Clinical features and diagnosis of hepatocellular carcinoma

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a primary tumor of the liver that usually develops in the setting of chronic liver disease, particularly in patients with cirrhosis due to alcohol use, chronic hepatitis B or C virus infections, or nonalcohol-associated steatohepatitis (NASH) [1,2]. (See "Epidemiology and risk factors for hepatocellular carcinoma".)

HCC is the fourth leading cause of cancer-related deaths in the world, according to the World Health Organization GLOBOCAN database, and the most rapidly growing cause of cancer deaths in the United States [3,4]. The prognosis of patients with this tumor remains poor, with a five-year survival rate of 18 percent [5]. HCC is frequently diagnosed late in its course for two reasons: the absence of symptoms in patients with early disease, and the reluctance of some clinicians to provide surveillance for high-risk patients. This reflects the ongoing debate regarding the benefit of surveillance among high-risk individuals [6,7]. It is estimated that in Western countries fewer than one-third of patients with cirrhosis undergo surveillance for HCC [8]. As a result, many patients have advanced disease at the time of diagnosis.

The diagnosis of HCC, which can be difficult, often requires the use of one or more imaging modalities. The goal is to detect the tumors when they are ≤2 cm in size so that the entire range of treatment options are available. The five-year survival rate for patients whose tumors are detected at an early stage and who receive treatment exceeds 70 percent [9]. (See "Overview of treatment approaches for hepatocellular carcinoma".)

This topic discusses the clinical and histologic features of HCC and methods for diagnosis. The selection of patients who warrant surveillance for HCC is discussed separately. (See "Surveillance for hepatocellular carcinoma in adults".)

Staging and treatment options for HCC are also discussed separately, as are the clinical features and diagnosis of fibrolamellar liver cancer:

- (See "Staging and prognostic factors in hepatocellular carcinoma".)
- (See "Overview of treatment approaches for hepatocellular carcinoma".)
- (See "Management of potentially resectable hepatocellular carcinoma: Prognosis, role of neoadjuvant and adjuvant therapy, and posttreatment surveillance".)
- (See "Surgical management of potentially resectable hepatocellular carcinoma".)
- (See "Localized hepatocellular carcinoma: Liver-directed therapies for nonsurgical candidates not eligible for local thermal ablation".)
- (See "Localized hepatocellular carcinoma: Liver-directed therapies for nonsurgical candidates who are eligible for local ablation".)
- (See "Systemic treatment for advanced hepatocellular carcinoma".)
- (See "Epidemiology, clinical manifestations, diagnosis, and treatment of fibrolamellar carcinoma".)

CLINICAL FEATURES

Patterns of presentation — There is a spectrum of clinical presentations for patients with HCC. Many patients have no symptoms related to the tumor, especially among those who have been undergoing regular surveillance and have HCC detected at an early stage. (See "Surveillance for hepatocellular carcinoma in adults".)

The majority of HCC cases occur in the setting of chronic liver disease [8]. In fact, cirrhosis is present in 90 percent of patients with HCC in Western countries [4]. Among patients with more advanced liver disease, symptoms and physical findings are often due to underlying cirrhosis rather than the tumor itself. The clinical manifestations of cirrhosis are discussed separately. (See "Cirrhosis in adults: Etiologies, clinical manifestations, and diagnosis", section on 'Clinical manifestations'.)

Patients with cirrhosis may develop features of liver decompensation (eg, variceal bleeding or ascites) due to the extension of HCC into the hepatic or portal veins as the initial manifestation of the tumor.

Symptomatic patients — Patients with advanced lesions may present with mild to moderate upper abdominal pain, weight loss, early satiety, or a palpable mass in the upper abdomen [10].

Paraneoplastic syndromes — Patients with HCC may occasionally develop a paraneoplastic syndrome that can manifest with the following features which (except for erythrocytosis) are generally associated with a poor prognosis [11]:

- **Hypoglycemia** – Hypoglycemia, which usually occurs in advanced HCC, is thought to result from the tumor's high metabolic needs. Hypoglycemia is typically mild and produces no symptoms; however, more severe reductions in plasma glucose can occur, resulting in lethargy and confusion.

  Less than 5 percent of tumors secrete insulin-like growth factor-II, which can cause severe, symptomatic hypoglycemia sometimes early in the course of the disease [12,13].

- **Erythrocytosis** – Erythrocytosis in HCC is probably due to tumor secretion of erythropoietin (EPO) [14]. Although raised serum EPO levels may be present in up to 23 percent of patients with HCC, elevations in hemoglobin concentration or packed cell volume are uncommon, and most patients are anemic at diagnosis because of other effects of the tumor [15]. (See "Diagnostic approach to the patient with erythrocytosis/polycythemia".)

- **Hypercalcemia** – Hypercalcemia can be present in association with osteolytic metastases, but it may also be seen in the absence of bony metastasis due to secretion of parathyroid hormone-related protein [16]. (See "Hypercalcemia of malignancy: Mechanisms".)

- **Diarrhea** – Patients with HCC may infrequently present with intractable diarrhea and associated electrolyte disturbances (eg, hyponatremia, hypokalemia, metabolic alkalosis) [17,18]. The underlying mechanism is not fully understood, but it may be related to secretion of peptides that cause intestinal secretion. These include vasoactive intestinal polypeptide, gastrin, and peptides with prostaglandin-like immunoreactivity [18].

- **Cutaneous features** – Although skin changes are rare in patients with HCC, several cutaneous manifestations have been described; however, none is specific for the diagnosis [19,20]. (See "Cutaneous manifestations of internal malignancy".)

  These include:

  - Dermatomyositis may present with a variety of cutaneous findings (eg, scaly, violaceous papules overlying bony prominences of the hands) and is associated with solid organ malignancies.

- Pemphigus foliaceus is a superficial blistering disease similar to pemphigus vulgaris, except it rarely involves the mucous membranes. Blisters often appear as shallow erosions associated with erythema, scale and crust formation, and the appearance may resemble severe seborrheic dermatitis.

- The sign of Leser-Trélat refers to the sudden appearance of multiple seborrheic keratoses, often with an inflammatory base in association with skin tags and acanthosis nigricans.

- Pityriasis rotunda, which is characterized by multiple, round or oval, sharply demarcated scaling patches has been reported in South African Black patients with HCC [21,22].

Other clinical presentations — The following clinical presentations may be seen in symptomatic patients with HCC:

- Intraperitoneal bleeding due to tumor rupture. Tumor rupture is often associated with sudden onset of severe abdominal pain with distension, an acute drop in the hemoglobin and hypotension, and is most commonly diagnosed by abdominal imaging. Computed tomography (CT) of the abdomen typically demonstrates a liver mass and free intraperitoneal blood [23]. Blood is best appreciated on CT without contrast, whereas the mass is best visualized on contrast-enhanced CT. Tumor rupture is a life-threatening complication, and control of bleeding may require emergent angiography and embolization of the bleeding vessel, or surgery (image 1) [24]. Although the risk of peritoneal dissemination is high, delayed resection may be considered, if feasible. (See "Surgical management of potentially resectable hepatocellular carcinoma" and "Management of potentially resectable hepatocellular carcinoma: Prognosis, role of neoadjuvant and adjuvant therapy, and posttreatment surveillance".)

- Obstructive jaundice caused by invasion of the biliary tree, compression of the intrahepatic duct, or rarely, as a result of hemobilia.

- Fever developing in association with central tumor necrosis.

- Pyogenic liver abscess (very rare) [25].

Extrahepatic metastases — For patients who do not undergo surveillance, extrahepatic metastases are present at the time of diagnosis in approximately 10 to 15 percent of cases [26-28]. Extrahepatic metastases are more common in patients with advanced stage primary tumors (>5 cm, large vessel vascular invasion) [27,29,30]. Extrahepatic metastases occur as a

component of disease recurrence after locoregional therapy in approximately 5 to 25 percent of patients [31-33].

The most common sites of extrahepatic metastases are lung, intra-abdominal lymph nodes, bone [34], and adrenal gland, in that order. Brain metastases are rare overall (0.2 to 2 percent), although a higher rate has been reported in patients who have already developed metastases elsewhere or with locally advanced HCC [35,36].

Perihepatic lymphadenopathy should not be assumed to represent extrahepatic metastases. In patients with cirrhosis related to hepatitis B or C virus infection, benign nodal enlargement may be present and most often involves the porta hepatis and portacaval space. (See "Surgical management of potentially resectable hepatocellular carcinoma", section on 'Determining the extent of tumor involvement'.)

Serum markers

Alpha-fetoprotein — The most commonly used serum marker for HCC is serum alpha-fetoprotein (AFP) concentration. AFP is a glycoprotein that is normally produced during gestation by the fetal liver and yolk sac, and the serum concentration can be elevated in patients with HCC.

An AFP level of 20 ng/mL is a commonly-used threshold to trigger evaluation for HCC in clinical practice [4]. In two studies including over 1800 patients with chronic liver disease and using a AFP cutoff level of 10 to 20 ng/mL, AFP had a sensitivity of approximately 60 percent and specificity of approximately 80 percent for the detection of HCC [37,38].

Data have suggested an increased risk for HCC in patients with chronic liver disease who have elevated AFP levels [39,40]. However, AFP is not used as the primary surveillance test for HCC because of low sensitivity and specificity. As an example, fewer than 20 percent of patients with early HCCs present with abnormal AFP levels. In addition, elevated AFP levels are not specific for HCC and may reflect viral hepatitis or decompensated liver disease [41].

Serum levels of AFP are typically higher for advanced HCC compared to early HCC, but overall, AFP levels do not correlate well with the clinical features of the tumor. Serum AFP levels >400 ng/mL in a high-risk patient are nearly diagnostic of HCC, with a specificity of >95 percent [10,42-44]. However, less than 20 percent of HCCs are associated with such AFP levels [45].

The differential diagnosis of an elevated AFP includes the following:

- Elevated serum AFP may be seen in patients with chronic liver disease such as acute or chronic viral hepatitis, but without HCC [46-49]. In a study of 357 patients with hepatitis C

virus infection but without HCC, 23 percent had an AFP >10 ng/mL [50]. The range was 0.3 to 241 ng/mL. Elevated levels were associated with the presence of stage 3 or 4 fibrosis, an elevated international normalized ratio, and an elevated serum aspartate aminotransferase level.

- Elevated serum AFP also occurs in pregnancy, with tumors of gonadal origin (both germ cell and non-germ cell [51]) and in a variety of other malignancies, of which gastric cancer is the most common [52]. (See "Serum tumor markers in testicular germ cell tumors", section on 'Alpha-fetoprotein' and "Ovarian germ cell tumors: Pathology, epidemiology, clinical manifestations, and diagnosis".)

AFP testing can be useful in conjunction with other tests to guide the management of patients in whom a diagnosis of HCC is suspected. An elevated AFP level in conjunction with suspicious, but not diagnostic, imaging results can have a positive predictive value in the absence of biopsy [53-55]. In addition, an AFP level >1000 ng/mL excludes potential transplant candidates from being eligible for routine HCC exceptions that result in a higher priority MELD score, although they can still be listed as transplant candidates. (See "Liver transplantation for hepatocellular carcinoma", section on 'United States'.)

Given the issues with sensitivity and specificity, most society guidelines do not use serum AFP as a diagnostic test for HCC [41,56-58]. The approach to HCC surveillance is discussed separately. (See "Surveillance for hepatocellular carcinoma in adults".)

Other markers — There is a need for additional biomarkers for the early detection of HCC. Serum markers of HCC used alone or in combination with serum AFP for diagnosis of HCC have included des-gamma-carboxy prothrombin [59] and lens culinaris agglutinin-reactive AFP (AFP-L3) [60-63]. Several other biomarkers have shown promise such a plasma microRNA expression [64,65], methylated DNA markers (MDMs) [66], circulating tumor DNA (ctDNA) [67-69], and circulating tumor cells [70].

In addition to individual biomarkers, the use of combinations of biomarkers have also shown promise in identifying patients with early stage HCC. These include the GALAD (gender, age, AFP-L3, AFP, and des-caboxy prothrombin) score [71], the Doylestown algorithm (age, gender, ALT, alkaline phosphatase, and AFP [72], and a modification, which adds lectin reactive low molecular weight (LMW) kininogen to the latter algorithm to increase accuracy in patients with low AFP values [73].

Emerging data have suggested potential for viral exposure signature (VES) of commonly-acquired viral infections in the early diagnosis of HCC among at-risk patients. In a cohort of 173

patients at risk for HCC, the VES had excellent diagnostic characteristics for predicting HCC prior to a clinical diagnosis with an area under the receiver operating curve of 0.91 [74].

The National Cancer Institute has proposed a five-stage validation program for promising strategies for HCC surveillance [3]. However, none of the above biomarkers and strategies have met the benchmark for clinical application.

DIAGNOSTIC APPROACH

Patients at high risk for HCC — For patients at high risk for developing HCC, the diagnosis can be made with dynamic contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) tailored for liver lesion evaluation. Contrast-enhanced abdominal ultrasound (US) can also be used for solitary lesions if the modality is available. If the lesion demonstrates specific imaging characteristics, a diagnosis of HCC can be made radiographically, obviating the need for a biopsy. (See 'Imaging diagnosis of HCC' below.)

High-risk patients are candidates for surveillance. This includes most patients with cirrhosis and subsets of those with chronic hepatitis B virus infection. Selecting patients for surveillance is discussed in more detail separately. (See "Surveillance for hepatocellular carcinoma in adults" and 'High risk patients' below.)

Surveillance typically uses US with or without alpha-fetoprotein (AFP) [41,56] at regular intervals to detect tumor at an earlier, potentially curable stage (algorithm 1). The diagnosis of HCC may be suspected because of a new lesion on US.

Our diagnostic approach to a solid liver lesion in a high-risk patient is determined initially by the size of the lesion, as detected on surveillance US:

- **Lesions <1 cm** – Lesions measuring <1 cm in diameter are too small to be definitively diagnosed by further imaging or biopsy. They should be monitored at short intervals (eg, every three to six months) for one to two years. If the lesion disappears or remains 1 cm, the patient may return to routine surveillance at six-month intervals (algorithm 1). If the lesion grows beyond 1 cm, or if a new ≥1 cm lesion develops, or if the AFP level is rising, we obtain dynamic contrast-enhanced CT or MRI of the liver tailored for liver lesion characterization. Contrast-enhanced US may be used instead of CT or MRI to characterize the lesion if the modality is available, with the caveat that a contrast-enhanced US exam will require a follow-up CT or MRI to stage the tumor burden in the liver.

- **Lesions ≥1 cm** – For high risk patients with an US showing a dominant, solid lesion ≥1 cm that has not been proven to be a hemangioma on a prior contrast-enhanced imaging study, we obtain dynamic contrast-enhanced CT or MRI of the abdomen tailored for liver lesion evaluation (image 2) [75]. Biopsy for histologic confirmation is not required if the lesion fulfills typical imaging criteria for HCC (ie, Liver Imaging Reporting and Data System (LI-RADS) LR-5 or Organ Procurement and Transplantation Network class 5 lesion). However, if the diagnosis is suspicious (but not certain) for a malignancy (ie, lesion is LI-RADS M or 4) and the results will affect the patient's management, a biopsy of the lesion may be indicated. The decision to biopsy should be arrived at in the context of multidisciplinary discussion with consideration of patient preferences, co-morbidities, and other relevant factors. (See 'Patients requiring additional evaluation' below.)

For patients with cirrhosis or other risk factors for HCC (eg, chronic HBV infection) who have a lesion detected by surveillance US, we agree with the approach to diagnosis of HCC as outlined in a guideline from the American Association for the Study of Liver Diseases (AASLD) [56]. Similar guidelines have been issued by the European Association for the Study of the Liver [41]. However, it should be emphasized that the imaging criteria developed for HCC diagnosis have not yet been validated in patients with chronic hepatitis B virus without cirrhosis.

Patients with chronic, nonviral liver disease and no cirrhosis — For patients who have chronic, noncirrhotic, nonviral liver disease, and who have a suspicious liver lesion (of any size) on US, we obtain a contrast-enhanced CT or MRI of the abdomen tailored for liver lesion imaging and AFP for further evaluation.

If the imaging characteristics are consistent with HCC and the AFP is >400 ng/mL, a biopsy may not be necessary in all patients, especially if the lesion appears to be resectable. (See 'Diagnosis on CT or MRI' below.)

If the diagnosis remains uncertain after obtaining advanced imaging, and the lesion is ≥1 cm, a biopsy can be obtained if the results are likely to affect the patient's management. If the lesion is <1 cm in size, we follow the lesion with repeat advanced imaging in three to six months because the yield of a biopsy is low in this setting. We continue advanced imaging at three to six-month intervals for a total of at least 24 months, provided that there is no change in the size or appearance of the lesion. If the lesion grows beyond 1 cm during follow-up, imaging may be able to establish a definitive diagnosis noninvasively; otherwise, a biopsy may be considered if the results might affect management.

Patients without chronic liver disease — Noncirrhotic livers are more frequently affected by metastases from an extrahepatic malignancy compared with cirrhotic livers [76]. The diagnostic

approach for lesions detected in patients without known liver disease includes a serologic evaluation for previously undiagnosed liver disease, tumor markers (AFP, CA 19-9, carcinoembryonic antigen), and imaging (a contrast-enhanced CT or MRI of the abdomen tailored for liver lesion evaluation). If the diagnosis remains uncertain after obtaining imaging, biopsy can be considered if the results are likely to affect the patient's management. The diagnostic workup and role of biopsy in these patients is discussed separately. (See "Approach to the adult patient with an incidental solid liver lesion".)

IMAGING

HCC can be diagnosed on contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI), or ultrasound (US). In most high-risk patients, HCC can frequently be diagnosed on imaging alone, obviating the need for biopsy. These are categorized as LR-5 in the Liver Imaging Reporting and Data System (LI-RADS) for high risk patients (table 1). (See 'High risk patients' below.)

In a non-high-risk patient, a lesion with the same features would be described as suspicious for HCC but usually requires biopsy for definitive diagnosis. (See 'Liver biopsy' below.)

Selection of imaging exam — The choice of modality should be individualized based on available scanner technology, imaging expertise, and patient contraindications and preferences. Contrast-enhanced CT, MRI, or US are all sufficiently accurate to diagnose HCC. Very few false positive diagnoses are observed with any of these modalities if the diagnostic criteria are rigorously applied [77-79].

In general, contrast-enhanced US (CEUS) is applied only to lesions that can be seen with noncontrast US. Moreover, unlike with CT or MRI, CEUS cannot be used to fully characterize unsuspected lesions in the remainder of the liver [80]. For this reason, CEUS is not useful for staging tumor burden.

Abdominal CT, MRI, or CEUS performed for other indications are often technically insufficient to enable HCC diagnosis. Specific scanner hardware, imaging protocols, and radiologist experience is required. For CT or MRI evaluation, the necessary expertise is available at most imaging centers, whereas CEUS availability is more limited. (See 'Modalities for HCC diagnosis' below.)

The American College of Radiology (ACR), The American Association for the Study of Liver Disease (AASLD), European Association for the Study of the Liver, Organ Procurement and Transplantation Network (OPTN), Asian-Pacific Association for the Study of the Liver, Japan Society of Hepatology, National Comprehensive Cancer Network [81] and others have all issued

guidelines for utilization of imaging and criteria for noninvasive diagnosis of HCC in patients at risk [41,56,82-84].

Prior AASLD guidelines [85], which categorize a lesion as positive, negative, or indeterminate for HCC, have been validated prospectively in single-center studies in patients with cirrhosis and with lesions detected during surveillance US [86,87]. They have not been validated in patients without cirrhosis or for additional lesions detected with multiphase CT or MRI. To improve standardization, most imaging centers have adopted ACR's Liver Imaging Reporting and Data System (LI-RADS) that is broadly consistent with, but more comprehensive than other guidelines and allows for continued updates as new data on liver lesion imaging becomes available [80,88]. Moreover, the 2018 AASLD guideline has adopted the LI-RADS criteria for HCC [56].

Modalities for HCC diagnosis — Contrast-enhanced CT, MRI or US of the liver are used to noninvasively diagnose HCC.

Computed tomography — Contrast-enhanced CT of the abdomen can be used for diagnosis of HCC (image 2).

The necessary equipment for liver lesion characterization with CT is available at most imaging centers. This includes a multidetector scanner with ≥8 detector rows and power injector for dynamic contrast imaging.

Iodinated contrast is administered intravenously at an injection rate of ≥3 mL per second with bolus tracking technology recommended for accurate timing. Reconstructed section thickness is ≤5 mm and liver images during the late arterial (hepatic artery and portal vein enhanced, hepatic vein not enhanced), portal venous (portal vein enhanced, hepatic parenchyma at peak enhancement) and delayed phase (2 to 5 minutes after injection) of contrast enhancement should be obtained (image 3). Other image sets (eg, precontrast, multiplanar reformations) are optional but not required.

Abdominal CT with contrast performed for other indications such as trauma or abdominal pain (but not for liver lesion characterization) are often technically insufficient for the diagnosis of HCC.

For HCC diagnosis with CT, per lesion sensitivity is 65 percent and specificity is 96 percent [77]. For lesions <2 cm, sensitivity decreases to 40 percent. For patients with cirrhosis undergoing evaluation for liver transplantation, the positive predictive value of CT for lesions measuring ≥2 cm is 92 percent.

Allergy to iodinated contrast is a relative contraindication to CT. Contrast-enhanced MRI is the alternative in these patients. (algorithm 2). (See "Patient evaluation prior to oral or iodinated intravenous contrast for computed tomography", section on 'Patients with past reactions to contrast'.)

Severely impaired renal function (ie, estimated glomerular filtration rate [eGFR] <30 mL/min/1.73m^2) is a relative contraindication to CT. If clinically feasible, imaging for HCC diagnosis should be avoided in these patients. However, if imaging is necessary, contrast-enhanced CT can be performed adhering to prophylactic safety measures (algorithm 3). (See "Patient evaluation prior to oral or iodinated intravenous contrast for computed tomography", section on 'Assessing risk for contrast-induced nephropathy'.)

Patients should be able to breath-hold for 10 to 15 seconds at a time for optimal image quality.

Effective radiation dose of CT for liver lesion evaluation is approximately 15 mSv which is comparable to five years of natural background radiation. This risk is unlikely to be clinically meaningful in patients with underlying co-morbidities of cirrhosis and elevated risk for HCC. (See "Radiation-related risks of imaging".)

Magnetic resonance imaging — MRI of the abdomen can be used for diagnosis of HCC (image 4).

The necessary equipment for liver lesion characterization with MRI is available at most imaging centers. This includes a scanner with magnet strength of ≥1.5 Tesla, a torso phased-array coil, and a power injector for dynamic contrast imaging. The accuracy of open MRI with magnet strength <1.5 Tesla has not been adequately studied, and they should not be used for HCC diagnosis unless there is no other safe, practical option.

Gadolinium contrast is administered intravenously at an injection rate of about 1 to 2 cc per second, depending on the agent, with bolus tracking technology or multiarterial phase technology recommended for accurate timing. Required image sets are axial precontrast unenhanced T1-weighted in- and out-of-phase images and T2-weighted images acquired at ≤8 mm section thickness. Then, axial T1-weighted images with fat suppression at ≤5 mm section thickness before contrast administration and during the late arterial (hepatic artery and portal vein enhanced, hepatic vein not enhanced), portal venous (portal vein enhanced, hepatic parenchyma at peak enhancement) and delayed phase (two to five minutes after injection) should be acquired. Other image sets (eg, diffusion-weighted images, non-axial imaging planes) are optional. T2-weighted images may be acquired before or after contrast injection; the use of fat suppression is optimal for these images.

Abdominal MRI with contrast performed for other indications such as characterization of a renal, pancreatic or adrenal lesion (but not for liver lesion characterization) are often technically insufficient to enable HCC diagnosis.

Some data have suggested that MRI was more accurate than CT for diagnosis of HCC ≤3 cm. In a study of 300 patients with histologically-confirmed HCC, MRI had higher sensitivity (79 versus 62 percent) and diagnostic accuracy (78 versus 67 percent) compared with CT [89].

In patients with severe chronic kidney impairment (ie, eGFR <30 mL/min/1.73 m^2), contrast-enhanced MRI should be undertaken with some caution as some types of gadolinium contrast agents are contraindicated. If clinically feasible, diagnostic imaging for HCC should be avoided in these patients. However, if imaging is necessary, contrast-enhanced MRI should be performed adhering to prophylactic safety measures (algorithm 4). The risk of adverse events with gadolinium administration is discussed in more detail separately. (See "Patient evaluation before gadolinium contrast administration for magnetic resonance imaging".)

A common limitation with MRI is claustrophobia. Patients must be able to lie still in the scanner for the duration of the exam (usually 30 to 40 minutes) and breath-hold for 20 to 25 seconds at a time. If the patient cannot do this and if the breath-hold times cannot be reduced to accommodate the patient, we obtain a contrast-enhanced CT scan as an alternative to MRI. If CT is also not possible, then open-magnet MRI can be attempted as a last resort with the understanding that diagnostic accuracy is not known.

Gadoxetate MRI — Gadoxetate disodium, an MRI contrast agent that is slightly different from other gadolinium contrast, can also be used for HCC diagnosis [90]. Gadoxetate is primarily taken up intracellularly by the hepatocytes and excreted in bile whereas other gadolinium contrast agents remain primarily extracellular and are excreted by the kidneys. This pharmacologic difference slightly alters the requirements for post-contrast imaging with gadoxetate. In addition to the image sets usually acquired for dynamic contrast administration, a hepatobiliary phase image set (usually 10 to 30 minutes after injection) is required.

In patients with elevated bilirubin in whom hepatocellular uptake of gadoxetate contrast may be impaired, accuracy of MRI using gadoxetate contrast may be reduced. Thus, while there are no widely accepted bilirubin values above which gadoxetate use is prohibited, we advise against using it for HCC diagnosis in patients with a bilirubin >3 mg/dL.

Ultrasound — Contrast-enhanced ultrasound (CEUS) of the liver can be used for diagnosis of HCC but cannot be used to evaluate a patient as a candidate for liver transplantation. (See 'Diagnosis on contrast-enhanced US' below.)

Generally, CEUS can be applied only to lesions that are visualized with noncontrast US, although some radiologists use CEUS to characterize such lesions using anatomic landmarks from contemporaneous CT or MRI. If the lesion proves to be an HCC, either CT or MRI would be needed to evaluate the remainder of the liver and the upper abdomen for staging [80]. This is because CEUS cannot evaluate the disease burden of the entire liver during the course of contrast enhancement. To detect and characterize a lesion, imaging is performed continuously for the first 60 seconds, then switched to intermittent imaging every 30 seconds for about four to five minutes after contrast infusion. With US, such rapid imaging of the entire liver volume, as opposed to a single index lesion, is not possible.

The necessary imaging expertise for liver lesion characterization with CEUS is available at select imaging centers. Operator experience with the technique is required for acceptable diagnostic performance. LI-RADS categorization applies to the use of pure blood-pool microbubble contrast agents and not combined blood-pool and Kupffer cell agents. (See "Sulfur hexafluoride lipid microspheres: Drug information" and "Perflutren lipid microspheres: Drug information".)

US microbubble contrast agents are well-tolerated. Contraindications are very rare but include known allergy.

Data suggest that the diagnostic performance of CEUS for diagnosing HCC is similar to that of other contrast-enhanced imaging modalities such as CT or MRI. In a systematic review of 23 studies including 6546 adults with chronic liver disease, the sensitivity of CEUS was 78 percent and the specificity was 94 percent for diagnosing a lesion of any size that was previously suspected on noncontrast US as HCC [91]. In studies limited to detecting resectable lesions (ie, <3 cm), the sensitivity of CEUS was 77.5 percent while the specificity was 93 percent. These data suggest that for lesions detected on antecedent ultrasound, CEUS can be used as an alternative to CT or MRI for lesion characterization. This might be useful in situations where CEUS can be performed more expeditiously than other contrast-enhanced imaging modalities. However, if the CEUS exam verifies that the lesion is HCC, additional imaging with CT or MRI will be necessary for staging. Moreover, there was a low degree of certainty in the results of the systematic review given the high risk of bias in the included studies, heterogeneity among studies, and the wide range of the 95% CIs, indicating imprecision. (See 'Magnetic resonance imaging' above.)

For detection and diagnosis of HCC in patients without previously identified liver lesions, the diagnostic performance of CEUS is unknown.

Imaging diagnosis of HCC — Imaging features used to diagnose an HCC include size, kinetics, and pattern of contrast enhancement, and growth on serial imaging [92]. Size is measured as

the maximum cross-section diameter on the image where the lesion is most clearly seen.

Diagnosis on CT or MRI — For a lesion to be considered suspicious for HCC (in a non-high risk patient) or definitely HCC or LR-5 (in a high-risk patient), it should be ≥1 cm and demonstrate non-rim arterial phase hyperenhancement relative to the liver parenchyma [93]. In addition, the following features are assessed (table 1):

- **Non-peripheral washout appearance** – Hypoenhancement when compared to liver in portal venous or delayed phase of contrast administration
- **Enhancing capsule appearance** – Smooth border around most or all of the lesion that enhances visibly in the portal venous or delayed phase of contrast administration
- **Growth** – ≥50 percent increase in size in ≤6 months (a threshold of ≥5 mm increase in size is recommended to ensure that the change represents biological growth and not measurement error). Assessment of growth cannot be made comparing the CT or MRI to a prior US or CEUS.

To be categorized as suspicious for HCC (in a non-high-risk patient) or definitely HCC or LR-5 (in a high-risk patient), a lesion must demonstrate non-rim hyperenhancement in the arterial phase, and fulfill the following size-related criteria:

- >2 cm and demonstrate one or more of the above features **or**
- ≥1 and <2 cm and demonstrate ≥50 percent increase in size in ≤6 months **or**
- ≥1 and <2 cm and demonstrate washout appearance

Lesions <1 cm in size and lesions demonstrating no hyperenhancement in the arterial phase cannot be diagnosed as definitely HCC even in the high-risk patient.

LR-4 and LR-5 categorization based on CT or MRI features are described in greater detail in Liver Imaging Reporting and Data System (LI-RADS).

Diagnosis on contrast-enhanced US — Imaging criteria for HCC diagnosis with CEUS are different from those applied to contrast-enhanced CT or MRI (table 1). To be considered suspicious for HCC (in a non-high-risk patient) or definitely HCC or LR-5 (in a high-risk patient), a lesion must be ≥1 cm, demonstrate diffuse internal enhancement during the arterial phase of contrast administration, and show mild and late (ie, ≥1 minute after injection) washout [94,95]. By comparison, marked or early (<60 seconds) washout is unusual for HCC and raises concern for a non-HCC malignancy. Thus, lesions with marked or early washout should be categorized LR-M. Growth and a presence of an enhancing capsule are not primary features for HCC diagnosis with this modality.

LR-4 and LR-5 categorization based on CEUS features are described in greater detail in Liver Imaging Reporting and Data System (LI-RADS).

High risk patients — LI-RADS offers guidelines for the performance, image interpretation, and reporting for diagnosis of HCC in patients at high risk.

LI-RADS patient criteria — LI-RADS should only be applied to patients with any of the following findings or risk factors:

- Cirrhosis (except for those groups noted below)
- Chronic hepatitis B virus infection
- Lesion identified on a surveillance US for HCC in a patient with cirrhosis (except for those groups noted below), chronic hepatitis B virus infection, or concurrent or prior diagnosis of HCC

LI-RADS should not be applied to the following patients:

- No risk factors for HCC
- Age less than 18 years
- Cirrhosis related to congenital hepatic fibrosis
- Cirrhosis secondary to a vascular disorder (eg, Budd-Chiari syndrome, chronic portal vein occlusion, cardiac congestion, hereditary hemorrhagic telangiectasia). In these patients, the altered hepatic blood flow results in formation of benign hypervascular nodules that resemble and sometimes cannot be distinguished by imaging from HCC.

LI-RADS categories — LI-RADS estimates the relative likelihood of HCC and malignancy associated with each LR category (table 1). The likelihood of HCC associated with each category was estimated in a systematic review of 14 studies of liver CT or MRI that included 2708 observations with 1841 HCCs [96]. The results are noted below. These data can provide guidance for subsequent management, with the assumption that decisions will be individualized to the patient and practice setting. However, risk estimates likely vary with each imaging examination [97-100].

Management tends to be governed by the largest, highest category lesion. Multidisciplinary discussion with consensus-based decision-making is necessary for optimal management, especially for LR-4, LR-5, and LR-M lesion. In particular, multidisciplinary discussion should

precede a choice either to biopsy or to treat presumptively as HCC without histologic confirmation [96].

- LR-NC, not categorized – Inadequate exam. Perform repeat imaging with same modality, if the cause of image omission or degradation is correctable, or an alternative modality in three months.

- LR-1, definitely benign (0 percent likelihood of HCC [96]) – No further workup is indicated. Patients should return to routine surveillance. Examples of lesions in this category include cyst and hemangioma with characteristic imaging features.

- LR-2, probably benign (0 percent likelihood of HCC [96]) – For most lesions, no further evaluation is indicated and most patients should return to routine surveillance. Examples of lesions in this category include focal nodular hyperplasia, hepatocellular adenoma, and hemangioma with most but not all the characteristic imaging features or rounded arterioportal shunts. A clinician may elect to perform imaging with an alternative modality in ≤6 months if the additional information is likely to allow categorization as definitely benign. For example, a lesion interpreted as a probable hemangioma on CT could be more definitively characterized as a hemangioma with MRI (see "Hepatic hemangioma"). Similarly, a rounded area of arterial phase hyperenhancement interpreted as a probable arterioportal shunt on MRI performed with an extracellular gadolinium agent could be proven to be an arterioportal shunt on gadoxetate-enhanced MRI.

- LR-3, intermediate risk (31 percent [95% CI 12-50 percent] likelihood of HCC) [96] – Perform repeat imaging with the same or alternative modality every three to six months. Continue serial imaging until the lesion can be downgraded by stability or evolving imaging features to LR-1 (definitely benign) or LR-2 (probably benign) or upgraded by growth or evolving imaging features to LR-4, LR-5, or LR-M.

- LR-4, probably HCC (64 percent [95% CI 47-80 percent] likelihood of HCC [96]) – Lesions in this category demonstrate most but not all of the characteristic features of a HCC. Such lesions merit multidisciplinary discussion for individualized management, which may include follow-up or alternative imaging, biopsy, or treatment as presumptive HCC (ie, resection) without biopsy. Factors informing the final decision include patient preferences, co-morbidities, eligibility for resection or liver transplantation and availability of other locoregional treatment options (ie, thermal ablation). Patients with an LR-4 lesion who are eligible for transplant will require a biopsy for listing. (See "Overview of treatment approaches for hepatocellular carcinoma".)

- LR-5, definitely HCC (95 percent [95% CI 93-96 percent] likelihood of HCC [96]) – Evaluate for treatment. Biopsy is not necessary to confirm the diagnosis. Lesions in this category demonstrate all the characteristic features of an HCC. In a cohort study of 220 patients with cirrhosis and either HCC or a non-HCC malignancy (confirmed by histopathology within 79 days of the MRI), LR-5 criteria demonstrate a sensitivity of 74 percent (95% CI 67-81 percent) and a specificity of 89 percent (95% CI 81-97 percent) for the diagnosis of HCC [101].

- LR-M, probably or definitely malignant but not definitely HCC (33 percent [95% CI 21-46 percent] likelihood of HCC [96]) – These lesions merit multidisciplinary discussion for individualized management, which usually includes biopsy to establish a specific diagnosis if the results would alter management. Non-HCC malignancies seen in this category are cholangiocarcinoma, mixed hepatocellular-cholangiocarcinoma, lymphoma, or metastasis. (See 'Patients requiring additional evaluation' below.)

  Imaging features suggestive of malignancy include rim but not central arterial phase hyperenhancement, peripheral washout appearance, delayed central enhancement, or a targetoid appearance on diffusion weighted, transitional phase, or hepatobiliary phase images. In a case-controlled cohort study of 220 patients with cirrhosis and either a non-HCC malignancy or HCC (confirmed by histopathology within 79 days of the MRI), LR-M criteria demonstrate a sensitivity of 89 percent (95% CI 81-97 percent) and a specificity of 48 percent (95% CI 40-56 percent) for the diagnosis of a non-HCC malignancy [101].

- LR-TIV, tumor in vein (54 percent [95% CI 30-77 percent] likelihood of HCC) [96] This category indicates that tumor, either HCC or another malignancy [102], is seen in a vein. These lesions merit multidisciplinary discussion for individualized management, which may include follow-up or alternative imaging, biopsy of the intravascular tumor, or presumptive treatment without biopsy. Imaging features include the presence of soft tissue in a vein showing unequivocal enhancement.

Prospective trials that validate these risk estimates and compare different potential treatment strategies have yet to be reported. However, the overall approach, which is based on the estimated risk of HCC for each LI-RADS risk category in high-risk patients, is in agreement with society guidelines.

Organ Procurement and Transplantation Network (OPTN) for transplant candidates — OPTN has described criteria by which HCC is diagnosed with imaging alone (table 2) [82]. The OPTN system is applied to patients with cirrhosis who are candidates for orthotopic liver transplantation.

Imaging criteria for definitive diagnosis of HCC with OPTN and LI-RADS are, for the most part, concordant. Most lesions classified as LI-RADS LR-5 (ie, definitely HCC) meet the criteria for OPTN class 5 (ie, meets radiologic criteria for HCC). One important difference is that LI-RADS includes 10 to 19 mm lesions with arterial phase hyperenhancement and washout appearance as meeting LR-5 criteria (ie, definitely HCC); in the OPTN system, such lesions are not considered HCC unless they also demonstrate a capsule. (See 'Imaging diagnosis of HCC' above.)

In defining the applicable scenarios for use, OPTN and LI-RADS are, for the most part, concordant. Important differences are:

- OPTN allows for use of the system in pediatric patients and those with vascular causes of cirrhosis whereas LI-RADS does not
- OPTN does not allow for use of contrast-enhanced US whereas LI-RADS does
- OPTN does not allow for MRI gadolinium agents with dominant hepatobiliary excretion (ie, gadoxetate disodium) whereas LI-RADS does (see 'Magnetic resonance imaging' above)
- OPTN has size criteria for defining an HCC that is potentially eligible for transplant while LI-RADS does not (ie, a solitary lesion <5 cm or up to three lesions but none over 3 cm)

Non-high-risk patients — Imaging features of HCC in this population do not differ from those in the high-risk category. However, as the prevalence of HCC is much lower, imaging may suggest HCC but the findings rarely obviate the need for additional testing, including a biopsy. On occasion, imaging may also yield a differential diagnosis that includes other tumors (eg, cholangiocarcinoma, metastases). Clinical evaluation, serum laboratories for tumor markers, biopsy of the lesion and, on occasion, the liver parenchyma for evidence of cirrhosis, are some of the options for subsequent management. (See "Approach to the adult patient with an incidental solid liver lesion".)

PATIENTS REQUIRING ADDITIONAL EVALUATION

Patients with LI-RADS LR-3 (intermediate risk for HCC), LR-4 (probably HCC), and LR-M (probably or definitely malignant, but not definitely HCC) lesions may require further evaluation to diagnose HCC (table 1). (See 'LI-RADS categories' above.)

Choice of evaluation strategy — Subsequent evaluation strategies include biopsy or followup imaging with the same or alternative imaging modality. Biopsy may be performed if the result would impact management. Presumptive therapy for HCC without added evaluation is an option

following multidisciplinary discussion in some high-risk patients with LR-4 lesions. (See 'LI-RADS categories' above.)

For LR-4 and LR-M lesions, the need for biopsy should be considered in the context of the clinical presentation and serum tumor marker levels. Multidisciplinary discussion for individualized decision-making is recommended prior to biopsy. For some patients with LR-4 lesions, where the clinical features of the presentation increase suspicion for underlying HCC and the alpha-fetoprotein is >400 ng/mL, a biopsy may not be needed and the lesion may be treated presumptively for HCC. In this setting, a biopsy may still be needed if the result would alter management. Examples include a patient who is potentially eligible for transplantation for whom listing requires biopsy confirmation of the diagnosis, or a patient who is being considered for nonsurgical locoregional therapies such as radiation therapy or thermal ablation.

For most LR-3 lesions, we suggest follow-up imaging with abdominal computed tomography (CT) or magnetic resonance imaging (MRI) with contrast for liver evaluation until the lesion is diagnosed as HCC, another malignancy, or a benign lesion. The majority of LR-3 lesions are benign [98].

For LR-M lesions, where about two-thirds are non-HCC malignancy and about one-third are HCC, biopsy often plays an important role [98].

Liver biopsy — A diagnosis of HCC can be made noninvasively for some patients because histologic confirmation with tissue obtained either at the time of surgery or percutaneous biopsy is not required [103]. There are several clinical scenarios, usually with LR-4 and LR-M lesions, where biopsy is pursued:

- Patient is not at high risk for HCC. (See 'Patients without chronic liver disease' above and "Approach to the adult patient with an incidental solid liver lesion".)
- Patient has cardiac cirrhosis, congenital hepatic fibrosis, or cirrhosis due to a vascular disorder (eg, Budd-Chiari syndrome, hereditary telangiectasia).
- Patient has elevated Cancer Antigen (CA) 19-9 or carcinoembryonic antigen with suspicion of intrahepatic cholangiocarcinoma (CCA) or a mixed HCC-CCA. (See "Clinical manifestations and diagnosis of cholangiocarcinoma", section on 'Tumor markers'.)
- Confirmation of metastatic disease could change the management.
- Histologic grading or molecular characterization of the tumor is desired.

- Nonsurgical, locoregional therapy (eg, ablation) is being considered. (See "Localized hepatocellular carcinoma: Liver-directed therapies for nonsurgical candidates who are eligible for local ablation".)

- Patient is undergoing liver transplantation evaluation. (See "Liver transplantation for hepatocellular carcinoma".)

Biopsy is not generally recommended for LR-1, LR-2, LR-3, or LR-5 lesions. (See 'LI-RADS categories' above.)

The diagnostic yield of image-guided percutaneous liver biopsy for lesions ≤2 cm can be as low as 70 percent [86]. However, studies report low rates of malignancy for these small lesions [104-106]. Use of core needles in addition to fine-needle aspiration increases the amount of tissue obtained and increases biopsy yield [107]. (See "Approach to liver biopsy".)

Risks — Risks of biopsy include immediate procedure-related complications, spread of tumor along the needle track, and the possibility of sampling errors leading to false negative diagnoses. These risks should be factored into the decision to perform a biopsy, especially in patients with lesions where imaging characteristics are highly suggestive but not diagnostic of HCC (eg, LR-4 lesions) and the patient is a potential candidate for liver transplantation, or if surgical resection is likely to be performed. (See "Surgical management of potentially resectable hepatocellular carcinoma" and "Liver transplantation for hepatocellular carcinoma".)

Major procedure-related complications include hemoperitoneum, symptomatic hypotension, pneumothorax, and biliary peritonitis. These occur in 1.5 to 2.6 percent of liver biopsies in patients with cirrhosis [108,109]. Biopsy-related death is estimated at 9 in 100,000 procedures. In a systematic review, the overall risk of needle track seeding with percutaneous needle biopsy was 2.7 percent (95% CI 1.8-4.0 percent) [110].

Histopathology — The histologic appearance of HCC can range from well-differentiated (with individual hepatocytes appearing nearly identical to normal hepatocytes) (picture 1) to poorly differentiated lesions consisting of pleomorphic tumor cells in a solid or compact growth pattern (picture 2). Central necrosis of large tumors is common. Bile globules (picture 3) and acidophilic (hyaline) inclusions (picture 4) are occasionally present. (See "Pathology of malignant liver tumors", section on 'Hepatocellular carcinoma'.)

In some cases, dysplasia, rather than carcinoma, is diagnosed. Dysplasia seen on a needle biopsy specimen may represent sampling error and warrants repeat biopsy or resection to avoid underdiagnosis. (See "Pathology of malignant liver tumors", section on 'Dysplastic nodules'.)

Follow-up imaging — Follow-up imaging should be acquired with contrast-enhanced CT or MRI. Imaging should be performed with the liver imaging protocol for the diagnosis of HCC. Generally, follow up should be done with same modality unless imaging with an alternative method is likely to be safer, better tolerated, or more accurate. (See 'Imaging' above.)

The schedule and preferred modality for followup is individualized (see 'LI-RADS categories' above).

Typically, repeat imaging is performed three to six months after the initial exam, with the time interval governed by lesion size (ie, six months for lesions <1 cm and three months for larger lesions). If lesions are stable on initial followup, the interval between imaging exams can be increased. Occasionally, a recommendation will be made by the radiologist to alter the modality or the gadolinium contrast for MRI.

CLINICAL PRACTICE GUIDELINES

Our diagnostic approach for high-risk patients is generally consistent with guidelines from the American Association for the Study of Liver Diseases (AASLD), the American College of Radiology's Liver Imaging Reporting and Data System (LI-RADS) and European Association for the Study of the Liver (EASL) [41,56,88].

EVALUATION AFTER HCC DIAGNOSIS

Once the diagnosis of HCC is made, further evaluation in a multidisciplinary setting is required to select therapy. History and physical examination, and serologic and imaging tests are obtained to assess the patient's liver reserve, performance status, co-morbidities, extent of tumor spread, and potential eligibility for liver transplantation. Multidisciplinary evaluation is essential. (See "Staging and prognostic factors in hepatocellular carcinoma", section on 'Staging and prognostic scoring systems' and "Surgical management of potentially resectable hepatocellular carcinoma", section on 'Preoperative assessment' and "Liver transplantation for hepatocellular carcinoma", section on 'Indications for transplantation'.)

Potential treatment options for HCC include [111] (see "Overview of treatment approaches for hepatocellular carcinoma"):

- Surgical resection
- Liver transplantation

- Locoregional ablation therapies:
  - Thermal ablation approaches (radiofrequency ablation, microwave ablation, cryoablation)
  - Percutaneous ethanol or acetic acid ablation
  - Irreversible electroporation
- Arterial-based therapies (bland embolization, chemoembolization, radioembolization)
- External beam radiotherapy
- Systemic chemotherapy and immunotherapy

Laboratory tests — The following laboratory tests should be obtained in a patient with a liver mass suspicious for HCC (see "Approach to the patient with abnormal liver biochemical and function tests", section on 'Liver enzymes' and 'Alpha-fetoprotein' above):

- Liver biochemical and function tests (ie, bilirubin, aminotransferases, alkaline phosphatase)
- Complete blood count, platelets
- Renal function tests (blood urea nitrogen and creatinine)
- Prothrombin time
- Albumin
- Tumor markers including alpha-fetoprotein, carbohydrate antigen (CA) 19-9, carcinoembryonic antigen
- Serology for hepatitis B virus and hepatitis C virus

Imaging — Extent of tumor spread may be evaluated with the following imaging exams:

- Contrast-enhanced abdominopelvic computed tomography (CT) or magnetic resonance imaging (MRI) tailored for liver lesion evaluation (see 'Modalities for HCC diagnosis' above).
- Chest CT without or with intravenous contrast. Either is appropriate depending on the clinical scenario of the imaging.
- Whole body technetium-99m bone scan, if clinically indicated.

In addition to liver imaging, we agree with the National Comprehensive Cancer Network guidelines [81] that recommend chest and abdominopelvic CT to evaluate for extrahepatic metastases, and reserve bone scan for patients with skeletal symptoms.

For patients who might be eligible for liver transplantation, in the United States, in an attempt to ensure that preoperative assessment is as accurate as possible, the Organ Procurement and Transplantation Network (OPTN) provides a set of specific requirements for listing patients with HCC for orthotopic liver transplantation (OLT). The patient must undergo a thorough assessment to evaluate the number and size of tumors, and to rule out extrahepatic spread and/or macrovascular involvement (ie, tumor in the portal or hepatic vein). This can be accomplished by contrast-enhanced CT, or MRI of the abdomen plus a contrast-enhanced chest CT. Bone scan is no longer required in the absence of skeletal symptoms as of December 2012. (See "Liver transplantation for hepatocellular carcinoma", section on 'United States'.)

Outside of the United States, practices are variable. This subject is discussed in detail elsewhere. (See "Liver transplantation for hepatocellular carcinoma", section on 'Outside of the United States'.)

Whole body fluorodeoxyglucose positron emission tomography is not recommended as it rarely detects extrahepatic disease not seen with conventional CT or MRI [112].

Chest CT and bone scan — The most frequent sites of extrahepatic disease spread are the lungs, abdominal lymph nodes, and bones, in that order. (See 'Extrahepatic metastases' above.)

However, the rate of extrahepatic spread is low overall (with the possible exception of tumors >5 cm), and the yield of routine chest CT and bone scan for detecting extrahepatic disease is also low [28,113,114].

The value of chest CT and bone scan in the staging workup of HCC was addressed in a prospective cohort of 381 patients newly diagnosed with HCC at a single Korean institution over a three-year period [28]. All patients underwent contrast-enhanced abdomen CT for liver assessment, chest radiograph followed by chest CT, and radionuclide bone scan. Abnormal findings on chest CT and bone scan were observed in 60 and 53 percent of the 381 patients, respectively. However, 19 of the 30, and 7 of the 8 patients with documented metastatic disease in the chest or bones, respectively, had the same lesions detected on CT or chest radiograph. Only three patients showed a shift in Barcelona Clinic Liver Cancer (BCLC) stage (from B [localized disease] to C [extrahepatic disease spread], 3 of 61 patients or 5 percent of those with BCLC stage B disease), and additional metastases were revealed in only 1.1, 14, and 5.6 percent of patients with American Joint Committee on Cancer stage T2, T3a, and T3b (table 3) disease, respectively. These data support the view that staging chest CT and bone scans do not provide additional information on metastases in patients who have localized HCC, especially those who fulfill the Milan criteria for transplantation. Nevertheless, routine chest CT (but not bone scan) is recommended by OPTN in the initial evaluation of eligibility for OLT in patients

with HCC. (See "Liver transplantation for hepatocellular carcinoma", section on 'Requirements for listing and management while on the wait list'.)

Staging — A number of systems have been proposed to predict the prognosis for HCC, none of which has been universally adopted. Issues related to staging and prognosis are discussed separately. (See "Staging and prognostic factors in hepatocellular carcinoma".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Hepatocellular carcinoma".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Liver cancer (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Clinical features** – There is a range of clinical presentations for patients with HCC, from being asymptomatic to presenting with a life-threatening illness such as variceal hemorrhage. Previously stable patients with cirrhosis may develop features of decompensation (eg, variceal bleeding or ascites) due to the extension of HCC into the hepatic or portal veins. (See 'Clinical features' above.)

Patients with HCC may develop a paraneoplastic syndrome that can manifest as hypoglycemia, erythrocytosis, hypercalcemia, or severe diarrhea. (See 'Paraneoplastic syndromes' above.)

- **Screening** – High-risk patients are candidates for surveillance. This includes most patients with cirrhosis and some with chronic hepatitis B virus infection. (See "Surveillance for hepatocellular carcinoma in adults".)

- **Diagnostic imaging** – Our approach to high-risk patients depends on lesion size (algorithm 1) (see 'Patients at high risk for HCC' above):

  - For high-risk patients with lesions measuring <1 cm in diameter, we monitor by obtaining a follow-up ultrasound (US) every three to six months for one to two years. If the lesion grows to ≥1 cm, we obtain dynamic contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen tailored for liver lesion characterization.

  - For high-risk patients with an US showing a dominant, solid lesion ≥1 cm that has not previously been diagnosed as a hemangioma on a contrast-enhanced imaging exam, we obtain dynamic contrast-enhanced CT or MRI of the abdomen tailored for liver lesion evaluation. Biopsy for histologic confirmation is not required in patients at high risk for HCC whose lesion(s) fulfill typical imaging criteria for HCC (ie, Liver Imaging Reporting and Data System (LI-RADS) LR-5 or Organ Procurement and Transplantation Network [OPTN] class 5 lesion).

  HCC can be diagnosed on contrast-enhanced CT, MRI, or US. In high-risk patients, HCC can sometimes be diagnosed on imaging alone, obviating the need for biopsy. These are categorized as LR-5 in the LI-RADS for high-risk patients (table 1). In a non-high-risk patient, a lesion with the same features would be described as suspicious for HCC but usually requires further evaluation (eg, serum tumor markers, biopsy) for definitive diagnosis. (See 'Imaging' above.)

  LI-RADS estimates the likelihood of HCC and malignancy associated with each LR category (table 1). Thus, it provides guidance for subsequent management, with the assumption that decisions will be individualized to the patient and practice setting. (See 'LI-RADS categories' above.)

- **Patients who are liver transplant candidates** – OPTN has described criteria by which HCC is diagnosed based upon imaging alone (table 2). The OPTN system is applied to

patients with cirrhosis who are candidates for orthotopic liver transplantation. (See 'Organ Procurement and Transplantation Network (OPTN) for transplant candidates' above.)

- **Indications for biopsy** – Biopsy is usually needed for LR-M (probably or definitely malignancy, not definitely HCC) lesions and sometimes for LR-4 (probably HCC) lesions if the result would alter clinical management. However, a multidisciplinary consultation may elect to treat LR-4 lesions presumptively as HCC without biopsy confirmation. In contrast, if the patient is eligible for liver transplantation or if nonsurgical local treatment modalities are under consideration (eg, thermal ablation), a biopsy may be needed to confirm the diagnosis.

  Biopsy is typically not performed for LR-1, LR-2, LR-3, or LR-5 lesions. We obtain follow-up imaging with abdominal CT or MRI with contrast for liver evaluation for most LR-3 lesions (intermediate risk for HCC) until the lesion is diagnosed radiographically as HCC, another malignancy, or a benign lesion. (See 'Patients requiring additional evaluation' above and 'LI-RADS categories' above.)

- **Pretreatment evaluation** – Following the diagnosis of HCC, further evaluation, usually in a multidisciplinary setting, is required to select therapy. History and physical examination, and serologic and imaging exams are obtained to assess the patient's liver reserve, performance status, comorbidities, extent of tumor spread, and eligibility for liver transplantation. (See 'Evaluation after HCC Diagnosis' above.)

  A number of systems have been proposed to predict the prognosis for HCC, none of which has been universally adopted. Issues related to staging and prognosis are discussed separately. (See "Staging and prognostic factors in hepatocellular carcinoma".)

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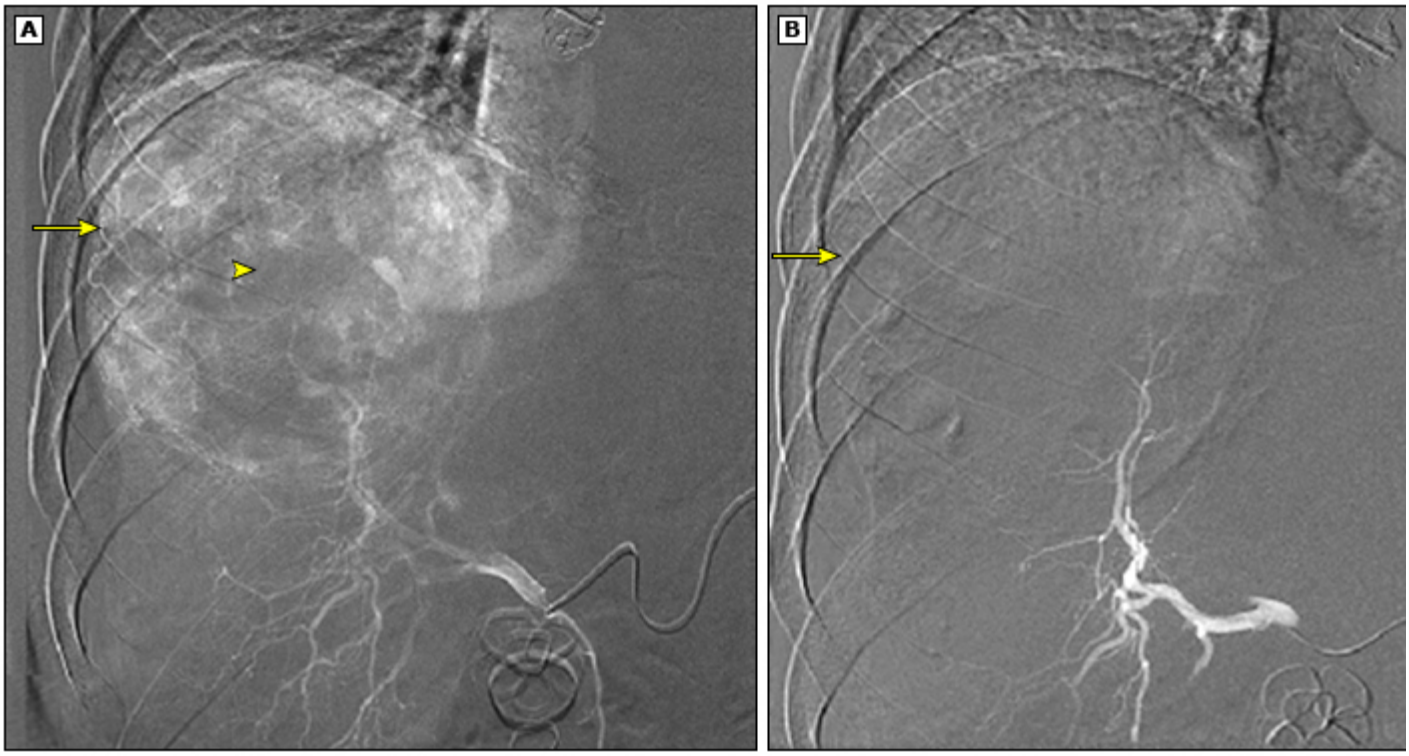
Topic 3597 Version 56.0

GRAPHICS

Hemorrhagic HCC treated with embolization

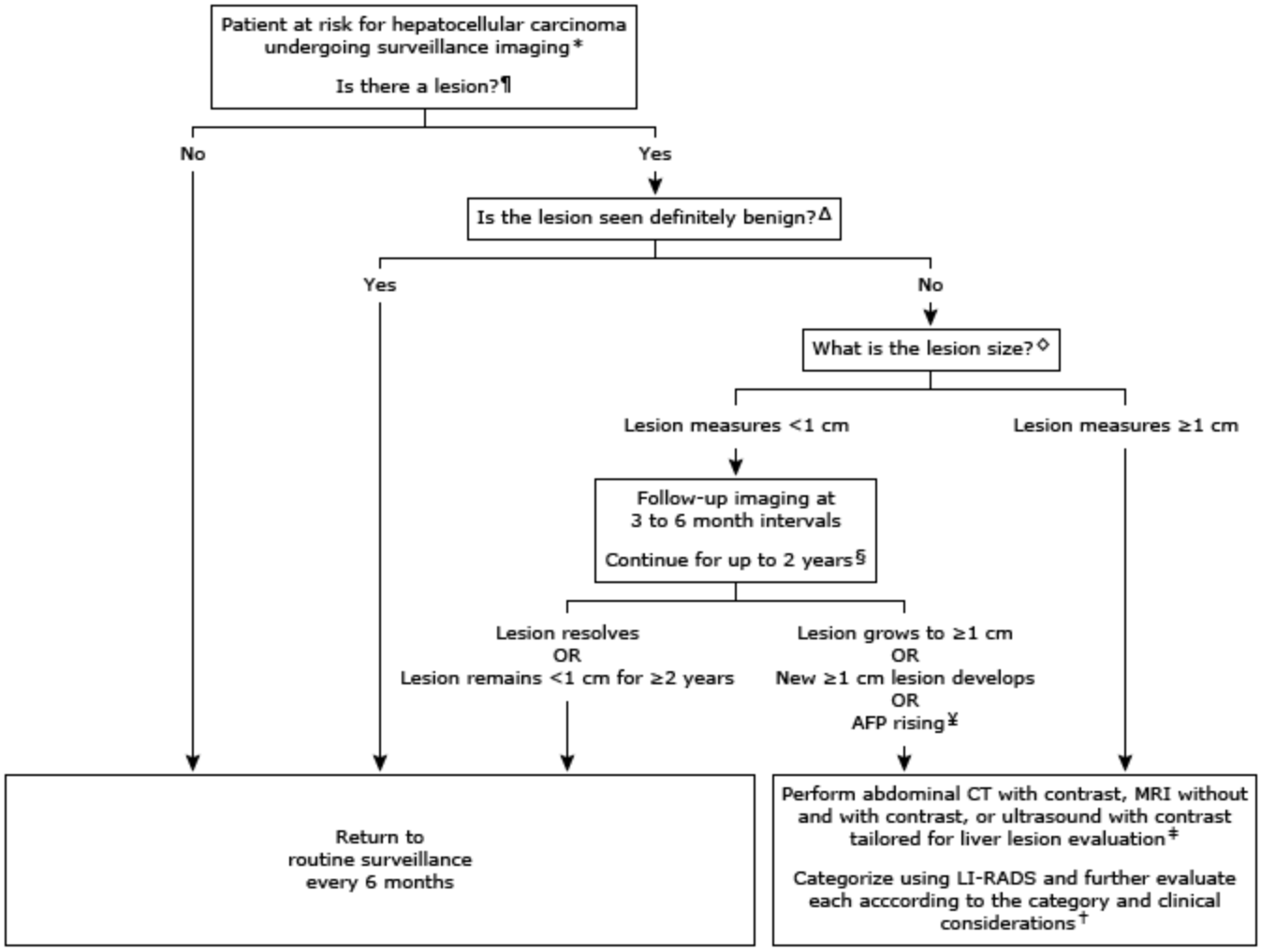


An angiogram of a hemorrhagic HCC (A) shows a hypervascular mass in the dome of the liver (arrow) with a central region of hypovascularity (arrowhead) likely representing intratumoral clot or necrosis. Image B is ar angiogram of the right hepatic artery following microsphere embolization and shows an avascular mass (arrow).

HCC: hepatocellular carcinoma.

Graphic 97795 Version 1.0

Surveillance imaging in adults at risk for hepatocellular carcinoma



AFP: alpha-fetoprotein; CT: computed tomography; MRI: magnetic resonance imaging; LI-RADS: Liver Imaging Reporting and Data System.

* Abdominal ultrasound is recommended in most patients. However, surveillance modalities (eg, addition of serum alpha fetal protein, abdominal CT, or MRI with intravenous contrast rather than ultrasound) are sometimes individualized as described elsewhere in UpToDate.

¶ If there are multiple lesions, this algorithm can be applied to each lesion. However, management choice is driven by the lesion that is the most suspicious (eg, largest and not definitely benign, growing).

Δ Examples of definitely benign lesions include simple cysts or those previously characterized on contrast-enhanced liver imaging or biopsy as definitely benign (eg, hemangioma).

◇ Size is defined as the maximum cross-section diameter measured on the image where the lesion is most clearly seen.

§ Same imaging modality should be used for initial follow-up, but subsequent imaging may involve a change in modality. While the two-year follow-up represents our practice, stability over that time does not confirm that a lesion is benign. For these patients, we resume routine surveillance imaging every six months.

¥ Practice varies on whether serum AFP is measured in this setting.

‡ Imaging technology and performance should adhere to standards required for liver lesion characterization which are more stringent than those for routine abdominal imaging and requires multiphase post-contrast imaging[1]. Modality choice depends on available scanner technology, imaging expertise, and patient contraindications. Contrast-enhanced CT and MRI demonstrate comparable accuracy. Contrast-enhanced ultrasound is more limited in availability and its diagnostic performance is not as well characterized.

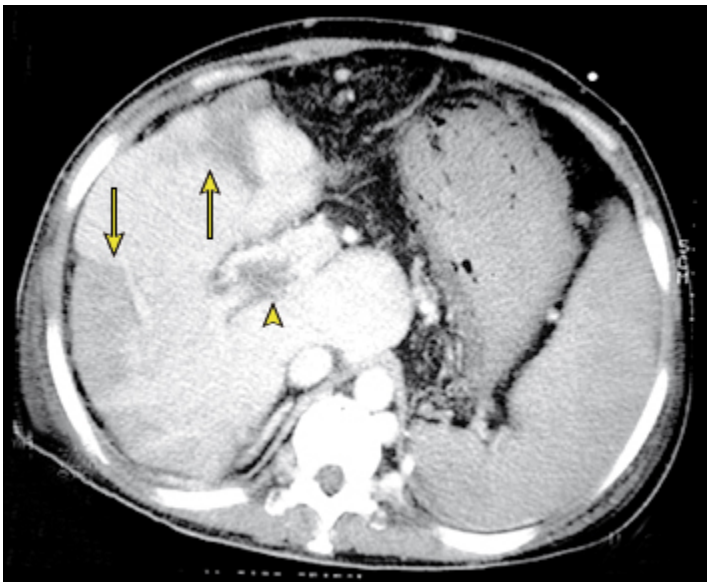
† Liver Imaging Reporting and Data System (LI-RADS) system to categorize, further evaluate, and diagnose liver lesions is described elsewhere in UpToDate. LI-RADS evaluation can involve biopsy or follow-up imaging with contrast-enhanced CT, MRI, or ultrasound.

Reference

1. *American College of Radiology. Liver Reporting & Data System v2017. https://www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/LI-RADS (Accessed on December 20, 2017)*

Graphic 117489 Version 2.0

CT of hepatocellular carcinoma invading the portal vein



Hepatocellular carcinoma. Contrast-enhanced CT of a cirrhotic liver demonstrates multifocal hypervascular masses (arrows) and a mass in the portal vein (arrowhead). The spleen is enlarged due to portal hypertension secondary to cirrhosis.

CT: computed tomography.

Courtesy of Jonathan Kruskal, MD.

Graphic 67676 Version 4.0

Liver lesion evaluation in patients at risk for hepatocellular carcinoma using Liver Imaging Reporting and Data System (LI-RADS) categorization[1]

Select the target population:

Patients who have a liver lesion on imaging (eg, ultrasound) and who are at risk for HCC due to at least one of the following:

- Cirrhosis, with certain exceptions*
- Chronic hepatitis B virus infection
- Concurrent or prior diagnosis of HCC

Perform one of the following studies, tailored for liver lesion evaluation:¶

- Contrast-enhanced CT
- Contrast-enhanced MRI
- Contrast-enhanced ultrasound (CEUS)‡

Categorize lesion(s) using LI-RADS

LI-RADS categorization of liver lesions in patients at risk for hepatocellular carcinoma

Category	Assessment	Diagnostic considerations	Action
LR-1	Definitely benign	Includes hemangiomas with characteristic features or cysts.	▪ Continue routine surveillance imaging for HCC Δ
LR-2	Probably benign	Includes hemangioma without characteristic features and wedge-shaped arterioportal shunts.	▪ For most patients, continue routine surveillance imaging for HCC Δ ▪ For some patients, image with a different modality or MRI contrast agent ◇
LR-3	Intermediate probability of malignancy	Includes dysplastic nodules, benign lesions without characteristic features, and rounded arterioportal shunts.	▪ Repeat contrast-enhanced CT, MRI, or ultrasound for liver lesion evaluation in 3 to 6 months¶ ▪ Continue serial imaging every 3 to 6 months while the lesion remains LR-3 for ≥2 years or until the lesion has a conclusive diagnosis§ ▪ If the lesion remains LR-3 for ≥2 years on imaging follow-up, return to routine surveillance imaging for HCC Δ

LR-4	Probably HCC	Includes HCC with some characteristic features.[¥]	▪ Multidisciplinary consultation to tailor further management. Options include: • Alternative or follow-up imaging • Biopsy the lesion • Presumptive treatment without conclusive diagnosis
LR-5	Definitely HCC[†]	HCC with characteristic features.**	▪ Treatment for HCC ▪ No biopsy needed
LR-M	Probably or definitely malignant, not specific for HCC	Most LR-M lesions are malignant. Includes HCC without characteristic features[¶¶] and other malignancies (eg, cholangiocarcinoma, combined hepatocellular carcinoma and cholangiocarcinoma, lymphoma, or metastasis).	▪ Multidisciplinary consultation to tailor further management. Options include: • Evaluate for underlying malignancy[ΔΔ] • Perform biopsy if it will alter management[◇◇]
LR-NC	Not categorizable	Images are insufficient for assessment. Common reasons include imaging protocol not tailored for liver lesion or images degraded from patient motion.	▪ Repeat imaging for liver lesion evaluation with same or alternate modality in ≤3 months
LR-TIV	Tumor in vein	Unequivocal enhancing soft tissue in vein indicating tumor, either from HCC or another malignancy.	▪ Multidisciplinary consultation to tailor further management. Options include: • Alternative or follow-up imaging • Biopsy the tumor in vein • Presumptive treatment without histologic confirmation

Evaluation of liver lesions in patients not at high risk for HCC is described elsewhere in UpToDate and is not addressed in this table. If there are multiple lesions, this table can be applied to each lesion. However, management choice is driven by the lesion that is the most suspicious (eg, growing, largest, and not definitely benign).

LI-RADS: Liver Imaging Reporting and Data System; HCC: hepatocellular carcinoma; CT: computed tomography; MRI: magnetic resonance imaging; OPTN: Organ Procurement and Transplantation Network.

* LI-RADS assessment should not be applied to patients <18 years old or those with cirrhosis from congenital hepatic fibrosis or secondary to vascular disorders (eg, Budd-Chiari syndrome, chronic portal vein occlusion, cardiac congestion, hereditary hemorrhagic telangiectasia).

¶ Imaging technology and performance should adhere to standards required for liver lesion characterization, which are more stringent than those for routine abdominal imaging. Contrast-enhanced CT or MRI is preferred over ultrasound (CEUS) to characterize lesions where index of suspicion for HCC or malignancy is high or in patients with multiple lesions requiring LI-RADs categorization. Should the lesion prove to be LR-4, LR-5, or LR-M, CEUS cannot evaluate the entire liver to assess tumor burden for treatment planning nor diagnose HCC using the OPTN criteria for transplant evaluation. In addition, for technical reasons, CEUS cannot categorize multiple lesions simultaneously.

Δ Surveillance imaging for adults at risk for HCC, usually performed with abdominal ultrasound without contrast, is described elsewhere in UpToDate.

◇ Choice of additional imaging should be made in consultation with the radiologist.

§ While the two-year follow-up represents our practice, stability over that time does not confirm that a lesion is benign.

¥ On contrast-enhanced CT or MRI, in order to be categorized as LR-4, lesions that measure <1 cm should be arterially enhancing and demonstrate at least one of these three features: nonperipheral washout, enhancing capsule, or growth. Lesions that are not arterially enhancing can also be categorized as LR-4 if they measure >2 cm and demonstrate one of the three features or measure <2 cm and demonstrate two of the three features. On CEUS, in order to be categorized as LR-4, lesions should be arterially enhancing without washout and measure >1 cm, arterially enhancing with late and mild washout and measure <1 cm, or not arterially enhancing with late and mild washout and measure >2 cm.

‡ If the lesion was diagnosed on CEUS, contrast-enhanced CT or MRI tailored for liver lesion evaluation should be performed to plan therapy.

† For patients who are candidates for liver transplant, most LR-5 lesions meet OPTN criteria for diagnosis of HCC. Refer to UpToDate content for description of pertinent exceptions.

** On contrast-enhanced CT or MRI, in order to be categorized as LR-5, lesions must be arterially enhancing and measure >1 cm. Additionally, those measuring >2 cm should demonstrate at least one of the following three features, and those measuring >1 but <2 cm should demonstrate at least two of the three features: non-peripheral washout, enhancing capsule, or growth. On CEUS, in order to be categorized as LR-5, lesions should measure >1 cm and demonstrate arterial enhancement

with late and mild washout. Growth is defined as ≥50% increase in size in ≤6 months with a threshold of ≥5 mm change to avoid error from measurement variability.

¶¶ Examples of HCC without characteristic features are those without arterial enhancement or those with both arterial and delayed enhancement suggesting cholangiocarcinoma.

ΔΔ Approximately 95% of LR-M lesions are malignant. Slightly less than one-half of malignant cases are HCC and the remainder are non-HCC malignancies (eg, cholangiocarcinoma, combined HCC-cholangiocarcinomas, lymphoma, or metastases).

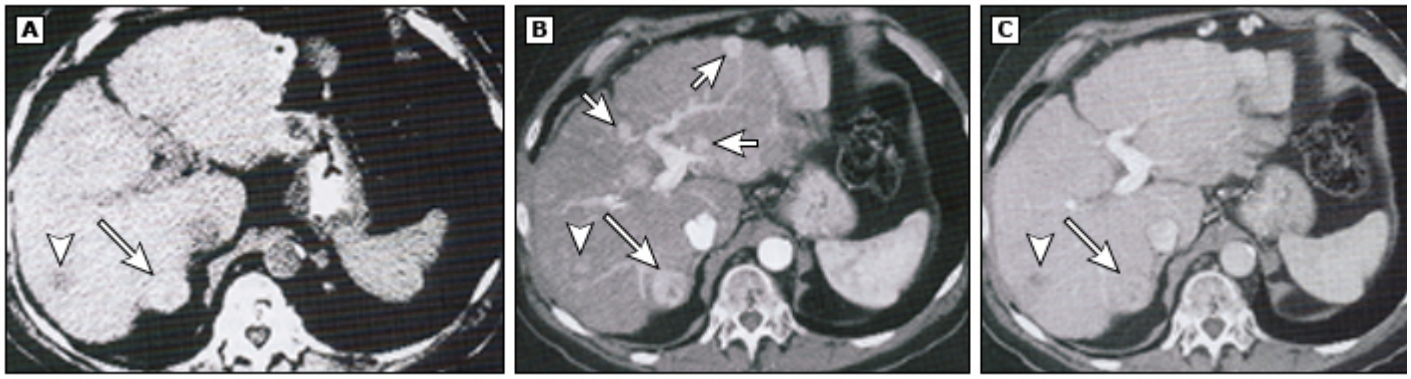
◇◇ Biopsy may alter management for patients being evaluated for liver transplant or for other nonsurgical locoregional therapies (eg, thermal ablation), or if serum tumor markers suggest intrahepatic cholangiocarcinoma or metastasis from an extrahepatic malignancy.

Reference:

1. *American College of Radiology. Liver Reporting & Data System v2018. https://www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/LI-RADS (Accessed on August 21, 2018).*

Graphic 116155 Version 3.0

CT of hepatocellular carcinoma



Hepatocellular carcinoma. CT images before and after dynamic contrast of a 74-year-old male with cirrhosis and a history of alcohol exposure.

(A) Unenhanced image of liver shows exophytic mass (arrow) and a hypoattenuating mass (arrowhead) in segment VII.

(B) Contrast-enhanced image of the liver during late arterial phase shows hyperenhancement of both lesion (arrowhead, arrow) and multiple other additional masses (short arrows). These are all suspicious for multifocal hepatocellular carcinoma.

(C) Imaging during the portal venous phase shows washout of contrast of one of the segment VII lesions (arrowhead) relative to the liver. Thus, this lesion (arrowhead) would be considered displaying all features diagnostic of hepatocellular carcinoma. The other segment VII lesion (arrow) does not yet show washout an would be considered only suspicious for hepatocellular carcinoma.

CT: computed tomography.

Szklaruk J, Silverman PM, Charnsangavej C. Imaging in the diagnosis, staging, treatment, and surveillance of hepatocellular carcinoma. Am J Roentgenol 2003; 180:441. Reprinted with permission from the American Journal of Roentgenology. Copyright © 200 American Roentgen Ray Society.

Graphic 73767 Version 13.0

Patient evaluation for contrast administration for computed tomography: Con

Clinical manifestations of acute contrast reaction

The most severe symptom predominates. If allergic-like and physiologic symptoms are mixed or cannot be determined (eg, cardiopulmonary collapse), reaction should be presumed allergic-like.

Mild, allergic-like
(self-limited, rarely requires treatment, may or may not recur)
- Transient urticaria, pruritis, or cutaneous edema
- Transient "itchy" throat, nasal congestion, sneezing, conjunctivitis, or rhinorrhea

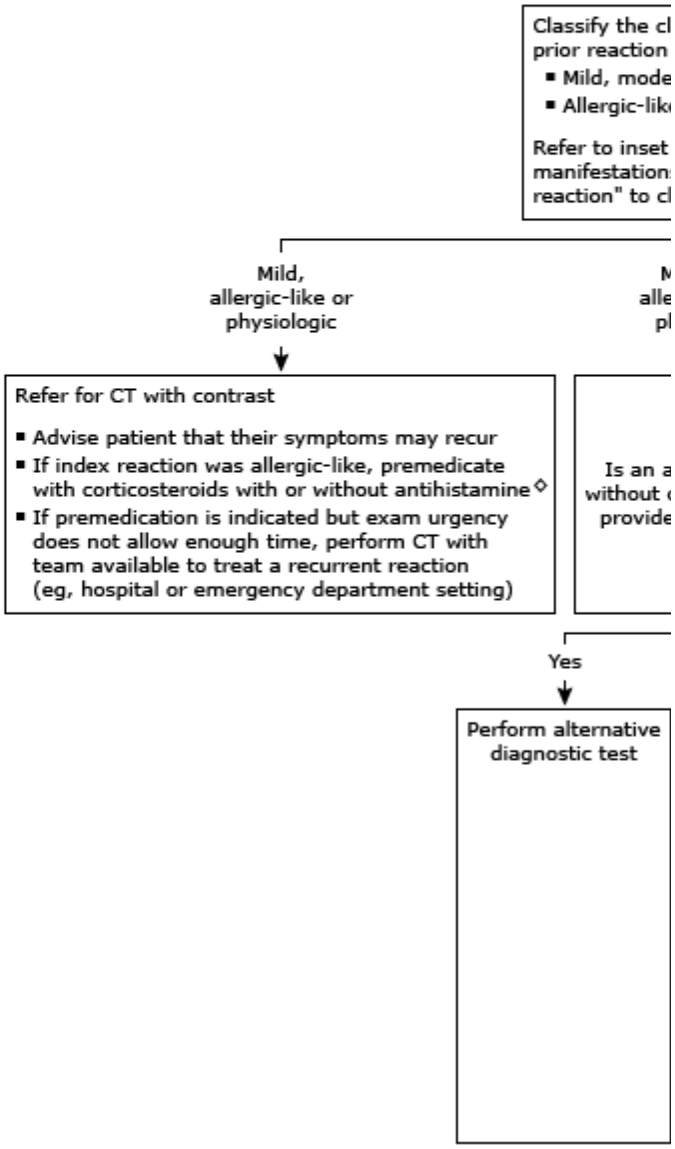
Mild, physiologic
(self-limited, rarely requires treatment, dose dependent)
- Transient nausea, vomiting
- Transient mild hypertension
- Transient flushing, warmth, chills, metallic taste, or headache
- Vasovagal reaction (ie, hypotension and bradycardia) not requiring treatment

Moderate, allergic-like
(usually requires treatment, may progress to severe, may or may not recur)
- Urticaria, pruritis, cutaneous edema, or diffuse erythema requiring treatment
- Wheezing, bronchospasm, hoarseness, or throat tightness without hypoxia
- Facial edema without dyspnea

Moderate, physiologic
(usually requires treatment, may progress to severe, dose dependent)
- Nausea or vomiting requiring treatment
- Hypertension requiring treatment
- Chest pain
- Vasovagal reaction (ie, hypotension and bradycardia) requiring and responsive to treatment

Severe, allergic-like
(life-threatening, associated with significant morbidity, may or may not recur)
- Diffuse cutaneous edema with dyspnea
- Diffuse erythema with hypotension
- Wheezing, bronchospasm, laryngeal spasm, or stridor with hypoxia
- Shock (hypotension and tachycardia)

Severe, physiologic
(life-threatening, associated with significant morbidity, dose dependent)
- Arrhythmia
- Hypertensive emergency
- Seizure
- Vasovagal reaction (ie, hypotension and bradycardia) resistant to treatment



Standards for patient preparation and indications for contrast vary somewhat with each practice. Referring p guidelines in patients with a history of an acute reaction to iodinated contrast.

CT: computed tomography.

* Refer to UpToDate topics or the American College of Radiology (ACR) Appropriateness Criteria for CT contr

¶ Acute reaction to contrast can occur after oral, intracavitary, or intravascular administration. Verify that th fluoroscopy, or angiography) rather than to noniodinated contrast used for other imaging modalities (eg, ga cross-reactivity between the two classes. If the reaction was delayed (>20 minutes) it is not considered an ac

Δ Refer to the inset box titled "Clinical manifestations of acute contrast reaction" to classify reaction.

◇ Refer to UpToDate topic for commonly used premedication prophylaxis regimens. For outpatients, one op and 1 hour prior to contrast administration; and 50 mg oral diphenhydramine administered one hour prior t

§ Imaging alternatives are CT without contrast, ultrasound, magnetic resonance imaging, or nuclear scintigr provide a diagnosis.

¥ Examples of such scenarios are extremely rare and may include CT angiography for diagnosis of acute aor

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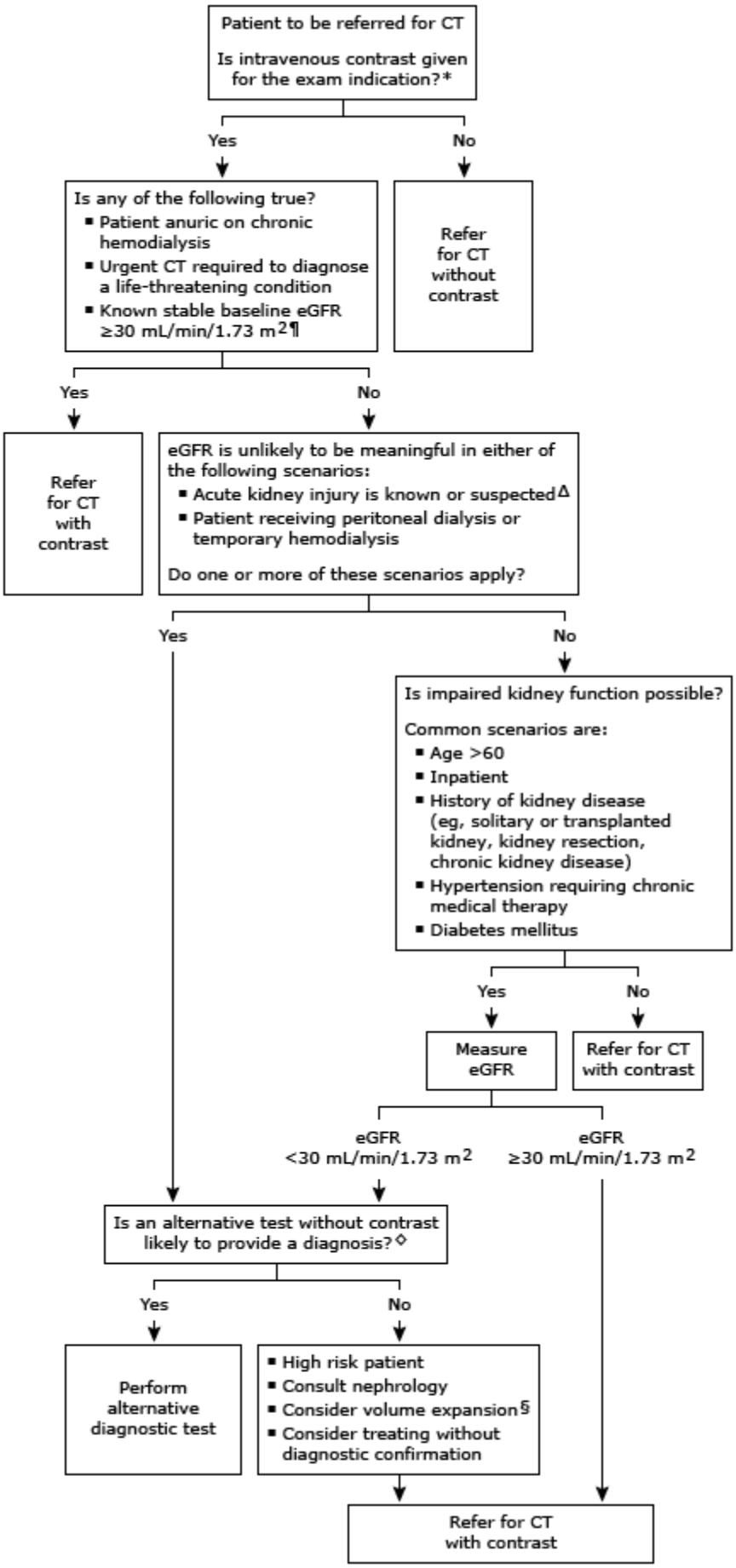
Graphic 113232 Version 3.0

Patient evaluation for contrast administration for computed tomography: Concern for contrast-associated acute kidney injury


Patient to be referred for CT
Is intravenous contrast given for the exam indication?*
Yes
No
Is any of the following true?
Patient anuric on chronic hemodialysis
Urgent CT required to diagnose a life-threatening condition
Known stable baseline eGFR ≥30 mL/min/1.73 m2¶
Refer for CT without contrast
Yes
No
Refer for CT with contrast
eGFR is unlikely to be meaningful in either of the following scenarios:
Acute kidney injury is known or suspectedΔ
Patient receiving peritoneal dialysis or temporary hemodialysis
Do one or more of these scenarios apply?
Yes
No
Is impaired kidney function possible?
Common scenarios are:
Age >60
Inpatient
History of kidney disease (eg, solitary or transplanted kidney, kidney resection, chronic kidney disease)
Hypertension requiring chronic medical therapy
Diabetes mellitus
Yes
No
Measure eGFR
Refer for CT with contrast
eGFR <30 mL/min/1.73 m2
eGFR ≥30 mL/min/1.73 m2
Is an alternative test without contrast likely to provide a diagnosis?◇
Yes
No
Perform alternative diagnostic test
High risk patient
Consult nephrology
Consider volume expansion§
Consider treating without diagnostic confirmation
Refer for CT with contrast

Standards for patient preparation and indications for contrast vary somewhat with each practice. Provider should refer to institutional policies for detailed guidelines in patients likely to require an intervention.

CT: computed tomography; eGFR: estimated glomerular filtration rate.

* Refer to UpToDate topics or the American College of Radiology (ACR) Appropriateness Criteria for CT contrast recommendations based on a specific exam indication. Enteric (oral or rectal) contrast is not associated with kidney injury.

¶ Medical judgment should be used to determine whether baseline kidney function is likely stable. In general, eGFR within 30 days in an outpatient and two days in an inpatient is likely to reflect baseline kidney function if the medical condition and treatments have not been changing in the interim.

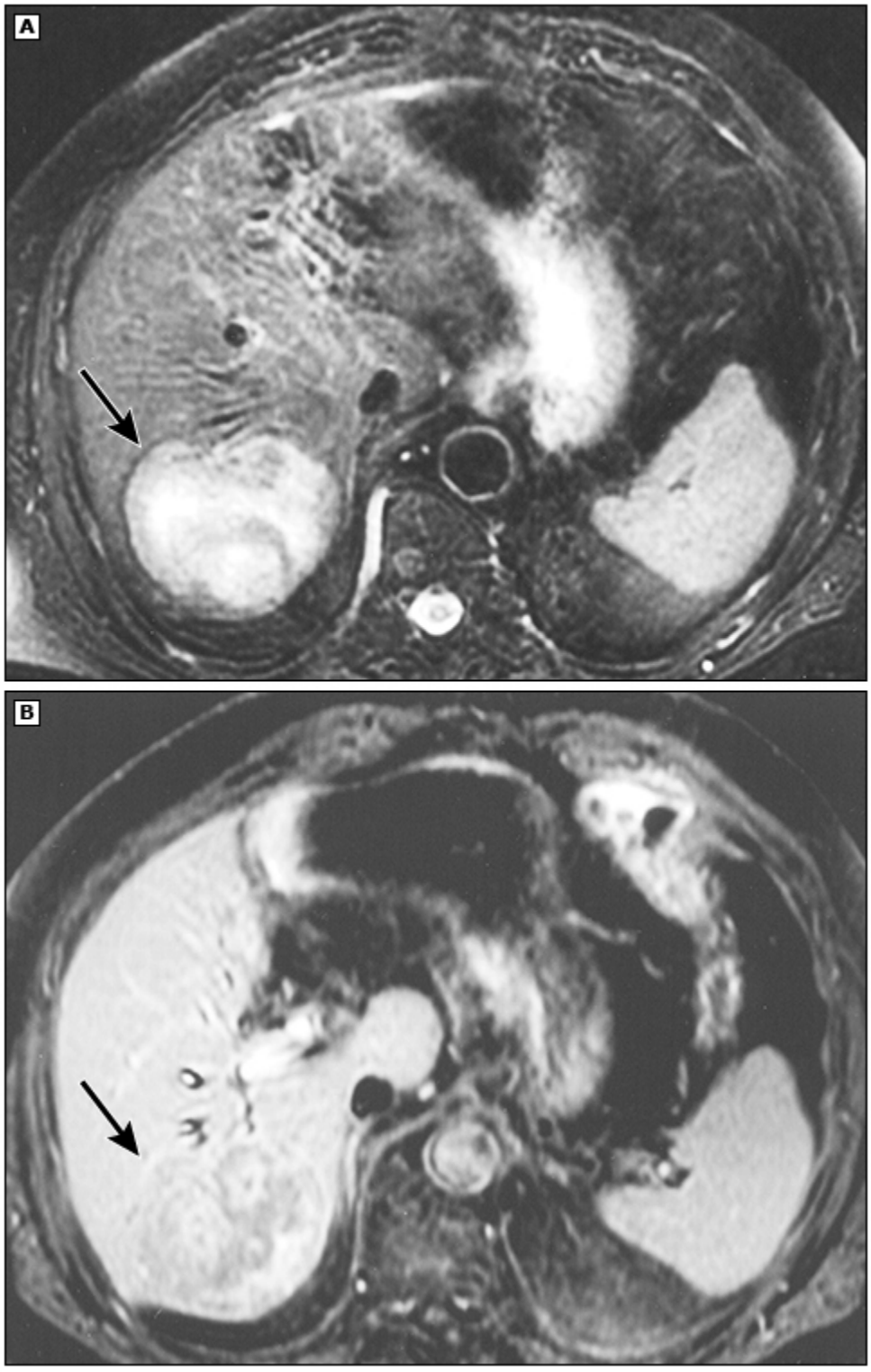
Δ Examples are patients with sepsis, myocardial infarction, or large volume hemorrhage.

◇ Imaging alternatives are CT without contrast, ultrasound, magnetic resonance imaging, or nuclear scintigraphy. Discuss with a radiologist whether any of these are likely to provide a diagnosis.

§ No standard regimen has been described. Examples are 100 cc/hour, beginning 6 to 12 hours before and continuing 4 to 12 hours after the exam in inpatients, and 500 cc bolus over 30 minutes to one hour before and during the exam in outpatients.

Graphic 113233 Version 4.0

MRI of hepatocellular carcinoma



Hepatocellular carcinoma. MRI of the liver without and with contrast in a 73-year-old male with hepatitis C virus and cirrhosis. Axial fast spin echo T2-weighted image with fat saturation (A) shows a hyperintense mass with a thin low signal intensity capsule (arrow). Axial T1-weighted fat-saturated image in the delayed phase of contrast administration (B) shows washout

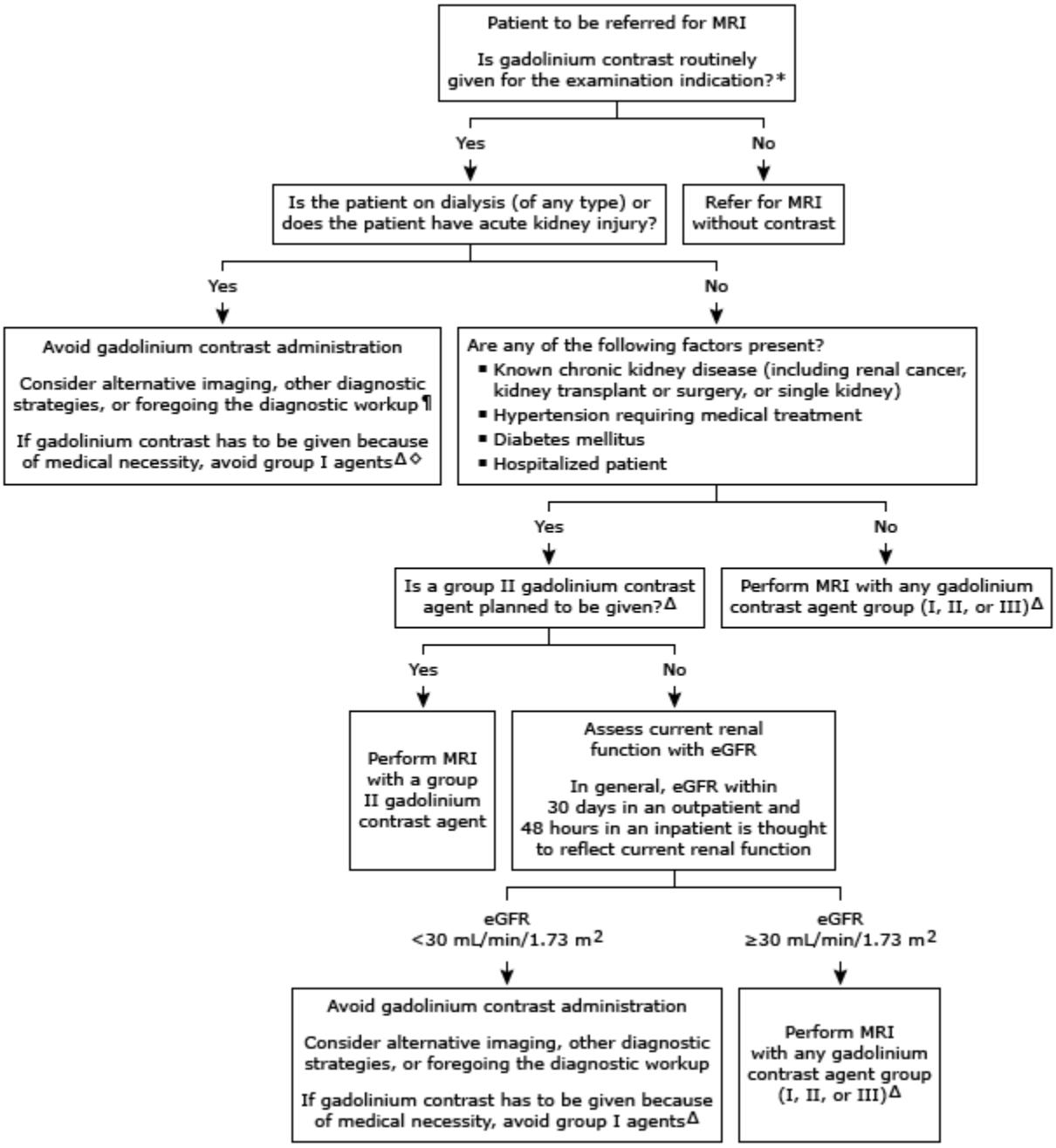
in the tumor relative to adjacent liver while the capsule remains enhancing (arrow).

MRI: magnetic resonance imaging.

Szklaruk J, Silverman PM, Charnsangavej C. Imaging in the diagnosis, staging, treatment, and surveillance of hepatocellular carcinoma. Am J Roentgenol 2003; 180:441. Reprinted with permission from the American Journal of Roentgenology. Copyright © 2003 American Roentgen Ray Society.

Graphic 75007 Version 18.0

Evaluation of kidney function before gadolinium contrast-enhanced magnetic resonance imaging: Concern for nephrogenic systemic fibrosis



Standards for patient preparation and indications for contrast vary somewhat with each practice. Referring provider should refer to institutional policies for detailed guidelines.

MRI: magnetic resonance imaging; eGFR: estimated glomerular filtration rate; CT: computed tomography.

* Refer to other UpToDate content or the American College of Radiology (ACR) Appropriateness Criteria for MRI contrast recommendations based on a specific examination

indication.

¶ Alternative imaging options include noncontrast MRI, CT, or ultrasound. If the patient is chronically anuric, an iodinated contrast-enhanced CT can be substituted, depending on the clinical indication for imaging. A discussion with a radiologist will likely be helpful.

Δ Refer to imaging provider (eg, radiology department) if the group of the gadolinium agent to be administered is unknown or needs to be specified, as availability will vary with site. For most examinations at most sites, group II agents are given preferentially. Group III agents are sometimes necessary for specific clinical indications. Group I and III agents are no longer marketed in the United States or Europe. Refer to other UpToDate content for description of the gadolinium contrast groups based on their associated risk of nephrogenic systemic fibrosis.

◇ If gadolinium contrast has to be given and the patient is on hemodialysis, schedule the hemodialysis to follow the imaging as close as possible.

Graphic 119424 Version 4.0

Classification system for nodules seen on images of cirrhotic livers from the Organ Procurement and Transplantation Network (OPTN)

Class and description	Additional requirements
OPTN class 0	
Incomplete or technically inadequate study	Repeat study required for adequate assessment; automatic priority MELD points cannot be assigned on basis of an imaging study categorized as OPTN class 0.
OPTN class 5	
Meets radiographic criteria for HCC, and potentially eligible for MELD exception points.	
Class 5A: ≥1 cm and <2 cm measured on late arterial or portal venous phase images	Increased contrast enhancement in late hepatic arterial phase and **either** washout during later phases of contrast enhancement and peripheral rim enhancement on delayed phase, **or** biopsy confirmation.
Class 5A-g: same size as OPTN class 5A HCC	Increased contrast enhancement in late hepatic arterial phase **and** growth by 50% or more documented on serial CT or MR images obtained ≤6 months apart.
Class 5B: maximum diameter ≥2 cm and ≤5 cm	Increased contrast enhancement in late hepatic arterial phase **and** either washout during later contrast phases **or** peripheral rim enhancement (capsule or pseudocapsule) **or** growth by 50% or more documented on serial CT or MR images obtained ≤6 months apart (OPTN class 5B-g) **or** biopsy confirmation.
Class 5T: prior regional treatment for HCC	Any class 5A, 5A-g, or 5B lesion that was automatically approved for MELD HCC exception points upon initial request or extension and has been subsequently ablated.
Class 5X: maximum diameter ≥5 cm	Increased contrast enhancement in late hepatic arterial phase **and** either washout during later contrast phases **or** peripheral rim enhancement (capsule or pseudocapsule). Not eligible for MELD HCC exception points.

NOTE: OPTN class number denotes whether an imaging examination is nondiagnostic (OPTN class 0) or the study includes an image that contains at least one treated or untreated HCC (OPTN class 5).

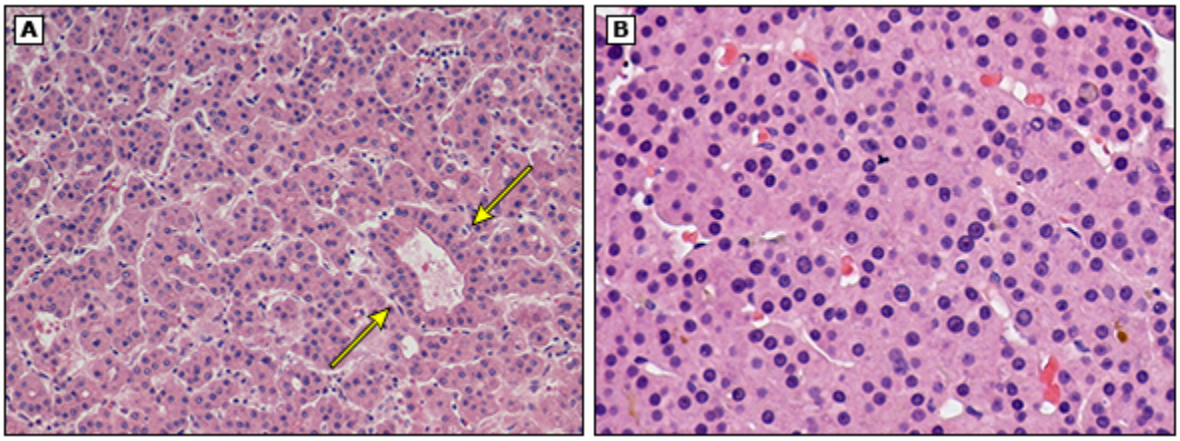
OPTN class 5 is further subdivided by adding a capital letter to denote UNOS stage 1 disease (OPTN class 5A), UNOS stage 2 disease (OPTN class 5B), a treated HCC (OPTN class 5T), or HCC beyond acceptable size for transplantation (OPTN class 5X). The *g* in OPTN class 5A-g and OPTN class 5B-g is used to indicate that growth was used to arrive at the HCC diagnosis.

MELD: Model for End Stage Liver Disease score; HCC: hepatocellular carcinoma; CT: computed tomography; MR: magnetic resonance; UNOS: United Network for Organ Sharing.

* As assessed according to the American Liver Tumor Study Group modification of the standard TNM staging system (stage II, T2N0M0).

Graphic 87919 Version 4.0

High power histology of a well-differentiated hepatocellular carcinoma



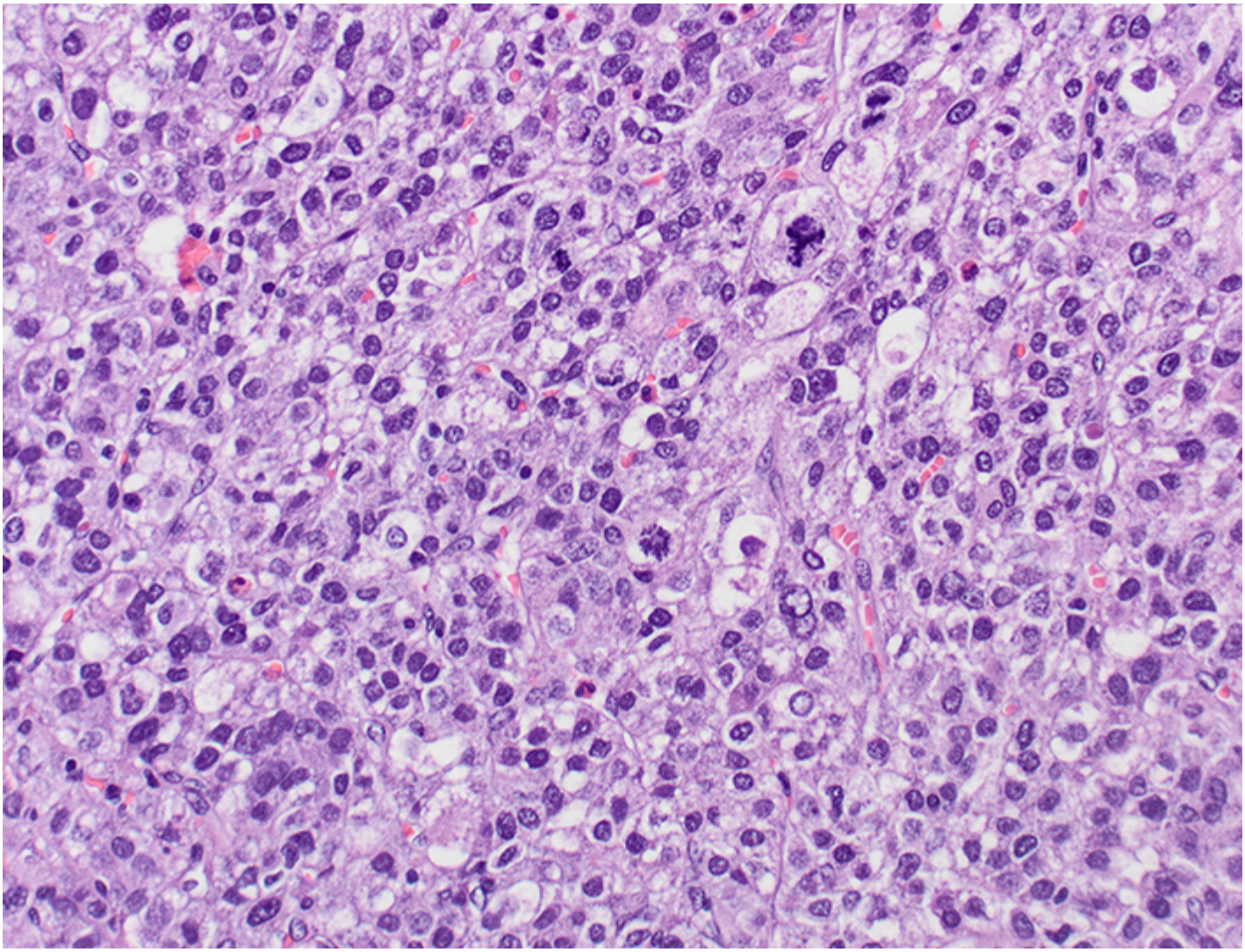
(A) Well-differentiated hepatocellular carcinoma, which is composed of tumor cells with mild atypia, a higher nuclear to cytoplasmic ratio than seen in normal hepatocytes, and rare pseudoglandular structures (arrows).

(B) At higher power, the tumor is composed of polygonal tumor cells with eosinophilic cytoplasm, arranged in trabeculae that are more than two cells thick.

HCC: hepatocellular carcinoma.

Graphic 97328 Version 1.0

Histology of poorly differentiated hepatocellular carcinoma

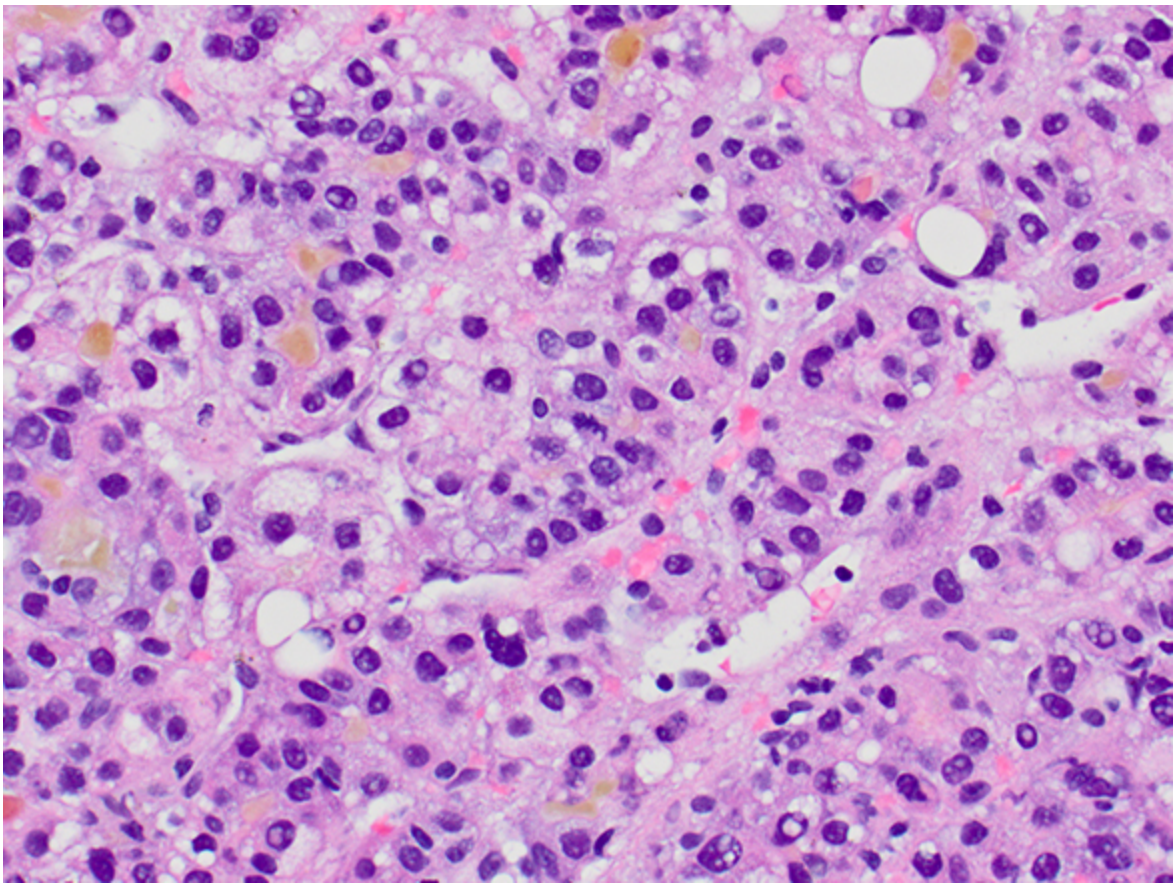


Poorly differentiated hepatocellular carcinoma with pleomorphic tumor cells in a solid growth pattern.

Courtesy of Arief Suriawinata, MD.

Graphic 97338 Version 2.0

Histology of a well-differentiated hepatocellular cancer making bile

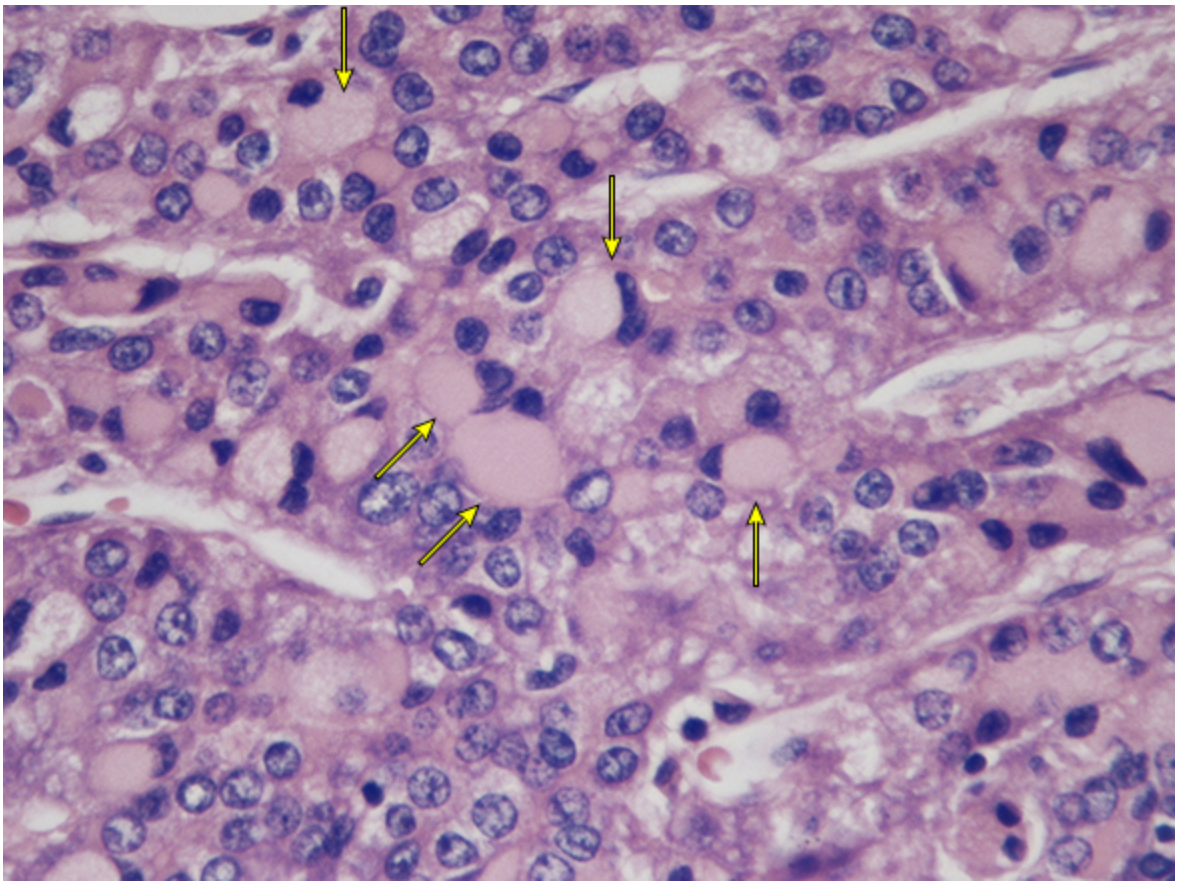


Brown-green bile in dilated bile canaliculi in HCC.

HCC: hepatocellular carcinoma.

Graphic 97329 Version 1.0

Histology of a well-differentiated hepatocellular carcinoma containing intracytoplasmic fibrinogen



Well-differentiated hepatocellular carcinoma containing intracytoplasmic fibrinogen inclusions (arrows).

Graphic 97334 Version 1.0

TNM staging for hepatocellular cancer

Primary tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
T1	Solitary tumor without vascular invasion		
T2	Solitary tumor with vascular invasion or multiple tumors none more than 5 cm		
T3a	Multiple tumors more than 5 cm		
T3b	Single tumor or multiple tumors of any size involving a major branch of the portal vein or hepatic vein		
T4	Tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum		
Regional lymph nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis		
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
Fibrosis score (F)*			
F0	Fibrosis score 0-4 (none to moderate fibrosis)		
F1	Fibrosis score 5-6 (severe fibrosis or cirrhosis)		
Anatomic stage/prognostic groups			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3a	N0	M0
Stage IIIB	T3b	N0	M0
Stage IIIC	T4	N0	M0
Stage IVA	Any T	N1	M0

Stage IVB	Any T	Any N	M1

Note: cTNM is the clinical classification, pTNM is the pathologic classification.

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* The fibrosis score as defined by Ishak is recommended because of its prognostic value in overall survival. This scoring system uses a 0-6 scale.

Graphic 63333 Version 12.0

Contributor Disclosures

Jonathan M Schwartz, MD No relevant financial relationship(s) with ineligible companies to disclose. **Robert L Carithers, Jr, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Claude B Sirlin, MD** Equity Ownership/Stock Options: Livivos [NASH imaging]. Grant/Research/Clinical Trial Support: ACR Innovation [Liver cancer]; Bayer [Liver cancer]; GE MRI [Fatty liver disease]; GE US [Fatty liver disease]; Gilead [Fatty liver disease]; Pfizer [Fatty liver disease]; Philips [Liver cancer]; Siemens [Fatty liver disease]. Consultant/Advisory Boards: Altimmune [Independent consultant on liver imaging]; AMRA [Institutional consultant on metabolic disease and health outcomes]; Ascelia AB [Independent consultant on liver cancer screening]; Blade [Liver fibrosis imaging]; Boehringer [NASH imaging]; Bristol Myers Squibb [Institutional consultant on fibrosis advisory board]; Enanta [NASH imaging]; Epigenomics [Independent consultant on liver cancer screening]; Gilead [NASH imaging]; Guerbet [Independent consultant on gadolinium-based contrast agents]; IBM Watson Health [Institutional consultant on deep learning, liver cancer]; ICON [NASH imaging]; Intercept [NASH imaging]; Nusirt [NASH imaging]; Pfizer [Institutional consultant on quantitative imaging]; Quantix Bio [NASH imaging]; Shire [NASH imaging]; Synageva [NASH imaging]; Takeda [Lab service agreements for fatty liver disease]. Other Financial Interest: Medscape [Honoraria for educational material]. All of the relevant financial relationships listed have been mitigated. **Sanjiv Chopra, MD, MACP** No relevant financial relationship(s) with ineligible companies to disclose. **Herbert Y Kressel, MD** Consultant/Advisory Boards: Canon Medical Systems [MRI]. All of the relevant financial relationships listed have been mitigated. **Kristen M Robson, MD, MBA, FACG** No relevant financial relationship(s) with ineligible companies to disclose. **Sonali M Shah, MD** No relevant financial relationship(s) with ineligible companies to disclose.

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