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REVIEW

Review of dynamic contrast-enhanced ultrasound guidance in ablation therapy for hepatocellular carcinoma

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Abstract

Local ablative techniques-percutaneous ethanol injection, microwave coagulation therapy and radiofrequency ablation (RFA)-have been developed to treat unresectable hepatocellular carcinoma (HCC). The success rate of percutaneous ablation therapy for HCC depends on correct targeting of the tumor *via* an imaging technique. However, probe insertion often is not completely accurate for small HCC nodules, which are poorly defined on conventional B-mode ultrasound (US) alone. Thus, multiple sessions of ablation therapy are frequently required in difficult cases. By means of two breakthroughs in US technology, harmonic imaging and the development of second-generation contrast agents, dynamic contrast-enhanced harmonic US imaging with an intravenous contrast agent can depict tumor vascularity sensitively and accurately, and is able to evaluate small hypervascular HCCs even when B-mode US cannot adequately characterize the tumors. Therefore, dynamic contrast-enhanced US can facilitate RFA electrode placement in hypervascular HCC, which is poorly depicted by B-mode US. The use of dynamic contrast-enhanced US guidance in ablation therapy for liver cancer is an efficient approach. Here, we present an overview of the current status of dynamic contrast-enhanced US-guided ablation therapy, and summarize the current indications and outcomes of reported clinical use in comparison with that of other modalities.

Key words: Dynamic contrast-enhanced ultrasound; Hepatocellular carcinoma; Percutaneous ethanol injection; Radiofrequency ablation

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INTRODUCTION

Hepatic resection forms part of the conventional treatment for patients with primary liver cancers; however, the majority of hepatocellular carcinomas (HCCs) are not suitable for curative resection at the time of diagnosis. Difficulties of surgical resection may be related to size, site, and number of tumors, vascular and extrahepatic involvement as well as liver function of the patient[1-4]. There is a need to develop a simple and effective technique for treatment of unresectable HCCs; therefore, local ablative techniques [percutaneous ethanol injection (PEI), microwave coagulation therapy (MCT) and radiofrequency ablation (RFA)] have emerged in clinical practice to expand the pool of patients considered for

liver-directed therapies[5-8]. In particular, RFA is not associated with some of the side-effects of other ablative techniques[9]. Thus, RFA is currently more widely accepted due to the ease of use, safety, reasonable cost and applicability to minimally invasive techniques[10].

Percutaneous ablation therapy for HCC is widely performed under real-time sonographic guidance. The success rate of percutaneous RF ablation depends on correct targeting *via* an imaging technique. However, multiple sessions of ablation therapy are often required for small HCCs, which are poorly defined on conventional B-mode ultrasound (US) alone[11]. There are two particular situations in which B-mode US cannot adequately characterize the tumors[12]. The first is the presence of residual HCC nodules after ablation, because B-mode US findings cannot adequately differentiate between treated and viable residual tumor tissue. The second is the presence of naïve HCC nodules among many large regenerated nodules in cirrhotic liver. Color Doppler and power Doppler have increased the sensitivity of hepatic lesion detection compared to that using gray-scale US, but these modalities do not provide levels of sensitivity comparable to those of contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI)[13-16]. However, two breakthroughs in US technology, harmonic imaging and the development of second-generation contrast agents, have demonstrated the potential to dramatically broaden the scope of US diagnosis of hepatic tumors[14-16]. Dynamic contrast harmonic US can depict tumor vascularity sensitively and accurately, and is able to evaluate small hypervascular HCCs even when B-mode US cannot adequately characterize the tumors[17-21]. Therefore, contrast-enhanced harmonic US is expected to improve the detectability of HCC nodules, and decrease the number of sessions required for ablation of HCC in difficult cases[22,23].

This paper reviews the evidence for the use of dynamic contrast-enhanced US guidance in ablation of HCC, and illustrates the potential of the techniques for improving the targeting in percutaneous ablation therapy.

DIAGNOSIS AND TREATMENT OF HEPATOCELLULAR CARCINOMA

HCC can be diagnosed radiologically, without the need for biopsy if the typical imaging features are present[20,24,25]. This requires a contrast-enhanced study (dynamic CT or MRI). HCC enhances more intensely than the surrounding liver in the arterial phase, whereas the presence of 'washout' persists in the delayed phase. Tumor markers including alpha-fetoprotein and descarboxyprothrombin have been used for the diagnosis of HCC.

The management of HCC involves multiple disciplines including hepatology, surgery, diagnostic and interventional radiology, oncology, and pathology[20,25-27]. One has to consider several patient and tumor factors including the severity of underlying liver disease, tumor bulk, and associated comorbidities, as well as several practice-setting factors including availability and expertise in surgical resection, transplantation, and ablative therapies. RFA is basically recommended for HCC nodules with a maximum diameter of 3 cm in patients with not more than three tumors who are contraindicated for surgery.

DYNAMIC CONTRAST-ENHANCED ULTRASOUND

Contrast agents

Levovist (Schering, Berlin, Germany) is a first-generation US agent made of galactose[28]. A trace of palmitic acid is added as a surfactant to stabilize the resultant microbubbles. These bubbles have a weak encapsulating shell and are easily destroyed by US exposure. The contrast effect of Levovist is based on the destruction of microbubbles by high mechanical index (MI) pulses. In addition, Kupffer cells phagocytose Levovist microbubbles; therefore, liver parenchymal findings are obtained as Kupffer imaging in the postvascular phase at least 10 min after administration.

Sulfur hexafluoride microbubbles (SonoVue; Bracco SpA, Milan, Italy), perflutren lipid microbubbles (Definity; Bristol-Myers Squibb, North Billerica, MA), perflutren protein microbubbles (Optison; GE Healthcare, Buckinghamshire, United Kingdom), and perfluorocarbon microbubbles (Sonazoid; Daiichi-Sankyo, Tokyo, Japan) are second-generation contrast agents[29-33]. These microbubbles provide stable nonlinear oscillation in a low power acoustic field because of the hard shell of these bubbles, producing great detail in the harmonic signals in real-time. The only second-generation contrast agent that can be taken up by Kupffer cells in the liver is Sonazoid. Sonazoid microbubbles accumulate in the liver parenchyma over time[34,35].

Generally, few drug toxicities have been reported; these being pain at the point of injection, sense of heat and sense of cold. The incidence of complications was shown not to differ from historical controls (1.7%, P = 0.867 by Fisher's exact probability test)[36].

Imaging and procedure

In point of fact, there is a clinical need for high resolution and real-time imaging for dynamic contrast-enhanced US guidance in ablation therapy.

Using Levovist, real-time images of tumor enhancement by the simultaneous collapse of microbubbles caused by high mechanical index pulses can be obtained in the early vascular phase only[28]. The collapse of microbubbles in viable HCC lesions is seen as white flashes on the screen[12]. However, maintaining real-time US imaging for guidance reduces the enhancement period to approximately one minute after injection because Levovist microbubbles are easily disrupted (Figure 1). Therefore, great skill is required because the procedure time is too short to search for enhanced HCC nodules and insert the probe.

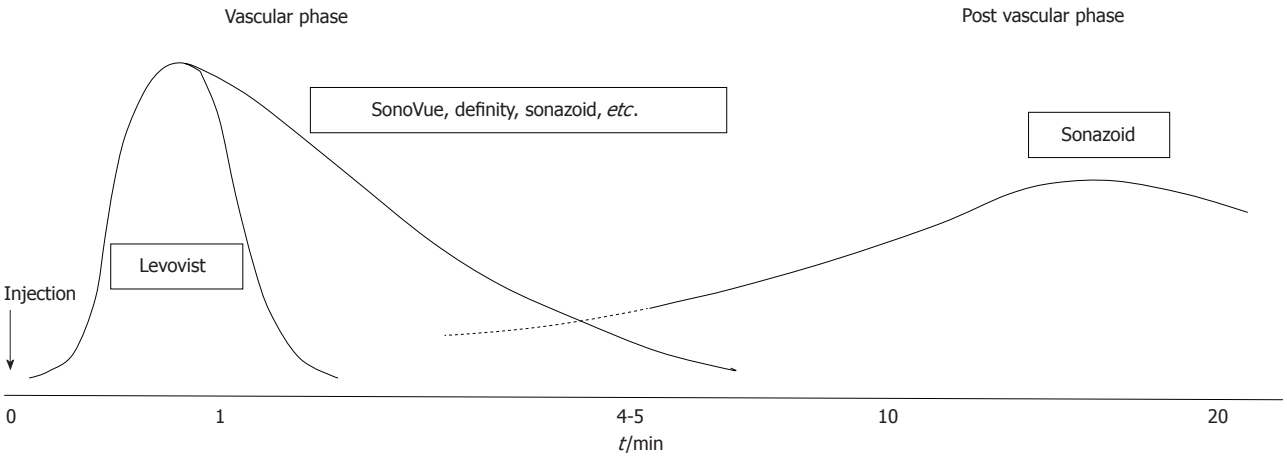

Figure 1 ***In vivo*** **kinetics of intravenous contrast ultrasound agents in the liver.**

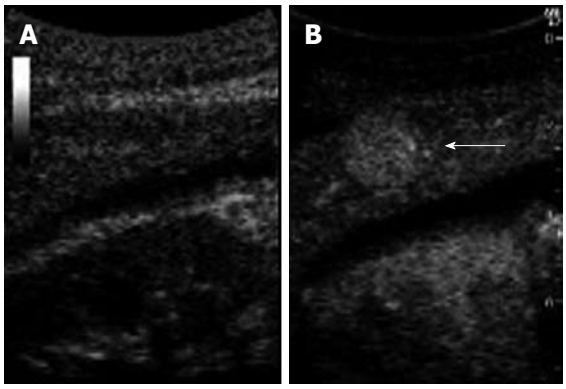

Figure 2 A 67-year-old man with a 1.5-cm hepatocellular carcinoma nodule located in segment 3 of the liver. A: B-mode ultrasound (US) cannot clearly depict the hepatocellular carcinoma (HCC) nodule; B: Contrast-enhanced US shows enhancement of HCC focus (arrow) in early vascular phase after administration of sonazoid.

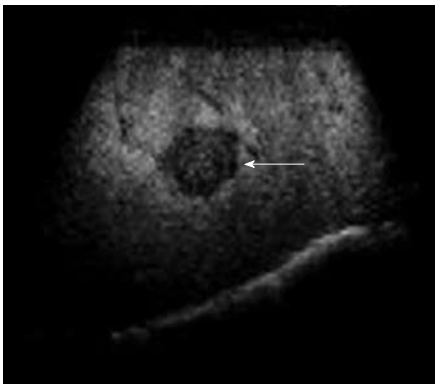

Figure 3 A 70-year-old man with a 2.0-cm hepatocellular carcinoma nodule located in segment 6 of the liver. Contrast-enhanced ultrasound using sonazoid shows the defect (arrow) imaging in post-vascular phase. The defect lesion can be targeted for insertion of a single needle by extending the time limitation.

Using second-generation contrast agents, real-time findings are better than those reported with Levovist[37] (Figure 1). Hypervascular HCC shows a short early arterial flushlike enhancement for less than 20 s, followed by homogeneous enhancement of the lesion in the late phase under low MI imaging (Figure 2). Needle insertion can be performed between the early arterial phase to late vascular phase in which maximum lesion conspicuity is observed[38]. In particular, HCCs have been visualized as defects in the liver parenchyma in the post-vascular phase only with Sonazoid use (Figure 1)[39-43]. Therefore, we can use these defect lesions as a target for insertion of a single needle (Figure 3). In patients who had previously undergone ablation for HCC, demonstration of viable nodules among all nodules detected in the post-vascular phase was achieved by injecting an additional new dose of Sonazoid in order to confirm tumor vascularity before needle insertion[44]. This defect-reperfusion US imaging is extremely useful in the depiction and confirmation of HCCs that are otherwise undetectable on US.

CLINICAL OUTCOMES

Treatment sessions and local tumor progression

Table 1 shows the treatment sessions of percutaneous ablation guided by contrast-enhanced US for HCC in published papers[12,36,45-49]. Numata *et al*[45] first reported that nine HCC nodules were successfully treated with percutaneous ablation therapy guided by intravenous contrast-enhanced US. These nine lesions were not detected on conventional US but were depicted on real-time contrast-enhanced harmonic gray-scale US with Levovist (incomplete local treatment, $n = 4$; small new lesion, $n = 5$). Since 2004, second-generation contrast agents of US have been used in percutaneous ablation guided by contrast-enhanced US. Particularly with Sonazoid use, complete tumor necrosis has been achieved in 94% with a single session of RF ablation[49]. In cases of HCC that are not clearly demarcated by B-mode US, dynamic contrast-enhanced sonography-guided RFA and are efficient approaches for guiding ablation.

Table 1 Treatment sessions of percutaneous ablation guided by contrast-enhanced ultrasound for hepatocellular carcinoma

Author[Ref.]	Year	Procedure	*n*	Contrast agent	Tumor size (mean, cm)	Treatment sessions (mean)
Numata *et al*[45]	2003	PEI, RFA	9	Levovist	1.4	ND
Minami *et al*[12]	2004	RFA	21	Levovist	1.7	1.05
Solbiati *et al*[46]	2004	RFA	51	SonoVue	ND	ND
Numata *et al*[47]	2008	RFA	15	Sonazoid	ND	1.04
Maruyama *et al*[48]	2009	PEI, RFA	42	Sonazoid	1.3	ND
Miyamoto *et al*[49]	2009	RFA	52	Sonazoid	ND	1.04
Minami *et al*[50]	2010	RFA	108	Sonazoid	1.7	1.1
Masuzaki *et al*[36]	2010	RFA	291	Sonazoid	1.6	1.33

HCC: Hepatocellular carcinoma; ND: Not described; PEI: Percutaneous ethanol injection; RFA: Radiofrequency ablation.

Table 2 Local tumor progression rates of percutaneous ablation guided by contrast-enhanced ultrasound for hepatocellular carcinoma

Author[Ref.]	Year	Procedure	*n*	Tumor size (mean, cm)	Follow-up (mean, mo)	Local tumor progression (%)
Maruyama *et al*[48]	2009	PEI, RFA	42	1.3	8.6	0
Minami *et al*[50]	2010	RFA	108	1.7	4.3	0
Masuzaki *et al*[36]	2010	RFA	291	1.6	ND	2.1
Miyamoto *et al*[51]	2010	RFA	17	1.6	11	12

HCC: Hepatocellular carcinoma; ND: Not described; PEI: Percutaneous ethanol injection; RFA: Radiofrequency ablation.

The local tumor progression rates after RFA have ranged from 0% to 12% during the follow-up period[47,36,49,50] (Table 2). The risk of local tumor progression increases with size, but the local tumor progression rates of small HCCs were markedly dependent on whether or not the center of the HCC nodule was penetrated by the RF needle.

Dynamic contrast-enhanced US guidance vs conventional B-mode US guidance

The effectiveness of contrast harmonic sonographic guidance for RFA of HCC was evaluated in comparison with conventional B-mode US guidance[12,36,51] (Table 3) (Level of evidence: grade B, level 2b). Dynamic contrast-enhanced US significantly helps in the placement of RFA electrodes in hypervascular HCCs that cannot be adequately depicted by B-mode sonography. In a randomized controlled study, the number of treatment sessions was significantly lower in the contrast harmonic US group (mean, 1.1 ± 0.2 *vs* 1.4 ± 0.6, $P = 0.037$)[51]. Treatment analysis showed that the complete ablation rate after a single treatment session was significantly higher in the contrast harmonic US group than in the B-mode US group (94.7% *vs* 65.0%, $P = 0.043$). Moreover, Masuzaki *et al*[36] reported in a large-scale study that the detectability of tumor nodules was 83.5% in conventional US and 93.2% in contrast-enhanced US ($P = 0.04$). The number of RFA sessions was 1.33 ± 0.45 with contrast-enhanced US as compared to 1.49 ± 0.76 in the historical controls ($P = 0.0019$). The number of RFA sessions required for complete ablation could be decreased in contrast-enhanced US-assisted RFA.

Few toxicities using US contrast agents have been reported, therefore the incidence of complications did not differ from that reported in patients treated by RFA alone[12,51].

Advances in techniques: Tumors abutting the diaphragm

HCC nodules abutting the diaphragm are difficult to depict because of ultrasound scatter due to pulmonary air. However, contrast-enhanced US through artificial pleural effusion can depict tumor vascularity in HCC. Thus, percutaneous RFA guided by contrast-enhanced US with artificial pleural effusion is an efficient approach[36,52]. Thirteen tumors were treated by contrast-enhanced US-guided RFA with artificial pleural effusion, and complete tumor necrosis was achieved in a single session in 12 lesions (92.3%)[52]. It took approximately 1 wk for pleural effusions to spontaneously resolve.

OTHER MODALITIES

Computed tomography guidance and computed tomography fluoroscopy

CT has high spatial resolution, good contrast, wide field of view, good reproducibility, and applicability to bony and air-filled structures. Potential advantages of CT guidance include confirmation of probe placement in relation to the tumor, improved visualization of the extent of ablation, and good correlation with actual lesion size[53-56] (grade C, level 3b). The use of a CT-guided method can be expected to reduce the rate of local tumor progression associated with percutaneous RFA. Laspas *et al*[53] reported that the ablation success rate was 87.3% (281/322 HCC nodules), and the survival rates at 1 year, 3 years and 5 years were 94.8%, 73.1% and 51.1%, respectively. Another merit is that the efficacy of treatment can be evaluated using contrast-enhanced CT immediately after treatment. Despite the advantages of CT, there are several limitations such as the increased time that is necessary for the procedure and exposure of the patient to ionizing radiation.

CT fluoroscopy guidance combines the high spatial resolution and good contrast resolution inherent in contrast-enhanced CT with the immediacy of fluoroscopic monitoring. Under CT fluoroscopy using either CT arteriography or iodized oil injection, we can target and puncture hepatic malignancies using a percutaneous ethanol injection needle. Real-time CT fluoroscopy is useful to guide the needle puncture and to monitor ethanol injection in small hepatic malignancies (grade C, level 3b). Takayasu *et al*[57] reported that the overall success rate in puncturing the lesions was 94.4% (17/18 sessions), the average number of punctures was 3.3, and this significantly decreased after the introduction of a puncture guide compared with freehand puncture ($P < 0.01$). However, the operator's hands are directly exposed to the beam of CT fluoroscopy, posing a potentially serious problem.

Magnetic resonance imaging guidance

MRI with its high soft tissue contrast can be advanta-

Table 3 Treatment sessions of radiofrequency ablation: Dynamic contrast-enhanced ultrasound guidance *vs* conventional B-mode ultrasound guidance

Author[Ref.]	Year	Study type	*n* (CEUS/B-mode)	Tumor size, (mean, cm) (CEUS/B-mode)	Mean treatment sessions (CEUS *vs* B-mode)	*P* value
Minami *et al*[12]	2004	Case control study	21/25	1.7/1.7	1.05 *vs* 2.0	0.002
Minami *et al*[53]	2007	RCT	19/20	1.2/1.3	1.1 *vs* 1.4	0.043
Masuzaki *et al*[36]	2010	Case control study	291/291	1.9/1.9	1.33 *vs* 1.49	0.0019

CEUS: Contrast-enhanced ultrasound; HCC: Hepatocellular carcinoma; RCT: Randomized controlled trial.

geous, and the capability of MRI for multiplanar imaging can be of value for needle placement and surveillance of the ablation procedure. Most of the current open MR scanners operate between 0.2 and 0.5 T, while clinical MR systems with a closed cylindrical design allow for significantly higher field strengths of up to 3.0 T or even more. While open MR systems allow for online monitoring of the puncture and easy replacement of the RF needle within a wide range, closed-bore MR systems improve lesion conspicuity and tumor delineation[58-63] (grade C, level 3b). Wu *et al*[59] reported that MRI and optical navigation system-guided ablation procedures were successfully performed on all 32 patients (36 tumor sites), and the 6- and 12-mo overall survival rates were 96.8% and 90.6%, respectively. Although MRI can be used to obtain reference images in ablation therapy, RF needle puncture is actually performed under sonographic guidance. Therefore, an MR-guided system can be used for ablation monitoring, but not for puncture guidance.

CO_2-enhanced ultrasound (ultrasound angiography)

CO_2-enhanced sonography is a sensitive means of detecting small HCC lesions. Kudo *et al*[64] reported that the detection rate of tumor hypervascularity on CO_2-enhanced sonography (86%) showed that it was more sensitive than digital subtraction arteriography (70%) and CT with iodized oil (82%). Imari *et al*[65] reported that CO_2-enhanced sonography is useful for the detection of hypervascular HCC and PEI treatment of lesions not detectable by conventional US. After direct intra-arterial injection of CO_2, enhancement of the tumor lasts approximately 10-60 min. This enhancement provides sufficient time to perform percutaneous ablation therapy (grade C, level 3b). Chen *et al*[66] reported that thirty-four (64.2%) of the 53 tumors showed complete necrosis after treatment, and the cumulative 1-, 2- and 3-year survival rates of patients who underwent CO_2-enhanced sonographically-guided percutaneous ethanol injection were 81%, 71% and 44%, respectively. However, nodules may become unclear because bubbles become trapped and accumulated in sinusoids with repeated injections of CO_2 microbubbles[67,68]. In addition, this method involves angiographic procedures that are invasive.

Virtual computed tomography sonography

Cross-sectional multiplanar reconstruction images from almost isovoxel volume data can be used for virtual sonographic visualization. This technique is available for patients with HCCs that became enhanced in the arterial phase of dynamic CT but were not well visualized with conventional B-mode US. Virtual CT sonography using magnetic navigation [real-time virtual sonography (RVS); HITACHI Medico, Tokyo, Japan] provides cross-sectional images of CT volume data corresponding to the angle of the transducer in the magnetic field in real-time[69-70]. RVS displays a real-time synchronized multiplanar CT image in precisely the same slice of the US plane. Thus, RVS can be used for real-time needle insertion guidance, especially for nodules demonstrated on CT, but not on US (grade C, level 3b). It has been reported that the technical success rate after a single treatment session was significantly higher in the virtual CT sonography group ($P = 0.017$)[71]. However, RVS has a weakness in that imaging gaps might be attributable to variations in the depth of breath-holding on CT and US examinations, as well as in the fact that the distance error between the magnetic sensor attached to the ultrasonic transducer and the magnetic generator becomes greater on intercostal US examination.

CONCLUSION

Percutaneous ablation therapy guided by dynamic contrast-enhanced US is an efficient approach for HCCs that are not clearly demarcated by B-mode US in both untreated and locally recurrent HCC cases. Moreover, second-generation microbubbles could facilitate dynamic contrast-enhanced US guidance of ablation therapy by extending the time limitation, simplifying the procedure, and improving detectability. RF ablation guided by second generation microbubble-enhanced US could become easier and be an efficient approach for hepatic malignancies that are not clearly depicted on B-mode US.

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