Early detection of hepatocellular carcinoma (HCC) is important, since the most effective treatment for HCC is surgical resection or local ablation therapy when the tumor is small. Fortunately, recent advances in liver imaging techniques have facilitated the detection of small HCCs.

Recent progression of noninvasive imaging technology includes various techniques of harmonic ultrasound (US) imaging with several kinds of US contrast agents, multislice helical computed tomography (CT), and rapid high-quality magnetic resonance (MR) technique with new, tissue-specific contrast agents. These techniques seem to have a strong potential to improve detection and characterization of HCC.

In this review, the technique and efficacy of new imaging methods including contrast enhanced US, multislice CT, and recent MR techniques with new contrast agents for detecting and diagnosing HCC will be described.

Recent Progress in Imaging Techniques

Ultrasound

Tissue harmonic Ultrasound

Harmonic imaging is a new sonographic imaging method that exploits the effect of nonlinear propagation on the acoustic signal as it travels through the human body or tissue. It produces sonographic images by using second harmonic signals generated by tissue itself during this nonlinear propagation of insonated acoustic energy.1–4 The resultant advantages are improved lateral resolution, reduced side lobe artifact, and increased signal-to-noise ratio.5 Several methods are available for harmonic imaging: conventional tissue harmonic imaging (THI), pulse inversion harmonic imaging (PIHI), and coded harmonic imaging.

THI uses a receive filter to separate out the second harmonic signals from which the US images are reconstructed. In THI, the US beam former transmits at fundamental frequency and receives at twice that frequency, that is the second harmonic frequency. A bandpass filter is used to process the received signal so that only the returning high-frequency harmonic signal is used to produce the image. The returning harmonic echo is, therefore, lower in signal intensity than the fundamental frequency; however, the signal is higher in contrast resolution and contains fewer artifacts. A recent phantom study revealed that harmonic beams have lower side-lobe levels. This effect can significantly improve the conspicuity of hepatic cysts and reduce internal haze in fluid-filled structures since side-lobe artifacts generally are most evident in fluid-filled structures.5

On the other hand, the overall echo texture in THI is coarse compared to that in conventional imaging, probably owing to impaired axial resolution of THI. Axial resolution is determined by the bandwidth of the overall received signal: the broader the bandwidth is, the better the axial resolution becomes. Whereas the sonographic equipment uses the entire signal bandwidth on conventional imaging, THI filters out the fundamental component by a narrow bandpass filter; thus, it has to reduce some axial resolution. This might be one of the factors that interfere with improving the conspicuity of focal liver lesions.5

THI has been shown to have superior image quality over fundamental imaging in differentiation of solid masses versus cysts and in evaluation of various intraabdominal organs including liver.1,6,7 PIHI has the advantage of higher signal intensity compared with THI because two returned harmonic signals are added. PIHI is not affected by bandwidth limitation, which causes a conflict between contrast and image resolution in THI. Thus, superior spatial resolution can be achieved.

PIHI improved the conspicuity of both solid and cystic hepatic lesions compared to that of conventional imaging (Fig. 1). In PIHI, two or multiple identical
pulses with reversed polarity are transmitted down each ray line, instead of only a single pulse as is done with conventional imaging or THI. When these resultant returned waveforms are added, the harmonic component gives the multiplied harmonic level of a single waveform while all linear fundamental components are canceled out more effectively than those on THI. This technique, instead of using a narrow receive filter tuned around harmonic frequency components, allows the use of broader transmit and receive bandwidths for improved resolution. Therefore, PIHI can overcome the bandwidth limitations of THI.

Contrast-enhanced Ultrasound

At present, a number of manufacturers have produced forms of stabilized microbubbles for use as intravenous US contrast. Levovist (Schering AG, Berlin, Germany), which has gained regulatory approval in Asia and Europe, is a suspension of galactose microparticles in sterile water. When injected intravenously, the microbubbles (mean diameter, 2–3 μm) produce systemic enhancement of Doppler signal for 1 to 5 minutes. In addition to this vascular phase, Levovist has a late hepatosplenic parenchymal phase after blood pool clearance. The disruption of the bubbles creates a transient but very strong echo. A disadvantage of this is that there is less contrast left for further imaging. Another limitation of Levovist is the short duration of effective contrast enhancement. Multiple injections or continuous slow infusion of Levovist may prolong the enhancement duration.

Power Doppler sonography with Levovist. In our experience of 20 patients with nodular or massive HCCs, power Doppler (PD) US showed markedly enhanced tumor vascularity (95%) at 30 and 60 seconds after injection of Levovist, compared with noncontrast scans (Fig. 2). Enhanced vascular flow signals in the tumor changed from detour pattern to basket pattern. Limitations of the PD contrast-enhanced US include susceptibility to tissue motion artifact and color blooming artifact, which can degrade image quality.

Harmonic sonography with contrast enhancement. Harmonic US is a technique based on transmitting at frequency f and receiving at frequency 2f, the second harmonic. Since the contrast agent microbubbles generate far more harmonic energy than tissue does, harmonic imaging enhances the signals from contrast over those from tissue.

According to our study comparing conventional and harmonic PD US for HCCs, harmonic PD was superior to conventional mode in terms of PD artifacts. Thus, harmonic PD has advantages for lesions near the heart or great vessels or for patients who cannot hold their breaths.

Figure 2. Hepatocellular carcinoma with power Doppler ultrasound. A: Unenhanced power Doppler sonogram shows scanty intratumoral flow signals in hypoechoic mass. B: Contrast-enhanced power Doppler sonogram after injection of Levovist shows numerous intratumoral flow signals in the mass.
Pulse inversion harmonic sonography with contrast enhancement. Pulse inversion harmonic uses two identical pulses with opposed polarity. Adding the two resulting returned signals cancels the fundamental linear components and preserves the nonlinear harmonic components. In our recent studies of contrast-enhanced pulse inversion harmonic US in 61 focal hepatic lesions including HCC,11 HCCs showed homogeneous or heterogeneous enhancement with or without irregular intratumoral vessels.

New promising contrast enhanced sonographic technique. Real-time harmonic B-flow US is a new harmonic US technology for imaging contrast agents based on digitally encoded US technology.12 The technique, named as “Coded Harmonic Angio (CHA)”, is specific to the GE Logiq 700 scanner (GE Medical Systems, Waukesha, WI). CHA suppresses the unwanted fundamental signal return by isolating the coded return signal. This leaves only the harmonic return signal.

In our experience, CHA showed excellent dynamic enhancement of tumor vascularity of HCC (Fig. 3). One limitation of CHA was severe suppression in background grayscale signal. In some HCCs, CHA showed blood flow from supplying arterial branches into draining hepatic veins before injection of contrast material. Contrast markedly enhanced these blood flow signals, with peak enhancement on 35 to 45 seconds later, similar to the enhancement noted on early phase CT or angiography. Based on our experience, we believe CHA has good sensitivity to weak flow in small vessels. Limitations of CHA include inferior imaging resolution, lower frame rate, and significant microbubble destruction. Therefore, we used intermittent scanning and lower mechanical index (output power) to reduce bubble destruction.12

Recently, Acuson developed a microbubble-specific mode, “agent detection imaging,” for optimal detection of stimulated acoustic emission from fragile agents such as Levovist. Using agent detection imaging, we performed single level dynamic US in patients with HCC, by means of automatic intermittent triggering with 1-second intervals between each scan. The images were usually acquired in 2 phases including vascular and post-vascular late phase after a bolus injection. Our preliminary results showed that single level dynamic US using agent detection imaging was potentially useful in diagnosing HCC with excellent demonstration of intra- and peritumoral vascularity, early tumor staining, and, sometimes, delayed capsular enhancement.12

Multislice-helical (spiral) CT

When helical or spiral CT was introduced in medical field in early 1990, it greatly increased the speed of CT data acquisition by imaging continuously during patient transport through the scanner gantry. Faster data acquisition allowed faster administration of contrast media, which dramatically improved contrast enhancement. Large volumes of data could be acquired during a breath-hold, which reduced misregistration artifacts, and overlapping slice reconstruction could be performed without increasing patient dose, thus improving the quality of multiplanar reformatted images. In addition, 3-dimensional image reconstruction became practical with faster data acquisition, and patient throughput increase.

The next major advance in CT was multislice spiral scanner. The evolution of multislice spiral CT continued in late 1998, 4 slices simultaneously. These multislice scanners acquire 4 times more data per revolution than singleslice spiral scanners, and some have gantries that spin at 2 revolutions per second (twice the speed of most single-slice scanners), making them 8 times faster than most single-slice scanners.13 Recently, a 16 detector CT was introduced.

Multislice spiral CT is ideally suited to quickly imaging a large volume of interest with thin slices during the limited temporal window for optimal contrast enhancement.

Multiphase CT exams are becoming common for the diagnosis of HCC. Exams may include a noncontrast...
phase, an arterial phase, a portal venous phase, and a delayed phase (Fig. 4). Speed is essential, particularly for the arterial and venous phases. These must be performed during the rapid IV administration of contrast media, and the scanning must be performed quickly with thin slices to achieve good resolution with adequate separation of the arterial and venous phases. Multislice spiral CT is ideal for this application and produces excellent studies, such as liver evaluations in patients with hepatitis B or C who are at risk for developing HCC.14

In general, early arterial phase CT images show intense hepatic arterial enhancement, minimal portal venous enhancement, and essentially no hepatic venous or parenchymal enhancement. Late arterial phase images demonstrate substantial portal venous, slight parenchymal, and no hepatic venous enhancement. In theory, hypervascular hepatic tumors, such as HCC, are detected best during a phase of maximal tumor enhancement and minimal hepatic parenchymal enhancement. Multiphasic imaging is useful for visualizing specific tumor vascularity and helpful for tumor characterization. However, HCC may show variable vascularity because of its histologic tumor grade; therefore, multiphasic imaging can show HCC with variable vascularity on some phase images.15

Multidetector row helical CT allows acquisition of early and late arterial sets of liver images. Whereas late arterial phase images depict more hypervascular HCC lesions than the early phase, review of both arterial phase images produces the greatest sensitivity and positive predictive value.15

MRI

With the recent progress of rapid, high-quality scan techniques and the development of new, tissue-specific contrast agents, the applications of MR for liver imaging continues to expand. Although initially found to be complementary to CT scan for selective applications, MRI plays an important role for the detection and characterization of liver tumors.

MRI using a T1-weighted sequence, T2-weighted sequence, and serial gadolinium-enhanced gradient echo sequences is very effective at both detecting and characterizing HCC. Currently available chelates of gadolinium simultaneously shorten the T1 and T2 relaxation times. However, the effect is more pronounced on T1 time than on T2 time at low concentrations, and these materials are used as T1 contrast agents at doses of 0.1 mmol/kg.16 Gadolinium chelates are nonspecifically distributed in extracellular space; their enhancement effect depends on the blood supply during the early dynamic phase and the volume of the interstitial matrix in the delayed phase. However, analysis of the degree of enhancement and the pattern in dynamic imaging is critically important in the evaluation of focal hepatic lesions.

HCC is a hypervascular tumor supplied primarily by the hepatic arteries, whereas a normal liver is perfused primarily by the portal circulation. With the recent development of fast MRI techniques, it has become possible to obtain multiphase intravenous contrast-enhanced dynamic imaging of the liver including the phases of predominantly arterial hepatic perfusion, peak portal venous perfusion with maximal hepatic enhancement, followed by an equilibrium phase. A rapid intravenous administration of contrast material enables greater contrast enhancement of hypervascular tumors including HCC during the arterial phase and makes it possible to assess the time-dependent hemodynamics in the tumors and surrounding hepatic parenchyma.17
Most HCCs are characterized by contrast enhancement in the arterial phase, and well-timed arterial phase imaging is crucial for detection and characterization of HCCs during dynamic MRI (Fig. 5). Peterson et al.\(^\text{18}\) reported that the acquisition of multiple dynamic arterial and portal venous phase images increased the rate of HCC detection by 21% as compared with spin-echo T1- and T2-weighted images.\(^\text{18}\) Early stage HCCs, however, which are usually small and well differentiated, tend to be hypovascular, and they have been detected during the portal venous or delayed phase of serial imaging.\(^\text{19}\)

Dynamic gadolinium-enhanced MRI improves the characterization of several types of liver tumors by showing a typical enhancement pattern. Regenerative nodules and dysplastic nodules are supplied mainly by the portal veins, whereas HCC has a hepatic arterial supply (Fig. 5). Liver nodules that were enhanced during the arterial phase in a cirrhotic patient were considered HCCs.\(^\text{20}\) The characteristic findings of HCCs such as enhancement of a pseudocapsule and internal mosaic pattern are generally better visualized on delayed phase imaging.\(^\text{21}\) Because of the variation of signal intensity in HCC on T1-weighted images, unenhanced images are also important to determine whether the lesion is enhanced (Fig. 5).

Superparamagnetic iron oxide particles are tissue-specific MRI contrast agents that are taken up by Kupffer cells in the liver and macrophages in the spleen.\(^\text{22}\) Their strong T2 shortening effect darkens the normal liver on T2-weighted images and improves the contrast between lesions and liver tissues. They have been used in hepatic MRI mainly for the detection of hepatic tumors and have been shown to be superior to noncontrast MRI and as sensitive as CT during arterial portography (CTAP) in the depiction of liver metastases.

Hepatocyte-directed agents such as mangafodipir, or gadolinium-based hepatocyte agents have a limited role in hepatic MRI. However, superparamagnetic iron oxide-enhanced MRI might replace the more aggressive CTAP in the preoperative evaluation of metastasis. The combination of superparamagnetic iron oxide-enhanced and gadolinium chelate-enhanced dynamic MRI produces results comparable to those of CT hepatic arteriography (CTHA) and CTAP in the evaluation of malignant hepatic tumors including HCC.\(^\text{16}\) These tissue-specific agents in tissue characterization require further studies.

The use of a growing number of contrast agents has the potential to increase the sensitivity and specificity of liver MRI in HCC by improving morphological and functional information.

**Summary**

The recent availability of US contrast agents and the remarkable advances in US technology have led to the rapid development of new US imaging methods. Techniques currently available in the evaluation of HCC are
tissue harmonic imaging, harmonic power Doppler US, pulse inversion harmonic imaging, and coded harmonic angiography.

The most recent advance in CT was the multislice spiral (multidetector row helical) scanner. The evolution of multislice spiral CT continued through the 21st century with the capability of scanning 16 slices simultaneously. Multiphase CT examinations are becoming common for the diagnosis of HCC.

Recent advances in MR technology, including hardware and pulse sequence implementations, have allowed acquisition times to be reduced to 25 seconds or less, the time frame of 1 breathhold. For T1-weighted imaging, short acquisition times not only reduce respiratory artifacts but also allow dynamic contrast-enhanced imaging during select phases of enhancement, such as the hepatic arterial phase with various newly developed contrast agents, having a high possibility of improvement in detection and characterization of HCC.

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