

**American College of Radiology
ACR Appropriateness Criteria®**

Clinical Condition: Suspected Liver Metastases

Variant 1: Initial imaging test following detection of primary tumor.

Radiologic Procedure	Rating	Comments	<u>RRL*</u>
CT abdomen with contrast	8	Images are acquired during PVP. HAP imaging is useful for patients with a hypervascular primary tumor such as (but not limited to) renal cell, pancreatic islet cell, and thyroid carcinoma; carcinoid and other neuroendocrine tumors; and melanoma.	Med
MRI abdomen with contrast	7	Dynamic gadolinium-chelate-enhanced imaging is used most commonly. Delayed imaging after SPIO or gadolinium-BOPTA-enhanced imaging can be useful for staging patients with liver metastases. See comments regarding contrast in text under "Anticipated Exceptions."	None
FDG-PET whole body	6		High
CT abdomen without contrast	4		Med
MRI abdomen without contrast	4		None
US abdomen with or without Doppler	4		None
CT arterial portography liver	2		Med
CTA abdomen	2		Med
NUC In-111 somatostatin receptor scintigraphy	2	May be useful in patients with neuroendocrine tumors.	High
Rating Scale: 1=Least appropriate, 9=Most appropriate			*Relative Radiation Level

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Clinical Condition:**Suspected Liver Metastases****Variant 2:****Surveillance following treatment of primary tumor.**

Radiologic Procedure	Rating	Comments	<u>RRL*</u>
CT abdomen with contrast	8	Images are acquired during PVP. HAP imaging is useful for patients with a hypervascular primary tumor such as (but not limited to) renal cell, pancreatic islet cell, and thyroid carcinoma; carcinoid and other neuroendocrine tumors; and melanoma.	Med
MRI abdomen with contrast	7	Dynamic gadolinium-chelate-enhanced imaging is used most commonly. Delayed imaging after SPIO or gadolinium-BOPTA-enhanced imaging can be useful for staging patients with liver metastases. See comments regarding contrast in text under "Anticipated Exceptions."	None
FDG-PET whole body	6		High
CT abdomen without contrast	4		Med
MRI abdomen without contrast	4		None
US abdomen with or without Doppler	4		None
NUC In-111 somatostatin receptor scintigraphy	4	May be useful in patients with neuroendocrine tumors.	High
CT arterial portography liver	2		Med
CTA abdomen	2		Med
Rating Scale: 1=Least appropriate, 9=Most appropriate			*Relative Radiation Level

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Clinical Condition:**Suspected Liver Metastases****Variant 3:****Abnormal surveillance US, CT, or MRI, in PVP: high suspicion of malignancy.**

Radiologic Procedure	Rating	Comments	<u>RRL*</u>
INV percutaneous biopsy liver	8		IP
CT abdomen with contrast	8	Images are acquired during PVP. HAP imaging is useful for patients with a hypervascular primary tumor such as (but not limited to) renal cell, pancreatic islet cell, and thyroid carcinoma; carcinoid and other neuroendocrine tumors; and melanoma.	Med
MRI abdomen with contrast	8	Dynamic gadolinium-chelate-enhanced imaging is used most commonly. Delayed imaging after SPIO or gadolinium-BOPTA-enhanced imaging can be useful for staging patients with liver metastases. See comments regarding contrast in text under "Anticipated Exceptions."	None
FDG-PET whole body	8		High
MRI abdomen without contrast	4		None
US abdomen with or without Doppler	4		None
US abdomen intraoperative/laparoscopic	4		None
NUC In-111 somatostatin receptor scintigraphy	3	May be useful in patients with neuroendocrine tumors.	High
CT arterial portography liver	3		Med
CTA abdomen	3		Med
CT abdomen without contrast	2		Med
<u>Rating Scale:</u> 1=Least appropriate, 9=Most appropriate			*Relative Radiation Level

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Clinical Condition:**Suspected Liver Metastases****Variant 4:****Abnormal surveillance US, CT, or MRI in PVP: high suspicion of benignancy.**

Radiologic Procedure	Rating	Comments	RRL*
MRI abdomen with contrast	8	Dynamic gadolinium-chelate-enhanced imaging is used most commonly. Delayed imaging after SPIO or gadolinium-BOPTA-enhanced imaging can be useful for staging patients with liver metastases. See comments regarding contrast in text under "Anticipated Exceptions."	None
CT abdomen with contrast	8	Images are acquired during PVP. HAP imaging is useful for patients with a hypervascular primary tumor such as (but not limited to) renal cell, pancreatic islet cell, and thyroid carcinoma; carcinoid and other neuroendocrine tumors; and melanoma.	Med
MRI abdomen without contrast	5		None
INV percutaneous biopsy liver	4		IP
US abdomen with or without Doppler	4		None
NUC In-111 somatostatin receptor scintigraphy	3	May be useful in patients with neuroendocrine tumors.	High
CT arterial portography liver	3		Med
CTA abdomen	3		Med
US abdomen intraoperative/laparoscopic	3		None
FDG-PET whole body	2		High
CT abdomen without contrast	2		Med
Rating Scale: 1=Least appropriate, 9=Most appropriate			*Relative Radiation Level

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SUSPECTED LIVER METASTASES

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Summary of Literature Review

In the United States, metastatic disease is the most common cause of malignancy in the liver and is 20 to 50 times more common than primary liver cancer. The colon, stomach, pancreas, and breast are the most common primary sites. The appearance of a new lesion in the liver in a patient with a history of cancer strongly suggests hepatic metastasis. On the other hand, most small (1-1.5 cm) liver lesions, even in patients with known malignancy, are not malignant, especially if there are fewer than five lesions [1,2]. In most series, about one-third of patients who die with a malignancy have liver involvement.

The liver is susceptible to metastatic disease primarily due to the nature of the endothelial lining. The dual blood supply to the liver has an effect on the vascularity of liver metastases, with those supplied by the hepatic arterial system being more vascular than those supplied by the portal venous system. Most gastrointestinal cancer is spread through the portal venous system, whereas other tumors are spread through the hepatic arterial system [3]. Numerous imaging methods are available for detecting intrahepatic metastatic disease before, during, and after definitive therapy for the primary lesion. The usefulness of various imaging tests can vary significantly across institutions because of local radiological expertise, availability of equipment or personnel, and the wishes and biases of treating physicians and radiologists.

This document will review the broad variety of available imaging tests so that each can be rated by the consensus panel, realizing that many published scientific studies do not compare all imaging tests at the current state of the art [4,5].

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Ultrasound

Ultrasound (US) is the most available technique for liver imaging worldwide, and in many countries is the major imaging test used to search for liver metastases. In the United States, the relative availability of computed tomography (CT) and magnetic resonance imaging (MRI), limited physician involvement in the performance of US, and the lack of availability of US contrast agents contribute to a lesser role for US diagnosis. In the United States pretreatment and post-treatment screening for metastases is performed infrequently with US. Comparative studies demonstrate that unenhanced grey-scale US has high specificity but lower sensitivity than CT and MRI [4-6]. With US, metastases can be hypochoic, hyperechoic, cystic, or diffuse. Doppler may be useful, particularly in vascular lesions such as neuroendocrine tumors, sarcomas, and lymphomas.

Intraoperative/Laparoscopic Ultrasound

Intraoperative ultrasound (IOUS) is the most accurate imaging technique for detecting liver metastases at the time of primary tumor resection or resection of previously identified hepatic metastases. It is complementary to surgical inspection and palpation. Additionally, IOUS can be important for localization of tumors for ablative techniques or to guide intraoperative biopsy or surgical resection [4,5,7,8].

Laparoscopic US (LUS), an alternative to open IOUS, has shown promising results. In one study of 55 patients with primary and secondary liver neoplasms who underwent LUS as part of a tumor ablation procedure, LUS demonstrated all 201 liver tumors shown by triphasic CT and an additional 21 lesions not shown by CT [9].

Computed Tomography

CT is particularly suited for the evaluation of metastatic disease, because the liver and potential extrahepatic sites of tumor spread can be evaluated during the same examination. Multidetector helical CT (MDCT) is the preferred examination in the United States for surveillance for metastatic disease after treatment of the primary neoplasm. Because most hepatic metastases are relatively hypovascular compared with normal liver parenchyma, the lesions are hypoattenuating when imaged during the peak of hepatic parenchymal enhancement (portal venous phase). In general, therefore, imaging during the portal venous phase of hepatic enhancement is adequate to detect most hepatic lesions in most patients [10-12].

Hypervascular lesions are less common, and tumors in this group include metastases from renal cell carcinoma, carcinoid, islet cell carcinoma, thyroid carcinoma, melanoma, and neuroendocrine tumors. In a large series

of patients, small (<2 cm) hypervascular lesions were seen better in the arterial phase than in the portal venous phase [10]. With the widespread use of multidetector-row scanners, arterial phase scanning can be routine. Although metastases from breast carcinoma are sometimes hypervascular, two studies showed that arterial phase imaging was not necessary in this group [10,12]. Hypervascular lesions may be isoattenuating to liver during the portal venous phase of hepatic enhancement. With helical CT, both arterial and portal venous phase imaging is recommended for patients with hypervascular primary tumors. If helical CT is not available, a noncontrast scan can also be useful [13].

CT arterial portography is no longer used extensively, as it is an invasive angiographic technique that often yields confusing artifacts that decrease accuracy [4-6,13]. Newer arterial mapping techniques using MRI and CT angiography have largely replaced standard angiographic techniques for preoperative staging.

Magnetic Resonance Imaging

With MRI, most hepatic metastases are hypointense to normal liver on T1-weighted images and hyperintense to liver on T2-weighted images. Morphologic, signal intensity, and contrast enhancement features have been shown to be useful in distinguishing metastatic lesions from common benign lesions such as hemangiomas and cysts.

Contrast-enhanced imaging is an important part of the hepatic MRI examination for detection of metastases and is particularly useful in characterizing hepatic lesions that are identified. Gadolinium chelates, which are the most widely used MR contrast agents, are most useful when used with dynamic T1-weighted gradient echo sequences. Gadolinium-enhanced MRI and dynamic contrast-enhanced CT are comparable in their ability to identify patients with hepatic metastases. Most comparative studies, however, have shown MRI to be somewhat more sensitive than contrast-enhanced CT for detecting individual hepatic metastases [14-16], although comparative studies using state-of-the-art MDCT scanners are lacking. MRI using superparamagnetic iron oxide (SPIO) contrast agents, which are taken up selectively by the reticuloendothelial system, has been shown to be more sensitive than unenhanced MRI and equal to or more sensitive than gadolinium-enhanced MRI [17,18]. In one study SPIO-enhanced MRI also was more sensitive than 16-row MDCT for detecting liver metastases [19]. Delayed phase imaging during gadobenate dimeglumine (GD-BOPTA)-enhanced MRI [17] and mangafodipir trisodium (Mn-DPDP)-enhanced MRI [20,21] have been shown to be equivalent to SPIO-enhanced MRI for detecting liver metastases, but mangafodipir currently is not available in the United States.

Nuclear Imaging

Positron emission tomography (PET) has become more widely used in detecting metastatic disease. Two meta-analyses comparing CT, MRI, and 18F fluorodeoxyglucose (FDG) PET in patients with cancers of the gastrointestinal tract concluded that FDG-PET is the most sensitive imaging test for distinguishing hepatic metastases from colorectal cancer [22,23]. In addition, several studies have demonstrated that the addition of FDG-PET to a conventional staging evaluation in colorectal cancer patients with potentially resectable liver metastases results in a change in management of 20%-32%, mainly due to detection of unknown extrahepatic disease. PET also has been shown to be accurate in distinguishing benign from malignant liver tumors. A limitation of FDG-PET, however, is that it may fail to demonstrate small (<1 cm) liver metastases [24-27]. In addition, the sensitivity of FDG-PET for demonstrating hepatic metastases from colorectal cancer is reduced in patients who have undergone recent chemotherapy [28]. For staging and restaging patients with colorectal liver metastases, integration of CT and FDG-PET data, either by fusion or by integrated PET-CT imaging, enables better management guidance than with either technique alone.

Traditional reticulo-endothelial radionuclide imaging is no longer used for detecting liver metastases. Somatostatin receptor scintigraphy is capable of demonstrating hepatic metastases from endocrine tumors but is not as sensitive as CT and MRI [29].

Summary

Many radiologic techniques are available for preoperative detection of liver metastases and postoperative surveillance. Some of the less widely used screening techniques can be useful when there is a need for specific problem solving. Rapid technological and clinical advances in equipment, contrast agents, and radioisotopes make direct comparison of the various techniques difficult. In addition, local custom and equipment availability within communities or medical centers can be expected to lead to a variety of indications and applications in detecting hepatic metastatic disease.

Anticipated Exceptions

Nephrogenic systemic fibrosis (NSF), also known as nephrogenic fibrosing dermopathy) was first identified in 1997 and has recently generated substantial concern among radiologists, referring doctors and lay people. Until the last few years, gadolinium-based MR contrast agents were widely believed to be almost universally well tolerated, extremely safe and non-nephrotoxic, even when used in patients with impaired renal function. All available experience suggests that these agents remain generally very safe, but recently some patients with renal failure who have been exposed to gadolinium contrast

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agents (the percentage is unclear) have developed NSF [30-32], a syndrome that can be fatal. Further studies are necessary to determine what the exact relationships are between gadolinium-containing contrast agents, their specific components and stoichiometry, patient renal function and NSF. Current theory links the development of NSF to the administration of relatively high doses (eg, >0.2mM/kg) and to agents in which the gadolinium is least strongly chelated. The FDA has recently issued a “black box” warning concerning these contrast agents (http://www.fda.gov/cder/drug/InfoSheets/HCP/gcca_200705HCP.pdf).

This warning recommends that, until further information is available, gadolinium contrast agents should not be administered to patients with either acute or significant chronic kidney disease (estimated GFR <30 mL/min/1.73m²), recent liver or kidney transplant or hepato-renal syndrome, unless a risk-benefit assessment suggests that the benefit of administration in the particular patient clearly outweighs the potential risk(s) [31].

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. 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*	Effective Dose Estimate Range
None	0
Minimal	< 0.1 mSv
Low	0.1-1 mSv
Medium	1-10 mSv
High	10-100 mSv
*RRL assignments are not included for some examinations. The RRL assignments for the IP (in progress) exams will be available in future releases.	

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