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REVIEW ARTICLE

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Recent applications of ultrasound: diagnosis and treatment of hepatocellular carcinoma

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Abstract Ultrasound (US) has the advantages of real-time observation, simple technique, and a noninvasive procedure compared to other imaging modalities. The recent development of digital technologies has enabled the observation of sonograms with improved signal-to-noise ratio, penetration, and spatial and contrast resolutions. Furthermore, microbubble contrast agents have increased the diagnostic ability of US examination, and the use of three-dimensional sonograms is now not unusual. These advances have furthered the usefulness of US for liver tumors in clinical practice. This article reviews the recent applications of US in the diagnosis and treatment of hepatocellular carcinoma.

Key words Ultrasound (US) · Contrast agent · Microbubble · Three-dimensional image · Liver · HCC

Introduction

Recent advances in digital technologies have resulted in remarkable developments in the field of imaging modalities. Ultrasound (US) is one of the diagnostic tools that have shown significant improvement within the past decade.[1] For the diagnosis of liver tumors, US examination in clinical practice has the advantages of real-time observation, a simple technique, and noninvasiveness. It is being used worldwide, and at a high frequency, as a first-step, reliable method for the diagnosis of liver tumors. Further, the use of the Doppler method and/or microbubble contrast agents provides details of hemodynamics, which are useful for the detection and characterization of liver tumors.[2,3] In addition, current US systems now also allow the easy three-dimensional visualization of combined tissue structures and color blood-flow appearance.[4,5]

US guidance techniques allow the accurate percutaneous advancement of needle-like applicators for biopsy and treatment.[6,7] Moreover, studies of the use of US energy for therapeutic procedures that do not require puncture are currently in progress.[8–10] This article reviews the recent applications of US for the diagnosis and treatment of hepatocellular carcinoma (HCC), including newly developed techniques using contrast agents and three-dimensional imaging.

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Ultrasound (US) diagnosis of HCC

Gray-scale imaging

Two-dimensional gray-scale US is a basic and essential procedure as a first-step examination in the diagnosis of liver tumors. For a number of years now, tissue harmonic imaging (THI) has been in use as an optional tool for gray-scale imaging. Because THI improves both lateral resolution and contrast resolution, by narrowing the width of the US beam, accompanied by the reduction of reverberation and side-lobe artifacts, the margin and structure of the tumor nodule become clear, with distinct delineation.[11–14] Nowadays, THI plays a major role in the routine work of gray-scale US examination.

Advances in transducer performance are also important for improving the diagnostic ability of US. Recent digital technologies have provided control of the broad-frequency band, improved penetration and signal-to-noise ratio, and increased spatial and contrast resolution, all these features helping to raise the image qualities of sonograms.[1,2] In this regard, a small lightweight transducer is now desirable because of the increasing population of elderly people worldwide.

Table 1. US contrast agents

	Gas	Shell	Diameter[a]	Manufacturer
Al-700	Perfluorocarbon	Synthetic polymer	?	Acusphere (Watertown, MA, USA)
Albunex	Air	Cross-linked albumin	3–5 (4.3)	Molecular Biosystems (San Diego, CA, USA)
Biosphere	Air	Biodegradable polymer	?	Ponit Biomedical (San Carlos, CA, USA)
Definity	Perfluoropropane	Lipid	2.3	Bristol-Myers Squibb (N. Billerica, MA, USA) (DuPont Merck[b])
Echovist	Air	Galactose	3	Schering (Berlin, Germany)
Echo Gen	Dodecafluoropentane	Surfactant	0.4, 2–5[c]	Sonus Pharmaceuticals (Bothell, WA, USA)
Imavist	Perfluorohexane; physiological gases	Surfactant	<5	Alliance Pharmaceutical (San Diego, CA, USA)
Levovist	Air	Galactose; palmitic acid	1.3	Schering
Optison	Perfluoropropane	Cross-linked albumin	3.6–5.4 (4)	Molecular Biosystems
Sonavist	Air	Cyanoacrylate (polymer)	1	Schering
Sonazoid	Perfluorocarbon	Lipid	2.4–2.5	Nycomed-Amersham (Oslo, Norway)
SonoVue	Sulfur hexafluoride	Phospholipids	2.5	Bracco Diagnostics (Princeton, NJ, USA)
Quantison	Air	Albumin	3.2	Quadrant (Zurich, Switzerland)

[a] Diameter of microbubble (μm). Numbers in parentheses are mean diameters
[b] Previous manufacturer
[c] Echo Gen is the first phase-shift US contrast agent which has a boiling point significantly below body temperature. It has two different conditions, it is a liquid at room temperature (nonechogenic particles with a mean diameter of approximately 0.4 μm) and a gas at body temperature (echogenic microbubbles with a diameter of 2–5 μm)

Blood flow imaging: spectrum analysis and color flow images

The advent of the Doppler method has changed diagnostic US.[1,2,15–17] Waveform analysis was the initial application, and it was frequently used for the characterization of liver tumors. Then, color flow imaging with real-time observation added to the process of diagnosing liver tumors, and the power Doppler mode contributed to a better detectability of blood flow.[18–27] However, limitations in the detection of slow flow and in the detection of deeply located vessels far from the skin surface have prevented the wider application of the Doppler mode in the evaluation of tumor hemodynamics. Furthermore, artifacts caused by respiratory or cardiac motion sometimes affect the precise evaluation of hemodynamic information. At present, the application of the Doppler mode alone for detecting tumor blood flow is rare, as the more recent availability of microbubble contrast agents has assisted in overcoming the limits of the Doppler mode.

Contrast-enhanced US

A problem for US contrast agents: unstable microbubbles

Against the background described above, there has been considerable expectation that US contrast agents would improve the detectability of blood flow in liver tumors. In fact, since the first report of a US contrast agent, by Gramiak et al.,[28] there has been an ongoing challenge to establish contrast-enhanced US with microbubble agents.[29–31] While free gas bubbles are efficient scatterers of US, their utility has been limited because of their immediate removal by the lungs. Although colloidal suspensions and emulsions were developed, in the 1980s, for stabilized US contrast agents, their practical use was compromised by difficulties in controlling the size of the bubbles and in attaining stabilization of the contrast effects.[32–36] From the late 1980s to the 1990s, gray-scale contrast-enhanced US with carbon dioxide gained broad attention as an echo-enhancing technique, with high sensitivity for detecting tumor vascularity and high performance for the characterization of liver tumors.[37,38] However, the method requires an arteriography procedure, because carbon dioxide is easily soluble in blood. The development of microbubble contrast agents suitable for peripheral venous injection has been expected for practical use.

Next stage for contrast agents: stable microbubbles and hemodynamic features

The results with Albunex (Molecular Biosystems, San Diego, CA, USA) and Echovist (Schering, Berlin, Germany) after injection via the peripheral route were disappointing, because they did not provide sufficient enhancement in the left ventricle, aorta, and abdominal organs, due to their instability.[3,39,40] Finally, at the end of the twentieth century, a galactose-based US contrast agent (SHU 508; Levovist; Schering) was made available. It was a long-awaited material that provided a stable enhancement effect in abdominal organs with a peripheral injection. Subsequently, many microbubble contrast agents have been developed or are currently under development, as summarized in Table 1. These intravenously injectable agents improve the detectability of tumor blood flow and the depiction of characteristic flow patterns in Doppler mode or contrast-specific imaging mode and are associated with fewer safety concerns than iodinated contrast materials. It has become clear that some kinds of US contrast agents, as opposed to iodinated contrast medium, have a characteristic property of organ-specific accumulation.[41–46] Although the precise mechanism remains unclear, the reticuloendothelial system (i.e., phagocytosis by Kupffer cells) may be concerned with this phenomenon. Both Levovist and

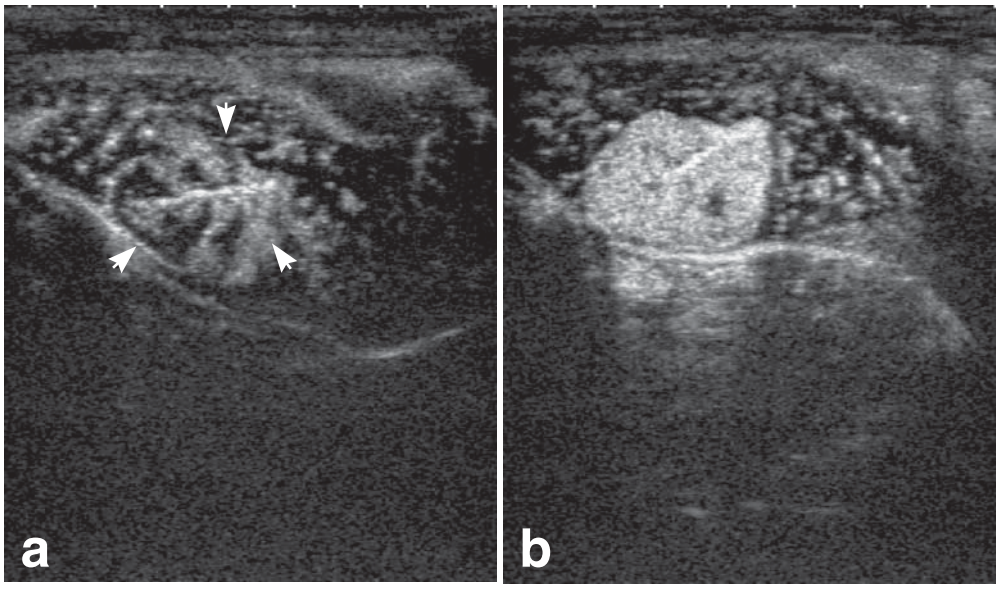

Fig. 1. Contrast-enhanced ultrasound (US) with Definity (pulse subtraction harmonic mode; Toshiba, Tokyo, Japan) of hypervascular liver tumor (VX-2 tumor, 12 mm, rabbit liver). *arrowheads*: **a** 8 sec; **b** 15 sec

Sonazoid (Nycomed-Amersham, Oslo, Norway) acc1umulate in the liver, and sonograms in this phase (late liver-specific parenchymal phase) are frequently used for the detection or characterization of liver tumors. In contrast, Definity (Bristol-Myers-Squibb, N. Billerica, MA, USA; available in Canada at present) and SonoVue (Bracco Diagnostics, Princeton, NJ, USA; a popular US contrast agent in Europe) do not accumulate in the liver, although Lim et al.[47] reported that the latter showed spleen-specificity in their clinical study with healthy volunteers.

Acoustic properties of microbubble agents and specific imaging mode

Microbubble agents have characteristic acoustic properties that depend on the size and kind of gas and shell used.[3,48] Contrast harmonic mode (with pulse inversion technique), which is based on the nonlinear scattering behaviors of microbubbles, provides high resolution with fewer artifacts compared to the simple Doppler technique,[49,50] and is now a typical specialized imaging method for microbubble contrast agents.

The behaviors of microbubbles are related to the acoustic power level (mechanical index [MI]) of the transmitted ultrasound. With Levovist, US transmission under a standard acoustic power level for routine US examination provides immediate disappearance of the microbubbles. This feature, "loss of correlation" ("stimulated acoustic emission"), is used in some imaging modes specialized for Levovist.[51,52] Additionally, the echo signal increases according to the lengthening of the interval between frames, as the intermission during US transmission reduces the destruction of microbubbles in the region of interest (ROI). With this methodology, an ingenious contrivance using an intermittent transmission technique has been developed to obtain strong echo-enhancement in the ROI as contrast-specific imaging.[53]

The next-generation contrast agents, such as SonoVue and Definity, show characteristic oscillation behavior under very low MI, which reduces the signals derived from tissues and microbubble breakdown. As a result, contrast harmonic imaging under a low MI level has received considerable attention of late as a useful method for the real-time observation of microbubble images, and the method is expected to improve the ability to diagnose liver tumors[54–58] (Fig. 1).

Clinical applications of contrast-enhanced US

Detection of vascularity in HCC. Microbubble contrast agents can increase the detectability of blood flow by US examination. Numata et al.[59] examined the relationship of enhancement patterns between contrast-enhanced harmonic gray-scale imaging with Levovist and helical computed tomography (CT), and they stated that the same results were obtained in 53 of 61 nodules (87%). More recent studies also showed over 80% concordance for tumor vascularity (Giorgio;[60] 82.4%; Bolondi;[61] 81%) between contrast-enhanced US under low MI level with SonoVue, and contrast-enhanced helical CT. The improved detectability of tumor vascularity with contrast-enhanced US contributes to the characterization of liver tumors and assessment of the therapeutic response.

Characterization of focal liver lesions. Many studies using contrast-enhanced US have been carried out for the characterization of focal liver lesions with early-phase images and/or delayed phase images (Table 2). Early-phase images provide characteristic vascular-enhancement patterns that are useful for specific diagnosis.[62–64] However, evaluation of the enhanced appearance in delayed-phase images is not always simple, owing to the fact that the accumulative property of microbubbles affects the enhancement findings in this phase. According to previous reports, focal nodular hyper-

Table 2. Characterization of focal liver lesions by contrast-enhanced US

Author	Contrast agent	No. of patients	Results[a]	
Bryant et al.[67]	Levovist	88	Sensitivity[a]	89, 93%
		54	Specificity[d]	80, 93%
		142	Accuracy[d]	88, 90%
Dietrich et al.[68]	Levovist	174	Sensitivity	100%
			Specificity	93%
Kim et al.[71]	Levovist	75	Sensitivity[d]	98, 98%
			Specificity[d]	85, 91%
			SD[b,d]	75, 79%
			CIT[c,d]	63, 72%
von Herbay et al.[65]	Levovist	67	Sensitivity	100%
			Specificity	63%
Nicolau et al.[70]	SonoVue	152	Sensitivity	98%
			Specificity	82%
			Accuracy	92.8%

[a] Discrimination of benign and malignant lesions
[b] Specific diagnosis: correct diagnosis was obtained by contrast-enhanced US
[c] Confirmatory imaging technique: the reader judged that no further imaging for lesion characterization was needed and that the lesion concerned had been correctly diagnosed
[d] Evaluation by two different readers

plasia (FNH) shows positive enhancement and metastatic tumor shows negative enhancement in the delayed phase with Levovist, a contrast agent that accumulates in the liver.[65–68] However, it is known that several enhancement patterns are observed in both HCC and hepatic hemangioma on liver-specific sonograms.[65–68] Irrespective of the various kinds of contrast agents used, the evaluation of combined multiphase images would improve the diagnostic ability of contrast-enhanced US.

Concerning the discrimination of malignant versus benign liver lesions by contrast-enhanced US, recent studies have reported sensitivities of 98% to 100% and specificities of 63% to 93% with Levovist,[65–69] and sensitivity of 98% and accuracy of 92.7% with SonoVue.[70] Furthermore, in a clinical study with two independent image reviewers, Kim et al.[71] reported that contrast-enhanced US (agent-detecting imaging mode with Levovist) provided a specific diagnosis in 75%–79% of 75 patients with focal hepatic lesions, and that the technique was successful as a confirmatory imaging technique in 63%–72% of the patients.

Nicolau et al.[72] reported that the phase-related echogenicity of HCC nodules on contrast-enhanced sonograms with SonoVue correlated well with the cellular differentiation. Regarding this point, small HCC nodules (less than 20 mm) sometimes present a hypovascular appearance on imaging diagnosis, and both dysplastic nodules and regenerative nodules also appear as hypovascular nodules.[61,73–75] Because high-grade dysplastic nodules are considered as potentially premalignant lesions, the characterization of such hypovascular nodules is very important in clinical practice.[76,77] However, the ability of contrast-enhanced US to discriminate between various types of hypovascular nodules is not yet clear, and therefore the significance of contrast-enhanced US for the early diagnosis of HCC has still not been established. At present, percutaneous needle biopsy under US guidance is frequently required for the characterization of small hepatic lesions in patients with chronic liver diseases.

Detection of tumor nodules in the liver. Some kinds of hepatic nodules, such as metastatic liver tumors, appear as hypo-enhanced nodules on liver-specific images of accumulated microbubbles in the liver. Gray-scale US sometimes fails to detect metastatic tumor nodules because of their small size and iso-echoic appearance, and so liver-specific sonograms assist in detecting occult tumor nodules on gray-scale images.[50,78–82] This application of contrast-enhanced US contributes to the staging of the disease by a noninvasive procedure.

As Levovist microbubbles disappear instantly just after US transmission under a suitable MI level (standard acoustic power level for routine work), it is very difficult to observe liver-specific images repeatedly with this agent. In this regard, as neither Definity nor SonoVue (blood-pool contrast agents) accumulate in the liver, repeated observation of delayed-phase images with these agents under a low MI level is possible because there is less microbubble breakdown. The general application of contrast-enhanced US under low MI with blood-pool contrast agents for the detection of metastatic liver tumors is expected to take place as a matter of course.[83,84]

Transit time analysis using a microbubble contrast agent was proposed by Albrecht et al.[85,86] as a noninvasive method for the evaluation of liver hemodynamics. In cirrhotic patients, as shortened arrival time in the hepatic vein was observed with Doppler spectral analysis after the injection of Levovist, they concluded that their technique had potential as a noninvasive test for cirrhosis. They also suggested the applicability of their technique for detecting metastasis in the liver, on the basis of arterio-venous shunt in association with tumor nodules. Thus, the application of US contrast agents for detecting tumor nodules can be expected in terms of functional aspects as well as morphological diagnosis.

One of the clinical problems with contrast-enhanced US examination is the limited duration of the contrast-enhanced effect. Most of the agents are given by bolus

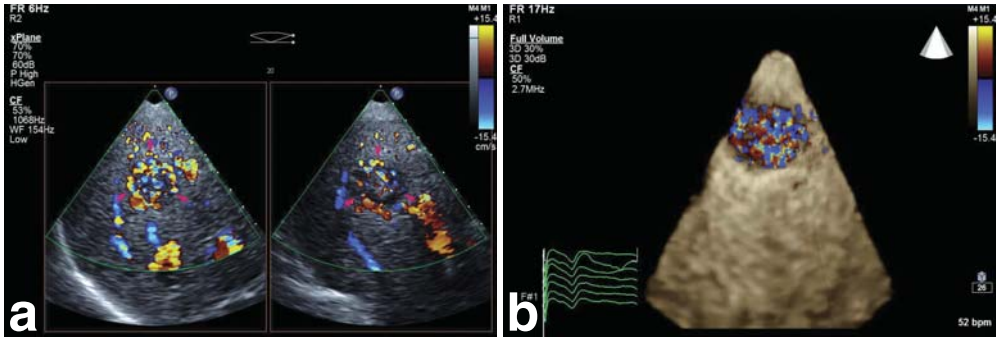

Fig. 2a,b. Novel imaging using X-matrix transducer (iu22; Philips, Andover, MA, USA). **a** Biplane imaging of hepatocellular carcinoma (*arrowheads*: HCC; X-plane, color Doppler with Levovist). The "biplane imaging" shows two different planes simultaneously on the display. The additional image (*right side*) demonstrates the plane parallel to the regular image (*left side*), and the same blood-flow pattern was observed in the two different planes (the angle between these two planes was 20° in this case). This technique makes it easy to characterize a tumor nodule. **b** Real-time three-dimensional imaging (Live 3D, color Doppler with Levovist) of HCC

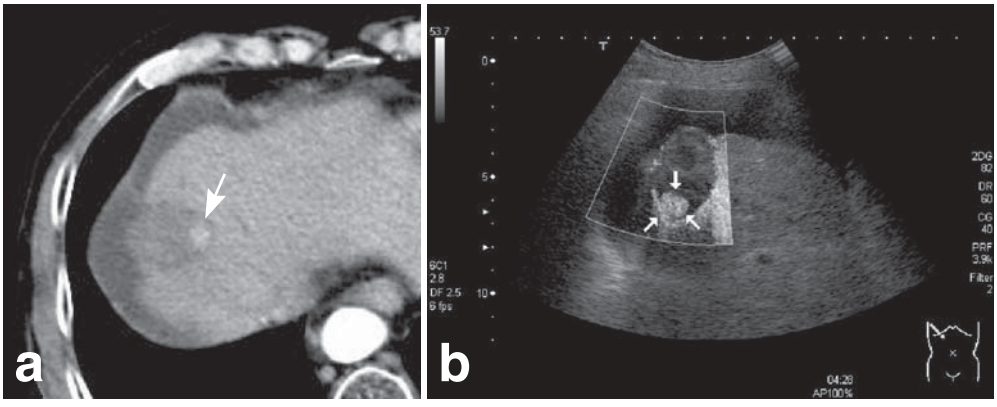

Fig. 3a,b. Assessment of therapeutic response after percutaneous ethanol injection (PEI) for HCC. **a** Contrast-enhanced computed tomography (CT) with dynamic study. **b** Contrast-enhanced US (advanced dynamic flow with Levovist). Contrast-enhanced CT showed enhanced appearance within the treated area (**a**, *arrow*), and contrast-enhanced US demonstrated a similar finding (**b**, *arrows*)

injection, but a drip infusion method would be helpful for prolonging the contrast-enhanced effect.[87,88]

Three-dimensional US and other digital technologies. Recent advances in digital technologies have made it possible to acquire three-dimensional images simply and rapidly with various radiological modalities.[89] At present, many US systems can easily demonstrate the combined images of gray-scale tissue structures and color blood-flow appearance.[90–94] These images provide additional anatomical information about the tumor and tumor-associated vessels on any plane from multiple directions. With the use of Levovist, contrast-enhanced three-dimensional (3D) fusion US presents tumor-specific vascular flow patterns that assist in the characterization of liver tumors.[95]

Thanks to the remarkable progress in microelectronic technology, the US transducer has achieved full digital specification (Matrix transducer, 1–3 MHz, iu22; Philips, Andover, MA, USA) with 3000 elements. Including built-in micro-beam forming composed of a 150-computer board, it can visualize both "biplane imaging (X-plane)" and "live 3D". The former simultaneously shows two different planes on the display (Fig. 2). The additional image next to the regular image presents a cross-sectional plane or a parallel plane, making it possible to demonstrate any angle by rolling the track ball without tilting the probe. In clinical practice, this technique can reduce the operator's time for image acquisition by echocardiography,[96–98] and the same benefit can be expected in the abdominal field. Tracking the needle tip during percutaneous needle advancement under US-guidance may be an additional application of this technique. "Live 3D" means real-time 3D images with volume rendering for pyramidal volume (40*20 angles). 3D hemodynamic views of tumor vessels or vascular abnormalities are visible from any angle on the display. However, because the system was designed for echocardiography, this application has image limitations within a narrow angle or within several cardiac beats that rely on an ECG monitor. Improvement of the system would be needed for its practical use in liver disease.

Application of US for the treatment of HCC

1. Percutaneous needle puncture technique

As the majority of patients with HCC have liver dysfunction, surgery is not always an appropriate treatment choice.[99–101] In addition, recurrence of HCC is an insepa-

Table 3. Assessment of therapeutic response after percutaneous treatment for HCC using contrast-enhanced US with Levovist

Author	Treatment	No. of patients/ No. of lesions	Results[a]	
Bartolozzi[120]	PEI	40/47	Sensitivity	92%
			Specificity	100%
			Accuracy	98%
Choi[122]	RFA	40/45	Diagnostic agreement	100%
Kim[124]	RFA	90/94	Diagnostic concordance[c]	99%
Meloni[125]	RFA	25/43	Sensitivity	83.3%
			Specificity	100%
Solbiati[121]	RFA	20/20[b]	Sensitivity	50%
			Specificity	100%
			Diagnostic agreement	85%
Wen[123]	RFA	67/91	Sensitivity	95.3%
			Specificity	100%
			Accuracy	98.1%

[a] Comparison with contrast-enhanced helical CT
[b] Solitary colorectal liver metastases
[c] 1-Month follow-up CT

rable companion in post-treatment patients. Against such backgrounds, percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA) were developed, and they are now widely used in clinical practice as minimally invasive methods,[102–107] as a first-line, favored approach that has an efficient therapeutic effect on HCC.[108–114]

Percutaneous needle puncture under US guidance is frequently performed for biopsy, as well as for the treatment of patients with liver diseases.[6,115,116] Although detection of the needle shaft or at least the needle tip on the sonogram is required for the technique, in practice this is not always easily to achieve. Recently, the use of a polymer coating has led to improvements in the visualization of both the needle shaft and tip sonographically.[117–119] This distinctive invention regarding the needle should result in a high success rate of the percutaneous procedure under US guidance.

2. Assessment of therapeutic response by US

With high sensitivity and specificity for detecting tumor vascularity, contrast-enhanced US has come to be frequently applied for the evaluation of therapeutic response in HCC nodules (Table 3). For percutaneous treatment, Bartolozzi et al.[120] reported that contrast-enhanced US (color Doppler with Levovist) showed sensitivity of 92%, specificity of 100%, and accuracy of 98% compared to the results of spiral CT and biopsy, in the detection of residual (viable) tumor tissue in 47 HCC lesions (40 patients) treated with PEI. Solbiati et al.[121] reported that the sensitivity and specificity of contrast-enhanced US (color or power Doppler with Levovist) were 50% and 100%, respectively, in comparison with contrast-enhanced helical CT, and the diagnostic agreement with CT was 85%, 24 h after ablation therapy in 20 patients with colorectal cancer and liver metastases. A study by Choi et al.[122] revealed that diagnostic agreement between contrast-enhanced US (power Doppler with Levovist, 14–23 h after ablation therapy) and immediate follow-up CT (within 30 min after ablation) was achieved in 100% of the 45 HCC nodules in 40 patients. In an assessment of therapeutic response after RFA, Wen et al.[123] compared the results of contrast-enhanced US (coded harmonic angio mode with Levovist) for detecting residual tumor in 91 HCC nodules (67 patients) 5 to 7 days after RFA with the results of dynamic CT; the sensitivity, specificity, and diagnostic accuracy of the contrast-enhanced US were 95.3%, 100%, and 98.1%, respectively. In the clinical course after RFA, Kim et al.[124] reported that the diagnostic concordance between contrast-enhanced US (agent-detection imaging with Levovist) performed within 24 h (mean, 18 h) after RFA and 1-month follow-up CT was 99% in 90 patients with 97 HCC nodules. They concluded that contrast-enhanced US was potentially useful for evaluating the early therapeutic effect of RFA for HCC. However, five (5%) of the 94 ablated HCC nodules, which showed no residual tumor on either contrast-enhanced US or 1-month follow-up CT after the initial RFA, had findings of local tumor progression at a subsequent follow-up CT. Therefore, they noted that their method had limitations in predicting local tumor progression in treated tumors. According to a study by Meloni et al.,[125] the sensitivity and specificity of contrast-enhanced US (pulse inversion harmonic imaging with Levovist) were 83.3% and 100%, respectively, for detecting residual nonablated tumor at 4 months after treatment in 35 patients with 43 HCC nodules, compared with helical CT findings.

For the assessment of therapeutic response after transarterial chemoembolization (TACE), it is well known that contrast-enhanced US has the advantage of not being limited by iodized oil deposition, which affects the evaluation of contrast-enhanced CT findings. Minami et al.[126] reported that contrast-enhanced US (coded phase-inversion harmonic sonography with Levovist) had a significantly higher sensitivity in depicting residual blood flow in HCC about 1 week after TACE compared with dynamic CT and dynamic magnetic resonance (MR) imaging: contrast-enhanced US, 38 of 44 (86%) lesions; dynamic CT, 19 of 44 (43%) lesions; dynamic MR imaging, 10 of 20 (50%)

lesions. They also noted that the contrast-enhanced US findings were predictive of HCC local recurrence in the clinical course after treatment. Morimoto et al.[127] compared the results of contrast-enhanced US (harmonic wideband gray-scale sonography with Levovist) with histologic findings; the sensitivity and specificity for discerning viable and nonviable HCC after TACE in 29 HCC nodules were 100% and 81%, respectively. With the use of SonoVue, Pompili et al.[128] reported that contrast-enhanced US resulted in diagnostic agreement in 53/56 cases (94.6%), with sensitivity and specificity of 87.0% and 98.4%, respectively, after nonsurgical treatments for HCC (PEI, RFA, TACE, TACE followed by PEI, RFA followed by PEI), compared with contrast-enhanced CT findings.

As mentioned above, the diagnostic ability of contrast-enhanced US and its capacity for the assessment of therapeutic response in HCC are now sufficient, and its findings are equivalent to contrast-enhanced CT findings. However, there are some limitations to evaluation with contrast-enhanced US. The main problem is the difficulty of determining whether the enhancement is located inside or outside the tumor area. Arterial vascularity within the tumor area and focal areas with irregular peripheral enhancement within the ablation zones are signs indicative of residual tumor. However, the treatment itself (especially a percutaneous procedure) causes an unclear margin of the tumor nodule. While distinct enlargement of the treated area may indicate successful treatment, US observation lacks the ability to achieve spatial localization of the nodule. The issue of assessment of a sufficient safety margin by US remains to be solved. In addition, the therapeutic response after RFA needs to be assessed at least several hours after the treatment, because artificial signals caused by the procedure affect early detailed observations.[121,122,124] The possibility of an immediate assessment of the therapeutic effect during or just after RFA is eagerly awaited.

New therapeutic approach with US energy

High-intensity focused ultrasound (HIFU) is an alternative treatment procedure using US energy without a needle puncture technique.[129] A successful result with HIFU means necrosis of the tumor at the focus alone, without damage to surrounding tissues. While some clinical studies have been carried out using HIFU for the treatment of liver tumors, several hurdles need to be crossed.[130–132] The main problem is difficulty with focusing the US beam in the liver, as the focusing is affected by the ribs and respiratory motion. If clinical efficacy were to be established after overcoming these problems, current treatments such as PEI and RFA might be replaced by this new method.

It is known that US transmission can activate some types of drugs, such as thrombolytics (used for the treatment of vascular disease).[10] This activating technique is expected to deliver an efficient medical effect to the target organ. Additionally, US energy allows the sonoporation phenomenon, which is US-induced membrane porosity. In sonoporation, the presence of microbubbles helps to increase the permeability of the cell membrane; intracellular drug delivery and nonviral gene transfection procedures are expected to benefit from this increase in permeability.[133–136]

Conclusion

There have been outstanding advances in the US field, and possibilities for the application of US technology are considered to be almost unlimited. On the basis of the development of US systems and the application of US contrast agents, US is sure to play a leading role in the diagnosis and treatment of HCC.

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