Recent Advances in the Imaging Diagnosis of Hepatocellular Carcinoma (HCC)

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I. Introduction

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 agent, and multislice helical CT. These techniques seem to have a strong potential to improve detection and characterization of HCC.

Another recent interesting field in the imaging diagnosis of HCC is the study of intranodular hemodynamics of HCC because pathological findings and grade of malignancy of HCC are closely related to intranodular hemodynamics.

In this review, the efficacy of new imaging techniques including contrast enhanced US and multislice CT for diagnosing HCC will be described. In addition, intranodular hemodynamic imaging of HCC will be discussed with focus on the premalignant lesions; dysplastic nodule.

II. Recent Progress in Imaging Technique

1. Ultrasound (US)

   1) Contrast-enhanced Harmonic Power Doppler US

   Harmonic US has higher signal to noise ratio and higher lateral resolution than fundamental mode (1). However, the returning harmonic echo is lower in signal intensity than the echo with fundamental frequency (2). When employing microbubble contrast agents, the magnitude of the backscattered contrast-enhanced signal at the harmonic frequency is much greater than that of the tissue. This is due to the fact that harmonics generated from microbubble contrast agents result from asymmetric expansion and contraction of the microbubbles (non-linear motion), a
resonance phenomenon completely different from the mechanism of harmonic generation within tissue (2, 3).

At the small expense of some sensitivity to detect vascular flow, compensated by the enhancement of PD signals by the contrast agent, the harmonic PD US effectively overcomes the problem of artifacts. The use of harmonic mode in contrast-enhanced PD US can effectively reduce artifacts including blooming and motion-related artifacts. This technique was also applicable to lesions near the heart or great vessels without reducing PD gain too much, thus harmonic mode was superior to conventional mode in demonstrating intratumoral vessels in that area. Additionally, in harmonic mode, continuous scanning during patient’s quiet breathing was possible without producing considerable motion-related artifacts, therefore, this technique could be more easily used in patients with poor breath-holding ability than conventional technique.

2) Pulse Inversion Harmonic US

The resolution and sensitivity of harmonic imaging is limited by a fundamental compromise in the frequency filtering approach. Similar to conventional harmonic US, pulse inversion harmonic US displays the amplitude of the harmonic signals resulting from the nonlinear echoes. However, rather than using frequency filtering on receive, this method uses the nonlinear propagation on transmit as well. Two identical pulses with reverse polarity are transmitted in the media, adding the two resulting returned signals yields to the cancellation of the fundamental linear components and preserves the nonlinear harmonic components. Since no filtering technique is used, the broadband information is preserved delivering overall improved resolution and furthermore improved sensitivity is also achieved because of better rejection of the fundamental component.

It is now understood that the US field, if its peak pressure is sufficiently high, is capable of disrupting a bubble shell and hence destroying it (4). Most microbubbles consist of a gas bubble surrounded by a thin stabilizing shell. These shells are very thin and break easily when the microbubble expands under insonation, allowing the gas to diffuse more rapidly into the blood. The disruption of the bubbles creates a transient but very strong echo that is rich in harmonics, an effect referred to as stimulated acoustic emission (SAE) (5, 6). However, it causes the bubble to disappear. Stimulated acoustic emission does not rely on the movement of the microbubble and can be observed equally well from stationary microbubbles. This fact can be exploited as a way of detecting microcirculation. The blood pool in microvasculature is, however, moving very slowly, and has not had time to refuse the bed before the next US frame is created. It is therefore necessary to interrupt the scanning process for a sufficient time (interval delay imaging) to allow the agent to wash in to the capillary tissue (7). Each transmitted US pulse in interval delay imaging will produce the best possible harmonic signals because it can be arranged to allow areas of slow flow to fill with intact microbubbles during the imaging pause. SAE can be maximized because the high intensity US induces resonance and disruption in all the microbubbles in the imaging field simultaneously. This transient response, a signal with high
amplitude, is exploited highly effectively by pulse inversion harmonic US.

3) Real-time Harmonic B-Flow (Coded Harmonic Angio)
   
   This new US technique, coded harmonic angio, combines benefits of coded harmonic and B-flow. Coded harmonic technology is able to precisely suppress the unwanted fundamental return signal by transmitting sequence, isolating the coded fundamental return signal and suppressing this signal. This leaves only the harmonic return signal.

   B-flow is a new technique developed to image blood flow. B-flow directly images blood reflectors providing a real time picture of flow in a display that resembles an angiogram.

   Coded harmonic angio uses codes to suppress the fundamental signal, and uses decoding techniques optimized for contrast agents, to suppress tissue signal, thus, improving sensitivity and uniquely optimizing for contrast signal visualization in dynamic flow states.

   Therefore, coded harmonic angio with US contrast agent visualizes superb arterial architecture like a digital subtraction angiography.

2. Multislice Helical (Spiral ) CT
   
   When helical or spiral CT was introduced in medical field in early '90, 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, three-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, four slices simultaneously. These quad-slice scanners acquire four times more data per revolution than singleslice spiral scanners, and some have gantries that spin at two revolutions per second (twice the speed of most single-slice scanners), making them eight times faster than most single-slice scanners(8).

   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 venous phase, and a delayed phase. 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 (9).

Multislice spiral CT increases the diagnostic efficacy over single-slice spiral CT for liver applications, and will become the imaging method of choice for a growing list of indication.

III. Intranodal Hemodynamics in Precancerous Lesion of HCC (Dysplastic Nodule)

Most dysplastic nodules are hypovascular (10, 11) at angiography or sonographic angiography with intraarterial infusion of carbon dioxide microbubbles, which is one of the most sensitive methods in detecting vascularity of tumors. According to Matsui et al. (11), only one (4%) of 25 adenomatous hyperplasias showed hypervascular arterial supply. In our series (10), two (12%) of 16 nodules showed faint vascular stain, whereas 14 (88%) nodules showed hypovascularity at angiography.

The blood supply of hepatocellular carcinoma (HCC) is primarily arterial. Recent studies based on histopathologic examinations (12, 13) reported differences of vascular, especially arterial, supply among low- and high-grade dysplastic nodules and HCC. Unpaired arteries were rare in cirrhotic nodules, significantly more common in dysplastic nodules, and most common in HCC. Sinusoidal capillarization was least common in cirrhotic nodules, significantly more common in dysplastic nodules, and most common in HCC. These findings showed that distributions of sinusoidal capillarization and unpaired arteries in dysplastic nodules are intermediate between those in cirrhotic nodules and HCC, supporting dysplastic nodules as premalignant lesions. Another previous study reported a morphometric analysis of vascular supply in adenomatous hyperplasia and HCC (14). In ordinary AHs, cumulative areas of arterial lumen and portovenous lumen were almost equal to or less than those in the surrounding liver in two thirds of our cases. In a majority of atypical AHs, the cumulative area of arterial lumen was equal to, and that of portovenous lumen was less than, the cumulative area in the surrounding liver. In most HCC nodules, the number and cumulative luminal area of arteries were much more, and those of portal veins were much less, than the number and cumulative area in the surrounding liver. The relative number and cumulative luminal area of abnormal arteries compared with all arteries showed a stepwise increase in the following order: ordinary AH (20.7% and 17.5%), atypical AH (46.8% and 52.5%) and HCC (93.6% and 92.0%). These data suggest that ordinary AH, atypical AH, and HCC are different in vascular supply, and that these differences may reflect sequential changes in the hemodynamic state during hepatocarcinogenesis.

The relationship between the portal and arterial blood supplies in the hepatocellular nodules in cirrhotic liver was considered to be reciprocal (11). Intranodular portal blood flow tends to decrease and arterial blood flow tends to decrease initially and then increase as the grade of malignancy increase form regenerative nodules through
Intermediate steps of dysplastic nodules to HCCs (14). However, the distinctions, including angiogenesis and histopathology, between each step are not always clear, which suggests a continuous transition in the pathway of hepatocarcinogenesis. Recently, several studies based on CTA and CTAP shows different results in terms of the portal and arterial supplies to dysplastic nodules (15, 16). Hayashi et al (15) reported statistically significant correlation between the blood supply and grade of malignancy while Lim et al (16) reported no consistent pattern regarding the portal and arterial supplies to the dysplastic nodules. Therefore, some dysplastic nodules may have an arterial blood flow from the hepatic artery, although the mechanism for this phenomenon is not yet fully understood.

References


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**Major Interest** Diagnosis and Treatment of Hepatocellular Carcinoma