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**American College of Radiology
ACR Appropriateness Criteria®
Chronic Liver Disease**

Variant 1: Chronic liver disease. Diagnosing liver fibrosis.

Radiologic Procedure	Rating	Comments	RRL*
MR elastography abdomen	8	This procedure is the most accurate method for diagnosing liver fibrosis noninvasively but may be influenced by iron overload.	○
US elastography ARFI abdomen	7	This procedure can be used to diagnose liver fibrosis and cirrhosis in patients with obesity, ascites, and NAFLD.	○
ID transient elastography abdomen	7	This procedure is less reliable in diagnosing liver fibrosis and cirrhosis in patients with obesity or ascites.	○
MRI abdomen without IV contrast	6	This procedure can be performed with MR elastography.	○
MRI abdomen without and with IV contrast	6	This procedure can assess for cirrhosis and diagnose hepatocellular carcinoma and can be performed with MR elastography.	○
MRI abdomen without and with hepatobiliary contrast	6	This procedure can assess for cirrhosis and diagnose hepatocellular carcinoma and can be performed with MR elastography.	○
US abdomen	6	Sonographic appearance of hepatic steatosis and cirrhosis often overlap. Interobserver variability may be present. This procedure can be performed with US ARFI.	○
CT abdomen with IV contrast	5	This procedure is part of the liver protocol.	☼☼☼
CT abdomen without IV contrast	4		☼☼☼
CT abdomen without and with IV contrast	4	This procedure is part of the liver protocol.	☼☼☼☼
<u>Rating Scale:</u> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			*Relative Radiation Level

Variant 2:**Chronic liver disease. Screening and surveillance for hepatocellular carcinoma (HCC). No prior diagnosis of HCC.**

Radiologic Procedure	Rating	Comments	RRL*
MRI abdomen without and with IV contrast	8	Consider surveillance by CT or MRI when US is limited by obesity, NAFLD, or nodular cirrhotic liver or if the patient is at very high risk of HCC.	○
MRI abdomen without and with hepatobiliary contrast	8	Decreased dose of contrast can be given in patients with impaired renal function.	○
US abdomen	7	Sensitivity of ultrasound is low on a single study and needs to be repeated every 6 months. This procedure is limited for HCC detection in patients with obesity, NAFLD, or nodular cirrhotic livers.	○
CT abdomen with IV contrast	7	This procedure is used in the liver protocol. Consider surveillance by CT or MRI when US is limited by obesity, NAFLD, or nodular cirrhotic liver or if the patient is at very high risk of HCC.	⊕⊕⊕
CT abdomen without and with IV contrast	7	This procedure is used in the liver protocol. Consider surveillance by CT or MRI when US is limited by obesity, NAFLD, or nodular cirrhotic liver or if the patient is at very high risk of HCC.	⊕⊕⊕⊕
MRI abdomen without IV contrast	6	MRI without contrast may be able to detect but not diagnose HCC in patients who cannot receive contrast. This procedure must include DWI. If IV contrast is contraindicated, MRI with DWI is better than unenhanced CT.	○
MR elastography abdomen	5	This procedure can be performed with MRI for HCC screening if there is a need for diagnosis of fibrosis and cirrhosis at the same time.	○
US elastography ARFI abdomen	4	This procedure can be performed with US for HCC screening if there is a need for diagnosis of fibrosis and cirrhosis at the same time.	○
CT abdomen without IV contrast	3		⊕⊕⊕
FDG-PET/CT whole body	3		⊕⊕⊕⊕
1D transient elastography abdomen	2		○
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			*Relative Radiation Level

Variant 3:

Chronic liver disease. Surveillance for hepatocellular carcinoma (HCC). Previous diagnosis of HCC.

Radiologic Procedure	Rating	Comments	RRL*
MRI abdomen without and with IV contrast	9	Multiphase CT or MRI is used to assess response 1 month after resection or therapy, followed by imaging every 3 months for at least 2 years.	○
CT abdomen with IV contrast	8	Multiphase CT or MRI is used to assess response 1 month after resection or therapy, followed by imaging every 3 months for at least 2 years. This procedure includes 3 phases: arterial, portal venous, and delayed.	☼☼☼
MRI abdomen without and with hepatobiliary contrast	7	Multiphase CT or MRI is used to assess response 1 month after resection or therapy, followed by imaging every 3 months for at least 2 years.	○
CT abdomen without and with IV contrast	7	Multiphase CT with a noncontrast phase is more helpful than postcontrast phases in patients who have received liver-directed therapy. Consider dual-energy CT to avoid additional radiation dose. This procedure includes 4 phases: noncontrast, arterial, portal, and delayed.	☼☼☼☼
MRI abdomen without IV contrast	6	MRI without contrast may be able to detect but not diagnose HCC in patients who cannot receive contrast. This procedure must include DWI. If IV contrast is contraindicated, MRI with DWI is better than unenhanced CT.	○
US abdomen	4	This procedure is useful in some situations (eg, >2 years post-treatment.) It is limited for HCC detection in patients with obesity, NAFLD, or nodular cirrhotic livers.	○
MR elastography abdomen	3		○
CT abdomen without IV contrast	3		☼☼☼
US elastography ARFI abdomen	2		○
1D transient elastography abdomen	2		○
FDG-PET/CT whole body	2		☼☼☼☼
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			*Relative Radiation Level

CHRONIC LIVER DISEASE

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Summary of Literature Review

Introduction/Background

Chronic liver disease is an important cause of morbidity and mortality both worldwide and in the United States. Patients with hepatitis C, hepatitis B, alcoholism, nonalcoholic fatty liver disease (NAFLD), autoimmune hepatitis, and others are at risk for developing hepatic fibrosis. In the United States, nearly 2 million deaths annually are attributable to chronic liver disease, and liver-related mortality has been underestimated during the past 2 decades in the United States [1,2], particularly in nonwhite and Hispanic patients. In the United States, 1.3% of the population is chronically infected with hepatitis C, and hepatitis C morbidity and mortality are increasing because of the aging of persons who were infected in past decades [3-5]. In a study examining ultrasound (US) in a national health survey in the United States from 1988 to 1994, the rates of prevalence of hepatic steatosis and NAFLD were 21.4% and 19.0%, respectively, corresponding to estimates of 32.5 million adults with hepatic steatosis and 28.8 million adults with NAFLD nationwide [6].

Hepatic fibrosis slowly progresses to cirrhosis, typically over a period of decades. Once thought to be irreversible, hepatic fibrosis is now known to be a dynamic process that, if diagnosed in an early stage, can be treated and potentially reversed. The gold standard for diagnosing liver fibrosis and cirrhosis is liver biopsy [7]. However, liver biopsy is not an ideal method for diagnosis as it is disliked by patients, has complications, and is plagued by sampling error [8,9]. More importantly, it also is not practical to be used repeatedly to monitor patients' response of liver fibrosis to treatment.

Noninvasive assessment of liver fibrosis can be done with serologic tests or imaging [10]. Serologic tests include the serum aspartate aminotransferase to platelet ratio index, FibroTest (Biopredictive, Paris, France)/FibroSure (LabCorp, Burlington, NC), and others. However, these serum tests are not reliable because several factors not related to fibrosis (eg, active hepatitis or Gilbert syndrome) can contribute to false-positive test results and the serum tests cannot distinguish between different levels of fibrosis [11].

Traditional imaging options to diagnose cirrhosis include assessment for morphologic features on cross-sectional imaging, including US, computed tomography (CT), and magnetic resonance imaging (MRI). Imaging techniques currently being used to diagnose liver fibrosis and cirrhosis include US elastography and magnetic resonance (MR) elastography. Novel imaging techniques being investigated to diagnose liver fibrosis but not yet validated include MRI using diffusion, perfusion, and hepatobiliary contrast agents and CT using dual energy and perfusion.

Patients at risk of developing cirrhosis require screening for hepatocellular carcinoma (HCC) [12]. HCC is the fifth most common cancer in men, the seventh most common cancer in women, and the third leading cause of cancer mortality globally [13,14]. In the United States, HCC related to hepatitis C has recently become the fastest-rising cause of cancer-related death, and during the past 2 decades, the incidence of HCC has tripled while the 5-year survival rate has remained below 12% [15]. Worldwide, most cases of HCC (approximately 80%) are associated with chronic hepatitis B or hepatitis C infections [13]. However, NAFLD is becoming a common cause of cirrhosis in the United States. There is epidemiologic evidence to support an association between NAFLD and an increased risk of HCC in individuals with cirrhosis [16].

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Variant 1: Chronic liver disease. Diagnosing liver fibrosis.

Certain morphologic features of cirrhosis can be assessed on US, CT, or MRI. These include liver surface nodularity, particularly of the anterior left lobe [17,18]; an atrophic right lobe and hypertrophied caudate lobe and lateral segment left lobe [19]; an atrophied medial segment left lobe [20]; a right hepatic posterior “notch” [21,22]; an expanded gallbladder fossa [23,24]; narrow hepatic veins (right hepatic vein <5 mm) [25]; an enlarged caudate to right lobe ratio (modified ratio >0.90) [26,27]; and enlargement of the hilar periportal space (>10-mm thickness) [28,29]. Although these morphologic features are fairly good at diagnosing cirrhosis, they are subjective and are present only in later stages of fibrosis.

Ultrasound

Conventional grayscale and Doppler US are safe and can be used to diagnose cirrhosis. In addition to the morphologic signs described above, a coarsened or heterogeneous hepatic echotexture has been associated with cirrhosis [30,31]. However, this is subjective and the appearance of coarsening is often US machine dependent. Furthermore, the sonographic appearance of hepatic steatosis and cirrhosis often overlap, with a “fatty-fibrotic” pattern [31,32]. Evaluation of the liver with conventional US is also limited in obese patients because of poor penetration of the US beam. This limits assessment for cirrhosis and liver lesions. US can also assess for splenomegaly and other signs of portal hypertension.

Color Doppler US can be helpful in diagnosing signs of portal hypertension in the main portal vein, including slow velocity or hepatofugal (reversed) direction of flow [33]. However, these findings will be seen only in advanced cirrhosis and not in early stages of fibrosis. Decreased phasicity of the hepatic venous waveforms in spectral Doppler US correlates with hepatic fibrosis as well as steatosis [34,35]. Doppler US measurements for diagnosis of hepatic fibrosis have not been shown to be helpful in all studies [36].

US elastography includes shear-wave elastography and strain elastography. Shear-wave elastography can quantify elasticity, whereas strain elastography is semiquantitative and determines elasticity relative to other structures. Types of shear-wave elastography used to diagnose liver fibrosis include 1-dimensional (1D) transient elastography (TE) and acoustic radiation force impulse (ARFI) elastography.

US elastography attempts to predict the histologic stage of hepatic fibrosis, typically the METAVIR score (F0–F4, where \geq F2 is clinically significant fibrosis and F4 is cirrhosis). This score helps predict the response to treatment, since F3 and F4 patients are less likely to respond, and determines if the patient has cirrhosis and requires screening for HCC. Noninvasive monitoring of hepatic fibrosis is also helpful for patients taking hepatotoxic drugs.

The most commonly used types of US elastography for assessment of liver fibrosis are TE and ARFI. TE is predominantly performed with FibroScan (Echosens, Paris, France) and can be performed at point of care during a patient’s clinic visit without any additional equipment. TE was developed before ARFI and has been heavily studied and validated more than the other elastography methods as a method of diagnosing liver fibrosis. TE has a sensitivity and specificity of 70% and 84%, respectively, for diagnosing significant fibrosis (\geq F2) and 87% and 91%, respectively, for diagnosing cirrhosis (F4) [37]. TE is not reliable in patients with obesity or ascites and cannot distinguish between intermediate stages of fibrosis [38]. An extra-large probe for TE is now available for obese patients, which tries to overcome some limitations of TE [39].

Unlike TE, ARFI can be combined with conventional US and can be used in patients with obesity, ascites, and NAFLD [40–42]. Since ARFI is 2-dimensional/B-mode US, specific larger areas of the liver can be chosen for study compared with TE, which has a single-element US transducer. In a meta-analysis comparing TE and ARFI, rates of unreliable examinations were 3 times higher with TE as compared with ARFI (6.6% versus 2.1%, $P<0.001$) [43]. One limitation of ARFI is that it is operator dependent. In this document, it is assumed all studies are performed by an expert.

It should be noted that liver stiffness measurements on elastography can be influenced not only by fibrosis but also by edema, inflammation [44], extrahepatic cholestasis [45], and passive congestion [46]. Patients undergoing US elastography should be fasting [47,48]. The studies performed to validate US elastography have used liver biopsies as the reference standard. Thus, this imaging technique may be subject to the same sampling error that plagues liver biopsies.

Contrast-enhanced US (CEUS) has also been used to diagnose fibrosis and cirrhosis. An US contrast agent has recently been approved in the United States and some institutions use US contrast off-label. Discussion of the role

of CEUS is beyond the scope of this document. CEUS can exclude cirrhosis using contrast agent transit or disappearance times but cannot be used for staging fibrosis [31].

Computed tomography

Multiphase CT is predominantly performed in patients with chronic liver disease for diagnosis of HCC, as discussed in variant 2 below. However, cirrhosis can be assessed for using the morphologic features described above either on noncontrast CT, contrast-enhanced single-phase CT, or multiphase CT. Similar to MRI, bands of fibrosis will appear as linear areas of enhancement in portal venous or delayed phases. CT performs better than US for assessment of cirrhosis in obese patients.

CT perfusion and dual-energy CT have recently been used to assess for fibrosis and cirrhosis with some promising results [49-52]. CT perfusion has been able to distinguish between stages of fibrosis [49]. As CT perfusion requires significant postprocessing, this is not used clinically.

Magnetic resonance imaging

MRI is more accurate than US for the evaluation of cirrhosis in obese patients and patients with NAFLD. MRI can assess for morphologic features of cirrhosis, and fibrosis can be evaluated on dynamic contrast-enhanced (DCE) sequences with extracellular gadolinium contrast agents. Bands of fibrosis will be seen as linear areas of high T2 signal and enhancement on delayed-phase sequences [53]. Although visible fibrosis can be seen in later stages of fibrosis and cirrhosis, earlier stages of fibrosis will not be visible on conventional MRI with contrast.

MR elastography has also been used to noninvasively diagnose hepatic fibrosis and cirrhosis with good reliability. Although the other imaging techniques and modalities including US elastography can often distinguish well between cirrhosis or severe fibrosis and normal liver, MR elastography is the most accurate technique for diagnosing intermediate stages of fibrosis [31].

Compared with US elastography, MR elastography performs better for diagnosing fibrosis in obese patients and patients with ascites, has the fewest unreliable examinations, is able to assess fibrosis throughout the largest amount of liver parenchyma, and can evaluate for HCC at the same time [54]. The diagnostic capability of MR elastography is unaffected by obesity, whereas with US elastography, unreliable measurements were found in 35.4% of TE examinations in obese patients [55] and 17.6% of ARFI examinations in obese patients [56]. In a recent meta-analysis, MR elastography could also distinguish between levels of hepatic fibrosis, with good sensitivity (73%–91%) and specificity (79%–85%) [54]. The main limitation in MR elastography is that it is not accurate in patients with hepatic iron deposition [57], contributing to a failure rate of 4.3% [54].

Diffusion-weighted imaging (DWI) in MRI can be used to diagnose fibrosis and cirrhosis as well, either with qualitative subjective evaluation or quantitatively measuring the apparent diffusion coefficient (ADC) value, and it is mostly of research interest at this time. DWI is better at distinguishing between cirrhotic and normal livers than distinguishing between stages of fibrosis [58,59]. One study showed a positive predictive value, negative predictive value, and overall accuracy of 100%, 99.9%, and 96.4%, respectively, for diagnosing cirrhosis compared with controls with DWI [60]. However, a meta-analysis showed that DWI distinguished F0–F1 from F2–F4 with a sensitivity of 77%, specificity of 78%, and summary receiver operating characteristic of 0.83 [58]. DWI image quality can suffer particularly in patients with cirrhosis, ascites, and difficulty breath holding. ADC values are dependent on the particular MRI scanner as well, so published ADC results are not generalizable to all scanners.

Hepatobiliary MRI contrast agents such as gadoxetate disodium (Eovist; Bayer Healthcare, Wayne, NJ) and gadobenate dimeglumine (MultiHance; Bracco Diagnostics, Princeton, NJ) are not as widely used as extracellular agents, but research is ongoing regarding their use in diagnosing fibrosis [61]. MR elastography has been shown to be superior to MRI with gadoxetate disodium for staging hepatic fibrosis [62].

Assessing liver fibrosis with MR perfusion has also been studied in recent years. Arterial blood flow, arterial fraction, portal venous fraction, distribution volume, and mean transit time in 1 study were significantly different between patients with and without severe fibrosis [63]. Another study showed that DCE-MRI with gadoxetate disodium can be used to stage liver fibrosis [64]. The combination of DCE-MRI and DWI was able to accurately diagnose cirrhosis in 1 study [65]. However, perfusion analysis is laborious, so this is mostly a research interest and not clinically utilized at this time.

As with US elastography, studies of these MR techniques use liver biopsies as the reference standard.

Variant 2: Chronic liver disease. Screening and surveillance for hepatocellular carcinoma (HCC). No prior diagnosis of HCC.

Patients with cirrhosis and selected chronic liver disease patients without cirrhosis, such as chronic hepatitis B patients at high risk, need to be screened for HCC. More intense surveillance for HCC may be required for patients on the transplant waiting list regardless of etiology of cirrhosis. Cirrhotic patients whose liver contains small nodules are at increased risk for HCC as well [66]. The American Association for the Study of Liver Diseases (AASLD) reports that surveillance is cost effective if the expected HCC risk exceeds 1.5% per year in patients with cirrhosis and 0.2% per year in patients with hepatitis B [12]. Studies have shown that patients who have been screened for HCC have improved detection of HCC, improved receipt of curative therapy, improved survival, and lower mortality [67-71].

The accurate diagnosis of HCC with imaging is important because a liver lesion meeting strict diagnostic imaging criteria for HCC does not need to be biopsied. Using the Milan criteria, patients with one 2- to 5-cm HCC or 2 to 3 HCCs measuring up to 3 cm may be assigned priority for transplantation according to the Organ Procurement and Transplantation Network (OPTN) and the United Network of Organ Sharing (UNOS) [72,73]. HCCs invading portal veins and extrahepatic metastases are not eligible for transplantation, according to OPTN/UNOS. Although HCC can be diagnosed on imaging without a confirmatory biopsy prior to initiating treatment, including transplantation, the diagnosis of HCC cannot be made on US alone. Multiphase CT or MRI is necessary. Biopsy is reserved for indeterminate nodules on CT or MRI, particularly nodules 1 to 2 cm in size [74]. Biopsy results can be falsely negative in small HCCs and carry the risk of potential complications, including needle tract seeding and bleeding [75-77].

The American College of Radiology (ACR) Liver Imaging Reporting and Data System (LI-RADS) was created in part to standardize the reporting of CT and MRI for HCC in order to encourage consistent terminology and reduce image interpretation errors [78]. LI-RADS uses diagnostic algorithms to characterize liver lesions and diagnose HCC. It should be noted that the ACR Appropriateness Criteria® “[Liver Lesion — Initial Characterization](#)” [79] also discusses various scenarios about how to characterize incidentally found liver lesions. Detailed descriptions of imaging characteristics of HCC are beyond the scope of this document but will be briefly described below. OPTN/UNOS also encourages structured reporting regarding CT or MRI imaging diagnostic of HCC, representing “class 5” lesions [72]. It is also important to provide information on conventional versus variant vascular anatomy when reporting CT and MRI for HCC since this impacts the approach for local-regional therapy and surgery.

Potential noninvasive diagnostic modalities used for screening and diagnosing HCC include US, CT, MRI, and serum biomarkers. It should be noted that screening with α -fetoprotein (AFP) alone is not recommended because of the inadequate sensitivity of AFP, and the addition of AFP to US screening does not show a statistically significant improvement in HCC detection [80-82]. One review showed AFP >20 ng/mL to have a sensitivity of 41% to 65% and specificity of 80% to 94% for HCC screening [82].

Ultrasound

Although most international groups recommend US screening and surveillance for HCC, the evidence to support this practice is weak. The recommendation for screening with US every 6 months by the AASLD [12] is based on a prospective Chinese study of hepatitis B patients that showed that patients who had an US survived longer [83]. However, there is no good evidence to show that these results apply to the population in the United States, which has a much higher percentage of obese patients as well as fewer patients with chronic hepatitis B and many more with alcoholic cirrhosis, often with hepatitis C and NAFLD. US is insensitive for detection of HCC in patients with hepatic steatosis as well as nodular cirrhotic livers who are undergoing surveillance [84]. The regenerative nodules in cirrhotic livers alter the background hepatic echotexture, making HCC difficult to detect. Another inherent limitation of US is its operator dependence [85]. In this document, it is assumed all studies are performed by an expert.

Some international guidelines permit surveillance by CT or MRI when US is limited by obesity or other factors [86-88] or if the patient is at very high risk of HCC [87,89]. Patients may present with HCC, including advanced HCC (T stages T1–T4), even if US findings are negative within 1 year prior to diagnosis [90].

US can be unreliable in detection of HCC, as studies have shown sensitivity ranging from 21% to 94% [81,91-93]. At the low end, Yu et al [91] in 2011 calculated the sensitivity of US to detect HCC <2 cm to be 21% but for all sizes to be 46%, whereas sensitivity for detection of HCC of all sizes at CT and MR was 65% and 72%,

respectively. Another study showed that pooled sensitivity of US, CT, and MRI for facilitating the diagnosis of HCC was 60%, 68%, and 81%, respectively, and concluded that US is highly specific but insufficiently sensitive to detect HCC in many cirrhotic patients or to support an effective surveillance program [93]. At the high end, 1 meta-analysis showed a 94% sensitivity for US detection of HCC of all sizes but a sensitivity of 63% for early HCC [81].

CEUS can be used for liver lesion characterization and diagnosis of HCC with high specificity in a few studies, 92% to 100% [94-96], although another more recent, larger study had concerns regarding the sensitivity and accuracy of CEUS for HCCs <2.0 cm [97]. CEUS may be helpful to diagnose HCC in patients who cannot receive intravenous iodinated contrast for CT and cannot receive gadolinium for MRI. However, CEUS is not practical for screening, as is difficult or impossible to examine the entire liver during the arterial phase to look for hyperenhancing nodules [98].

Computed tomography and magnetic resonance imaging

Multiple international groups recognize the limitations of US, and once a liver lesion >1 cm is found on US in a patient at risk for HCC, all international guideline groups recommend multiphase CT or MRI for diagnosis and staging [12,86-88,99,100]. Additionally, many institutions in the United States provide multiphase CT or MRI for screening of cirrhotic patients for HCC when ordered by their physicians, as long as the practice can accommodate a large volume of patients for imaging. It is unknown whether routine and/or repeated use of multiphase CT for HCC screening is justified with regards to ionizing radiation.

The diagnosis of HCC on multiphase CT and MRI is made on postcontrast imaging when there is late hepatic arterial-phase hyperenhancement, venous- or delayed-phase washout appearance, and venous- or delayed-phase capsule appearance. The specificity and positive predictive value of this appearance on CT or MRI for HCC is nearly 100% [75,76,101,102]. For HCC of all sizes, the sensitivity of MRI is 59% to 95% [76,103-107] and the sensitivity of multiphase CT is 43% to 63% [103,104,108]. For HCCs >2 cm, sensitivity of MRI is 100% [106] and of multiphase CT is 98% [108]. For HCCs <2 cm, sensitivity of MRI is 58% to 100% [99,101,102,105,106,109-113] and sensitivity of CT is 53% to 68% [99,112,113]. These studies show a diagnostic advantage of MRI over multiphase CT. Studies also show improved sensitivity by using a delayed phase rather than the venous phase [114,115].

Advantages of multiphase CT compared with MRI include that it is a rapid test and easier to interpret. Disadvantages of CT include repeated exposure of patients to ionizing radiation and lower soft-tissue contrast [75], as well as risk of contrast nephropathy in patients with renal insufficiency.

Advantages of MRI include better chances for lesion detection and characterization, no radiation, and higher soft-tissue contrast [116]. Disadvantages of MRI include increased sensitivity for hypervascular lesions that are not HCC (often transient shunts that are often subcapsular), that it takes more time than CT, and that it is more frequently affected by artifacts (especially when there is moderate to severe ascites) [75].

Multiphase computed tomography

In order to accurately diagnose HCC on multiphase imaging, both late hepatic arterial and portal venous postcontrast phases are absolutely necessary. The addition of a delayed phase is considered by most to be essential to increase conspicuity of the HCC's washout and capsular appearance [114] and helps to distinguish HCC from cholangiocarcinoma as well [117]. This delayed phase is recommended by the UNOS [72]. A noncontrast phase is unnecessary if the patient has not received previous liver treatment [118,119]. Multiphase CT has been advocated in the past for screening cirrhotic patients on the transplant waiting list [120-122]. However, this does increase overall radiation exposure with repeated surveillance scans and is less preferable than MR. Exposure to ionizing radiation is a concern with multiphase CT, particularly in patients with chronic liver disease who are undergoing multiple CT scans for screening, diagnosis, and/or staging.

Magnetic resonance imaging

MRI has become more accessible in recent years, and more radiologists are comfortable with interpreting MRI than in the past, particularly with the efforts of ACR's LI-RADS [78]. Liver MRI for the diagnosis of HCC should include pre- and postcontrast T1-weighted and T2-weighted sequences, and DWI is helpful as well [123]. Gadolinium is needed in order to distinguish dysplastic nodules, early HCC, and small progressed HCC [89] and distinguishes between these diagnoses better than CT [124,125]. If gadolinium cannot be administered because of renal function or gadolinium allergy, T2-weighted sequences and DWI can be helpful in identifying liver lesions. DWI in MRI can be used for problem solving or increasing confidence when other MR sequences are equivocal.

Increased conspicuity of lesions on DWI increases sensitivity and justifies its routine use in MRI in detection of HCC [123,126-128].

Although extracellular gadolinium agents are most commonly used in liver MRI to diagnose HCC, hepatobiliary contrast agents such as gadoxetate disodium (also called gadoteric acid, Gd-EOB-DTPA) and gadobenate dimeglumine (also called Gd-BOPTA) have also been used in recent years. An advantage of hepatobiliary agents compared with traditional extracellular agents is their decreased dose of contrast in patients with impaired renal function. Gadobenate dimeglumine can be given at half dose in patients with impaired renal function. The dose of gadoxetate disodium is one-quarter of the dose of extracellular agents.

An advantage of hepatobiliary contrast agents is that they can detect early HCC that shows relative hypoenhancement on the hepatobiliary phase, when there is not yet arterial enhancement or venous-phase washout, enhancing the sensitivity and accuracy for HCC diagnosis [110,129]. Hepatobiliary phase hypointensity favors a malignant or premalignant lesion rather than a low-grade dysplastic or cirrhotic nodule in studies with both hepatitis B and C patients [89,113,130-132]. MRI with hepatobiliary contrast may be the most sensitive imaging method to detect small HCCs and premalignant lesions that could progress to HCC, and adding the hepatobiliary phase improves sensitivity of HCC detection by 5% to 16% compared with MRI using the other DCE sequences [109,133-135]. One recent meta-analysis regarding diagnosis of HCC using hepatobiliary contrast showed sensitivity of 91% and specificity of 95% [136], and another meta-analysis showed higher sensitivity for HCC diagnosis with hepatobiliary contrast (93%) compared with contrast-enhanced CT (78%) [137]. Most hypoenhancing lesions on the hepatobiliary phase will progress to an arterial-enhancing HCC within 12 months [75,138] or during the follow-up period [139], which has important treatment implications.

A limitation of hepatobiliary contrast agents is that in patients with severe cirrhosis, where there is decreased liver function, the hepatocytes do not take up the hepatobiliary contrast agent well, and lesions may not be as conspicuous [140-142]. A disadvantage of decreasing the volume of contrast injected with gadoxetate disodium is that the arterial and portal venous enhancement can be suboptimal. Additionally, the findings gleaned from hepatobiliary contrast agent use in MR have not been integrated into the UNOS criteria for the diagnosis of HCC. Distinguishing HCC from cholangiocarcinoma can be challenging with hepatobiliary contrast as well, as intrahepatic cholangiocarcinomas are often arterial enhancing in cirrhotic compared with normal livers [143].

The combination of hepatobiliary MRI and DWI was more accurate and sensitive in detecting small HCCs than each MRI technique alone in 1 study [126], and in another study the combination of hyperintensity on DWI and hypointensity on the hepatobiliary phase predicted progression to HCC [128].

MR elastography is primarily used for diagnosis of liver fibrosis and cirrhosis rather than diagnosis of HCC, although attempts have been made to characterize liver lesions/HCC with elastography. No association was found between MR elastography stiffness and HCC presence in at least 1 study [144]. Emerging data indicate that elevation of stiffness is associated with future development of liver-related decompensation, HCC, and death [145].

Positron emission tomography

Positron emission tomography/CT (PET/CT) is not an appropriate screening test for HCC. PET/CT is also of limited utility in the diagnosis of HCC, since HCC uptake of fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG) PET is variable [146-148]. One study, however, showed that PET/CT in HCC may be useful for predicting prognosis and treatment responses and for planning treatment in patients with locally advanced HCC [149]. Another study showed that combining choline 11 and FDG-PET/CT detected HCC with high sensitivity compared with FDG-PET/CT alone because of the variability of FDG-PET/CT uptake in HCC [150].

Variant 3: Chronic liver disease. Surveillance for hepatocellular carcinoma (HCC). Previous diagnosis of HCC.

Treatment options for HCC include surgical resection, liver transplant, liver-directed therapy, and systemic therapy [12]. Liver-directed therapy can include treatments such as chemoembolization, radioembolization with yttrium 90, thermal ablation, or percutaneous ethanol ablation, amongst others. These various treatment options are thoroughly discussed in the ACR Appropriateness Criteria® [“Radiologic Management of Hepatic Malignancy”](#) [151] and are beyond the scope of this document.

Surveillance for HCC is required for patients who have received liver-directed therapy, surgical resection, medical treatment, or a transplant for HCC. Potential noninvasive diagnostic modalities used for HCC surveillance and

diagnosis are the same as for HCC screening and include US, CT, MRI, and serum biomarkers. These modalities have the same strengths and weaknesses for surveillance as for HCC screening and surveillance prior to treatment, as discussed in variant 2. However, because of the higher risk of tumor recurrence, US is not typically used for surveillance for HCC in the first 2 years after treatment because of the low sensitivity of US. Similarly, US has low sensitivity in patients who are obese, have NAFLD, or have very nodular cirrhotic livers, as discussed above.

CT and MRI play an important role in surveillance for recurrence of HCC and are necessary for further HCC treatment planning in the case of tumor progression, notably when planning liver-directed therapy. In HCC patients who have already received liver-directed therapy, recurrence is 6.5 times more likely in the first year after treatment than in the second year.

There is currently a lack of evidence regarding the optimal follow-up strategy for patients treated with liver-directed therapy for HCC. There is variability in the interventional radiology community with regards to the type of and frequency of imaging follow-up after treatment for HCC [152,153].

Results of a survey of Society of Interventional Radiology members showed that CT or MRI was typically performed for follow-up after HCC treatment [153]. Most commonly, the first follow-up imaging was at 1 month post-treatment, followed by 3 months post-treatment. This was followed by imaging every 3 months with CT or MRI. This strategy of imaging for HCC surveillance every 3 months after treatment is also supported by other society guidelines, including the European Association for the Study of the Liver (EASL) and the National Comprehensive Cancer Network (NCCN) [86,154]. NCCN guidelines recommend at least 3-phase high-quality CT or MRI every 3 to 6 months for 2 years and then every 6 to 12 months after HCC resection, based on the consensus that earlier identification of disease may facilitate treatment [154]. EASL recommends multiphase CT or MRI to assess response 1 month after resection or locoregional or systemic therapies, followed by 1 imaging technique every 3 months to complete at least 2 years and then regular US every 6 months [86]. A separate paper recommended the optimal schedule for follow-up after HCC treatment at 2, 4, 6, 8, 11, 14, 18, and 24 months with either CT or MRI, reporting that this reduces diagnostic delay and is cost effective [155]. However, this schedule is more frequent than some of the other society recommendations and the most common practice amongst interventional radiologists (every 3 months) [153].

Regarding multiphase CT after treatment for HCC, a noncontrast phase is strongly recommended, particularly if the patient has received liver-directed therapy [118,119]. This can result in a patient having 4-phase CT examinations, including noncontrast, arterial, portal venous, and delayed phases. Dual-energy CT has the advantage of making virtual unenhanced images and/or iodine maps, which decrease the amount of radiation per multiphase CT, particularly for those patients who have previously undergone treatment for HCC [89]. Patients with HCC who are receiving treatment may undergo additional multiphase CT examinations to assess response to treatment with increased risk of lifetime exposure to ionizing radiation. Perfusion CT can calculate hepatic blood flow and portal blood flow using a color-coded display and thus analyze tumor angiogenesis and assess tumor response to treatment [156]. However, this is currently predominantly used in research and not used in surveillance for HCC.

Many centers treating HCC prefer MRI over multiphase CT in post-treatment surveillance of HCC because the lipiodol used in transarterial chemoembolization can make assessment for tumor recurrence difficult on CT, whereas the presence of lipiodol will not confound the assessment for tumor recurrence on MRI. Subtraction images on MRI can help to diagnose new HCC or tumor recurrence in patients with previous liver-directed therapy or T1 hyperintense dysplastic nodules [157].

CEUS can be used for assessing for local tumor progression and treatment planning after focal ablation of HCC lesions [158,159] but is not practical for surveillance of the whole liver [98]. Also, the sensitivity of CEUS in detecting local tumor recurrence and new intrahepatic recurrence after percutaneous ablation therapy is relatively low in comparison with multiphase CT [160]. After radiofrequency ablation and percutaneous ethanol ablation, tumor response can be evaluated with CEUS immediately after the procedure, after 1 day, after 1 month, or later [159]. Interestingly, the pattern of HCC on CEUS after cryoablation appears different compared to after radiofrequency ablation because the margins of the lesions are less well defined and shrink significantly faster than radiofrequency ablation lesions [161].

Summary of Recommendations

- Because liver fibrosis can now be treated, it is more important than ever to be able to diagnose liver fibrosis noninvasively and monitor response to treatment. Liver biopsy is plagued by sampling error and complications, and serology tests have significant limitations. Although US (grayscale and Doppler) can diagnose cirrhosis, it does so unreliably using morphologic and sonographic features and cannot diagnose earlier stages of fibrosis. TE can more reliably diagnose cirrhosis compared with grayscale and Doppler US but is unreliable in patients with obesity and ascites, which is a significant portion of cirrhotic patients living in the United States. ARFI elastography can reliably diagnose cirrhosis and can stage hepatic fibrosis as well, and ARFI is added to grayscale and Doppler US. MR elastography is the most accurate method for diagnosing liver fibrosis noninvasively because it assesses the whole liver and can stage liver fibrosis.
- All international organizations recommend US for screening for HCC. However, US is particularly limited for identifying HCC in patients with obesity, NAFLD, and nodular cirrhotic livers, which is a large portion of the United States cirrhotic population receiving screening. In these patient groups as well as patients who are on the liver transplant wait list, US is so limited that consideration should be made for screening for HCC with either MRI or multiphase CT. If a suspicious liver lesion >1 cm is identified on a screening US, the diagnosis of HCC cannot be made on US alone and the HCC diagnosis needs to be confirmed on MRI or multiphase CT. Although MRI is preferable because of its slightly increased accuracy compared with CT, ability to detect premalignant nodules, and lack of ionizing radiation, multiphase CT can accurately diagnose HCC as well. Many MRI centers now include techniques that further increase accuracy of HCC diagnosis, including DWI and hepatobiliary contrast.
- Patients who have been previously diagnosed with and treated for hepatocellular carcinoma require continued surveillance for recurrent hepatocellular carcinoma. Given the high rate of recurrence (particularly within the first year after treatment) and insensitivity of US, multiphase CT or MRI is suggested to assess response 1 month after resection or therapy, followed by imaging every 3 months for at least 2 years. Many centers treating HCC prefer MRI over multiphase CT in post-treatment surveillance of HCC because the lipiodol used in transarterial chemoembolization can make assessment for tumor recurrence difficult on CT.

Summary of Evidence

Of the 161 references cited in the *ACR Appropriateness Criteria® Chronic Liver Disease* document, 142 are categorized as diagnostic references including 4 well-designed studies, 50 good-quality studies, and 49 quality studies that may have design limitations. Additionally, 5 references are categorized as therapeutic references. There are 44 references that may not be useful as primary evidence. There are 14 references that are meta-analysis studies.

The 161 references cited in the *ACR Appropriateness Criteria® Chronic Liver Disease* document were published from 1986 through 2016.

Although there are references that report on studies with design limitations, 54 well designed or good quality studies provide good evidence.

Relative Radiation Level Information

Potential adverse health effects associated with radiation exposure are an important factor to consider when selecting the appropriate imaging procedure. Because there is a wide range of radiation exposures associated with different diagnostic procedures, a relative radiation level (RRL) indication has been included for each imaging examination. The RRLs are based on effective dose, which is a radiation dose quantity that is used to estimate population total radiation risk associated with an imaging procedure. Patients in the pediatric age group are at inherently higher risk from exposure, both because of organ sensitivity and longer life expectancy (relevant to the long latency that appears to accompany radiation exposure). For these reasons, the RRL dose estimate ranges for pediatric examinations are lower as compared to those specified for adults (see Table below). Additional information regarding radiation dose assessment for imaging examinations can be found in the *ACR Appropriateness Criteria® [Radiation Dose Assessment Introduction](#)* document.

Relative Radiation Level Designations		
Relative Radiation Level*	Adult Effective Dose Estimate Range	Pediatric Effective Dose Estimate Range
○	0 mSv	0 mSv
⊕	<0.1 mSv	<0.03 mSv
⊕⊕	0.1-1 mSv	0.03-0.3 mSv
⊕⊕⊕	1-10 mSv	0.3-3 mSv
⊕⊕⊕⊕	10-30 mSv	3-10 mSv
⊕⊕⊕⊕⊕	30-100 mSv	10-30 mSv

*RRL assignments for some of the examinations cannot be made, because the actual patient doses in these procedures vary as a function of a number of factors (eg, region of the body exposed to ionizing radiation, the imaging guidance that is used). The RRLs for these examinations are designated as “Varies”.

Supporting Documents

For additional information on the Appropriateness Criteria methodology and other supporting documents go to www.acr.org/ac.

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The ACR Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those examinations generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the FDA have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.