The capabilities and limitations of imaging techniques for the liver, including ultrasound, CT, MRI, and nuclear medicine, are reviewed, with an emphasis on their role in hepatocellular carcinoma.

Imaging of the Liver for Hepatocellular Cancer

Eric K. Outwater, MD

Background: Imaging of the liver is a key component in the detection, diagnosis, management, and follow-up of patients with hepatocellular carcinoma. Methods: The author uses his own experience as well as a review of pertinent literature to describe the capabilities and the limitations of the principal currently available imaging techniques for the liver. Results: Ultrasound is widely available, but sensitivity and specificity for small nodules are limited. Computed tomography effectively demonstrates extrabiliary lesions and can differentiate between cysts or hemangiomas and hepatocellular carcinomas. Magnetic resonance imaging better characterizes hepatic lesions, but positron emission tomography is of limited value. Conclusions: Cross-sectional imaging with ultrasound, CT, or MRI is critical for nodule characterization in the cirrhotic liver, surgical planning of HCC, and treatment response evaluation.

Introduction

Current technologies provide a wide range of possibilities for liver imaging, chief among them being computed tomography (CT), ultrasound, and magnetic resonance imaging (MRI). Advanced imaging research is focused on expanding the range of options from largely anatomical techniques — ultrasound and CT — to techniques that focus on tissue characterization and physiology — MRI, spectroscopy, specialized MRI contrast agents, positron emission tomography (PET) agents, and new techniques such as hyperpolarized MRI. These newer techniques will probe physiologic functions of tumors and other abnormal tissues and will guide treatment by customizing patient treatment based on specific tumor characteristics. They image such diverse physiological processes such as receptor function, pyruvate/lactate metabolism, apoptosis, oxygen levels, diffusion, and perfusion. This review focuses on current techniques for liver imaging, with an emphasis on hepatocellular carcinoma (HCC). It also highlights newer imaging techniques in nuclear medicine and MRI.

Ultrasound of the Liver

Ultrasound is a fundamental technique for imaging the liver, biliary tree, and gallbladder. Its advantages are speed and simplicity. Its disadvantages, which include somewhat limited resolution for small liver lesions and limitations of specificity of conventional ultrasound, can be overcome with the use of ultrasound contrast agents. Ultrasound is a basic technique for image-guided procedures such as biopsy and ablation (Fig 1). When the transducer is applied directly to the liver during an operation, the highest resolution is obtained, and this technique is generally more sensitive than CT or MRI for small liver lesions (Fig 2).
Several transducer frequencies are used to image the liver. The transducer is the hand-held device that transmits and receives the ultrasound signals used to reconstruct the image. Typically 3 to 5 MHz transducers are used for imaging the liver. Higher-frequency transducers can be used when they are directly applied to the liver in the operating room (Fig 2). Lower-frequency transducers scan image more deeply into the body, whereas higher-frequency transducers image with higher resolution. Lower-frequency transducers — necessarily lower resolution — are needed to image deeper structures and are necessary for large or obese patients.

Doppler ultrasound images flow and register speed by using the Doppler principle to measure direction and velocity of flow by the higher or lower frequency of ultrasound shifts received from moving fluid. The technique can be used to measure the spectral frequencies of flow as in pulsed-wave Doppler or to map velocity and direction of flow as in color Doppler imaging. Power Doppler imaging is another technique to map flow in an image. Power Doppler registers the amplitude of the Doppler shift rather than the velocity. This technique is more sensitive than color Doppler imaging for registering flow in tumors.

Contrast agents can also be used in ultrasound, similar to contrast agents given for CT or MRI. These agents are injected while imaging the liver or a selected part of the liver to register the arrival of the contrast agents in the liver or tumor. Many kinds of ultrasound contrast agents have been devised, most involving the use of coated microbubbles as an acoustic reflector. These agents appear echogenic on the ultrasound image. They can increase the sensitivity of the image for color flow mapping and power Doppler imaging. Contrast agents can increase the sensitivity and specificity of the examination for the diagnosis of HCC and dysplastic nodules. Hypervascularity in these tumors can be shown and graded after administration of the contrast agent. The grading of the vascularity in HCC corresponds with the vessel intensity as seen on angiography. Characterization of HCC on cirrhosis is now possible only with contrast-enhanced ultrasound (CEUS) for nodules > 2 cm in diameter when enhancement of the lesion is seen during arterial phase with washout during the portal phase. For nodules from 1 to 2 cm in diameter, a specific diagnosis of HCC in the cirrhotic liver can be established when two dynamic imaging modalities (CEUS, enhanced CT, and/or MRI) are coincident without the need of liver biopsy.

Ultrasound is an invaluable tool for real-time guidance of interventional procedures in the liver. Specifically, biopsy, percutaneous ethanol injection, and radiofrequency ablation procedures can be performed under ultrasound guidance (Fig 1). When applied as open procedures in the operating room, these techniques can be performed with higher-frequency transducers and can provide excellent resolution of even small lesions.
Ultrasound is an excellent technique for characterizing liver disease, particularly cirrhosis. Complications of portal hypertension such as ascites, recanalization of the paraumbilical veins, gastrohepatic ligament varices, and splenomegaly are easily visualized. HCCs generally appear as slightly hypoechoic nodules or masses in the heterogeneous cirrhotic liver (Fig 1).13-15 The appearance is variable, however, and hyperechoic nodules can result from fatty deposition in the tumor. Necrotic tumors are typically heterogeneous.15 Not all nodules found on ultrasound in cirrhotic livers are HCC nodules.16 Dysplastic nodules can appear similar to small HCC nodules. Increased vascularity shown on power Doppler imaging or with contrast enhancement may distinguish these. A minority of dysplastic nodules will progress to HCC, although the incidence is higher for high-grade dysplasia.17,18

Computed Tomography of the Liver
CT scanning is commonly used to assess masses in the liver and to evaluate cirrhotic livers for HCC. CT of the liver evaluates the entire liver equally and, unlike ultrasound, is not hindered by ribs or gas. In addition, compared with ultrasound, CT provides a more systemic evaluation of extrhepatic metastasis.

Modern CT scanners use helical technology arrayed in multiple rows of the x-ray detectors, termed multidetector CT scanners. Therefore, generally speaking, a 64-slice scanner is 64 times as fast as the older single-row helical CT scan. Similarly, a 16-slice CT scanner is one-quarter as fast as a 64-slice scanner. Imaging speed is important in a number of ways when using CT to scan the liver. Faster imaging allows for faster scanning to give complete scans of the liver during different phases of enhancement; a bolus of contrast material, typically 100 to 150 cc of contrast, is injected rapidly, and the liver is imaged when the contrast is in the arterial, portal, or other phase of enhancement. Faster scanning also allows for improved motion-free images as the complete scans can be performed in a breath-holding period. Also, faster scanning allows for thinner sections to be obtained during a breath-holding period. Because CT is a volume acquisition, images can be reformatted in any plane, such as the coronal plane, if the CT data are acquired with sufficient thinness. In addition, volume measurements can be obtained with appropriate software so that the liver volume or the volume of liver segments or lobes is measured. These may be of use in surgical planning.

Intravenous contrast is necessary to evaluate for HCC, and HCC may appear as higher or lower attenuation (ie, enhancing more or less) than the surrounding liver, depending on the timing of the scan after contrast injection. CT systematically evaluates the liver parenchyma, the hepatic veins, the portal veins, and the hepatic arteries, if done as a multiphasic examination.19-22 Multiphasic refers to scanning that is done during the arterial-predominant phase of contrast enhancement (when the hepatic arterial tree is filled with contrast before there is substantial portal vein enhancement of the liver) and then during the portal-predominant phase of contrast enhancement (when the bulk of injected contrast has reached the liver via the portal vein).21 For cirrhotic patients, it is also helpful to obtain a delayed phase since many HCCs may be most obvious on this phase of enhancement.23 The separate phases will optimally demonstrate the hepatic arteries, portal veins, and hepatic veins separately.

Because the enhancement characteristics of HCC vary, scanning through the liver and multiple phases increases sensitivity for small HCCs (Fig 3).20 Small HCCs will commonly show hypervascularity during the arterial phase of enhancement due to tumor-induced angiogenesis, but some do not, and many will be most obvious on a delayed phase. The delayed phase of enhancement shows tumors that demonstrate increased washout of contrast, ie, contrast leaves the tumor more than the surrounding cirrhotic liver. Therefore, HCC nodules may appear as low-attenuation lesions relative to the surrounding liver. Pseudocapsules may be demonstrated as low-attenuation, thin rims around well-differentiated tumors, with delayed enhancement.24

CT can demonstrate the location, arterial supply, and venous drainage of HCCs. Invasion of the hepatic and portal veins, as well as local metastases to periporal lymph nodes and nearby sites, can be demonstrated.
Tidetector CT has largely supplanted invasive techniques such as CT arterial portography, CT angiography, and conventional angiography for diagnosis and evaluation of HCC.\textsuperscript{24} Scanning is also useful for the evaluation of HCC after local therapies such as resection and ablation procedures. Loss of contrast enhancement indicates loss of vascularity, from either embolization, infarction such as radiofrequency ablation, or chemotherapy. Persistence of enhancement or the development of new nodular areas of enhancement can indicate a recurrence of tumor.

Like ultrasound, CT easily demonstrates the manifestations of cirrhosis and portal hypertension. Also like ultrasound, liver fibrosis is not directly imaged but rather inferred by the presence of surface nodularity, hepatic parenchymal heterogeneity, or signs of portal hypertension. Enhancing venous varices in any location, ascites, and splenomegaly are all easily imaged with CT.

CT can also distinguish HCCs from cysts and hemangiomas, the most common incidental liver lesions. Cysts show a well-defined wall, low attenuation, and no enhancement. Hemangiomas typically show nodular peripheral enhancement that gradually expands into the tumor. CT images obtained at different phases of enhancement will show this progression. Distinguishing these lesions from malignancies is difficult when the lesions are small and the enhancement characteristics are indeterminate.\textsuperscript{25} Other lesions such as dysplastic nodules or small arterial portal shunts, which are common in cirrhotic livers, may be difficult to distinguish from HCCs.\textsuperscript{16}

CT has some lack of specificity in distinguishing HCC from tumors such as metastases, focal nodular hyperplasia, and hepatic adenomas. In general the clinical and radiographic setting indicates which of these is likely in a given patient, as these tumors are rare in cirrhotic liver and HCC is uncommon in the nondiseased liver. No imaging feature will reliably distinguish these tumors based on tumor morphology alone.

![Fig 4. — MRI of HCC. (A) T1-weighted in-phase image shows the tumor in segment II of the liver (arrow). (B) Opposed phase image shows lower signal in the tumor (arrow), indicating steatosis. (C) Arterial-phase image after contrast injection shows enhancement of the tumor, a sign of neovascularity and arterial supply (arrow). (D) Delayed image shows washout of enhancement (arrow).](image-url)
Magnetic Resonance Imaging of the Liver

MRI uses radiofrequency power in the presence of a strong magnetic field to perturb protons, either in water or in fatty acid chains, and to induce them to produce a radiofrequency signal in return. This signal can be registered with the use of receiver coils. Gradients can be applied during the application of the radiofrequency pulse or during the reception of this signal to spatially encode it and create a map of the signal in the body. Tissue characteristics such as T1, T2, magnetic...

Fig 5. — MRI of HCC. (A) T2-weighted image shows the tumor mass (arrows) as higher signal intensity than the surrounding liver. (B) Diffusion-weighted image shows the high signal intensity mass (arrow), indicating restricted diffusion. (C) Apparent diffusion coefficient (ADC) map of the tumor shows lower ADC of the tumor (arrow). (D) Arterial-phase gadoxetate (a biliary uptake agent) enhanced image shows the enhancing tumor around a nonenhancing necrotic core from prior ablation. Additional foci of tumor (arrow) are seen that are not evident on other sequences. (E) Delayed-phase image shows washout of contrast from the main tumor mass. There is some uptake of contrast by the tumor, indicating hepatocellular function.
susceptibility, and resonant frequencies produced by fat, water, and other compounds can be detected on the image. Because MRI does not involve ionizing radiation, as CT does, extended imaging can be obtained, probing many different characteristics of tissues, organs, and tumors. For this reason, MRI is more powerful than CT in characterizing tissue and tumors.

MRI uses many different types of images to characterize tissues and tumors. If images are produced with different types of imaging parameters, such as repetition time (TR) and echo time (TE), images can be designed to show different types of tissue characteristics such as T1 and T2. For example, an image produced with an appropriately short TE and TR will produce a T1-weighted image. Choices of other imaging parameters can produce images that are T2-weighted, diffusion-weighted, or magnetic susceptibility-weighted (produced by iron in the tissues). Images can be produced to show lipid (such as steatosis), iron, or perfusion (Fig 4). MR contrast agents act by shortening T1, thus appearing bright on the image, or by increasing magnetic susceptibility, thus appearing dark on the image. Contrast agents such as gadopentetate, which diffuse into the interstitium, can be used to show perfusion and interstitial uptake similar to CT contrast agents (Figs 4 and 5). In addition, a number of more physiologically specific agents have been developed that have biliary uptake or Kupffer cell uptake, which can be useful in liver imaging (Fig 6). Because MRI is more sensitive to the gadolinium effect than CT is to iodinated agents, lower amounts of the agent can be used. The gadolinium can be bound to a variety of agents that have physiologic significance such as biliary uptake and secretion (Fig 7).

MRI is dependent on the amplitude of the received radiofrequency signal. Contrast agents increase the amplitude of this signal, and so does magnetic field strength. MRI is typically performed at 1.5 Tesla, although lower field strengths are sometimes used to provide an open configuration that can accommodate larger or claustrophobic patients. Signal-to-noise increases in proportion to field strength, providing an impetus to scanning at higher field strengths such as 3 Tesla or higher. Higher signal-to-noise can be used to generate images with higher resolution or greater time resolution in dynamic studies such as perfusion studies, or to image processes that have intrinsically low signal-to-noise, such as functional imaging or spectroscopic imaging. Another way to dramatically increase signal-to-noise is to increase the magnetization, or polarization, of a molecule above that conventionally available at thermal equilibrium in the body. Magnetization can be dramatically increased under specialized conditions (eg, by dynamic nuclear polarization at low temperatures and high field strength) and then injected and imaged before thermal equilibrium occurs. Such techniques are

Fig 6. — MRI of fibrolamellar HCC in a 25-year-old man with a reticuloendothelial contrast agent. (A) T1-weighted image shows the left lobe liver mass (arrow) (B) T2-weighted image shows a heterogeneous mass in the left lobe of the liver (arrow). (C) T2-weighted image after injection of Ferridex superparamagnetic contrast agent. This was performed because prior imaging suggested possible nodular hyperplasia. The liver and spleen become low signal intensity (darker) because of the agent, but the tumor does not (arrow). (D) Surface of the resected tumor shows band-like fibrous scars corresponding to the low signal intensity bands on the T2-weighted image.
termed hyperpolarization MRI and are a fertile area of research, although they are not currently applicable to liver imaging in humans. Hyperpolarization has been performed in gases such as xenon that are inhaled and then used to image lung ventilation in humans. Hyperpolarized compounds such as pyruvate can be made and then injected to image the conversion of pyruvate to lactate. Many other compounds can theoretically be made to image various aspects of tumor biology.

On T1-weighted images, the liver has a higher signal intensity (brighter) than the spleen or kidneys, reflecting its shorter T1. On T2-weighted images, the liver is darker than the spleen (lower signal intensity), indicating a shorter T2. Cirrhosis causes the liver to be heterogeneous and to have a longer T1 and longer T2 overall. Individual regenerative nodules can be seen. More well-differentiated HCCs typically appear as masses that are higher signal intensity than the liver on T1-weighted images, due in part to mineral content, and higher signal intensity than the liver on T2-weighted images. MRI demonstrates such features as a pseudocapsule or steatosis within some HCCs. Steatosis within a liver tumor indicates that it is a hepatocellular tumor although not necessarily carcinoma, as hepatic adenomas and dysplastic nodules can sometimes have steatosis. More poorly differentiated tumors will be infiltrative and are typically lower signal intensity on the T1-weighted images.

Specialized MR contrast agents have been developed, most of them for liver imaging. In addition to the standard interstitial agents that leave the vasculature, enter the interstitium of tissues and tumor, and are renally excreted, agents that have biliary uptake or Kupffer cell uptake have been developed. The biliary agents use gadolinium as the contrast mechanism and are designed to show uptake in the hepatic parenchyma so that most tumors appear as low signal intensity nodules or masses against the background of a high signal intensity liver (Fig 5). The biliary tree is also imaged as a very high signal intensity structure. Typically, delayed imaging over 15 to 20 minutes demonstrates the biliary uptake and excretion. Agents with Kupffer cell uptake employ superparamagnetic compounds to image the liver. T2-weighted images will
thus demonstrate the liver parenchyma as very low signal intensity so that lesions such as metastases or HCCs will show significantly higher signal intensity (Fig 6). HCCs, fibronodular hyperplasia, and hepatic adenomas may take up both of these agents, thus establishing that they are hepatocellular tumors (Fig 5).35,36

While enhancement characteristics of HCCs are variable, increased vascularity manifested as increased enhancement on arterial phase images are typical. Regenerative nodules and low-grade dysplastic nodules do not have much enhancement on arterial phase images, similar to the surrounding liver. Well-differentiated HCCs tend to enhance diffusely on arterial-phase images. As on CT, some HCCs may be manifested on MRI by increased washout on delayed images. Contrast agents that display biliary secretion, eg, gadoxetic acid (Eovist), show uptake in hepatocellular neoplasms such as fibronodular hyperplasia or hepatic adenoma.37-43 HCCs tend not to take up the agent, but often some degree of uptake is seen, establishing its hepatocellular origin (Fig 5). These agents may be more sensitive than multidetector CT for detecting small HCCs.37 Similarly, agents that show Kupffer cell uptake such as superparamagnetic iron oxides show slight and patchy uptake with HCC.35

As with CT, not every enhancing abnormality in the cirrhotic liver is necessarily HCC.16 Incidentally identified arterial-enhancing lesions that are not tumor are generically termed transiently hyperintense defects (THIDs).44,45 Some dysplastic nodules can demonstrate enhancement, although most are distinguishable from HCCs.16,46 Small arterial portal shunts show enhancement that typically is morphologically unlike HCCs47 but may be difficult to distinguish from small HCCs in

![Fig 8. — MRI of hemangioma and malignant tumors. (A) T2-weighted image shows right lobe liver mass (black arrow) that is high signal intensity and multiple intermediate-signal intensity metastases (white arrows). (B) Heavily T2-weighted image accentuates the difference in signal intensity between the hemangioma with long T2 (black arrow) and the metastases with shorter T2 (white arrows). (C) Arterial phase image after gadopentetate administration shows the nodular peripheral enhancement typical of hemangioma (white arrow) that is different from the diffuse enhancement of the malignant lesions (black arrows). (D) Delayed image fill-in of the hemangioma (white arrow) is shown with washout of contrast from the metastases (black arrows). Washout is typical of malignancies including HCC.](image-url)
some cases. A majority of small enhancing nodular lesions in cirrhotic livers will prove to be nonmalignant.48 High-flow or hypervascular hemangiomas can appear to be similar to HCCs that typically demonstrate intense arterial phase and enhancement and are hyperintense on T2-weighted images, unlike most HCCs.49 Common liver lesions such as hemangiomas, cysts, bile duct hamartomas, and focal fatty infiltration can easily be distinguished from HCCs on MRI (Fig 8).50-54

Newer MR sequences such as diffusion-weighted imaging (DWI) may prove helpful in characterizing liver lesions.27,55,56 DWI uses gradients to suppress signal from water that is free to move, such as Brownian motion. DWI can be used to differentiate high fluid tumors such as hemangiomas from solid tissue such as HCC (Fig 5). DWI with calculation of diffusion coefficient may be an early marker of tumor response to therapy.56-58 For example, DWI correlates with apoptosis in xenografts targeted with apoptosis-inducing antibodies.59

**Nuclear Medicine**

A variety of nuclear medicine agents are used for imaging the liver, although no standard agents have particular importance for imaging HCC. Standard PET imaging, 18F-fluorodeoxyglucose (18F-FDG) PET, has a high false-negative rate in the detection of HCC, averaging 40% to 50% (Fig 9).60,61 Part of the reason for this low sensitivity is the relatively high normal uptake of 18F-FDG in the liver, which can obscure smaller liver lesions. In many cases, 18F-FDG may show extrahepatic metastases or residual activity after interventional therapy.62

Older nuclear medicine agents such as labeled sulfur colloid, with uptake by Kupffer cells, and labeled red blood cell scans have limited applicability for HCC in general, but they may be helpful for the diagnosis of focal nodular hyperplasia and hepatic hemangiomas, respectively. Other tumor-specific agents such as 99mTc-octreotide are useful for imaging neuroendocrine tumor metastases such as carcinoma tumors.53 Fusion imaging with CT can be helpful for localizing tumors in the liver (Fig 10). To date, such tumor-specific agents for HCC have not been developed, although similar fusion techniques may be useful in the future.

Other PET agents such as acetate have been developed for tumor imaging and applied to hepatocellular imaging.64 This agent appears promising but has not
been extensively tested. Other newer agents have been developed to image apoptosis (eg, monitoring of tumor response to chemotherapy in vivo by a novel small-molecule detector of apoptosis).

Conclusions

Ultrasoundography, CT, and MRI are the mainstays of liver imaging. Sonography with adjuncts of Doppler and ultrasound contrast agents is helpful for detecting HCC and guiding interventions. CT provides a systematic evaluation of the chest and abdomen for metastatic disease and is helpful for assessing tumor response to therapy. MRI provides the most information about tumor characterization in general, and it is most helpful in distinguishing liver tumor types and in assessing tumor response.

References


