American College of Radiology
ACR Appropriateness Criteria®
Liver Lesion-Initial Characterization

Variant: 1 Indeterminate, greater than 1 cm liver lesion on initial imaging with US. Normal liver. No suspicion or evidence of extrahepatic malignancy or underlying liver disease.

Procedure	Appropriateness Category	Relative Radiation Level
US abdomen with IV contrast	Usually Appropriate	O
MRI abdomen without and with IV contrast	Usually Appropriate	O
CT abdomen with IV contrast multiphase	Usually Appropriate	☢☢☢☢
MRI abdomen without IV contrast	May Be Appropriate	O
Image-guided biopsy liver	Usually Not Appropriate	Varies
CT abdomen without IV contrast	Usually Not Appropriate	☢☢☢
DOTATATE PET/CT skull base to mid-thigh	Usually Not Appropriate	☢☢☢
Liver spleen scan	Usually Not Appropriate	☢☢☢
RBC scan abdomen and pelvis	Usually Not Appropriate	☢☢☢
CT abdomen without and with IV contrast	Usually Not Appropriate	☢☢☢☢
FDG-PET/CT skull base to mid-thigh	Usually Not Appropriate	☢☢☢☢
Octreotide scan with SPECT or SPECT/CT chest and abdomen	Usually Not Appropriate	☢☢☢☢

Variant: 2 Indeterminate, greater than 1 cm liver lesion on initial imaging with CT (noncontrast or single-phase) or noncontrast MRI. Normal liver. No suspicion or evidence of extrahepatic malignancy or underlying liver disease.

Procedure	Appropriateness Category	Relative Radiation Level
MRI abdomen without and with IV contrast	Usually Appropriate	O
CT abdomen with IV contrast multiphase	Usually Appropriate	☢☢☢☢
US abdomen	May Be Appropriate (Disagreement)	O
US abdomen with IV contrast	May Be Appropriate	O
Image-guided biopsy liver	Usually Not Appropriate	Varies
DOTATATE PET/CT skull base to mid-thigh	Usually Not Appropriate	☢☢☢
Liver spleen scan	Usually Not Appropriate	☢☢☢
RBC scan abdomen and pelvis	Usually Not Appropriate	☢☢☢
CT abdomen without and with IV contrast	Usually Not Appropriate	☢☢☢☢
FDG-PET/CT skull base to mid-thigh	Usually Not Appropriate	☢☢☢☢
Octreotide scan with SPECT or SPECT/CT chest and abdomen	Usually Not Appropriate	☢☢☢☢

Variant: 3 Indeterminate, greater than 1 cm liver lesion on initial imaging with US. Known history of an extrahepatic malignancy.

Procedure	Appropriateness Category	Relative Radiation Level
MRI abdomen without and with IV contrast	Usually Appropriate	O
CT abdomen with IV contrast multiphase	Usually Appropriate	☢☢☢☢
US abdomen with IV contrast	May Be Appropriate	O
Image-guided biopsy liver	May Be Appropriate	Varies
MRI abdomen without IV contrast	May Be Appropriate	O

DOTATATE PET/CT skull base to mid-thigh	May Be Appropriate	☢☢☢
CT abdomen without and with IV contrast	May Be Appropriate	☢☢☢☢
FDG-PET/CT skull base to mid-thigh	May Be Appropriate	☢☢☢☢
Octreotide scan with SPECT or SPECT/CT chest and abdomen	May Be Appropriate	☢☢☢☢
CT abdomen without IV contrast	Usually Not Appropriate	☢☢☢
Liver spleen scan	Usually Not Appropriate	☢☢☢
RBC scan abdomen and pelvis	Usually Not Appropriate	☢☢☢

Variant: 4 Indeterminate, greater than 1 cm liver lesion on initial imaging with CT (noncontrast or single-phase) or noncontrast MRI. Known history of an extrahepatic malignancy.

Procedure	Appropriateness Category	Relative Radiation Level
MRI abdomen without and with IV contrast	Usually Appropriate	O
CT abdomen with IV contrast multiphase	Usually Appropriate	☢☢☢☢
FDG-PET/CT skull base to mid-thigh	Usually Appropriate	☢☢☢☢
US abdomen	May Be Appropriate	O
US abdomen with IV contrast	May Be Appropriate	O
Image-guided biopsy liver	May Be Appropriate	Varies
DOTATATE PET/CT skull base to mid-thigh	May Be Appropriate	☢☢☢
CT abdomen without and with IV contrast	May Be Appropriate	☢☢☢☢
Octreotide scan with SPECT or SPECT/CT chest and abdomen	May Be Appropriate	☢☢☢☢
Liver spleen scan	Usually Not Appropriate	☢☢☢
RBC scan abdomen and pelvis	Usually Not Appropriate	☢☢☢

Variant: 5 Incidental liver lesion, greater than 1 cm on US, noncontrast or single-phase CT, or noncontrast MRI. Known chronic liver disease.

Procedure	Appropriateness Category	Relative Radiation Level
US abdomen with IV contrast	Usually Appropriate	O
MRI abdomen without and with IV contrast	Usually Appropriate	O
CT abdomen with IV contrast multiphase	Usually Appropriate	☢☢☢☢
Image-guided biopsy liver	May Be Appropriate	Varies
DOTATATE PET/CT skull base to mid-thigh	Usually Not Appropriate	☢☢☢
Liver spleen scan	Usually Not Appropriate	☢☢☢
RBC scan abdomen and pelvis	Usually Not Appropriate	☢☢☢
CT abdomen without and with IV contrast	Usually Not Appropriate	☢☢☢☢
FDG-PET/CT skull base to mid-thigh	Usually Not Appropriate	☢☢☢☢
Octreotide scan with SPECT or SPECT/CT chest and abdomen	Usually Not Appropriate	☢☢☢☢

Variant: 6 Indeterminate, less than 1 cm liver lesion on initial imaging with US. Known history of an extrahepatic malignancy.

Procedure	Appropriateness Category	Relative Radiation Level
MRI abdomen without and with IV contrast	Usually Appropriate	O
US abdomen with IV contrast	May Be Appropriate	O
MRI abdomen without IV contrast	May Be Appropriate	O
CT abdomen with IV contrast multiphase	May Be Appropriate	☢☢☢☢

Image-guided biopsy liver	Usually Not Appropriate	Varies
CT abdomen without IV contrast	Usually Not Appropriate	☢☢☢
DOTATATE PET/CT skull base to mid-thigh	Usually Not Appropriate	☢☢☢
Liver spleen scan	Usually Not Appropriate	☢☢☢
RBC scan abdomen and pelvis	Usually Not Appropriate	☢☢☢
CT abdomen without and with IV contrast	Usually Not Appropriate	☢☢☢☢
FDG-PET/CT skull base to mid-thigh	Usually Not Appropriate	☢☢☢☢
Octreotide scan with SPECT or SPECT/CT chest and abdomen	Usually Not Appropriate	☢☢☢☢

Variant: 7 Indeterminate, less than 1 cm liver lesion on initial imaging with CT (noncontrast or single-phase) or noncontrast MRI. Known history of an extrahepatic malignancy.

Procedure	Appropriateness Category	Relative Radiation Level
MRI abdomen without and with IV contrast	Usually Appropriate	O
CT abdomen with IV contrast multiphase	Usually Appropriate	☢☢☢☢
US abdomen with IV contrast	May Be Appropriate	O
Image-guided biopsy liver	May Be Appropriate	Varies
US abdomen	Usually Not Appropriate	O
DOTATATE PET/CT skull base to mid-thigh	Usually Not Appropriate	☢☢☢
Liver spleen scan	Usually Not Appropriate	☢☢☢
RBC scan abdomen and pelvis	Usually Not Appropriate	☢☢☢
CT abdomen without and with IV contrast	Usually Not Appropriate	☢☢☢☢
FDG-PET/CT skull base to mid-thigh	Usually Not Appropriate	☢☢☢☢
Octreotide scan with SPECT or SPECT/CT chest and abdomen	Usually Not Appropriate	☢☢☢☢

Variant: 8 Incidental liver lesion, less than 1 cm on US, noncontrast or single-phase CT, or noncontrast MRI. Known chronic liver disease.

Procedure	Appropriateness Category	Relative Radiation Level
MRI abdomen without and with IV contrast	Usually Appropriate	O
CT abdomen with IV contrast multiphase	Usually Appropriate	☢☢☢☢
US abdomen with IV contrast	May Be Appropriate	O
Image-guided biopsy liver	Usually Not Appropriate	Varies
DOTATATE PET/CT skull base to mid-thigh	Usually Not Appropriate	☢☢☢
Liver spleen scan	Usually Not Appropriate	☢☢☢
RBC scan abdomen and pelvis	Usually Not Appropriate	☢☢☢
CT abdomen without and with IV contrast	Usually Not Appropriate	☢☢☢☢
FDG-PET/CT skull base to mid-thigh	Usually Not Appropriate	☢☢☢☢
Octreotide scan with SPECT or SPECT/CT chest and abdomen	Usually Not Appropriate	☢☢☢☢

Panel Members

Victoria Chernyak, MD, MS[a]; Jeanne M. Horowitz, MD[b]; Ihab R. Kamel, MD, PhD[c]; Hina Arif-Tiwari, MD[d]; Mustafa R. Bashir, MD[e]; Brooks D. Cash, MD[f]; James Farrell, MD[g]; Alan Goldstein, MD[h]; Joseph R. Grajo, MD[i]; Samir Gupta, MD[j]; Nicole M. Hindman, MD[k]; Aya Kamaya, MD[l]; Michelle M. McNamara, MD[m]; Kristin K. Porter, MD, PhD[n]; Lilja Bjork. Solnes, MD, MBA[o]; Pavan K. Srivastava,

MD[p]; Atif Zaheer, MD[q]; Laura R. Carucci, MD.[r]

Summary of Literature Review

Introduction/Background

Incidental liver masses are commonly discovered on imaging performed for other indications. Because the prevalence of benign focal liver lesions in adults is high, with at least one lesion seen in up to 15% of patients, accurate characterization of incidentally detected lesions is an important objective of diagnostic imaging [1].

Benign lesions are very common in the liver, and even in patients with primary malignancy, benign lesions unrelated to the known malignancy can be found in nearly 30% of patients [2]. Common benign liver masses include cysts, hemangiomas, and focal nodular hyperplasia (FNH). Common malignant tumors include metastases and hepatocellular carcinomas (HCCs). Less common liver masses include hepatocellular adenoma, intrahepatic cholangiocarcinoma, fibrolamellar HCC, biliary cystadenoma and cystadenocarcinoma, lymphoma, stromal tumors, and a variety of sarcomas. On occasion, benign lesions and pseudolesions may mimic liver tumors. These mimics include focal fat deposition or sparing, intrahepatic vascular shunts, transient hepatic attenuation/intensity difference, abscess, hematoma, and peliosis hepatis. Patients with cirrhosis are a special patient population in whom certain benign (regenerating nodules), premalignant (dysplastic nodules), malignant (HCC), and nontumorous (confluent hepatic fibrosis) masses as well as pseudolesions (vascular shunts) are more prevalent than in the general population [3].

For each of the variants in this document, it is assumed that an imaging study has identified a lesion that was not fully characterized by the study that detected it. Prior imaging studies may include ultrasonography (US) with color-flow evaluation, noncontrast or contrast-enhanced multidetector helical CT, or noncontrast or contrast-enhanced MRI.

Management recommendations of incidental liver lesions were addressed in a recent white paper by the ACR Incidental Findings Committee (Management of Incidental Liver Lesions on CT: A White Paper of the ACR Incidental Findings Committee) [4]. The document addressed management guidance for incidental liver lesions detected on CT only. In contrast, this document addresses approaches to characterization of hepatic lesions detected with various modalities and in various clinical scenarios.

For purposes of increased clarity in this document, we combined the low-risk and average-risk individual into one category using the definitions as stated in the white paper (any age with no known malignancies, hepatic dysfunction, risk factors for HCC, or symptoms attributable to the liver). The definition of a high-risk individual in this document differs from that in the white paper in that we separate those individuals with pre-existing liver disease (cirrhosis and chronic hepatitis B without cirrhosis) from those with a known primary malignancy.

Special Imaging Considerations

When considering a definitive diagnosis of liver lesions, the dynamic pattern of lesion enhancement can guide the final diagnosis. Therefore, at least two dynamic imaging phases (ie, dual-phase) are required for characterization of most liver lesions. These phases include hepatic

arterial phase and portal venous phase and are applicable to CT, MRI, and contrast-enhanced US (CEUS). For CT and MRI, late arterial phase is preferred over the early arterial phase, as maximal lesion enhancement compared with precontrast occurs more frequently during the late arterial phase [5]. It is important to note that these phases are required for assessment of liver lesions in patients with chronic liver disease, as stated in the *Liver Imaging Reporting and Data System* (LI-RADS®) [6].

For MRI, extracellular gadolinium-based contrast agents are commonly used in a variety of clinical settings. However, hepatobiliary contrast agents were developed to assist with detection and characterization of liver lesions. Two such agents are available: gadoxetate disodium and gadobenate dimeglumine. Hepatobiliary agents have the advantage of hepatobiliary phase (HBP) in addition to the dynamic postcontrast phases. In the HBP, parenchymal uptake of the contrast agent provides avid enhancement of the liver and therefore the ability to detect nonhepatocellular lesions. Of the two agents, gadoxetate is used more widely for HBP imaging as its HBP occurs approximately 20 minutes after injection as compared with 1 to 2 hours when using gadobenate.

CEUS has been recently approved for use in the United States, and has been used in Europe and Asia for >10 years [7]. Contrast agents used for CEUS are gas-filled microbubbles, stabilized by the shell of albumin, surfactants, or phospholipids [7]. Microbubbles are exclusively intravascular, and because of their small diameter (>7μm) are able to circulate in the capillary beds [7].

A positron-emitting radioisotope-labeled somatostatin analogue called Ga-68-DOTATATE utilized in PET/CT is designed to image neuroendocrine tumors (NETs). It offers a higher spatial resolution and considerably shorter imaging times compared with In-111 somatostatin receptor or metaiodobenzylguanidine scintigraphy [8].

Discussion of Procedures by Variant

Variant 1: Indeterminate, greater than 1 cm liver lesion on initial imaging with US. Normal liver. No suspicion or evidence of extrahepatic malignancy or underlying liver disease.

Variant 1: Indeterminate, greater than 1 cm liver lesion on initial imaging with US. Normal liver. No suspicion or evidence of extrahepatic malignancy or underlying liver disease.
A. CT Abdomen

In some cases, establishing the benign nature of the lesion, rather than a definitive diagnosis is sufficient. In differentiation between malignant and benign lesions, contrast-enhanced CT is accurate in 74% to 95% of cases [9,10]. Definitive diagnosis can be established on contrast-enhanced CT in 71% of patients, with additional imaging recommended in 10% of patients [11]. For patients with incidental liver lesions, multiphase contrast-enhanced CT has 91% to 95% accuracy for diagnosis of hemangioma, 85% to 93% accuracy for the diagnosis of FNH, and 96% to 99% accuracy for diagnosis of HCC [10,12]. For lesions detected on grayscale US, contrast-enhanced CT has sensitivity of 72% to 91%, specificity of 38% to 82%, positive predictive value (PPV) of 92%, negative predictive value (NPV) of 80%, and accuracy of 80% to 88% for establishing a definitive diagnosis [9,13]. CT of the abdomen with and without IV contrast is not recommended for this clinical scenario because there is no added value for unenhanced images.

Variant 1: Indeterminate, greater than 1 cm liver lesion on initial imaging with US. Normal liver. No suspicion or evidence of extrahepatic malignancy or underlying liver disease.

B. FDG-PET/CT Skull Base to Mid-Thigh

There is no relevant literature to support the use of fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG)-PET/CT in this clinical scenario.

Variant 1: Indeterminate, greater than 1 cm liver lesion on initial imaging with US. Normal liver. No suspicion or evidence of extrahepatic malignancy or underlying liver disease.
C. DOTATATE PET/CT Skull Base to Mid-Thigh

There is no relevant literature to support the use of Ga-68-DOTATATE PET/CT in this clinical scenario.

Variant 1: Indeterminate, greater than 1 cm liver lesion on initial imaging with US. Normal liver. No suspicion or evidence of extrahepatic malignancy or underlying liver disease.
D. Octreotide Scan with SPECT or SPECT/CT Chest and Abdomen

There is no relevant literature to support the use of In-111 somatostatin receptor scan with single-photon emission computed tomography (SPECT) or SPECT/CT in this clinical scenario.

Variant 1: Indeterminate, greater than 1 cm liver lesion on initial imaging with US. Normal liver. No suspicion or evidence of extrahepatic malignancy or underlying liver disease.
E. MRI Abdomen

In lesions detected on grayscale US, one study of MRI with and without intravenous (IV) contrast has sensitivity of 82% and specificity of 43% for establishing an exact diagnosis [14]. In another series, MRI with and without IV contrast is able to establish a definitive diagnosis in 95% of liver lesions, which is significantly higher than contrast-enhanced CT [11]. Furthermore, only 1.5% of patients with MRIs require recommendation for further imaging as opposed to 10% with CT [11]. Performance characteristics of MRI depend on the sequences and type of contrast, as well as the lesion itself. A combination of diffusion-weighted imaging (DWI) and HBP allows correct classification of lesions as benign or malignant in 91% of cases and exact characterization in 85% of cases [15]. Gadoxetate-enhanced MRI has an accuracy of 95% to 99% for diagnosis of hemangioma, accuracy of 88% to 99% for the diagnosis of FNH, and accuracy of 97% for diagnosis of HCC in patients with incidentally discovered liver lesions [10,12]. For differentiation between adenoma and FNH, low signal on HBP is 100% specific, 92% sensitive, and 97% accurate for hepatocellular adenoma [16]. However, it should be noted that inflammatory adenoma can mimic FNH on MRI [17]. For the diagnosis of a hemangioma, MRI with extracellular gadolinium contrast has sensitivity of 93%, specificity of 99%, accuracy of 98%, PPV of 96%, and NPV of 99% [18]. Although apparent diffusion coefficient (ADC) values of solid benign lesions are higher than those of the solid malignant lesions, there is a considerable overlap of the ADC values between the two groups [19]. Therefore, in patients without a history of malignancy, the value of DWI for differentiating solid liver masses may be limited.

There is no relevant literature that has assessed the performance of MRI without IV contrast specifically for this clinical scenario. Therefore, the committee recommendations on the use of MRI without IV contrast are based primarily on expert opinion. In some cases, MRI without IV contrast may be appropriate, particularly if the initial US has a high index of suspicion for the diagnosis of a cyst.

Variant 1: Indeterminate, greater than 1 cm liver lesion on initial imaging with US. Normal liver. No suspicion or evidence of extrahepatic malignancy or underlying liver disease.
F. Image-Guided Biopsy Liver

An indeterminate liver lesion detected on US is often further evaluated with a diagnostic CT or MRI prior to biopsy, in order to avoid biopsy of solid benign liver lesions such as hemangiomas or areas of FNH [4].

Percutaneous image-guided biopsy may be necessary to establish the diagnosis, particularly when the imaging features on a CT or MRI examination indicate possibility of malignancy. In some liver lesions, such as lymphoma, histopathologic analysis is the only technique that can make a definitive diagnosis [20]. Various techniques exist for guidance of the biopsy, and US and CT are the most commonly utilized modalities for biopsy guidance. When a biopsy is performed to diagnose or rule out malignancy in indeterminate lesions, the overall technical success rate under grayscale US guidance is 74%, which can be increased to 100% under CEUS guidance [21,22].

The percentage of tumor cells in the biopsy sample is greater with a higher number of collected biopsy samples [23]. Furthermore, for lesions not seen on grayscale US, the success rate for CEUS-guided biopsy can be as high as 88% to 96% [24,25]. US fusion with CT or MRI, can be used for percutaneous biopsy of lesions with poor sonographic conspicuity, with a 96% technical success rate [25]. Lesions that are isointense on CT can also present a challenge for CT-guided biopsy; however, use of anatomic landmarks or IV contrast can achieve accuracy of 96% to 98% [26].

Image-guided biopsies carry a risk of postbiopsy bleeding, which may be as high as 9% to 12%, particularly with hypervascular lesions [27,28]. In addition, a very small risk of needle-track seeding exists.

Variant 1: Indeterminate, greater than 1 cm liver lesion on initial imaging with US. Normal liver. No suspicion or evidence of extrahepatic malignancy or underlying liver disease.
G. RBC Scan Abdomen and Pelvis

There is no relevant literature to support the use of a Tc-99m red blood cell (RBC) scan in this clinical scenario.

Variant 1: Indeterminate, greater than 1 cm liver lesion on initial imaging with US. Normal liver. No suspicion or evidence of extrahepatic malignancy or underlying liver disease.
H. Liver Spleen Scan

There is no relevant literature to support the use of a Tc-99m sulfur colloid scan in this clinical scenario.

Variant 1: Indeterminate, greater than 1 cm liver lesion on initial imaging with US. Normal liver. No suspicion or evidence of extrahepatic malignancy or underlying liver disease.
I. US Abdomen with Contrast

For patients with a lesion on grayscale US, addition of CEUS reduces the number of indeterminate diagnoses from 57% to 6%, and the sensitivity and specificity improve from 49% and 25% at baseline US to 93% and 75% with CEUS, respectively [29]. Furthermore, CEUS can reach a specific diagnosis in 77% to 93% and distinguish benign versus malignant lesions in 89% to 97% of indeterminate liver lesions discovered on grayscale US [9,30-32]. Of the complex cystic lesions found on grayscale US, CEUS correctly categorizes 95% of the malignant cases [33]. CEUS is comparable to CT for establishing a diagnosis for lesions detected on grayscale US, with sensitivity of 94% to 96%, specificity of 75% to 83%, PPV of 92%, NPV of 88%, and accuracy of 88% to 90% [13,14,29]. CEUS can definitively characterize an additional 41% of hemangiomas that are deemed indeterminate on a grayscale US [34].

For specific diagnoses, CEUS correctly characterizes 89% of areas of focal fat, 80% to 90% of hemangiomas, 87% of complex cysts, 78% of hepatic adenomas, 84% to 94% of FNHs, 86% of abscesses, and 60% of hematomas [14,30,35]. Typical pattern of enhancement on CEUS (eg, centripetal fill in during the arterial phase, hyper-enhanced lesion during venous and late phases) has 88% to 90% sensitivity, 99% specificity, 94% to 95% PPV, 97% to 98% NPV, and 97% accuracy for the diagnosis of hemangiomas [18,36]. In noncirrhotic patients, the hypoechoic pattern in portal and sinusoidal phase (rapid wash-out) or the markedly hypoechoic or anechoic pattern in sinusoidal phase (marked late wash-out) showed a sensitivity, specificity, and accuracy of 97%, 100% and 98%, respectively, for the diagnosis of malignancy [37].

Variant 2: Indeterminate, greater than 1 cm liver lesion on initial imaging with CT (noncontrast or single-phase) or noncontrast MRI. Normal liver. No suspicion or evidence of extrahepatic malignancy or underlying liver disease.

Variant 2: Indeterminate, greater than 1 cm liver lesion on initial imaging with CT (noncontrast or single-phase) or noncontrast MRI. Normal liver. No suspicion or evidence of extrahepatic malignancy or underlying liver disease.

A. CT Abdomen

Contrast-enhanced CT correctly differentiates between malignant and benign lesions in 74% to 95% of lesions [9,10]. For patients with incidental liver lesions, multiphasecontrast-enhanced CT has 91% to 95% accuracy for diagnosis of hemangioma, 85% to 93% accuracy for the diagnosis of FNH, and 96% to 99% accuracy for diagnosis of HCC [10,12]. CT of the abdomen with and without IV contrast is not recommended for this clinical scenario because there is no added value for unenhanced images.

Variant 2: Indeterminate, greater than 1 cm liver lesion on initial imaging with CT (noncontrast or single-phase) or noncontrast MRI. Normal liver. No suspicion or evidence of extrahepatic malignancy or underlying liver disease.

B. FDG-PET/CT Skull Base to Mid-Thigh

There is no relevant literature to support the use of FDG-PET/CT in this clinical scenario.

Variant 2: Indeterminate, greater than 1 cm liver lesion on initial imaging with CT (noncontrast or single-phase) or noncontrast MRI. Normal liver. No suspicion or evidence of extrahepatic malignancy or underlying liver disease.

C. DOTATATE PET/CT Skull Base to Mid-Thigh

There is no relevant literature to support the use of Ga-68-DOTATATE PET/CT in this clinical scenario.

Variant 2: Indeterminate, greater than 1 cm liver lesion on initial imaging with CT (noncontrast or single-phase) or noncontrast MRI. Normal liver. No suspicion or evidence of extrahepatic malignancy or underlying liver disease.

D. Octreotide Scan with SPECT or SPECT/CT Chest and Abdomen

There is no relevant literature to support the use of In-111 somatostatin receptor scan with SPECT or SPECT/CT in this clinical scenario.

Variant 2: Indeterminate, greater than 1 cm liver lesion on initial imaging with CT (noncontrast or single-phase) or noncontrast MRI. Normal liver. No suspicion or evidence of extrahepatic malignancy or underlying liver disease.

E. MRI Abdomen

For small (≤2 cm) lesions deemed indeterminate on CT with and without IV contrast, MRI with and without IV contrast has sensitivity, specificity, PPV, and NPV of 68%, 94%, 76%, and 91%, respectively, for the correct classification of the lesion as benign or malignant [38]. Combination of DWI and HBP allows correct classification of lesions as benign or malignant in 91% of cases, and exact characterization in 85% of cases [15]. Compared with noncontrast MRI, gadoxetate-enhanced MRI allows for improved characterization of FNH with an accuracy of 68% versus 88%, respectively [12]. For patients with incidental liver lesions, gadoxetate-enhanced MRI has 95% to 99% accuracy for diagnosis of hemangioma, 95% to 99% accuracy for the diagnosis of FNH, and 97% accuracy for diagnosis of HCC [10]. Although ADC values of solid benign lesions are higher than that of the solid malignant lesions, there is a considerable overlap of the ADC values between the two groups [19]. Therefore, in patients without a history of malignancy, the value of DWI for differentiating solid liver masses may be limited.

Variant 2: Indeterminate, greater than 1 cm liver lesion on initial imaging with CT (noncontrast or single-phase) or noncontrast MRI. Normal liver. No suspicion or evidence of extrahepatic malignancy or underlying liver disease.
F. Image-Guided Biopsy Liver

Percutaneous image-guided biopsy may be necessary to establish the diagnosis, particularly when the imaging features on a CT or MRI examination indicate possibility of malignancy. In some liver lesions, such as lymphoma, histopathologic analysis is the only technique that can make a definitive diagnosis [20]. Various techniques exist for guidance of the biopsy, and US and CT are the most commonly utilized modalities for biopsy guidance. When a biopsy is performed to diagnose or rule out malignancy in indeterminate lesions, the overall technical success rate under grayscale US guidance is 74%, which can be increased to 100% under CEUS guidance [21,22].

The percentage of tumor cells in the biopsy sample is greater with a higher number of collected biopsy samples [23]. Furthermore, for lesions not seen on grayscale US, the success rate for CEUS-guided biopsy can be as high as 88% to 96% [24,25]. US fusion with CT or MRI, can be used for percutaneous biopsy of lesions with poor sonographic conspicuity, with a 96% technical success rate [25]. Lesions that are isointense on CT can also present a challenge for CT-guided biopsy; however, use of anatomic landmarks or IV contrast can achieve accuracy of 96% to 98% [26].

Image-guided biopsies carry a risk of postbiopsy bleeding, which may be as high as 9% to 12%, particularly with hypervascular lesions [27,28]. In addition, a very small risk of needle-track seeding exists.

Variant 2: Indeterminate, greater than 1 cm liver lesion on initial imaging with CT (noncontrast or single-phase) or noncontrast MRI. Normal liver. No suspicion or evidence of extrahepatic malignancy or underlying liver disease.
G. RBC Scan Abdomen and Pelvis

There is no relevant literature to support the use of a Tc-99m RBC scan in this clinical scenario.

Variant 2: Indeterminate, greater than 1 cm liver lesion on initial imaging with CT (noncontrast or single-phase) or noncontrast MRI. Normal liver. No suspicion or evidence of extrahepatic malignancy or underlying liver disease.
H. Liver Spleen Scan

There is no relevant literature to support the use of a Tc-99m sulfur colloid scan in this clinical scenario.

Variant 2: Indeterminate, greater than 1 cm liver lesion on initial imaging with CT (noncontrast or single-phase) or noncontrast MRI. Normal liver. No suspicion or evidence of extrahepatic malignancy or underlying liver disease.
I. US Abdomen

Diagnostic accuracy of grayscale US is 41% to 68% for specific diagnosis and 86% for differentiation between malignant and benign lesions [9,29]. US can be helpful in some cases due to its ability to characterize a lesion as a cyst. Doppler evaluation of flow is an integral part of the clinical grayscale US examination. However, none of the reviewed studies specifically compared performance of US examinations with and without the addition of Doppler.

Variant 2: Indeterminate, greater than 1 cm liver lesion on initial imaging with CT (noncontrast or single-phase) or noncontrast MRI. Normal liver. No suspicion or evidence of extrahepatic malignancy or underlying liver disease.
J. US Abdomen with Contrast

In a small retrospective study of solid indeterminate lesions detected on contrast-enhanced CT in patients without parenchymal liver disease, addition of CEUS improves diagnostic accuracy from 43% to 49% to 89% to 92% [39]. CEUS is able to provide correct diagnosis in 89% of cases and can distinguish between benign and malignant lesions in 97% of cases [9]. In noncirrhotic patients, the hypoechoic pattern in portal and sinusoidal phase (rapid wash-out) or the markedly hypoechoic or anechoic pattern in sinusoidal phase (marked late wash-out) showed a sensitivity, specificity, and accuracy of 97%, 100%, and 98%, respectively, for the diagnosis of malignancy [37].

Variant 3: Indeterminate, greater than 1 cm liver lesion on initial imaging with US. Known history of an extrahepatic malignancy.

Variant 3: Indeterminate, greater than 1 cm liver lesion on initial imaging with US. Known history of an extrahepatic malignancy.
A. CT Abdomen

In patients with a history of primary malignancy, contrast-enhanced CT can differentiate between metastases and benign lesions with 74% accuracy [40]. Specifically, in patients with a history of colon cancer, lesion characterization on contrast-enhanced CT is correct in 77% of cases [41]. When metastases are suspected based on US, the sensitivity and specificity of contrast-enhanced CT for detection of metastases are 88% and 17%, respectively [42].

In patients with hypervascular liver metastases, addition of noncontrast CT can improve the confidence level for lesion characterization by 4% to 15%; however, it does not change the diagnostic accuracy [43]. The addition of noncontrast CT can increase sensitivity for breast cancer metastases by 5% to 23% but does not improve sensitivity for melanoma metastases [44]. Sensitivity of noncontrast CT alone is 61% to 100% for breast cancer metastases, 62% to 100% for melanoma metastases, and 17% to 88% for NET metastases [44]. In comparison, contrast-enhanced CT has sensitivity of 77% to 95% for breast cancer metastases, 86% to 100% for melanoma metastases, and 44% to 77% for NET metastases [44,45].

Variant 3: Indeterminate, greater than 1 cm liver lesion on initial imaging with US. Known history of an extrahepatic malignancy.
B. FDG-PET/CT Skull Base to Mid-Thigh

In patients with a history of primary malignancy, FDG-PET/CT can differentiate between malignant and benign lesions with an accuracy of 75% [40]. When metastases are suspected based on US, the

sensitivity and specificity of PET/CT in the detection of hepatic metastases is 97% and 75%, respectively, which is higher, compared with contrast-enhanced CT alone with sensitivity and specificity of 88% and 17%, respectively [42].

Variant 3: Indeterminate, greater than 1 cm liver lesion on initial imaging with US. Known history of an extrahepatic malignancy.
C. DOTATATE PET/CT Skull Base to Mid-Thigh

In patients with primary NET, Ga-68-DOTATATE PET/CT demonstrates sensitivity of 80% to 100% and of specificity 82% to 100% [8]. Specifically, Ga-68-DOTATATE PET/CT is more sensitive than FDG-PET/CT, with sensitivities of 72% to 100% versus 54% to 78%, respectively [8]. Ga-68-DOTATATE PET/CT is not used in assessment metastases from primary cancers other than NET.

Variant 3: Indeterminate, greater than 1 cm liver lesion on initial imaging with US. Known history of an extrahepatic malignancy.
D. Octreotide Scan with SPECT or SPECT/CT Chest and Abdomen

Sensitivity of In-111 somatostatin receptor scan with SPECT or SPECT/CT varies depending on the specific histologic type of the primary NET. For example, detection rates are >75% in small-cell-lung cancer and carcinoid metastases and 40% to 75% in insulinoma and medullary thyroid cancers [46].

Variant 3: Indeterminate, greater than 1 cm liver lesion on initial imaging with US. Known history of an extrahepatic malignancy.
E. MRI Abdomen

In patients with a history of primary malignancy, noncontrast MRI can differentiate between malignant and benign lesions with an accuracy of 71% [47]. The accuracy increases to between 83% and 91% with the addition of dynamic postcontrast sequences and further increases to 94% with the addition of HBP [47,48]. In patients with a history of colon cancer, the lesion characterization on contrast-enhanced MRI is correct in 89% of cases [41]. In patients with suspected colorectal liver metastases, the combination of gadoxetate-enhanced MRI and DWI shows significantly higher accuracy (90%–93%) for the preoperative detection of small colorectal liver metastases than DWI alone [49]. In patients with known primary cancer, ADC values can help to distinguish between metastasis and benign solid hepatic lesions [50].

Variant 3: Indeterminate, greater than 1 cm liver lesion on initial imaging with US. Known history of an extrahepatic malignancy.
F. Image-Guided Biopsy Liver

Percutaneous image-guided biopsy may be necessary to establish the diagnosis, particularly when the imaging features on a CT or MRI examination indicate a possibility of malignancy. In some liver lesions, such as lymphoma, histopathologic analysis is the only technique that can make a definitive diagnosis [20]. Various techniques exist for guidance of the biopsy, where US and CT are the most commonly utilized modalities for biopsy guidance. When a biopsy is performed to diagnose or rule out malignancy in indeterminate lesions, the overall technical success rate under grayscale US guidance is 74%, which can be increased to 100% under CEUS guidance [21,22].

The percentage of tumor cells in the biopsy sample is greater with a higher number of collected biopsy samples [23]. Furthermore, for lesions not seen on grayscale US, the success rate for CEUS-guided biopsy can be as high as 88% to 96% [24,25]. US fusion with CT or MRI can be used for percutaneous biopsy of lesions with poor sonographic conspicuity with a 96% technical success

rate [25]. Lesions which are isointense on CT can also present a challenge for CT-guided biopsy; however, use of anatomic landmarks or IV contrast can achieve accuracy of 96% to 98% [26].

Image-guided biopsies carry a risk of postbiopsy bleeding, which may be as high as 9% to 12%, particularly with hypervascular lesions [27,28]. In addition, a very small risk of needle-track seeding exists.

Variant 3: Indeterminate, greater than 1 cm liver lesion on initial imaging with US. Known history of an extrahepatic malignancy.
G. RBC Scan Abdomen and Pelvis

There is no relevant literature to support the use of a Tc-99m RBC scan in this clinical scenario.

Variant 3: Indeterminate, greater than 1 cm liver lesion on initial imaging with US. Known history of an extrahepatic malignancy.
H. Liver Spleen Scan

There is no relevant literature to support the use of a Tc-99m sulfur colloid scan in this clinical scenario.

Variant 3: Indeterminate, greater than 1 cm liver lesion on initial imaging with US. Known history of an extrahepatic malignancy.
I. US Abdomen with Contrast

Depending on the appearance of the lesion on the initial US, CEUS may be performed for lesion characterization. CEUS can differentiate between malignant and benign lesions in 90% of lesions [48]. Diagnostic accuracy of CEUS for metastases is 83% compared with 76% for MRI with extracellular contrast agent [35]. In noncirrhotic patients, the hypoechoic pattern in portal and sinusoidal phase (rapid wash-out) or the markedly hypoechoic or anechoic pattern in sinusoidal phase (marked late wash-out) showed a sensitivity, specificity, and accuracy of 97%, 100%, and 98%, respectively, for the diagnosis of malignancy [37].

Variant 4: Indeterminate, greater than 1 cm liver lesion on initial imaging with CT (noncontrast or single-phase) or noncontrast MRI. Known history of an extrahepatic malignancy.

Variant 4: Indeterminate, greater than 1 cm liver lesion on initial imaging with CT (noncontrast or single-phase) or noncontrast MRI. Known history of an extrahepatic malignancy.
A. CT Abdomen

In patients with a history of primary malignancy, contrast-enhanced CT can differentiate between metastases and benign lesions with 74% accuracy [40]. Specifically, in patients with a history of colon cancer, lesion characterization on contrast-enhanced CT is correct in 77% of cases [41].

In patients with hypervascular liver metastases, adding a noncontrast CT phase to a contrast-enhanced CT examination can improve the confidence level for lesion characterization by 4% to 15%; however, it does not change the diagnostic accuracy [43]. The addition of noncontrast CT can increase sensitivity for breast cancer metastases by 5% to 23% but does not improve sensitivity for melanoma metastases [44]. Sensitivity of noncontrast CT alone is 61% to 100% for breast cancer metastases, 62% to 100% for melanoma metastases, and 17% to 88% for NET metastases [44]. In comparison, contrast-enhanced CT has a sensitivity of 77% to 95% for breast cancer metastases, 86% to 100% for melanoma metastases, and 44% to 82% for NET metastases [44,45].

Variant 4: Indeterminate, greater than 1 cm liver lesion on initial imaging with CT (noncontrast or single-phase) or noncontrast MRI. Known history of an extrahepatic malignancy.
B. FDG-PET/CT Skull Base to Mid-Thigh

In patients with a history of primary malignancy, FDG-PET/CT can differentiate between malignant and benign lesions with an accuracy of 75% [40]. In patients with a history of primary cancer and indeterminate lesions found by either CT or MRI, FDG-PET/CT has an accuracy of 75% with a high sensitivity of 96% and a limited specificity of 33% [40].

The sensitivity and specificity of FDG-PET/CT in the detection of hepatic metastases is 97% and 75%, respectively, which is higher compared with contrast-enhanced CT alone (which as a sensitivity and specificity of 88% and 17%, respectively) [42].

Variant 4: Indeterminate, greater than 1 cm liver lesion on initial imaging with CT (noncontrast or single-phase) or noncontrast MRI. Known history of an extrahepatic malignancy.
C. DOTATATE PET/CT Skull Base to Mid-Thigh

In patients with primary NET, Ga-68-DOTATATE PET/CT demonstrates sensitivity of 80% to 100% and specificity of 82% to 100% [8]. Specifically, Ga-68-DOTATATE PET/CT is more sensitive than FDG-PET/CT, with sensitivities of 72% to 100% versus 54% to 78%, respectively [8].

Variant 4: Indeterminate, greater than 1 cm liver lesion on initial imaging with CT (noncontrast or single-phase) or noncontrast MRI. Known history of an extrahepatic malignancy.
D. Octreotide Scan with SPECT or SPECT/CT Chest and Abdomen

Sensitivity of a In-111 somatostatin receptor scan with SPECT or SPECT/CT varies depending on the specific histologic type of the primary NET. For example, detection rates are >75% in small-cell-lung cancer and carcinoid metastases and 40% to 75% in insulinoma and medullary thyroid cancers [46].

Variant 4: Indeterminate, greater than 1 cm liver lesion on initial imaging with CT (noncontrast or single-phase) or noncontrast MRI. Known history of an extrahepatic malignancy.
E. MRI Abdomen

In patients with a history of primary malignancy, noncontrast MRI can differentiate between malignant and benign lesions with accuracy of 71% [47]. The accuracy increases by between 83% and 91% with the addition of dynamic postcontrast sequences and further increases to 94% with addition of HBP [47,48]. In patients with a history of colon cancer, the lesion characterization on contrast-enhanced MRI is correct in 89% of cases [41]. In patients with suspected colorectal liver metastases, the combination of gadoxetate-enhanced MRI and DWI shows significantly higher accuracy (90% to 93%) for the preoperative detection of small colorectal liver metastases than DWI alone [49]. In patients with known primary cancer, ADC values can help to distinguish between metastasis and benign solid hepatic lesions [50].

Variant 4: Indeterminate, greater than 1 cm liver lesion on initial imaging with CT (noncontrast or single-phase) or noncontrast MRI. Known history of an extrahepatic malignancy.
F. Image-Guided Biopsy Liver

Percutaneous image-guided biopsy may be necessary to establish the diagnosis, particularly when the imaging features on a CT or MRI examination indicate possibility of malignancy. In patients with a history of primary malignancy, 91% of biopsies are positive for malignancy, 5% of which can be different from the primary cancer [51]. Up to 6% of biopsies in patients with primary malignancy are nondiagnostic [51].

In some liver lesions, such as lymphoma, histopathologic analysis is the only technique that can make a definitive diagnosis [20]. Various techniques exist for guidance of the biopsy, and US and CT are the most commonly utilized modalities for biopsy guidance. When a biopsy is performed to diagnose or rule out malignancy in indeterminate lesions, the overall technical success rate under grayscale US guidance is 74%, which can be increased to 100% under CEUS guidance [21,22].

The percentage of tumor cells in the biopsy sample is greater with a higher number of collected biopsy samples [23]. Furthermore, for lesions not seen on grayscale US, the success rate for CEUS-guided biopsy can be as high as 88% to 96% [24,25]. US fusion with CT or MRI, can be used for percutaneous biopsy of lesions with poor sonographic conspicuity, with a 96% technical success rate [25]. Lesions that are isointense on CT can also present a challenge for CT-guided biopsy; however, use of anatomic landmarks or IV contrast can achieve an accuracy of 96% to 98% [26].

The image-guided biopsies carry a risk of postbiopsy bleeding that may be as high as 9% to 12%, particularly with hypervascular lesions [27,28]. In addition, a small risk of needle-track seeding exists. In patients with HCC, the rate of seeding is 0.1% to 0.7% [52-54].

Variant 4: Indeterminate, greater than 1 cm liver lesion on initial imaging with CT (noncontrast or single-phase) or noncontrast MRI. Known history of an extrahepatic malignancy.
G. RBC Scan Abdomen and Pelvis

There is no relevant literature to support the use of a Tc-99m RBC scan in this clinical scenario.

Variant 4: Indeterminate, greater than 1 cm liver lesion on initial imaging with CT (noncontrast or single-phase) or noncontrast MRI. Known history of an extrahepatic malignancy.
H. Liver Spleen Scan

There is no relevant literature to support the use of a Tc-99m sulfur colloid scan in this clinical scenario.

Variant 4: Indeterminate, greater than 1 cm liver lesion on initial imaging with CT (noncontrast or single-phase) or noncontrast MRI. Known history of an extrahepatic malignancy.
I. US Abdomen

Grayscale US is able to provide correct diagnosis in 68% of liver lesions [9]. For differentiation between malignant and benign lesions, US is correct in 86% of cases [9].

Variant 4: Indeterminate, greater than 1 cm liver lesion on initial imaging with CT (noncontrast or single-phase) or noncontrast MRI. Known history of an extrahepatic malignancy.
J. US Abdomen with Contrast

In noncirrhotic patients, the hypoechoic pattern in portal and sinusoidal phase (rapid wash-out) or the markedly hypoechoic or anechoic pattern in sinusoidal phase (marked late wash-out) showed a

sensitivity, specificity, and accuracy of 97%, 100%, and 98%, respectively, for the diagnosis of malignancy [37].

In a small retrospective study of patients with primary pancreatic adenocarcinoma, CT and CEUS have similar sensitivities for detection of metastases (73% versus 80%, respectively) [2]. However, CEUS is able to more accurately differentiate between an incidental benign lesion (eg, cysts, vascular shunts) from metastases, resulting in fewer false-positive diagnoses and therefore higher PPV (60% versus 92%) [2]. The accuracy of CEUS for diagnosis of metastases is 76% [35].

Variant 5: Incidental liver lesion, greater than 1 cm on US, noncontrast or single-phase CT, or noncontrast MRI. Known chronic liver disease.

Evaluation of liver lesions detected in a patient with chronic liver disease should be performed based on the algorithm set forth by the most recent version of LI-RADS [6,55].

Variant 5: Incidental liver lesion, greater than 1 cm on US, noncontrast or single-phase CT, or noncontrast MRI. Known chronic liver disease.
A. CT Abdomen

The sensitivity of a dual-phase contrast-enhanced CT for diagnosing a small HCC (<2 cm) is 53% [56]. In patients with chronic liver disease, triple-phase contrast-enhanced CT correctly characterizes lesions in 49% to 68% of cases and has a sensitivity of 61% to 73% for lesion detection [57]. Delayed phase wash-out on CT is important in HCC diagnosis [58]. For 1- to 2-cm lesions in patients with cirrhosis detected on screening US, the addition of noncontrast CT to dynamic postcontrast phases (CT without and with IV contrast) does not increase sensitivity or accuracy for HCC [59].

Variant 5: Incidental liver lesion, greater than 1 cm on US, noncontrast or single-phase CT, or noncontrast MRI. Known chronic liver disease.
B. FDG-PET/CT Skull Base to Mid-Thigh

FDG-PET/CT has a limited role in characterization of liver lesions in patients with parenchymal liver disease [6]. Once the diagnosis of HCC is established, tumor FDG activity may predict microvascular invasion [60].

Variant 5: Incidental liver lesion, greater than 1 cm on US, noncontrast or single-phase CT, or noncontrast MRI. Known chronic liver disease.
C. DOTATATE PET/CT Skull Base to Mid-Thigh

There is no relevant literature to support the use of Ga-68-DOTATATE PET/CT in this clinical scenario.

Variant 5: Incidental liver lesion, greater than 1 cm on US, noncontrast or single-phase CT, or noncontrast MRI. Known chronic liver disease.
D. Octreotide Scan with SPECT or SPECT/CT Chest and Abdomen

There is no relevant literature to support the use of In-111 somatostatin receptor scan with SPECT or SPECT/CT in this clinical scenario.

Variant 5: Incidental liver lesion, greater than 1 cm on US, noncontrast or single-phase CT, or noncontrast MRI. Known chronic liver disease.
E. MRI Abdomen

In patients with chronic liver disease, noncontrast MRI has a sensitivity of 46% to 59% for lesion detection; addition of postcontrast phases with gadoxetate increases sensitivity to 68% to 80%

[57]. Gadoxetate-enhanced MRI demonstrates a higher proportion of correctly characterized lesions (50%–72%) than noncontrast MRI (30%–50%) [57].

MRI with extracellular agents has a sensitivity of 78% to 83% and specificity of 100% [35,61]. Addition of HBP improves sensitivity and accuracy for nodules <2 cm [62]. The sensitivity of MRI with gadoxetate for diagnosing a small HCC (<2 cm) is 76% to 97% [56,63]. Addition of HBP improves detection of HCC and differentiation between HCC and dysplastic nodules [64,65]. Furthermore, addition of HBP improves sensitivity and accuracy for diagnosis of HCC, compared with the dynamic images alone [66,67]. Gadoxetate-enhanced MRI allows for correct characterization of liver lesions in 87% to 91% of cases [63]. However, the HBP on gadoxetate-enhanced MRI can be limited in the setting of poor liver function, and transient hepatic enhancement differences can cause artifacts in the HBP in cirrhotic patients [68,69].

In patients with chronic liver disease, the mean ADC values in benign solid lesions are higher than those in malignant lesions [70]. In small (<3 cm) lesions, presence of high signal intensity on both T2-weighted imaging and DWI helps differentiate atypical HCCs from dysplastic nodules, with the resultant sensitivity of 80%, specificity of 100%, PPV of 100%, and NPV of 78.3% [71]. For lesions <3 cm in patients with cirrhosis, the sensitivity and accuracy to differentiate the dysplastic nodule from HCC are 46% to 82% and 57% to 75%, respectively [72,73]. The addition of DWI to dynamic sequences improved its ability to distinguish between HCC and dysplastic nodules compared with dynamic sequences alone, with a resultant accuracy of 93% and sensitivity of 97% [73].

Variant 5: Incidental liver lesion, greater than 1 cm on US, noncontrast or single-phase CT, or noncontrast MRI. Known chronic liver disease.
F. Image-Guided Biopsy Liver

Biopsy plays a minor role in establishing the diagnosis of HCC because the imaging criteria of LI-RADS category 5 (definite HCC) can establish such diagnosis with nearly 100% specificity and PPV [6,74]. Biopsy may be necessary if the imaging features of the lesion do not meet the criteria for LI-RADS 5 (definite HCC) category or for molecular analysis to determine clinical trial eligibility or to guide treatment [74]. Overall risk of bleeding for image-guided biopsy can be as high as 12% [27]. An additional risk in biopsy of HCC is a risk of needle-tract seeding, with track seeding incidence being 2.7% overall and 0.1% to 0.9% per year [52-54,75].

Variant 5: Incidental liver lesion, greater than 1 cm on US, noncontrast or single-phase CT, or noncontrast MRI. Known chronic liver disease.
G. RBC Scan Abdomen and Pelvis

There is no relevant literature to support the use of a Tc-99m RBC scan in this clinical scenario.

Variant 5: Incidental liver lesion, greater than 1 cm on US, noncontrast or single-phase CT, or noncontrast MRI. Known chronic liver disease.
H. Liver Spleen Scan

There is no relevant literature to support the use of a Tc-99m sulfur colloid scan in this clinical scenario.

Variant 5: Incidental liver lesion, greater than 1 cm on US, noncontrast or single-phase CT, or noncontrast MRI. Known chronic liver disease.
I. US Abdomen with Contrast

For indeterminate liver lesions detected on US, CEUS can provide definitive diagnosis in 77% to

93% of cases and can distinguish between benign and malignant lesions in 89% to 96% of cases [31,32]. The sensitivity of CEUS for diagnosing a small HCC (<2 cm) is 68% compared with 53% for contrast-enhanced CT and 77% for gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid MRI in the same study [56]. Diagnostic accuracy of CEUS for HCC is 79% [35].

Assessment of nodule vascularity on CEUS can help determine the progression from regenerative nodules, dysplastic nodules and HCC in lesions measuring 1 to 3.5 cm [76]. For lesions <3 cm in patients with cirrhosis, the sensitivity and accuracy to differentiate the dysplastic nodule from HCC on CEUS are 59% and 67%, respectively [72]. For small nodules (1–2 cm) in cirrhosis, the sensitivity, specificity, and accuracy of CEUS for diagnosing HCC are 87%, 100%, and 93%, respectively [77].

On CEUS, HCC typically shows a global arterial hyperenhancement and a delayed contrast wash-out, whereas intrahepatic cholangiocarcinoma shows an initial contrast enhancement primarily at the tumor periphery followed by an early portal-venous contrast wash-out in the tumor center [78]. CEUS can accurately differentiate between intrahepatic cholangiocarcinoma and HCC [79].

Variant 6: Indeterminate, less than 1 cm liver lesion on initial imaging with US. Known history of an extrahepatic malignancy.

Variant 6: Indeterminate, less than 1 cm liver lesion on initial imaging with US. Known history of an extrahepatic malignancy.
A. CT Abdomen

Typically, resolution of CT does not allow for definitive characterization of lesions <1 cm. For instance, small hypervascular metastases may be difficult to distinguish from flash-filling hemangiomas [80]. However, between 78% and 84% of small (lesions ≤1 cm in diameter are deemed too small to characterize by the interpreting radiologist) hypodense lesions in patients with primary malignancy are benign [81-83].

CT of the abdomen with and without IV contrast is not recommended for this clinical scenario because there is no added value for unenhanced images.

Variant 6: Indeterminate, less than 1 cm liver lesion on initial imaging with US. Known history of an extrahepatic malignancy.
B. FDG-PET/CT Skull Base to Mid-Thigh

In patients with a history of primary malignancy, FDG-PET/CT may be indicated to evaluate for presence of metastases beyond the liver. Current literature does not support the use of FGD-PET/CT specifically to characterize subcentimeter liver lesions due to its limited sensitivity for lesions <1 cm.

Variant 6: Indeterminate, less than 1 cm liver lesion on initial imaging with US. Known history of an extrahepatic malignancy.
C. DOTATATE PET/CT Skull Base to Mid-Thigh

Ga-68-DOTATATE PET/CT is sensitive for detection of metastases in patients with primary NET; however, there is no relevant literature on assessment of subcentimeter liver lesions.

Variant 6: Indeterminate, less than 1 cm liver lesion on initial imaging with US. Known history of an extrahepatic malignancy.
D. Octreotide Scan with SPECT or SPECT/CT Chest and Abdomen

In patients with a history of primary NET, In-111 somatostatin receptor scan with SPECT or

SPECT/CT can detect liver metastases; however, there is no relevant literature to support the use of this procedure in characterization of subcentimeter liver lesions.

Variant 6: Indeterminate, less than 1 cm liver lesion on initial imaging with US. Known history of an extrahepatic malignancy.
E. MRI Abdomen

On MRI with gadoxetate, the combination of HBP and DWI has the highest accuracy for detection of subcentimeter liver lesions [15]. ADC values can help differentiate benign versus malignant subcentimeter liver lesions with 92% to 93% accuracy [84].

There is no relevant literature that has assessed the performance of MRI without IV contrast specifically for this clinical scenario. Therefore, the committee recommendations on the use of MRI without IV contrast are based primarily on expert opinion. In some cases, MRI without IV contrast may be appropriate as it can differentiate between small cysts and solid lesions.

Variant 6: Indeterminate, less than 1 cm liver lesion on initial imaging with US. Known history of an extrahepatic malignancy.
F. Image-Guided Biopsy Liver

Tissue sampling may be necessary to establish the definitive diagnosis in patients with a history of primary malignancy and indeterminate subcentimeter liver lesions. However, the role of percutaneous biopsy is limited in the evaluation of subcentimeter liver lesions because such lesions are typically difficult to target under image guidance. Furthermore, there is no relevant literature to assess performance of percutaneous biopsy techniques for subcentimeter liver lesions.

Variant 6: Indeterminate, less than 1 cm liver lesion on initial imaging with US. Known history of an extrahepatic malignancy.
G. RBC Scan Abdomen and Pelvis

There is no relevant literature to support the use of a Tc-99m RBC scan in this clinical scenario.

Variant 6: Indeterminate, less than 1 cm liver lesion on initial imaging with US. Known history of an extrahepatic malignancy.
H. Liver Spleen Scan

There is no relevant literature to support the use of a Tc-99m sulfur colloid scan in this clinical scenario.

Variant 6: Indeterminate, less than 1 cm liver lesion on initial imaging with US. Known history of an extrahepatic malignancy.
I. US Abdomen with Contrast

Compared with a baseline grayscale US, CEUS can detect 6.5 times more subcentimeter metastases [9]. For indeterminate liver lesions discovered on grayscale US, CEUS reached a specific diagnosis in 83% of cases and distinguished benign versus malignant in 90% of cases [30]. For the benign diagnoses, CEUS correctly characterized 89% of areas of focal fat, 90% of hemangiomas, 87% of complex cysts, 78% of hepatic adenomas, 90% of FNHs, 86% of abscesses, and 60% of hematomas [30]. CEUS correctly characterized 86% of metastases [30].

Variant 7: Indeterminate, less than 1 cm liver lesion on initial imaging with CT (noncontrast or single-phase) or noncontrast MRI. Known history of an extrahepatic malignancy.

Variant 7: Indeterminate, less than 1 cm liver lesion on initial imaging with CT (noncontrast or single-phase) or noncontrast MRI. Known history of an extrahepatic malignancy.

A. CT Abdomen

Subcentimeter liver lesions in patients with primary malignancy are seen on contrast-enhanced CT in 13% of patients, and of these, 12% are metastases [82]. Among patients with a history of colorectal and breast cancers, small hepatic lesions were metastatic in 14% and 22% of cases, respectively [82]. Subcentimeter liver lesions in women with breast cancer can be found in 29%, and if no obvious liver metastases are present, 93% to 97% of these subcentimeter liver lesions are benign [85].

CT of the abdomen with and without IV contrast is not recommended for this clinical scenario because there is no added value for unenhanced images.

Variant 7: Indeterminate, less than 1 cm liver lesion on initial imaging with CT (noncontrast or single-phase) or noncontrast MRI. Known history of an extrahepatic malignancy.
B. FDG-PET/CT Skull Base to Mid-Thigh

In patients with a history of primary malignancy, FDG-PET/CT may be indicated to evaluate for the presence of metastases beyond the liver. There is no relevant literature to support the use of FDG-PET/CT specifically to characterize subcentimeter liver lesions due to its limited sensitivity for lesions <1 cm.

Variant 7: Indeterminate, less than 1 cm liver lesion on initial imaging with CT (noncontrast or single-phase) or noncontrast MRI. Known history of an extrahepatic malignancy.
C. DOTATATE PET/CT Skull Base to Mid-Thigh

Ga-68-DOTATATE PET/CT is sensitive for detection of metastases in patients with primary NET; however, there is no relevant literature on assessment of subcentimeter liver lesions.

Variant 7: Indeterminate, less than 1 cm liver lesion on initial imaging with CT (noncontrast or single-phase) or noncontrast MRI. Known history of an extrahepatic malignancy.
D. Octreotide Scan with SPECT or SPECT/CT Chest and Abdomen

In patients with a history of primary NET, In-111 somatostatin receptor scan with SPECT or SPECT/CT can detect liver metastases; however, there is no relevant literature on assessment of subcentimeter liver lesions.

Variant 7: Indeterminate, less than 1 cm liver lesion on initial imaging with CT (noncontrast or single-phase) or noncontrast MRI. Known history of an extrahepatic malignancy.
E. MRI Abdomen

For subcentimeter liver lesions detected on CT, the sensitivity, specificity, PPV, and NPV for differentiation of benign from malignant lesions for contrast-enhanced MRI are 83%, 98%, 92%, and 94%, respectively [86]. In patients with a history of colon cancer, MRI has a sensitivity of 60% for detection of subcentimeter metastases [87].

There is no relevant literature that has assessed the performance of MRI without IV contrast specifically for this clinical scenario. Therefore, the committee recommendations on the use of MRI without IV contrast are based primarily on expert opinion.

Variant 7: Indeterminate, less than 1 cm liver lesion on initial imaging with CT (noncontrast or single-phase) or noncontrast MRI. Known history of an extrahepatic malignancy.
F. Image-Guided Biopsy Liver

Tissue sampling may be necessary to establish the definitive diagnosis in patients with a history of primary malignancy and indeterminate subcentimeter liver lesions. However, the role of

percutaneous biopsy is limited in the evaluation of subcentimeter liver lesions because such lesions are typically difficult to target under image guidance. Furthermore, published data are not available to assess performance of percutaneous biopsy techniques for subcentimeter liver lesions.

Variant 7: Indeterminate, less than 1 cm liver lesion on initial imaging with CT (noncontrast or single-phase) or noncontrast MRI. Known history of an extrahepatic malignancy.
G. RBC Scan Abdomen and Pelvis

There is no relevant literature to support the use of a Tc-99m RBC scan in this clinical scenario.

Variant 7: Indeterminate, less than 1 cm liver lesion on initial imaging with CT (noncontrast or single-phase) or noncontrast MRI. Known history of an extrahepatic malignancy.
H. Liver Spleen Scan

There is no relevant literature to support the use of a Tc-99m sulfur colloid scan in this clinical scenario.

Variant 7: Indeterminate, less than 1 cm liver lesion on initial imaging with CT (noncontrast or single-phase) or noncontrast MRI. Known history of an extrahepatic malignancy.
I. US Abdomen

In patients with a history of primary malignancy and indeterminate, subcentimeter focal liver lesions on CT, grayscale US is able to prove cystic nature of the lesion in 67% of cases [88].

Variant 7: Indeterminate, less than 1 cm liver lesion on initial imaging with CT (noncontrast or single-phase) or noncontrast MRI. Known history of an extrahepatic malignancy.
J. US Abdomen with Contrast

In patients with a history of primary malignancy and indeterminate, subcentimeter focal liver lesions on CT that were proven to be noncystic on grayscale US, CEUS correctly characterizes 95% of lesions overall, and 98% of metastases [88]. Compared with a baseline dual-phase contrast-enhanced CT, CEUS can detect 6.5 times more subcentimeter metastases [9].

Variant 8: Incidental liver lesion, less than 1 cm on US, noncontrast or single-phase CT, or noncontrast MRI. Known chronic liver disease.

Evaluation of liver lesions detected in a patient with chronic liver disease should be performed based on the algorithm set forth by the most recent version of LI-RADS [6,55]. Please note that a size ≥10 mm is required for definitive diagnosis of HCC [89].

Variant 8: Incidental liver lesion, less than 1 cm on US, noncontrast or single-phase CT, or noncontrast MRI. Known chronic liver disease.
A. CT Abdomen

If imaging assessment is desired in this clinical scenario, multiphase CT is appropriate, per LI-RADS technical recommendations. Triple-phase contrast-enhanced CT has a sensitivity of 26% to 47% for detection of subcentimeter liver lesions in patients with chronic liver disease [57]. Contrast-enhanced CT has an accuracy of 60%, sensitivity of 56%, and specificity of 67% for diagnosing HCC ≤1 cm [90].

CT of the abdomen with and without IV contrast is not recommended for this clinical scenario because there is no added value for unenhanced images.

Variant 8: Incidental liver lesion, less than 1 cm on US, noncontrast or single-phase CT, or noncontrast MRI. Known chronic liver disease.
B. FDG-PET/CT Skull Base to Mid-Thigh

There is no relevant literature to support the use of FDG-PET/CT in this clinical scenario.

Variant 8: Incidental liver lesion, less than 1 cm on US, noncontrast or single-phase CT, or noncontrast MRI. Known chronic liver disease.
C. DOTATATE PET/CT Skull Base to Mid-Thigh

There is no relevant literature to support the use of Ga-68-DOTATATE PET/CT in this clinical scenario.

Variant 8: Incidental liver lesion, less than 1 cm on US, noncontrast or single-phase CT, or noncontrast MRI. Known chronic liver disease.
D. Octreotide Scan with SPECT or SPECT/CT Chest and Abdomen

There is no relevant literature to support the use of In-111 somatostatin receptor scan with SPECT or SPECT/CT in this clinical scenario.

Variant 8: Incidental liver lesion, less than 1 cm on US, noncontrast or single-phase CT, or noncontrast MRI. Known chronic liver disease.
E. MRI Abdomen

Dynamic MRI has an accuracy of 66%, sensitivity of 58% to 91%, and specificity of 29% for diagnosing HCC ≤1 cm [90,91]. Gadoxetate-enhanced MRI is superior for detection of subcentimeter liver lesions compared with triple-phase contrast-enhanced CT, with the sensitivities of 38% to 55% versus 26% to 47%, respectively [57]. Addition of HBP can improve the detection of HCCs <1 cm from 85% to 96% [67].

There is no relevant literature that has assessed the performance of MRI without IV contrast specifically for this clinical scenario. Therefore, the committee recommendations on the use of MRI without IV contrast are based primarily on expert opinion.

Variant 8: Incidental liver lesion, less than 1 cm on US, noncontrast or single-phase CT, or noncontrast MRI. Known chronic liver disease.
F. Image-Guided Biopsy Liver

As with other liver lesions, percutaneous biopsy of small HCCs may be technically challenging. In small HCCs (≤20 mm), the initial biopsy is diagnostic in 70% of cases [92]. There is no relevant literature evaluating percutaneous biopsy for subcentimeter liver lesions. Even after a successful biopsy, the interpretation of the pathology specimen may not be straightforward, with the overwhelming diagnostic challenge for hypovascular liver nodules on pathology being the differentiation of high-grade dysplastic nodules from well-differentiated small HCC [93]. Overall risk of bleeding for image-guided biopsy is as high as 12% [27]. An additional risk in the biopsy of HCCs is the risk of needle-tract seeding, with track seeding incidence of 2.7% overall and 0.1% to 0.9% per year [52-54,75].

Variant 8: Incidental liver lesion, less than 1 cm on US, noncontrast or single-phase CT, or noncontrast MRI. Known chronic liver disease.
G. RBC Scan Abdomen and Pelvis

There is no relevant literature to support the use of a Tc-99m RBC scan in this clinical scenario.

Variant 8: Incidental liver lesion, less than 1 cm on US, noncontrast or single-phase CT, or noncontrast MRI. Known chronic liver disease.
H. Liver Spleen Scan

There is no relevant literature to support the use of a Tc-99m sulfur colloid scan in this clinical

scenario.

Variant 8: Incidental liver lesion, less than 1 cm on US, noncontrast or single-phase CT, or noncontrast MRI. Known chronic liver disease.
I. US Abdomen with Contrast

For indeterminate liver lesions discovered on US, CEUS reached a specific diagnosis in 83% and distinguished benign versus malignant in 90% of cases [30]. For the benign diagnoses, CEUS correctly characterized 89% of areas of focal fat, 90% of hemangiomas, 87% of complex cysts, 78% hepatic adenomas, 90% of FNHs, 86% of abscesses, and 60% of hematomas [30]. CEUS correctly characterized 76% of HCCs and 25% of intrahepatic cholangiocarcinomas [30]. CEUS can distinguish between HCC and FNH with 82% accuracy and 87% sensitivity [94].

Summary of Recommendations

- **Variant 1:** CT abdomen with IV contrast multiphase, MRI abdomen without and with IV contrast, or US abdomen with IV contrast is usually appropriate for the imaging of an indeterminate >1 cm liver lesion on initial imaging with US in a normal liver with no suspicion or evidence of extrahepatic malignancy or underlying liver disease. These procedures are equivalent alternatives (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient's care).
- **Variant 2:** CT abdomen and pelvis with IV contrast multiphase or MRI abdomen without and with IV contrast is usually appropriate for the imaging of an indeterminate >1 cm liver lesion on initial imaging with CT (noncontrast or single-phase) or noncontrast MRI in a normal liver with no suspicion or evidence of extrahepatic malignancy or underlying liver disease. These procedures are equivalent alternatives (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient's care). The panel did not agree on recommending US abdomen in patients in this clinical scenario. There is insufficient medical literature to conclude whether or not these patients would benefit from this procedure. This procedure is controversial but may be appropriate.
- **Variant 3:** MRI abdomen without and with IV contrast or CT abdomen with IV contrast multiphase is usually appropriate for the imaging of an indeterminate >1 cm liver lesion on initial imaging with US for patients with a known history of an extrahepatic malignancy. These procedures are equivalent alternatives (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient's care).
- **Variant 4:** MRI abdomen without and with IV contrast, CT abdomen with IV multiphase, or FDG-PET/CT skull base to mid-thigh is usually appropriate for the imaging of an indeterminate >1 cm liver lesion on initial imaging with CT (noncontrast or single-phase) or noncontrast MRI in patients with a known history of an extrahepatic malignancy. These procedures are equivalent alternatives (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient's care).
- **Variant 5:** MRI abdomen without and with IV contrast, CT abdomen with IV contrast multiphase, or US abdomen with IV contrast is usually appropriate for the imaging of an incidental liver lesion >1 cm on US, noncontrast, or single-phase CT, or noncontrast MRI in patients with known chronic liver disease. These procedures are equivalent alternatives (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient's care).
- **Variant 6:** MRI abdomen without and with IV contrast is usually appropriate for the imaging

of an indeterminate <1 cm liver lesion on initial imaging with US in patients with a known history of an extrahepatic malignancy.

- **Variant 7:** MRI abdomen without and with IV contrast or CT abdomen with IV contrast multiphase is usually appropriate for the imaging of an indeterminate <1 cm liver lesion on initial imaging with CT (noncontrast or single-phase) or noncontrast MRI in patients with a known history of an extra hepatic malignancy. These procedures are equivalent alternatives (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient's care).
- **Variant 8:** MRI abdomen without and with IV contrast or CT abdomen with IV contrast multiphase is usually appropriate for the imaging of an incidental liver lesion <1 cm on US, noncontrast or single-phase CT or noncontrast MRI in patients with known chronic liver disease. These procedures are equivalent alternatives (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient's care).

Supporting Documents

The evidence table, literature search, and appendix for this topic are available at https://acsearch.acr.org/list. The appendix includes the strength of evidence assessment and the final rating round tabulations for each recommendation.

For additional information on the Appropriateness Criteria methodology and other supporting documents, please go to the ACR website at https://www.acr.org/Clinical-Resources/Clinical-Tools-and-Reference/Appropriateness-Criteria.

Appropriateness Category Names and Definitions

Appropriateness Category Name	Appropriateness Rating	Appropriateness Category Definition
Usually Appropriate	7, 8, or 9	The imaging procedure or treatment is indicated in the specified clinical scenarios at a favorable risk-benefit ratio for patients.
May Be Appropriate	4, 5, or 6	The imaging procedure or treatment may be indicated in the specified clinical scenarios as an alternative to imaging procedures or treatments with a more favorable risk-benefit ratio, or the risk-benefit ratio for patients is equivocal.
May Be Appropriate (Disagreement)	5	The individual ratings are too dispersed from the panel median. The different label provides transparency regarding the panel's recommendation. "May be appropriate" is the rating category and a rating of 5 is assigned.
Usually Not Appropriate	1, 2, or 3	The imaging procedure or treatment is unlikely to be indicated in the specified clinical scenarios, or the risk-benefit ratio for patients is likely to be unfavorable.

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, because of both 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 with 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 [95].

Relative Radiation Level Designations		
Relative Radiation Level*	**Adult Effective Dose Estimate Range**	**Pediatric Effective Dose Estimate Range**
O	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."		

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Disclaimer

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.

[a]Montefiore Medical Center, Bronx, New York. [b]Northwestern University, Chicago, Illinois. [c]Panel Chair, Johns Hopkins University School of Medicine, Baltimore, Maryland. [d]University of Arizona, Banner University Medical Center, Tucson, Arizona. [e]Duke University Medical Center, Durham, North Carolina. [f]University of Texas Health Science Center at Houston and McGovern Medical School, Houston, Texas; American Gastroenterological Association. [g]Interventional Endoscopy and Pancreatic Diseases, New Haven, Connecticut; American Gastroenterological Association. [h]UMass Medical School, Worcester, Massachusetts. [i]University of Florida College of Medicine, Gainesville,

Florida. [j]Rush University Medical Center, Chicago, Illinois; American College of Surgeons. [k]New York University Medical Center, New York, New York. [l]Stanford University Medical Center, Stanford, California. [m]University of Alabama Medical Center, Birmingham, Alabama. [n]University of Alabama Medical Center, Birmingham, Alabama. [o]Johns Hopkins Bayview Medical Center, Baltimore, Maryland; Commission on Nuclear Medicine and Molecular Imaging. [p]University of Illinois College of Medicine, Chicago, Illinois; American College of Physicians. [q]Johns Hopkins Hospital, Baltimore, Maryland. [r]Specialty Chair, Virginia Commonwealth University Medical Center, Richmond, Virginia.