Recent Advances in the Imaging and Ablation of Hepatocellular Carcinoma

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I. INTRODUCTION

Early detection of hepatocellular carcinoma (HCC) has improved with recent non-invasive imaging modalities, such as ultrasonography (US), CT, and MRI. Liver imaging techniques basically play five roles in the management of HCC: a) screening for HCC, b) confirmation or differentiation of HCC from other tumors, c) evaluation of malignancy grade of HCC or borderline (hyperplastic) lesions, d) staging of HCC, and e) evaluation of the therapeutic response and detection of recurrence of HCC (1, 2). Study of intranodular hemodynamics is important as pathological findings and malignancy grade of HCC are closely related to intranodular hemodynamics. As is well known, the biological character of HCC is quite different from other malignant tumors; the liver has dual blood supply and other organs are fed by the artery and drained by the vein. The presence of portal venous flow in the liver may also be related to human hepatocarcinogenesis, since a premalignant lesion has portal flow within the nodule unlike over HCC. From this point of view, intranodular hemodynamic imaging is important in the differentiation and pathological assessment of liver tumors.

II. RECENT PROGRESS IN IMAGING TECHNIQUES

1) Intraarterial contrast-enhanced US (US angiography)
US angiography is a combination of US and angiography, and is an extremely sensitive method in the diagnosis of hepatic arterial vascularity within the nodule (3, 4). It is also a useful technique in the differentiation of HCC from other hepatic tumors such as dysplastic nodule, hemangioma, metastasis, or focal nodular hyperplasia (5, 6, 7). US angiography is performed by injecting microbubbles of CO2 through a catheter placed in the hepatic artery following conventional hepatic angiography. It is sensitive, but an invasive method, which is a major drawbacks of this technique. US angiography is, therefore, regarded as a gold standard or final goal of intravenous contrast-enhanced US.

2) Intravenous contrast-enhanced US

a. Enhanced Doppler US

Enhanced color Doppler US by an intravenous injection of US contrast agent improves the sensitivity of color Doppler US in the detection of arterial and portal blood flow within an HCC nodule. Inflow constant waveform signals were detected in 100% (in 4 of 4) of dysplastic nodules and well-differentiated HCCs, in which the presence of portal blood flow was previously confirmed by CTAP. Similarly, detection of intranodular arterial vascularity is much improved by enhanced color Doppler US compared to un-enhanced color Doppler US (4, 8). Detection of the vascularity of viable cancer cells by US imaging is useful in US-guided therapies for HCC as well.

b. Tumor Parenchymal Flow imaging

Contrast-enhanced Second Harmonic Imaging.

In hepatic tumors, evaluation of intranodular hemodynamics is important for differential diagnosis, selection of the treatment method and evaluation of therapeutic effectiveness. Fundamental color and power Doppler US are not always satisfactory for evaluating tumor vascularity compared with dynamic CT, dynamic MR or invasive imaging techniques (1, 2). However, US with a contrast-agent is a promising method in depicting tumor vascularity because of not only its non-invasiveness but also its advantage in providing dynamic flow information on a tomographic plane basis. Furthermore, since non-surgical local therapies such as percutaneous ethanol injection (PEI) therapy, percutaneous microwave coagulation
therapy (PMCT), or radiofrequency ablation (RFA) therapy are usually performed under US guidance. US vascular imaging is extremely important. Intermittent harmonic imaging makes use of two fortuitous properties of ultrasound contrast agents. Firstly, at the second harmonic, the signal from the bubble approaches, and in some circumstances equals, the signal at the fundamental frequency; i.e., as opposed to tissue which has a markedly lower signal at the second harmonic than at the fundamental frequency. This facilitates the signal from the bubble to discriminate from that of tissue at the second harmonic frequency. Secondly, the bubbles can be destroyed at power levels within the diagnostic range, yielding a signal much larger than that from an injected bubble. Intermittent harmonic imaging with bubble destruction uses intermittent transmission with a flexible interval to destroy most of the bubbles in a region of interest with high acoustic power and to permit replacement of bubbles on the scan plane due to fresh blood inflow during the non-transmission period (9–14). Therefore, intermittent harmonic power Doppler US is a combination of intermittent transmission and harmonic power Doppler, which maps a parameter directly related to the number of scatters in the blood, i.e., the total integrated power of the Doppler spectrum enhanced by the microbubbles. In contrast, digital frame subtraction gray-scale imaging can extract only the blood flow echoes created from collapse of microbubbles while echoes from tissue are effectively cancelled out (11, 12, 14).

Flash Echo Imaging

Flash echo imaging is also a newly developed technique for visualizing tissue perfusion flow. A very large echo signal (like a flash) is produced by collapsed microbubbles in the power of the transmitted ultrasound beam.

If the transmission of ultrasound wave is waited for sometime, microbubbles fill the nodule. At that time, an increased brightness is obtained within the tumor parenchyma by the transmitted beam, which depends on the stopping time. A similar technique is called “Loss of Correlation Imaging”, which uses color Doppler and an auto-correlation method.

This technique requires certain suspension time for the transmission of ultrasound beam, which sacrifices the real time capability. However, a dual monitor method with
multi-shot digital subtraction method has been recently applied for clinical use, one monitor visualizes low acoustic power image and another monitor visualizes flash echo images with intermittent transmission of the ultrasound beam. Therefore, this technique made it a routine clinical study for the diagnosis of tumor parenchymal flow in the clinical setting.

Real-time Gray-scale Harmonic Imaging (Coded Harmonic Angio).

Real-time vascular imaging technique called Coded Harmonic Angio has been developed by a combination of phase inversion harmonics and coded excitation technology, which transmits and receives coded ultrasound pulses.

This technique is a microbubble-specific approach, which overcomes conflict between requirements of contrast and resolution in harmonic imaging to enhance sensitivity. In phase-inversion harmonic imaging, two identical pulses with reverse polarity are transmitted in rapid succession into tissue. The scanner detects and summates the echoes from these two successive pulses. As a result, linear scattering from the tissue results in a signal void while non-linear signals from microbubbles predominate. Phase-inversion harmonic imaging depicts signals from microbubbles sensitively with a good spatial resolution without Doppler-related artifacts (15–17). It displays the amplitude of harmonic signals generated from the nonlinear echoes by simply brightening the gray-scale image. This technique with a combined use of Levovist, visualizes extremely beautiful arterial architecture, just like a microangiography. It can demonstrate tumor vessel and tumor parenchymal flow, unlike enhanced Doppler technique.

Application of Harmonic Imaging to the Treatment of HCC

Evaluation of Treatment Response.

Areas of residual tumor after RFA or PEI therapies are not distinguishable from necrotic tissue on US (18, 19). The sonographic findings of gray-scale, color Doppler and power Doppler scanning after RFA or PEI therapies do not correlate well with the overall necrotic shape, or with the volume or extent of induced coagulation necrosis (18–20). Therefore, contrast-enhanced CT or MR imaging is generally required to assess effectiveness of the treatment. Absence of enhanced area on
contrast-enhanced CT indicates disappearance of the blood supply and thus successful treatment. Conversely, focal areas of persistent contrast enhancement usually indicate viable tumor cells, and the needs for further treatment to achieve complete tumor necrosis are warranted. Harmonic gray-scale images can extract only the blood flow echoes created from the destruction of microbubbles, and echoes from tissue are effectively cancelled. This mode makes it possible to clearly depict residual blood flow in tumors after therapy (12, 21). Because contrast-enhanced harmonic sonography is easy to perform and provides real-time needle-insertion guidance, it may be preferable to perform after localized therapy to monitor treatment response, which may result in the reduction of unnecessary CT (21).

Real-time Needle Insertion Guidance for Local Treatment of HCC

Although contrast-enhanced CT can clearly depict residual areas in tumors after RFA or PEI therapies (18–22), it does not enable real-time guidance of percutaneous therapy. Furthermore, retention of Lipiodol in HCC lesions sometimes makes it difficult to distinguish the hyperattenuating area of contrast enhancement from that of Lipiodol when the retention of iodized oil in the tumor is incomplete (23, 24). Contrast-enhanced harmonic gray-scale images revealed tumor vascularity in patients with HCC after TAE and percutaneous therapy with high sensitivity and accuracy when compared with those of dynamic CT. This capability of harmonic imaging to depict residual cancer cells in treated HCC provides a great opportunity to guide needle insertion correctly on the US monitor, which can not be achieved by any other imaging modalities such as CT or MRI.

III. HEMODYNAMICS OF OVERT HCC AND PREMALIGNANT / BORDERLINE LESION

1) Afferent and Intranodular Hemodynamics

The afferent blood vessel in an overt HCC is the hepatic artery. Therefore, the characteristics of intranodular hemodynamics in HCC are arterial neovascularization and absence of portal blood flow. In contrast, the characteristic hemodynamic
pattern of a premalignant lesion (dysplastic nodule) or a borderline lesion is poor arterial vascularity and the presence of portal supply. The imaging diagnosis of HCC is based on the demonstration of this characteristic intranodular hemodynamics.

Angiography is not an effective in demonstrating arterial hypovascularity or presence of portal venous flow in small nodules less than 1.5 cm as previously thought. US angiography and CTA are more sensitive in detecting intranodular arterial vascularity and CTAP also sensitive in detecting portal perfusion within the nodule, enabling differentiation between overt HCC and a premalignant lesion (1, 2, 25).

2) Hemodynamics of early–stage HCC

It is known that most early–stage HCCs (26) do not show tumor stains on angiography or retention of Lipiodol within the tumor, making the diagnosis difficult. It is also known that some of early–stage HCCs are fed by the portal vein system, not by the hepatic artery, as in dysplastic nodule (27). Therefore, some hypovascular HCCs (early–stage HCC) show no perfusion defect on CTAP and may appear like benign nodules with a "benign appearing" vascular pattern. Except for these nodules having a "benign appearing" hemodynamic pattern, the diagnosis of HCC itself is possible even in its early stage by a combined use of tomographic vascular imagings, such as US angiography, CTA, and CTAP.

IV. Radiofrequency Ablation (RFA) for HCC

Radiofrequency ablation (RFA) for HCC has recently become available for the treatment of HCC in the routine clinical setting. We have introduced this technique for the treatment of HCC since June 1999. A total of 150 patients were treated by this technique (28). This technique is superior to other percutaneous local treatment for HCC such as PEI or PMCT as much larger coagulation area can be obtained with less side effect, less treatment sessions and less local recurrence rate. Thus, it will be the main local control therapy for HCC hereafter. In some instances, residual cancer cells are extremely difficult to differentiate from necrotic normal liver tissue or
coagulated tumor cells. In that occasion, RFA under harmonic image guidance is an extremely useful technique as mentioned earlier.

A combination therapy with RFA and LpTAE is greatly advantageous since much larger coagulative area can be obtained (28).

V. CONCLUSION

Perfusion imaging techniques, such as contrast second harmonic imaging, or Coded Harmonic Angio have recently become available for a routine clinical use. With these techniques, all of the 5 fundamental roles of imaging, that includes lesion detection, confirmation, staging, evaluation of malignancy grade, and follow-up after treatment, will be much simplified. They may reduce the requirement for dynamic CT or MRI, and replace some of their roles in the future. Especially, if the viable cancer cells are accurately imaged on the US monitor by sensitive perfusion imaging techniques, contrast harmonic imaging will be a great advantage in US-guided treatment procedures for HCC. Taking account of the present status in which percutaneous intervention therapy such as ethanol injection therapy and microwave or radiofrequency coagulation therapy totally depends on US guidance, the advance in ultrasound vascular imaging technique will lead to a more accurate diagnosis and a more affective treatment of HCC.

Finally, RFA will totally replace most of the PEIT or PMCT since it has a great advantage with fewer disadvantages in the management of HCC less than 4 cm in diameter.

REFERENCES


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