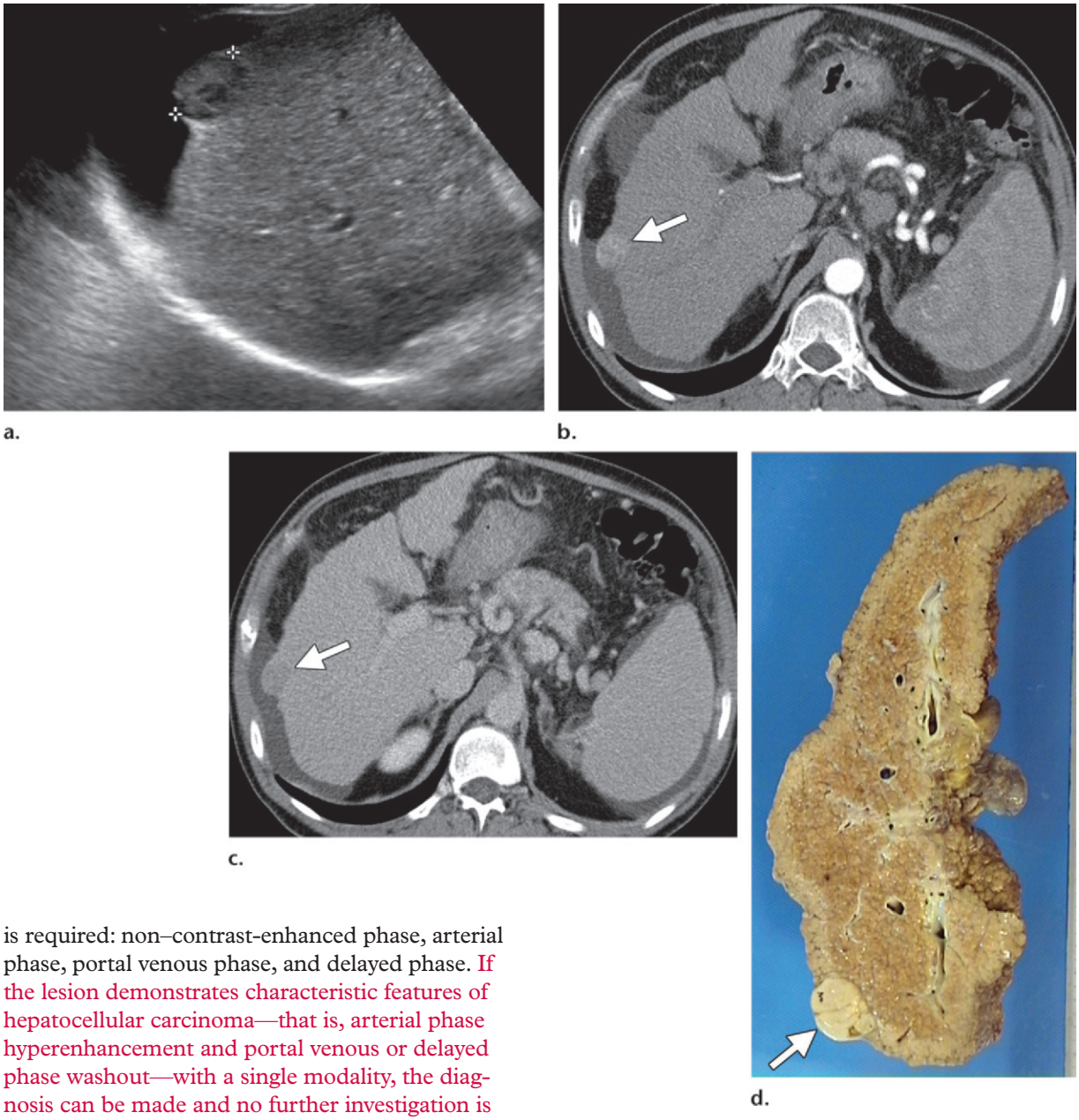
Teaching Point

## AASLD Criteria for Diagnosis of Hepatocellular Carcinoma in Cirrhosis

Teaching Point

The radiologic diagnosis of hepatocellular carcinoma can be made at either CT or MR imaging, provided that a multiphasic contrast material–enhanced study is used. Characteristically, hepatocellular carcinoma enhances during the arterial phase because of its blood supply from abnormal hepatic arteries. Contrast medium in the surrounding liver parenchyma is diluted during this phase because the parenchymal blood supply arises mostly from the portal veins, which are not yet opacified. In the portal venous phase, the surrounding liver parenchyma becomes relatively hyperattenuated and the lesion is perceived to be hypoattenuated because of its lack of portal venous supply. This appearance is the so-called washout effect. Occasionally, washout is evident only during a delayed phase sequence. Thus, a four-phase imaging study

**Figure 3.** Hepatocellular carcinoma in a 45-year-old man with hemophilia and hepatitis C cirrhosis. **(a)** Surveillance US scan shows a focal 2.6-cm hypoechoic exophytic nodule (calipers) in a coarse liver, as well as ascites. **(b)** Axial arterial phase CT scan from a multiphasic study shows hyperenhancement of the exophytic mass (arrow). **(c)** Delayed phase CT scan shows washout of contrast agent within the mass (arrow). The patient underwent orthotopic liver transplantation. **(d)** Hepatocellular carcinoma (arrow) is clearly evident in the excised specimen, as shown in the photograph.




Teaching Point

is required: non–contrast-enhanced phase, arterial phase, portal venous phase, and delayed phase. If the lesion demonstrates characteristic features of hepatocellular carcinoma—that is, arterial phase hyperenhancement and portal venous or delayed phase washout—with a single modality, the diagnosis can be made and no further investigation is required (Fig 3). If both of these features are not seen and if the imaging findings are not consistent with a benign process (eg, hemangioma), a second imaging study should be performed with an alternate modality.

Much diagnostic dilemma surrounds the concept of hypovascular small hepatocellular carcinoma. A small hepatocellular carcinoma is one that measures less than 2 cm in diameter. A minor subset of these tumors has been classified as early hepatocellular carcinoma, which has been defined as a histologically distinct, well-differentiated, and vaguely nodular hepatocellular carcinoma (10). Early hepatocellular carcinoma has been demonstrated histologically to have fewer unpaired arteries and, therefore, radiologically appears hypovascular (10–12). Yoon et al (13) evaluated the multidetector CT enhancement pattern of hepato-

**Table 1**
**Pathologic Findings Seen in the Diagnosis of Hepatocellular Carcinoma, Including Useful Immunohistochemical Markers**

| Pathologic Analysis | Findings | Comments |
|---|---|---|
| Macroscopy | Varying from discrete nodular (single vs multiple) to infiltrative tumor | Small HCC (<2 cm) is a distinct entity, subcategorized as early (vaguely nodular) or progressed (distinctly nodular) HCC |
| Microscopy | Elevated nuclear to cytoplasmic ratio, nuclear polymorphism, multinucleation or trabecular architecture | Degree of cellular atypia allows grading of tumor |
| Stromal invasion | Presence of tumor in peritumoral portal tracts or fibrous septa | Especially helpful in biopsy material |
| Silver staining | Absent, decreased, or abnormal stain pattern of reticulin | Distinguishes benign liver lesions from malignant lesions; occasional normal staining has been described in HCC |
| Immunohistochemical markers: HepPar1, polyclonal CEA | Positive staining for HepPar1 or polyclonal CEA | Establishes origin of cell as being from the liver; does not help distinguish benign from malignant liver disease; may stain negative if tumor is poorly differentiated |
| Immunohistochemical marker: CD34 | Positive staining for CD34 | Stains sinusoidal vascular endothelium; may stain negative in early HCC |
| Immunohistochemical markers: glypican 3, heat shock protein 7, glutamine synthase | Used in combination: a finding of two positive markers out of three is relatively sensitive and highly specific for HCC | Emerging tumor markers; generally reserved for problem solving in cases of small or atypical HCC |

Note.—CEA = carcinoembryonic antigen, HCC = hepatocellular carcinoma, HepPar1 = hepatocyte paraffin antigen.

cellular carcinomas smaller than 3 cm in diameter in patients with cirrhosis. They found that the classic enhancement pattern was present in 24% of tumors less than 1 cm in diameter, 28% of tumors that were 1–2 cm, and 47% of tumors that were greater than 2 cm. Occasionally, large hepatocellular carcinoma may be hypovascular. In cases in which imaging features are equivocal, that is, the perfusion pattern specific for hepatocellular carcinoma is not evident with both MR imaging and CT, the AASLD recommends that targeted biopsy be performed. Pathologic analysis of hepatocellular carcinoma includes macroscopic, microscopic, and immunohistochemical evaluation (Table 1). At our institution, typical microscopic morphology and reticulin pattern, along with the presence of CD34 and hepatocyte paraffin antigen markers, are considered to be essential components in establishing a diagnosis of hepatocellular carcinoma.

In Europe, Canada, and Asia, contrast-enhanced US has been used as a third imaging modality to demonstrate the enhancement pattern that is diagnostic of hepatocellular carcinoma. The microbubble contrast agent employed in contrast-enhanced US is not currently approved for use in the United States. It has recently been shown that intrahepatic cholangiocarcinoma in patients with cirrhosis may exhibit a vascular enhancement pattern similar to that of hepatocellular carcinoma at contrast-enhanced US; for this reason, contrast-enhanced US is excluded from the updated AASLD guidelines as an accepted alternative diagnostic modality (14).

In the original 2005 guidelines, use of both CT and MR imaging was required to evaluate lesions measuring 1–2 cm because of concern about whether the specific vascular pattern in these smaller nodules could be recognized with a single modality. More recent studies report that application of a single contrast-enhanced imaging technique has sensitivity similar to that of two contrast-enhanced imaging techniques in the assessment of 1–2-cm lesions (15). Therefore, the revised AASLD guidelines state that the diagnosis of hepatocellular carcinoma can be made on the basis of a single study that shows the typical contrast enhancement pattern of hepatocellular carcinoma in any lesion over 1 cm in diameter.

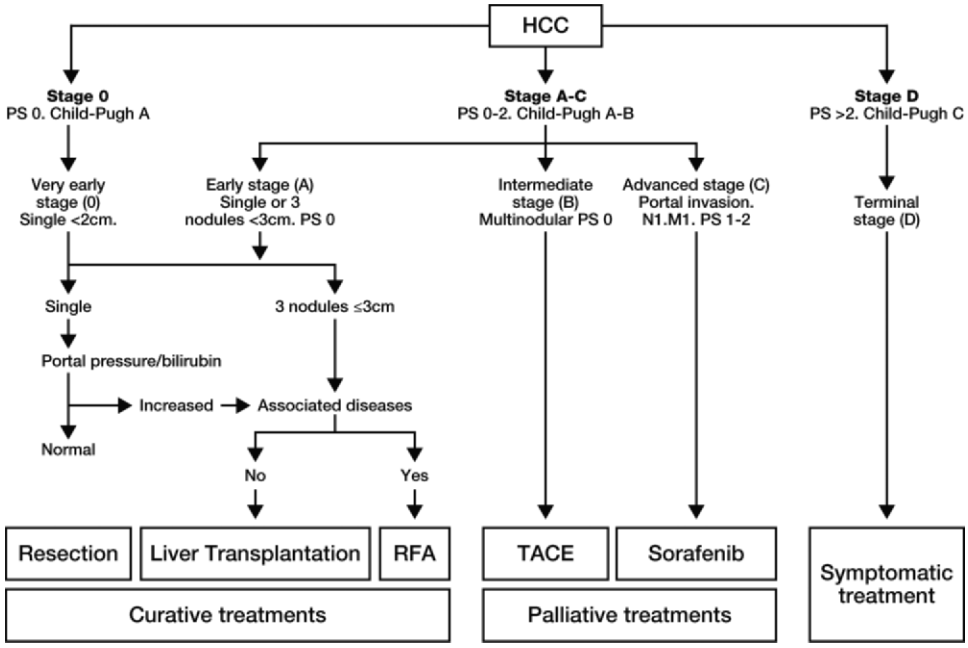



**Figure 4.** BCLC staging system and treatment allocation algorithm. *HCC* = hepatocellular carcinoma, *PS* = performance status, *RFA* = radiofrequency ablation, *TACE* = transcatheter arterial chemoembolization. (Reprinted, with permission, from reference 9.)

## Dynamic Enhanced CT and MR Imaging Techniques for Detection of Hepatocellular Carcinoma

Use of state-of-the-art equipment and protocols is important to ensure accurate characterization of focal liver lesions in cirrhotic livers. Detailed acceptable CT and MR imaging techniques have previously been published (16,17). In addition on the basis of a consensus of experts, the Organ Procurement and Transplantation Network has proposed minimum technical requirements for scanner hardware and protocols for the diagnosis of hepatocellular carcinoma (18).

CT should be performed with a multi–detector array scanner with a minimum of eight detector rows. The minimum reconstructed section thickness is 5 mm, although thinner sections are preferred. Use of a mechanical injector and a saline flush is advised to administer contrast material to achieve a minimum injection rate of 3 mL/sec for a total of 370 mg/mL of contrast medium. Bolus tracking software that monitors passage of contrast material through the descending aorta is recommended. Images should be acquired in four phases: non–contrast-enhanced phase (before the injection of contrast material), late arterial phase (about 20 seconds after the injection), portal venous phase (50 seconds after the injection), and delayed phase (>120 seconds after the injection). The optimal timing for image acquisition in the delayed phase is debated, varying between 2 and 15 minutes after contrast material injection. Contrast-enhanced US studies have shown that approximately 90% of hepatocellular carcinomas demonstrate washout by 5 minutes after injection of the microbubble contrast agent (19). Use of a 5-minute delay may be the practical choice for the timing of the delayed phase.

MR imaging should be performed with a multichannel phased-array body coil and at a magnetic field strength of 1.5 T or greater. A mechanical injector should be used to administer the gadolinium-based contrast agent at a rate of 2–3 mL/sec. Bolus tracking is recommended. Precontrast and dynamic postcontrast T1-weighted three-dimensional fat-suppressed gradient-echo sequences are required, in addition to T2 (with and without fat saturation) and T1 in-phase and opposed-phase imaging. Timing of the dynamic contrast-enhanced sequences is the same as that used for the CT examination. Emphasis on precise breath-holding is extremely important.

Systematic review has shown that MR imaging is more sensitive than CT in the diagnosis of hepatocellular carcinoma (81% vs 68%) (20). The disadvantages of MR imaging are its high cost, length of time required for image acquisition, and long duration of breath holds. Accessibility is also an issue in some healthcare centers. The main disadvantage of CT is that patients incur a radiation dose. Use of iodinated and MR imaging contrast media should be in line with the recommendations of the American College of Radiology manual on contrast media. Caution is advised in patients with renal failure.

**Table 2**
**Child-Turcotte-Pugh Score for Assessment of Liver Function**

| Clinical or Biochemical Parameter | One Point | Two Points | Three Points |
|---|---|---|---|
| Bilirubin (mg/dL) | <2 | 2–3 | >3 |
| Serum albumin (g/dL) | >3.5 | 2.8–3.5 | <2.8 |
| International normalized ratio | <1.7 | 1.7–2.3 | >2.3 |
| Ascites | None | Mild | Moderate to severe |
| Encephalopathy | None | Grade I–II | Grade III–IV |

Source.—Reprinted, with permission, from reference 25.
Note.—Severity of liver disease is graded as CTP A–C, on the basis of a patient's total score: A = 5–6, B = 7–9, and C = 10–15.

**Table 3**
**Eastern Cooperative Oncology Group Scale for Assessment of Patient Performance Status**

| Grade | Description of Performance Status |
|---|---|
| 0 | Fully active, able to complete all predisease performance tasks without restriction |
| 1 | Restricted in physically strenuous activity but ambulatory and able to complete work of a light or sedentary nature (eg, light house work, office work) |
| 2 | Ambulatory and capable of all self-care but unable to complete any work activities; up and active for more than 50% of waking hours |
| 3 | Capable of only limited self-care; confined to bed or chair more than 50% of waking hours |
| 4 | Completely disabled; cannot perform any self-care; totally confined to bed or chair |
| 5 | Dead |

Source. —Reprinted, with permission, from reference 26.

## Staging of Hepatocellular Carcinoma

Once the diagnosis of hepatocellular carcinoma has been made, clinical staging should be performed to assess prognosis and to guide therapeutic intervention. Many staging systems have been proposed over the years, including the Tumor Node Metastasis (TNM) system, the BCLC system, the Japanese Integrated System (JIS), Cancer of Liver Italian Program (CLIP), Groupe d'Etude de Traitement du Carcinoma Hepatocellulaire (GRETCH), the Chinese University Prognostic Index (CUPI), and the Okuda staging system; however, there is no worldwide consensus on which system to use. AASLD advocates use of the BCLC staging system because it is the only system that encompasses the three factors that have been shown to be independent predictors of survival—radiologic tumor extent, liver function, and patient's performance status—and thus has the best chance of predicting patient survival compared with other prognostic systems (21). The BCLC system is used in most major trials of hepatocellular carcinoma interventions, making it the reference staging system, and it is continuously updated to incorporate emerging changes (22,23). The BCLC system links each tumor stage with appropriate therapeutic interventions in a guideline format (Fig 4).

Teaching Point

The BCLC system assesses liver function by using the Child-Turcotte-Pugh (CTP) score, which grades the severity of liver disease from A to C. A range of biochemical and clinical parameters is assigned point values, which are then totaled to derive a patient's CTP score for liver function (24,25) (Table 2). A patient's performance status is assessed by using the Eastern Cooperative Oncology Group (ECOG) scale, which ranges from 0 to 5 and ranks a patient's abilities to complete activities of daily living (26) (Table 3). Radiologic tumor extent is evaluated on the basis of the maximum length of the lesion, the number of lesions, evidence of vascular invasion, and the presence of lymphatic or metastatic disease. Because this article is targeted to a radiology readership, the description of each BCLC

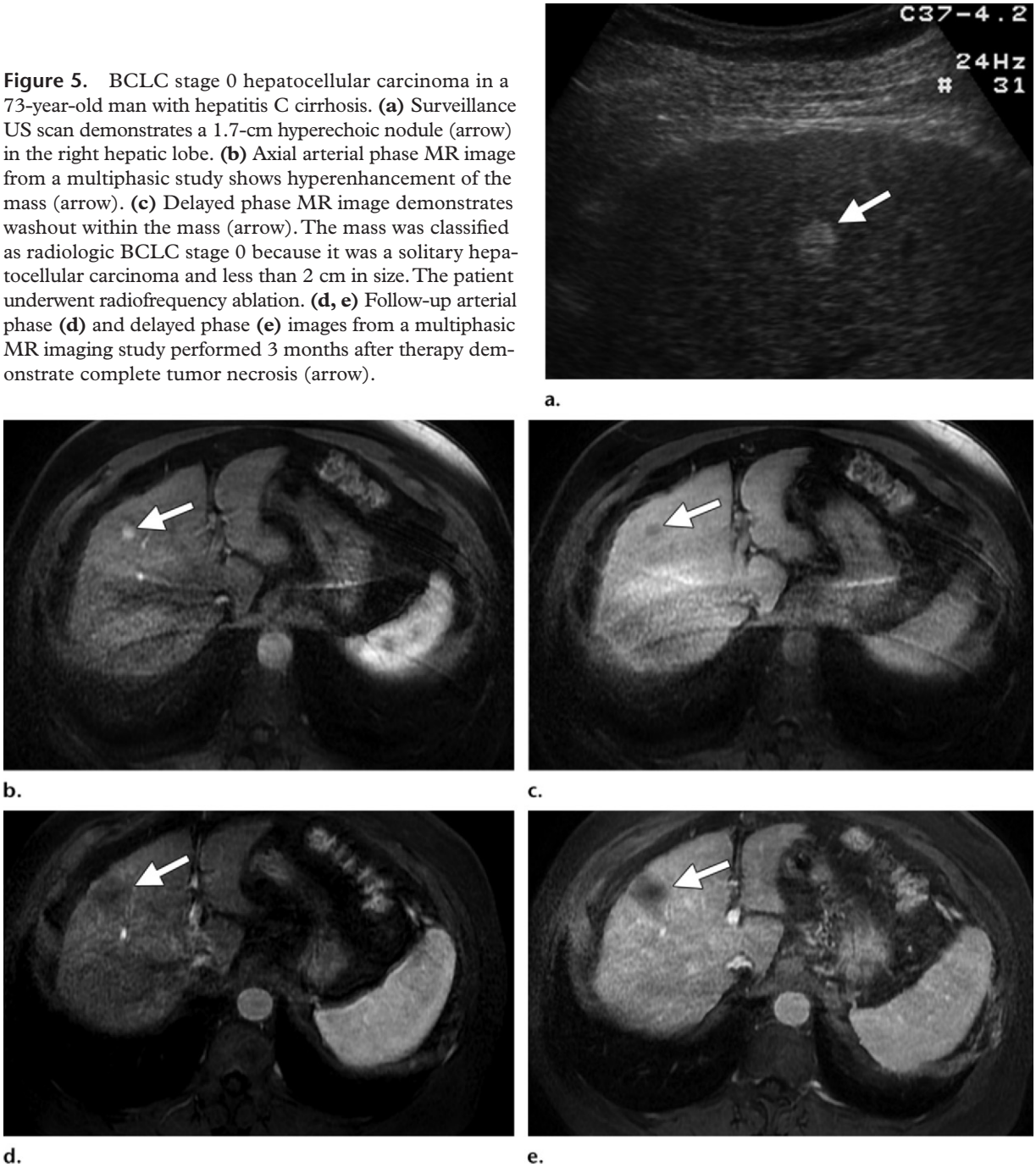



**Figure 5.** BCLC stage 0 hepatocellular carcinoma in a 73-year-old man with hepatitis C cirrhosis. **(a)** Surveillance US scan demonstrates a 1.7-cm hyperechoic nodule (arrow) in the right hepatic lobe. **(b)** Axial arterial phase MR image from a multiphasic study shows hyperenhancement of the mass (arrow). **(c)** Delayed phase MR image demonstrates washout within the mass (arrow). The mass was classified as radiologic BCLC stage 0 because it was a solitary hepatocellular carcinoma and less than 2 cm in size. The patient underwent radiofrequency ablation. **(d, e)** Follow-up arterial phase **(d)** and delayed phase **(e)** images from a multiphasic MR imaging study performed 3 months after therapy demonstrate complete tumor necrosis (arrow).

stage is presented from an imaging viewpoint; readers should note, however, that a patient's CTP or ECOG score can upstage each radiologic stage. Radiologic tumor extent is only an element of the BCLC stages 0, A, B, and C.

Radiologic BCLC stage 0 disease is a solitary lesion that measures less than 2 cm in diameter (Fig 5). Treatment options for a stage 0 lesion depend on the presence of portal hypertension or hyperbilirubinemia. If these conditions are absent, resection may be a suitable treatment option for the patient; if these conditions are present, transplantation is the preferred therapy. If the patient has associated comorbidities, a minimally invasive treatment option such as radiofrequency ablation may be more appropriate. Meta-analysis has demonstrated the superiority of radiofrequency ablation over percutaneous ethanol ablation in terms of patient survival and local tumor recurrence (27).

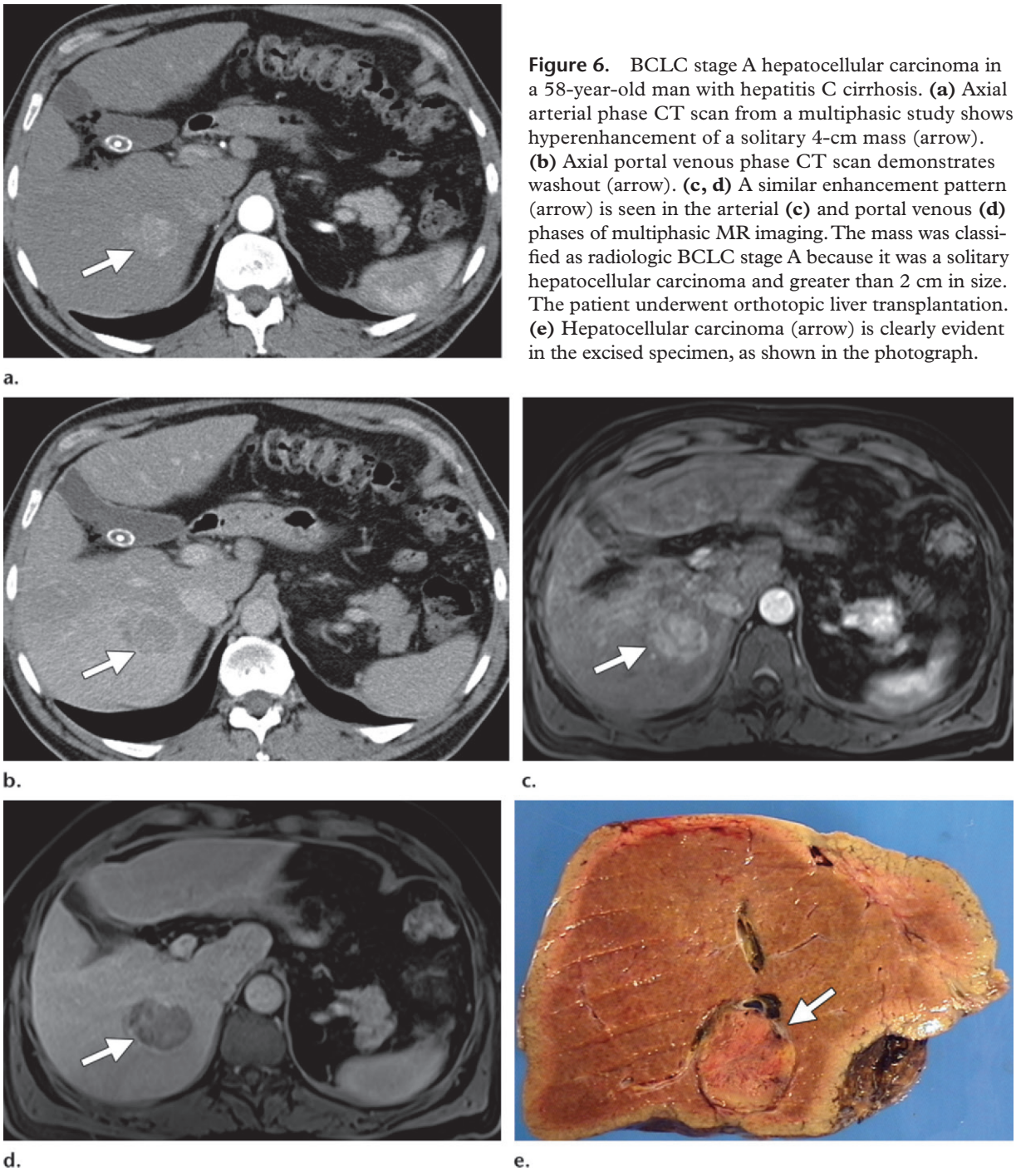
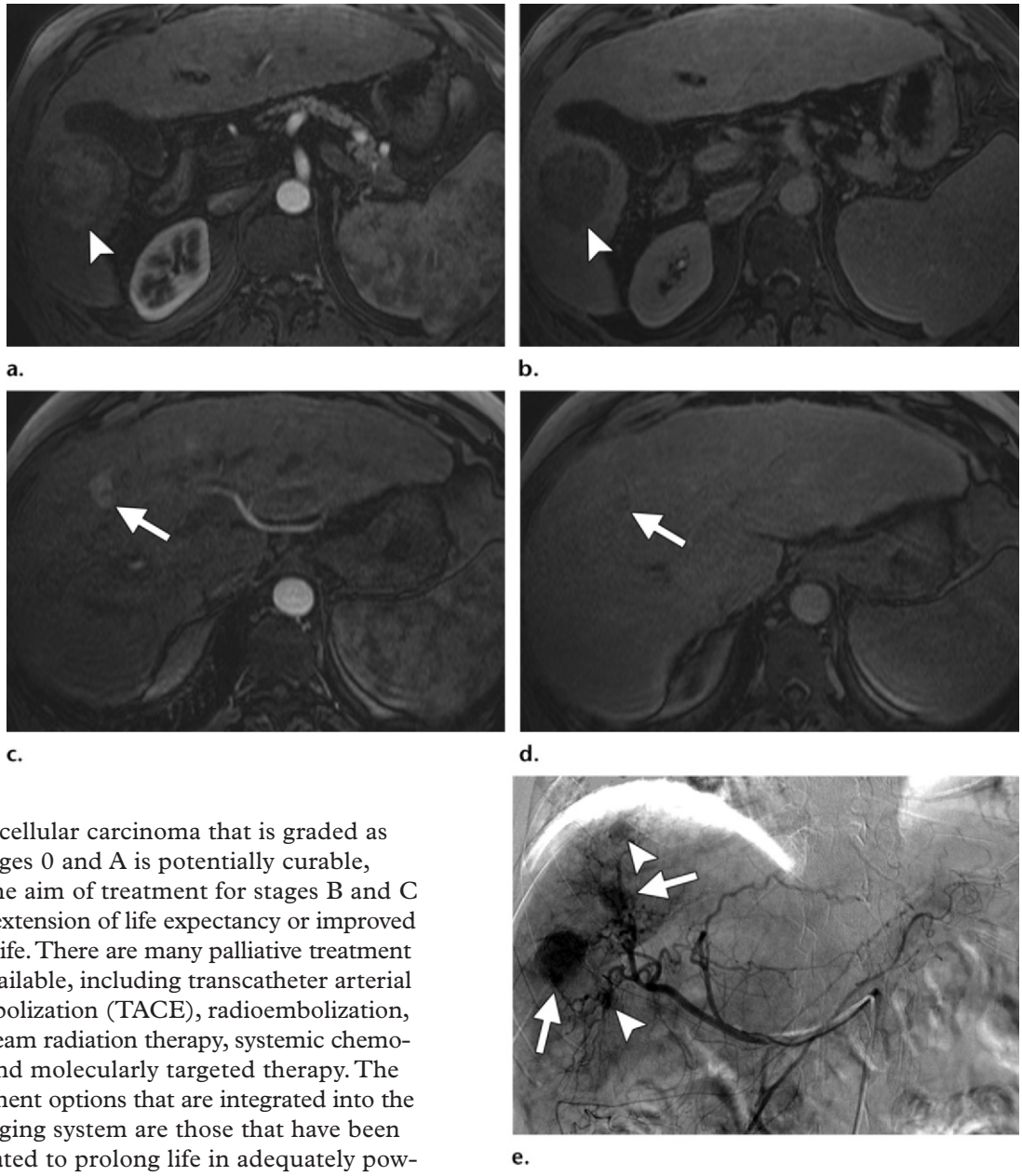


**Figure 6.** BCLC stage A hepatocellular carcinoma in a 58-year-old man with hepatitis C cirrhosis. **(a)** Axial arterial phase CT scan from a multiphasic study shows hyperenhancement of a solitary 4-cm mass (arrow). **(b)** Axial portal venous phase CT scan demonstrates washout (arrow). **(c, d)** A similar enhancement pattern (arrow) is seen in the arterial **(c)** and portal venous **(d)** phases of multiphasic MR imaging. The mass was classified as radiologic BCLC stage A because it was a solitary hepatocellular carcinoma and greater than 2 cm in size. The patient underwent orthotopic liver transplantation. **(e)** Hepatocellular carcinoma (arrow) is clearly evident in the excised specimen, as shown in the photograph.

Radiologic BCLC stage A disease is a solitary lesion that measures more than 2 cm in diameter or early multifocal disease that consists of up to three lesions, none of which measure more than 3 cm in diameter (Fig 6). As with stage 0 disease, suitable choices of therapeutic options depend on the presence of portal hypertension or hyperbilirubinemia. If these conditions are absent, resection remains a viable option for treating solitary BCLC stage A lesions. If portal hypertension is present, therapeutic options include transplantation and radiofrequency ablation, as with stage 0 disease. AASLD does not recommend expanding transplantation criteria beyond the widely used Milan criteria (ie, presence of a solitary hepatocellular carcinoma <5 cm, or up to three separate lesions, each <3 cm).

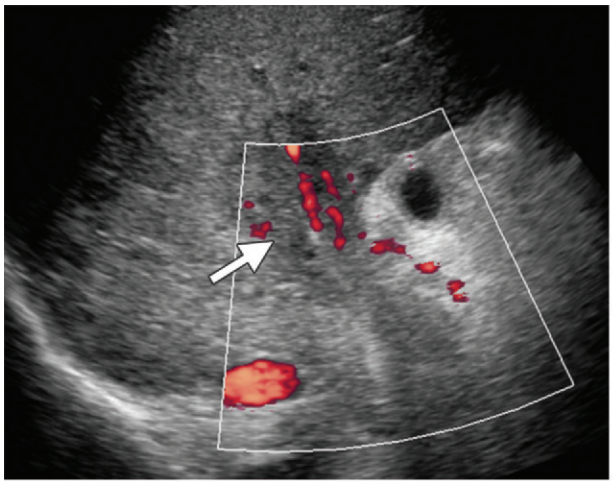
**Figure 7.** BCLC stage B hepatocellular carcinoma in a 63-year-old man with alcoholic cirrhosis. **(a)** Axial arterial phase MR image from a multiphasic study shows hyperenhancement of a 4.2-cm mass in the right hepatic lobe (arrowhead). **(b)** Delayed phase image from the same study demonstrates washout in the lesion (arrowhead). **(c)** Arterial phase MR image from the same study, but obtained at a more cranial level, shows an additional, arterially enhancing mass that measured 1.2 cm (arrow). **(d)** Delayed phase MR image demonstrates washout in this mass also (arrow). The disease stage was classified as radiologic BCLC stage B because the hepatocellular carcinoma was multifocal and one of the nodules was greater than 3 cm in size. The patient underwent TACE. **(e)** Selected angiographic image from the TACE procedure shows these two lesions (arrows), as well as two additional hypervascular lesions (arrowheads) in the right hepatic lobe.




Hepatocellular carcinoma that is graded as BCLC stages 0 and A is potentially curable, whereas the aim of treatment for stages B and C disease is extension of life expectancy or improved quality of life. There are many palliative treatment options available, including transcatheter arterial chemoembolization (TACE), radioembolization, external beam radiation therapy, systemic chemotherapy, and molecularly targeted therapy. The only treatment options that are integrated into the BCLC staging system are those that have been demonstrated to prolong life in adequately powered randomized trials: TACE and the molecularly targeted therapy with sorafenib.

Radiologic BCLC stage B disease is advanced multifocal disease that consists of more than one lesion, with at least one that is larger than 3 cm, or of more than three lesions regardless of size (Fig 7). Stage B disease is managed with TACE. Meta-analysis has demonstrated that patients who undergo TACE experience a statistically significant survival benefit, compared with those who receive

**Figure 8.** Malignant portal vein thrombus in a 65-year-old man with alcoholic cirrhosis and hepatocellular carcinoma. **(a)** Color Doppler US scan shows echogenic material and no flow within the main portal vein, a finding consistent with thrombus (arrow). **(b)** Axial arterial phase CT scan from a multiphasic study shows extensive peripheral enhancement of the main portal vein, a finding consistent with neovascularization (arrow). A large hypovascular mass is present in the right hepatic lobe (*). **(c)** Axial portal venous phase CT scan from the same study helps confirm the lack of flow in the main portal vein and washout of the enhancement (arrow) seen in the arterial phase. The large mass is more clearly seen (*). The mass represents radiologic BCLC stage C disease because of the presence of malignant portal vein thrombus.



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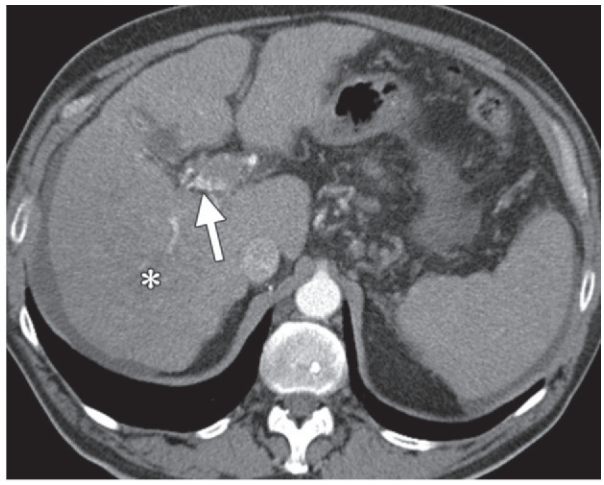

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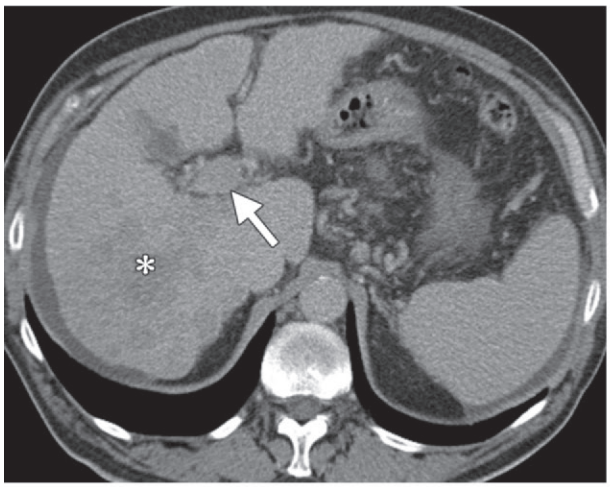

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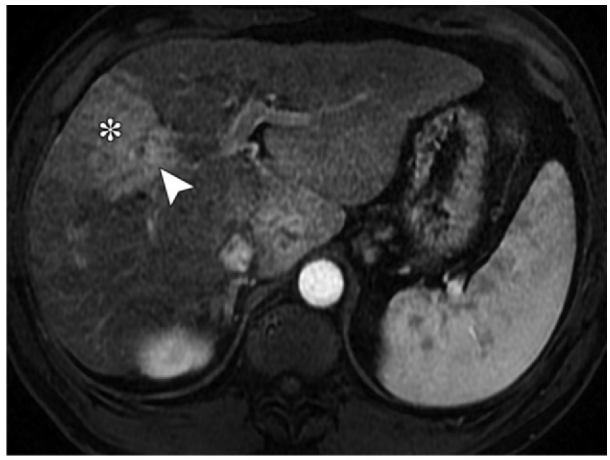
only supportive care, although survival benefit was not universal across all trial selection criteria and combination agents (28). Even without survival benefit, however, progression of symptomatic disease (ie, development of portal vein invasion and resultant ascites) is reduced by TACE (29). The evaluation of tumor response to local therapies such as radiofrequency ablation and TACE has evolved from assessment of morphologic size alone to encompass evaluation of posttreatment enhancement. The AASLD recommends use of the modified Response Evaluation Criteria in Solid Tumors (mRECIST) to assess tumor response (30).

Radiologic BCLC stage C disease is hepatocellular carcinoma with either vascular invasion or nodal or metastatic disease. In the staging system algorithm, this stage is linked with sorafenib, a multikinase inhibitor, which has been shown to produce a statistically significant survival benefit, compared with supportive treatment, in cases of advanced hepatocellular carcinoma (31). The survival benefit has been demonstrated only in patients with CTP grade A severity liver disease.

Evidence of vascular invasion (malignant thrombus) is used as a criterion to exclude liver transplantation as a treatment option; however, bland portal vein thrombus can occur in cirrhotic liver disease. Therefore, correctly distinguishing between benign and malignant portal vein thrombi is important. The characteristic imaging pattern of hepatocellular carcinoma—arterial hyperenhancement and venous or delayed phase washout—is maintained in tumor invasion of the portal vein (Fig 8). However, not all malignant thrombi will demonstrate this enhancement pattern (32). The additional observation of restricted diffusion at MR imaging supports the diagnosis of malignant thrombus (Fig 9). When uncertainty about the nature of thrombi arises that cannot be resolved with imaging, fine needle aspiration biopsy may be performed (33,34).

Teaching Point

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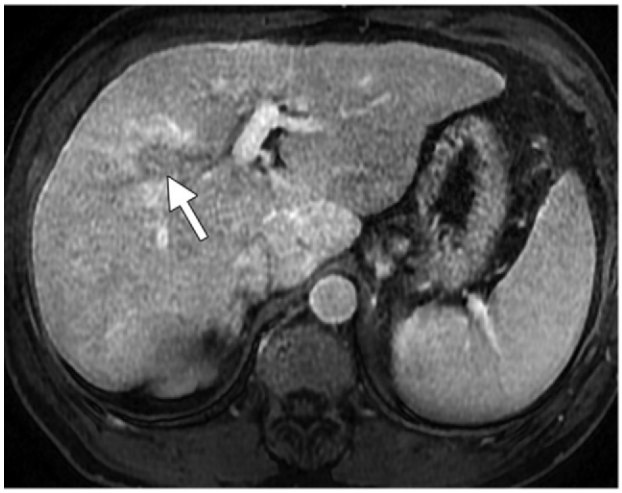

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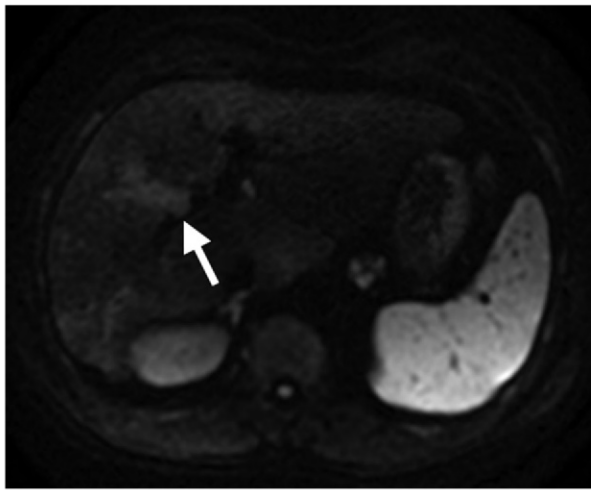

c.

**Figure 9.** Malignant portal vein thrombus in a 61-year-old man with alcoholic cirrhosis and hepatocellular carcinoma. Multiphasic MR images demonstrate anterior right segmental portal vein thrombosis that enhances in the arterial phase (arrowhead in **a**), washes out in the portal venous phase (arrow in **b**), and demonstrates restricted diffusion during the high *b* value diffusion-weighted sequence (arrow in **c**). On the arterial phase image **(a)**, parenchymal hypervascularity is seen adjacent to the segmental thrombosis, a finding that likely represents transient hepatic arterial compensation (*).

Distinguishing between benign and malignant thrombi is not always necessary. For example, in the setting of main portal vein thrombus in association with advanced multinodular hepatocellular carcinoma, differentiating between stage B disease (bland thrombus) and stage C disease (malignant thrombus) is not vital, because occlusion of the main portal vein is a relative contraindication to TACE and thus leaves only one treatment option available, that is, molecularly targeted therapy with sorafenib. Similarly, if nodal or metastatic disease is present, it is unnecessary to determine whether portal vein thrombus is benign or malignant (Fig 10).

BCLC stage D disease is not a radiologic stage. It is determined only on the basis of poor liver function and poor patient performance (CTP = C, ECOG > 2). Management should consist of only supportive therapies.

## Limitations of AASLD Guidelines

Advances in MR imaging have resulted in ancillary options for the assessment of hepatic nodules. Hepatocyte-specific contrast media (gadoxetate disodium [Eovist or Primovist], Bayer Healthcare, Berlin, Germany; and gadobenate dimeglumine [Multihance], Bracco Diagnostics, Princeton, NJ) have an extracellular distribution, but they are also taken up by hepatocytes and excreted in the biliary system. Hepatocellular carcinoma may or may not take up hepatocyte-specific contrast media, depending on the volume of functioning hepatocytes within the tumor (ie, tumor grade). Diffusion-weighted imaging provides information on tissue cellularity. Hepatocellular carcinoma typically demonstrates restricted diffusion; it is hyperintense on higher *b* value images and correspondingly hypointense on apparent diffusion coefficient maps. Well-differentiated or necrotic hepatocellular carcinoma may not demonstrate restricted diffusion (35).

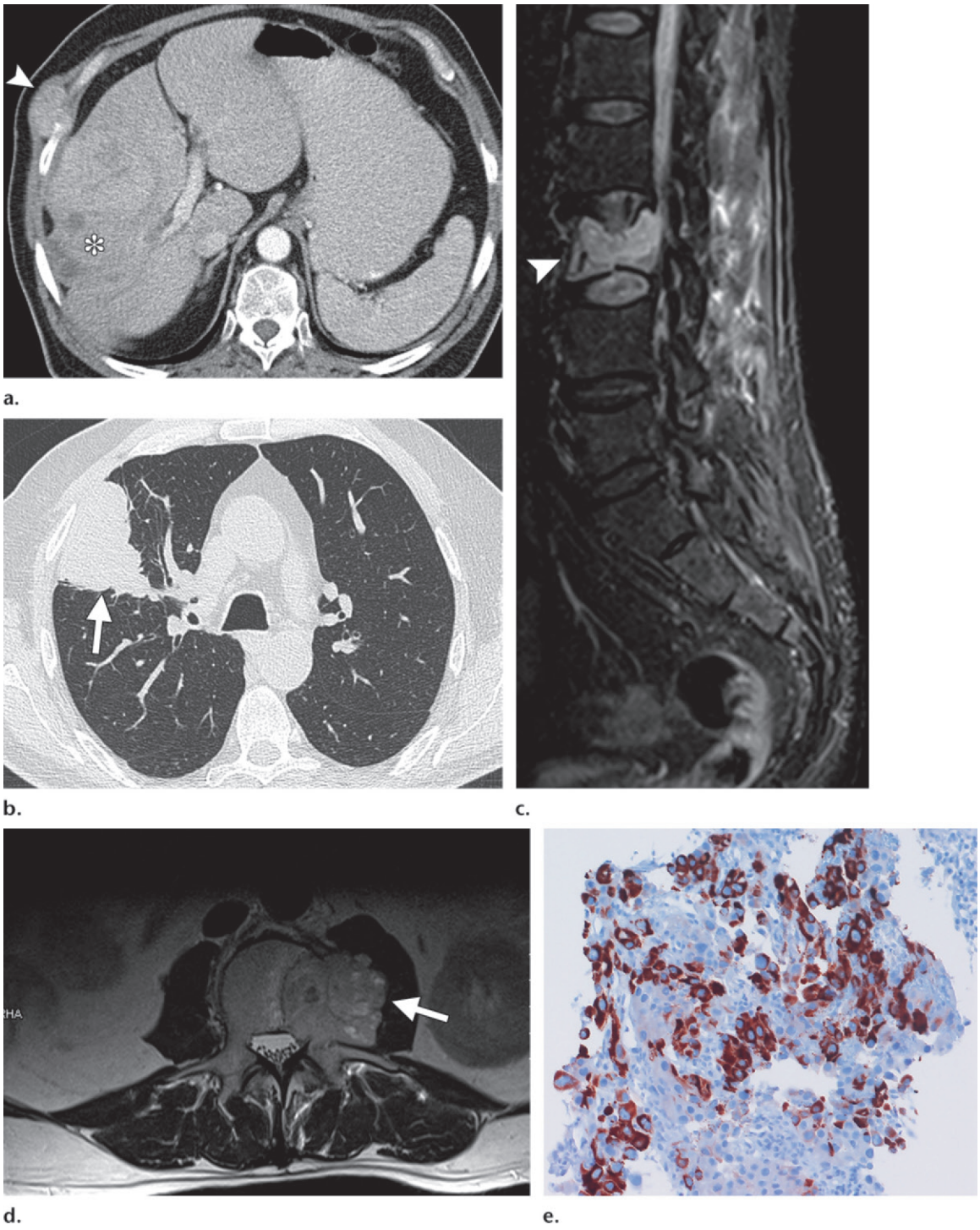


**Figure 10.** Metastatic hepatocellular carcinoma in two cases. **(a)** Portal venous phase CT scan of a 63-year-old man with cirrhosis caused by hemochromatosis shows an abdominal wall metastasis (arrowhead) and a large mass (*) in the right hepatic lobe. The patient had not undergone percutaneous liver biopsy, so this metastasis did not result from needle tract seeding. **(b–e)** Recurrent cancer in a 62-year-old man with nonalcoholic steatohepatitis cirrhosis who had undergone orthotopic liver transplantation for BCLC stage A hepatocellular carcinoma 3 years previously. **(b)** Contrast-enhanced CT scan of thorax demonstrates a large soft-tissue mass (arrow) in the right lung. **(c)** Sagittal short inversion time inversion-recovery image from an MR imaging study of the whole spine shows high signal and compression of the L3 vertebral body, findings consistent with a metastasis (arrowhead). **(d)** Axial T2-weighted image from same study, obtained at the level of L3, shows an extensive soft-tissue component that invades the left psoas muscle (arrow). Biopsy of the lung lesion was performed. **(e)** Photomicrograph of a histologic specimen demonstrates invasive adenocarcinoma with cytoplasmic positivity for hepatocyte paraffin antigen stain, findings consistent with metastatic hepatocellular carcinoma.

Currently, these newer techniques are not included in the AASLD guidelines; diagnosis of malignancy is made on the basis of perfusion characteristics alone. This practice may result in a degree of underdiagnosis and understaging (36,37). AASLD recognizes the subgroup of hypovascular hepatocellular carcinoma. It seems likely that the use of diffusion-weighted imaging and hepatocyte-specific contrast media will contribute to diagnostic accuracy in this subgroup (37). However, the evidence for this is under investigation; it is not comprehensive enough to be included in the diagnostic guidelines at this time.

The added benefit of diffusion-weighted imaging in the diagnosis of hepatocellular carcinoma is recognized by the American College of Radiology and is incorporated into its Liver Imaging Reporting and Data System (LI-RADS). LI-RADS provides a standardized, clear approach to assessment of cirrhotic nodules and allows the radiologist to classify nodules according to their probability of being hepatocellular carcinoma (38). LI-RADS 1 observations are definitely benign. LI-RADS 2–4 observations have increasing probability of being hepatocellular carcinoma, and LI-RADS 5 observations are definitely hepatocellular carcinoma.

## Comparison of AASLD Guidelines with Alternate Guidelines

Alternate guidelines exist for the diagnosis and staging of hepatocellular carcinoma, formulated by groups including the European Association for the Study of the Liver (EASL) and the National Comprehensive Cancer Network (NCCN) (39,40). There is considerable overlap between the AASLD system and these additional guidelines. They rely substantially on the same literature base, and some eminent specialists are members of both expert panels. Key similarities and differences are outlined.

1. ***Single versus dual modality for diagnosis.*** All three guidelines have been updated to allow diagnosis of hepatocellular carcinoma on the basis of findings from a single modality, provided that the nodule is larger than 1 cm and that the characteristic enhancement pattern has been demonstrated. EASL guidelines include the caveat that use of only one imaging modality to diagnose a 1–2-cm hepatocellular carcinoma is allowable only in healthcare centers with sophisticated (state-of-the-art) radiologic equipment.

2. ***Further investigation of new nodules seen at US surveillance.*** All three guidelines recommend that multiphasic imaging be performed immediately if the new nodule is larger than 1 cm in diameter. If the new nodule is smaller than 1 cm, AASLD recommends that US be performed at 3-month intervals for 2 years. If the nodule enlarges during this period, multiphasic imaging should be performed immediately. If the nodule is stable for the duration of the surveillance period, the schedule of routine surveillance examinations can be resumed. EASL recommends that nodules less than 1 cm should be monitored with US every 4 months for 1 year, and if they remain stable, routine surveillance should be resumed. NCCN recommends that multiphasic CT or MR imaging or contrast-enhanced US should be performed at 3–6-month intervals for nodules less than 1 cm. If the nodules remain stable, the NCCN advises that 3–6-month follow-up imaging be continued with the modality that originally demonstrated the lesion. The NCCN does not include a recommendation regarding the preferred time to return to routine surveillance.

3. ***Use of contrast-enhanced US for diagnosis of hepatocellular carcinoma.*** AASLD has eliminated use of contrast-enhanced US as a diagnostic technique. EASL guidelines state that contrast-enhanced US should be used with caution. NCCN supports its use when the modality is available.

4. ***Role of biopsy in diagnosis of hepatocellular carcinoma.*** All three guidelines recommend proceeding to biopsy for nodules that are greater than 1 cm in diameter if the enhancement pattern characteristic of hepatocellular carcinoma is not demonstrated with either multiphasic CT or MR imaging. The NCCN guidelines include an option of repeating imaging at 3 months if nodules are 1–2 cm.

5. ***Recommended staging system.*** AASLD and EASL advocate the use of the BCLC staging system, whereas NCCN does not use a specific staging system in its guidelines.

## Conclusions

Hepatocellular carcinoma is increasing in frequency. It is a malignancy encountered mainly in the setting of cirrhosis; therefore, US surveillance and monitoring of AFP levels are recommended for patients with cirrhosis. The AASLD has published guidelines for the management of focal liver lesions in cirrhosis, and they are described and illustrated in this article. The detection of focal liver lesions larger than 1 cm at routine US surveillance requires immediate further investigation with multiphasic CT or MR imaging. The characteristic imaging appearance of hepatocellular carcinoma is its enhancement pattern: arterial phase hyperenhancement and venous or delayed phase washout. The diagnosis of hepatocellular carcinoma can be

made from a single imaging study when the characteristic enhancement pattern is demonstrated. The BCLC system is the staging system of choice because it combines validated predictors of survival and links staging with treatment options. Stages are not determined on the basis of radiologic findings alone; imaging information is combined with clinical and biochemical parameters. In the future, as classification systems evolve further, the diagnostic roles of diffusion-weighted imaging and hepatocyte-specific MR imaging contrast media and the therapeutic role of newer interventional techniques will become better defined.

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# Hepatocellular Carcinoma: Illustrated Guide to Systematic Radiologic Diagnosis and Staging According to Guidelines of the American Association for the Study of Liver Diseases

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**Page 1655**
The nodules that are suspicious for hepatocellular carcinoma are new nodules that measure more than 1 cm or nodules that enlarge over a time interval. These suspicious nodules require immediate further investigation with multiphasic computed tomography (CT) or magnetic resonance (MR) imaging.

**Page 1655**
The radiologic diagnosis of hepatocellular carcinoma can be made at either CT or MR imaging, provided that a multiphasic contrast material–enhanced study is used.

**Page 1656**
If the lesion demonstrates characteristic features of hepatocellular carcinoma—that is, arterial phase hyperenhancement and portal venous or delayed phase washout—with a single modality, the diagnosis can be made and no further investigation is required.

**Page 1659**
AASLD advocates use of the BCLC staging system because it is the only system that encompasses the three factors that have been shown to be independent predictors of survival—radiologic tumor extent, liver function, and patient's performance status—and thus has the best chance of predicting patient survival compared with other prognostic systems.

**Page 1663**
Therefore, correctly distinguishing between benign and malignant portal vein thrombi is important.