Original Article

Role of Contrast Enhanced Ultrasound in Radiofrequency Ablation of Metastatic Liver Carcinoma

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ABSTRACT

Objective: To investigate the application of contrast enhanced ultrasound (CEUS) in planning and guiding for radiofrequency ablation (RFA) for metastatic liver carcinoma (MLC).

Methods: One hundred and thirty-five patients with clinically and pathologically diagnosed MLC (from gastrointestinal tumors) were included in the present study, and 104 of them had received CEUS prior to RFA to assess the number, size, shape, infiltration, location and enhancing features of the lesions. Among the 104 patients, 21 (20.1%) were excluded from RFA treatment due to too many lesions or large infiltrative range based on CEUS. The remaining 83 patients with 147 lesions underwent RFA (group A). During the same period, other 31 patients with 102 lesions serving as control group were treated based on findings of conventional ultrasound without contrast (group B). The patients underwent follow-up enhanced CT at the 1st month, and then every 3–6 months after RFA. The tumor was considered as early necrosis if no contrast enhancement was detected in the treated area on the CT scan at the 1st month.

Results: In group A, 72 of 147 MLC lesions (48.9%) showed increased sizes on CEUS. Among them, 48 lesions (66.6%) appeared enlarged in arterial phase, and 24 (33.3%) showed enlarged hypoechoic area in parenchymal phase. CEUS showed total 61 additional lesions in 35 patients (42.1%) (ranged from 8 to 15 mm) compared with conventional ultrasound (US), and 42 (68.8%) of them were visualized in parenchymal phase only. There were total 208 lesions in group A underwent RFA with CEUS planning, and the tumor necrosis rate was 94.2% (196/208). In this group, local recurrence was found in 16 lesions (7.7%) during 3–42 months' following up, and new metastases were seen in 30 cases (36.1%). For group B, the tumor necrosis rate was 86.3% (88/102), local recurrence in 17 lesions (16.7%), and new metastases in 13 cases (41.9%). Tumor early necrosis and recurrence rates were significantly different between the two groups (P=0.018, P=0.016, respectively).

Conclusion: CEUS played an important role in RFA for liver metastases by candidate selecting and therapy planning, which helped to improve the outcome of the treatment.

Key words: Contrast enhanced ultrasound (CEUS); Liver metastasis; Radiofrequency ablation (RFA)

INTRODUCTION

In the past few years, focal therapy for metastatic liver carcinoma (MLC) has been widely used in clinical practice. Among the various therapeutic methods, radiofrequency ablation (RFA) chemotherapy demonstrated its value in treating MLC with poor responds because of its multi-advantages of controllable treatment temperature, less damage to liver function and repeatability[1-4]. Chemotherapy combined with RFA is considered as a potentially promising pattern in the future[5, 6]. Studies showed that imaging guidance was critical in RFA[7, 8]. Solbiati, et al. first reported their experience in using contrast enhanced ultrasound (CEUS) before, during and after RFA treatment, and pointed out CEUS represented a

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significant improvement in detection of lesions, selection of patients for treatment and all steps of tumor ablative treatment[9]. Studies from our center[10, 11] also showed CEUS could provide valuable clinical information for planning treatment protocol and improve the treatment success rate for hepatocellular carcinoma (HCC).

However, there are few reports on the value of CEUS before RFA treatment of MLC. MLC has special biological feature and different outcome compared with HCC. Thus, this study is aimed to investigate the value and application of CEUS in planning and guiding RFA for MLC.

MATERIALS AND METHODS

Patients

From February 2006 to July 2011, 135 patients with MLC from gastrointestinal (GI) tumors were included in the study. The inclusion criteria for RFA was: the extrahepatic primary tumors have been resected before RFA; CEUS or enhanced CT/MRI showed enhanced viable tissue in MLC lesions; lesion number should be not more than 6; for patient with 4–6 lesions, the largest one should be less than 3 cm; for patient with 1–3 lesions, the largest lesion should be smaller than 7 cm; tumor location should be more than 5 mm to nearby organ or big vessel; and in patient laboratory test, prothrombin time (PT) should be more than 50%, platelet count more than 5×10^9/L. Among the 104 patients who received CEUS, 83 were confirmed as candidates for RFA (group A). During the same period, other 31 MLC patients, who did not received pre-RFA CEUS examination, served as the control group (group B). In group A, there were 47 males and 36 females, aged 41–78 years (mean, 58.0±10.3 years). Sixty-four patients were diagnosed as MLC by pre-RFA biopsy or surgical pathology, and the remaining 19 were verified by combination of at least two imaging methods and clinical presentations, such as enhanced CT/MRI or CEUS. MLC size was 0.9–7.0 cm (mean, 3.8±1.7 cm), and there were 2.5 lesions in each patient on average. Seventy-three patients (87.9%) had received chemotherapy before RFA. In group B, there were 22 males and 9 females, aged 38–75 years (mean, 60.0±11.2 years). MLC size was 1.0–6.9 cm (mean, 3.7±1.4 cm), and average 2.9 lesions per patient. No statistic differences were observed with respect to clinical profile and previous therapies (Table 1).

Table 1. Patient clinical profile before RFA in two groups

Groups	*n*	Age (year)	Sex (M/F, *n*)	Tumor size (cm)	Tumor number (*n*)
A (CEUS)	83	58.0±10.3	47/36	3.8±1.7	2.5±0.5
B (control)	31	60.0±11.2	22/9	3.7±1.4	2.9±0.9
t or χ^2 values		0.93	2.45	0.62	1.68
P values		0.37	0.14	0.53	0.16

M: males; F: females

CEUS Equipment and Methods

CEUS was performed with IU-22 (Philips, USA), Logiq-9 (GE Healthcare, USA) and Aloka α-10 (Aloka, Japan) ultrasound systems. SonoVue (Bracco, Italy) was used as contrast agent with bolus injection of 2.4 ml via peripheral vein. After contrast injection, continuous real-time recording was conducted to document enhancing patterns of the lesions in each phase, approximately total 6–8 min. A quick and thorough scan of the whole liver was then performed to detect potential lesion during parenchymal phase. MLC's shape, number, size, infiltration range, location and relationship with adjacent structures were evaluated for RFA planning.

RFA Equipment and Methods

RFA was performed under sonographic guidance with Aloka-5000 (Aloka, Japan) and α-10 systems. Three RFA systems were used in the study, included RITA-1500 (RITA Medical System, Mountain View, CA, USA) with a 14 gauge radiofrequency (RF) electrode that is able to ablate a lesion of 5 cm within 20 min; Radionics Coop-tip RF system (Tyco, USA) with water circulation cooling system which is able to treat a 3 cm×4 cm lesion within 12 min; and Olympus RF Multipolar system (Celon, Germany) that provides even thermal distribution and allows the operator to preset output power and design ablating area. The Olympus system is also able to ablate a lesion of 5 cm within 20 min.

Percutaneous ultrasound-guided RFA was conducted while the patient was under conscious sedation in the outpatient department. One to three lesions were treated in each RFA session. In patients with more than 3 lesions, multiple sessions were needed. For lesions larger than 5 cm, only one lesion was ablated in each session. The ablation area should cover the tumor and at least 0.5 cm of the surrounding

tissue, and the margin should even be more than 1 cm when MLC border was unclear[12]. In lesions with feeding vessels shown on CEUS, "accumulative multiple ablations" were used at the vessel sites[13]. Patients' vital signs were monitored during the procedure.

All RFA procedures were performed by three sonologists with more than 10-year experience in ultrasound-guided liver interventions. Anesthetists provided moderate sedation for the patients during RFA with intravenous administration of 2.5–5.0 mg Midazolam (Roche; Basel, Switzerland) and 50–100 μg Fentanyl (Fentaini; Renfu, Yichang, China). Local anesthesia was induced by 5–15 ml of 1% lidocaine (Liduokayin; Yimin, Beijing, China). Some patients with tumors adjacent to the diaphragm, hepatic hilum or ligament felt obvious local and right shoulder pain when the ablation was extended. Intravenous infusion of propofol (Diprivan; Zeneca, Macclesfield, UK) 1–2 mg/kg was used to temporarily enhance anesthesia.

During the ablation procedure, patients' vital signs, such as blood pressure, heart rate, respiration, and oxygen saturation, were continuously monitored. Generally, the patients stayed in the procedure room for observation for an hour after RFA, and were followed by 1–3 d for further observation.

Evaluation of Tumor Response and Follow up

To evaluate the tumor response to RFA therapy, contrast-enhanced CT was performed 1 month post-ablation and the early tumor necrosis was considered to be achieved if the scans revealed: (1) the ablation zone was beyond the tumor borders; (2) the margin of the ablation zone was well-defined and smooth; and (3) no contrast enhancement was detected within or around the tumor. Subsequently, the patients were monitored regularly for intrahepatic recurrence in the outpatient clinic by a follow-up protocol including serum alpha-fetoprotein (AFP), abdominal ultrasound (US) and enhanced CT every 2–3 months in the first year, and then AFP every 2–3 months, abdominal US and enhanced CT every 4–6 months after the first year. Biopsy may be indicated if suspicious lesion was found. Each case in this group was followed up for at least three months. When contrast enhancement was detected in the ablation margin on CT scan, it was considered local tumor recurrence. Residual tumor or local recurrences were retreated if the patients' physical conditions allowed another RF ablation session. The ablation was considered failed if repeated RFA still can not control tumor growth.

Statistical Analysis

The data are presented as $\bar{x}\pm s$ (range) or number (percentage). The Chi-square test and Fisher's exact test were used to analyze the difference in early necrosis rate, local recurrence and new lesion incidence rates. For comparison of continuous variables, we used the independent-samples t test. SPSS 10.0 software (SPSS, Inc., Chicago, IL, USA) was used to conduct data statistical analysis. A P value <0.05 was considered statistically significant.

RESULTS

In 104 patients who received CEUS, 15 lesions of 7 patients showed no intra- or peri-lesion enhancement after 6–10 sessions of chemotherapy (Figure 1), and 6 lesions were confirmed as necrosis by biopsy. In other

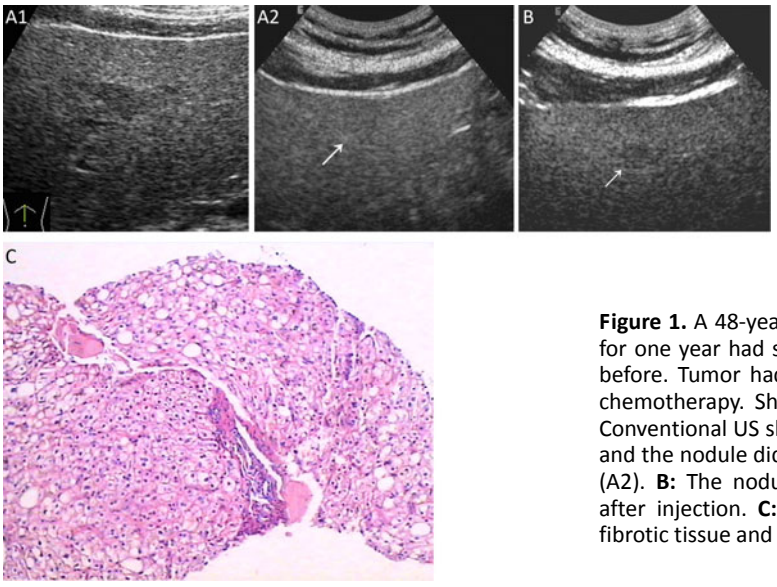

Figure 1. A 48-year-old female with liver metastasis for one year had surgery of colon cancer two years before. Tumor had no viability after six periods of chemotherapy. She was not candidate for RFA. **A:** Conventional US showed a small nodule in liver (A1) and the nodule did not enhance (↑) at artery phase (A2). **B:** The nodule slightly washed out at 4 min after injection. **C:** Biopsy pathology demonstrated fibrotic tissue and cell degeneration (HE, ×40).

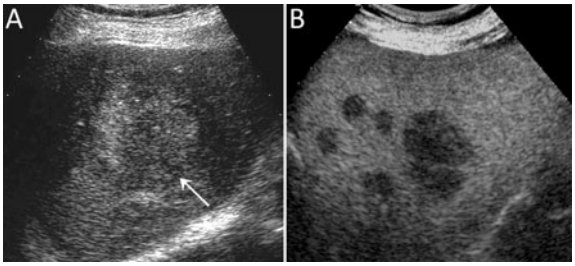

Figure 2. A 46-year-old male with liver metastasis from colon cancer. He was not candidate for RFA. **A:** Conventional US showed a heterogeneous solid tumor (↑) with a size of 6 cm. **B:** CEUS demonstrated multiple small metastases around the main tumor and the number of tumors increased to more than 6.

14 patients, CEUS showed either more than 7 MLC lesions in one patient, large lesion more than 7 cm, or tumor infiltration at the second liver hilum (Figure 2). These 21 patients (20.2%) were contraindicated for RFA after CEUS examination. The rest 83 patients with 147 MLC lesions underwent RFA and were included in group A.

In the 147 MLC lesions of group A, 53.7% showed nodular enhancement in arterial phase and turned hypoechoic in parenchymal phase (Figure 3), and 38.8% had ring-like enhancement in arterial and portal phase with enlarged echo-free area after wash-out (Figure 4). Only 7.5% lesions showed peripheral mild ring-like enhancement with poor-defined margin in parenchymal phase (Table 2).

Table 2. CEUS features of 151 MLCs

CEUS features	Number of MLC lesions (*n*, %)
Nodular enhancement and wash-out	79 (53.7)
Ring-like enhancement and wash-out	57 (38.8)
Peripheral mild ring-like enhancement	11 (7.5)

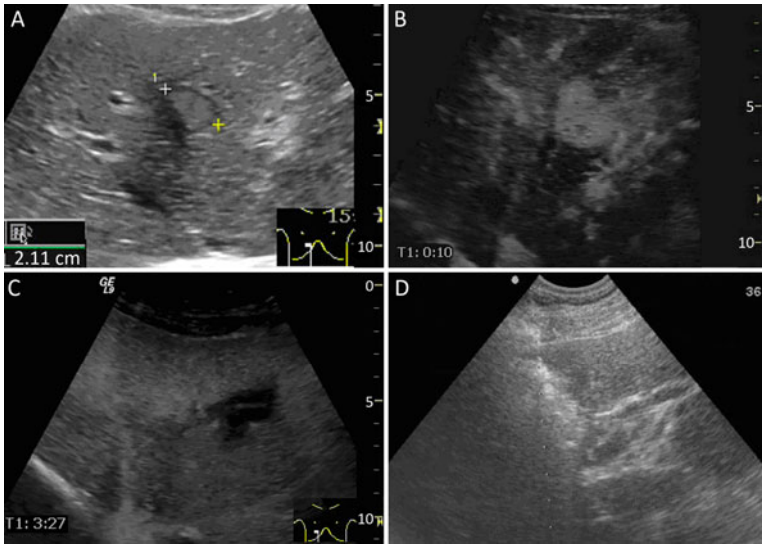

Figure 3. A 76-year-old male with liver metastasis from rectal cancer. **A:** Conventional US showed a 2 cm tumor with well defined margin in Segment IV. **B:** CEUS showed the enhanced tumor increased to 3.8 cm in size at artery phase. **C:** CEUS showed the tumor washed out and represented an irregular sphere at 196 seconds after injection. **D:** Extended ablation was performed to this tumor.

There were 72 MLC lesions (48.9%) showed enlarged sizes in CEUS, 48 (66.6%) shown in arterial phase, and 24 (33.3%) in parenchymal phase. Compared with the size shown in conventional sonogram, 32 MLCs (44.4%) appeared larger by 4–10 mm on CEUS, and 40 (55.6%) enlarged by 11–15 mm. CEUS detected 1–3 new lesions in 35 patients (42.1%), sizes ranged 8–15 mm, 67.7% of which were echo-free foci in parenchymal phase. For 208 MLC lesions in group A, RFA was planed based on CEUS findings (Tables 3 and 4).

There were 38 MLC (18.3%) in group A showed increased flow signals in or around the lesion on color Doppler ultrasound, 15 (7.2%) of which showed obvious feeding vessel in CEUS arterial phase.

Totally 148 RFA sessions were performed, including 95 sessions or 1.1/patient in group A and 53 sessions or 1.4/patient in group B (P>0.05). Eight patients in group A and 11 in group B underwent multi-session RFA (Table 5).

According to one-month enhanced CT, tumor necroses were obtained in 94.2% (196/208) of the patients in group A, and 86.2% (88/102) in group B (P=0.018). Local recurrence in 3–42 months' follow up period was seen in 7.7% (16/208) of the patients in group A, and 16.7% (17/102) in group B (P=0.016).

New developed MLC in group A was 36.1% (30/83) and 41.9% (13/31) in group B (P>0.05) (Table 6). RFA caused hemorrhage was seen in 3 patients (2.6%), including 1 in group A due to portal vein injury when ablating a nearby MLC, and 2 in group B during treating lesions near liver surface. Bleeding was controlled successfully in all 3 cases by ablation of bleeding site and conservative therapy. No RFA-related death occurred in this study.

Table 3. Size change of 151 MLC in CEUS (*n*, %)

MLC number	Enlarged lesion	Size change phase		Enlargement (mm)	
		Arterial	Parenchyma	4–10	11–15
147	72 (48.9)	48 (66.6)	24 (33.3)	32 (44.4)	40 (55.6)

Table 4. New MLC lesions showed on CEUS (*n*, %)

Patient number	Pre-CEUS MLC number	New MLC phase		New lesion size (mm)	
		Arterial*	Parenchyma	≤10	11–15
83	35 (42.1)	20 (32.3)	42 (67.7)	18 (29.1)	44 (70.9)

*including portal phase.

Table 5. Numbers of RFA sessions in group A and B

Groups	Patient (*n*)	MLC (*n*)	RFA sessions (*n*)	RFA session/patient
A (CEUS)	83	208	95	1.1
B (control)	31	102	53	1.4

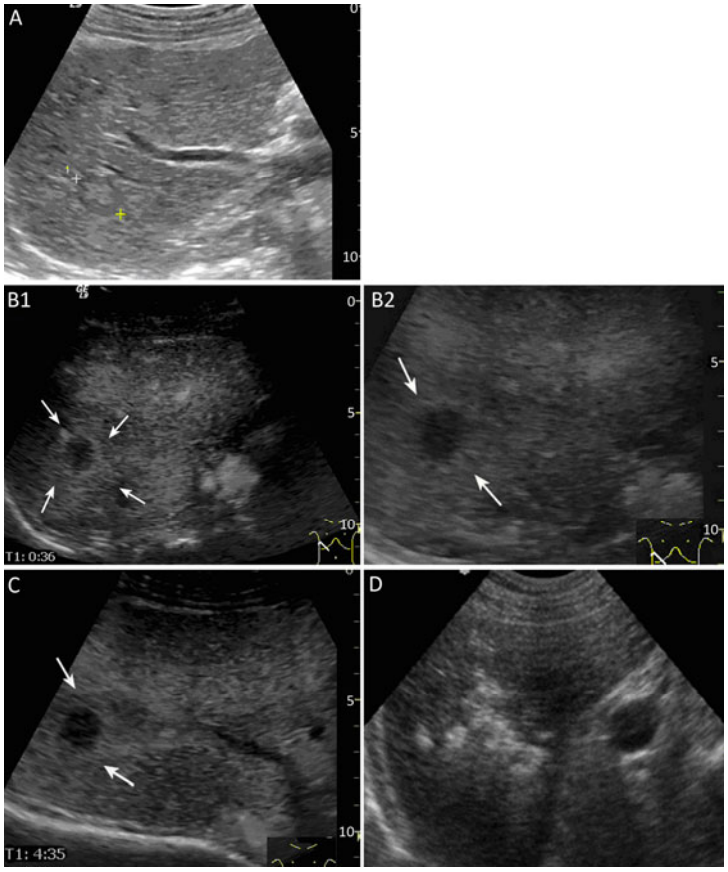

Figure 4. A 57-year-old male with liver metastasis from rectal cancer. **A:** Conventional US showed a 2.1 cm tumor with well-defined margin and "bull eye" sign in Segment VI. **B:** CEUS showed ring-like enhancement (↑) and enhanced range increased to 2.5 cm at 36 s (B1) and to 2.6 cm (↑) in portal phase (B2) compared with conventional US. **C:** CEUS showed the ring enhancement washed out and the hypoechoic range reached to 3.7 cm (↑). CEUS confirmed the tumor range demonstrated by conventional US was the necrotic area of the tumor. **D:** Extended ablation was performed to this tumor.

Table 6. RFA outcome for group A and B

Groups	*n*	MLC lesions (*n*)	Post-RFA necrosis		Recurrence (%)	New MLC (%)
			Lesions (*n*)	Rate (%)		
A (CEUS)	83	208	196	94.200	7.700	36.10
B (control)	31	102	88	86.200	16.700	41.90
χ^2 values				6.070	6.450	2.86
P values				0.018	0.016	0.17

DISCUSSION

Double blood supply of the liver makes it the most common organ with metastatic tumors. Traditionally, clinical treatment for MLC patients was mostly chemotherapy and/or radiation, which may not be applicable for all patients due to MLC location, number and poor general condition[2, 3]. Recently, with features of minimally invasive procedure, high necrosis rate, low complication rate, and repeatability, RFA has been widely used clinically[14].

Early stage small MLC is easily subjected to missed diagnosis on conventional US for its high incidence and no obvious symptom. For large-sized MLC, the overall outcome of RFA is not satisfactory because of poorly defined tumor margins and high recurrence. CEUS is a fast developing technology, which allows evaluation of liver microcirculation and tissue perfusion possible at capillary level[15, 16]. Studies showed that CEUS is sensitive in detecting MLC, and plays an important role in diagnosis and focal ablation of liver tumors. Additionally, CEUS has been shown to be of value in the assessment of patients who have received local therapy for HCC, particularly RFA. Solbiati, et al.[9] reported CEUS is important in RFA for liver cancer. Minami, et al.[8] reported their experience using CEUS in HCC cases with indistinct border, indicating that CEUS can improve detection and localization of the target lesion. Studies of our center also showed similar results in HCC [10, 11]. So far, there are few reports on the value of CEUS before RFA treatment of MLC. As shown in the present study, CEUS is demonstrated useful in RFA candidate screening and therapy planning in RFA for MLC.

CEUS for RFA Candidate Screening

Approximately 25%–50% of cancer patients had liver metastases when they were firstly diagnosed[17]. Therefore early detection of MLC is important for patient management. Clinical research showed that second harmonic imaging of CEUS provides useful information of tissue perfusion in both normal and abnormal liver parenchyma, and helps to differentiate lesion from surrounding tissue. Using low mechanical index (MI) real-time imaging, it is possible to monitor hemodynamic changes of tumor feeding vessels and perfusion of microcirculation, which improve early detection rate. In our data, 53.7% of the lesions showed arterial nodular enhancement in CEUS and became hypoechoic during wash-out phase, 38.8% were portal phase circular enhancement with echo-free appearance in wash-out phase, and 7.5% with mild circular enhancement without significant wash-out. The results indicate that findings of CEUS enhancement in arterial/portal phase are helpful in the diagnosis of MLC.

Large-sized and multi-focal MLCs are major factors affecting RFA outcome. In our data, among the 104 patients underwent CEUS screening, 14 were identified as non-RFA candidates due to more than 7 MLC lesions, or invasion area larger than 8 cm, or tumor infiltration of second liver hilum. CEUS is a sensitive tool not only for morphology, but also for tissue microcirculation evaluations, especially in thorough liver scanning during parenchymal phase. Small-sized tumor can usually be sensitively detected because there is little portal supply in small MLC lesion, causing its wash-out in parenchymal phase faster than normal liver. The small MLC cannot be well visualized with traditional gray scale ultrasound. And spatial and contrast resolution of CT and MRI also limit their capability in detecting small MLC[18]. Compared with conventional US and CT, additional 61 lesions were detected in 19 patients on CEUS in group A. These lesions were all smaller than 1.5 cm, and 67.7% of them were hypoechoic or echo-free in parenchymal or delayed wash-out phases. Therefore, the parenchymal phase seems to be a good period for early detection of small MLC. It is difficult to differentiate small MLC on initial CEUS, but additional injection of 1 ml contrast agent may be helpful for repeated evaluation of its features in arterial phase. Our data showed CEUS is better than conventional US in detecting small MLC. Pre-RFA CEUS provides accurate information of the number and location of MLC.

CEUS of RFA Planning

Most studies showed that it is helpful to ensure

RFA treated area 0.5–1.0 cm beyond tumor margin in reducing recurrence. Conventional US has difficulty in accurate measurement of tumor with poorly defined margins. CEUS is proved to be able to identify precise tumor margin and scope of infiltration of HCC, especially for those without capsules[10]. In our data, 72 MLCs (48.9%) showed larger sizes on CEUS, and 66.6% of them showed enlargement in arterial and portal phases with more significant enlargement than HCC. CEUS findings of MLC enlargement showed correlation with histology features of the lesion, where the MLC enhancing pattern on CEUS corresponds to its "bull eye sign" on conventional gray scale ultrasound due to possible central necrosis of the lesion (Figures 3 and 4). In our series, 33.3% MLCs showed enlargement in parenchymal phase. It may reflect the real invasive range of MLC when MLC showed mild ring-like enhancement in arterial phase, followed with enlargement of the hypoechoic area in parenchymal phase. Pathologically, there is no capsule in most MLCs due to tumor cell growth along the blood pool or Disse space in the lesion periphery[19], which makes imaging evaluation of tumor infiltration difficult. The capability of CEUS in demonstrating microcirculation of MLC improves identification of tumor margin and size, therefore provides important information for RFA planning.

MLC from hypovascular primary tumor usually showed ring-like enhancement on CEUS, and biopsy showed tumor infiltration in lesion periphery with central necrosis. On CEUS, the ring-like enhanced region appeared enlarged, while the hypo- or anechoic area without enhancement was verified as necrosis. Increased RFA area is required for these lesions to ensure complete ablation. MLC from hypervascular primary tumor usually showed nodular enhancement on CEUS, indicating hypervascularity in the lesion, and RFA with overlapping ablation was needed in these lesions. In group A, RFA was planned based on CEUS enhancing features of the MLC. Fifteen MLCs (7.2%) showed major feeding arteries in arterial phase of CEUS. In our center, we utilized focal "overlapping ablation" method for these lesions, the procedure is: 2–3 cm small ablating foci using high power were created at the inlet of feeding vessel to block the blood supply firstly; and regular ablation was performed for the rest lesions under the circumstance of decreased perfusion[13].

The average RFA session per lesion was 1.1 in group A and 1.4 in group B. Group A showed higher tumor necrosis rate of 94.2% (86.2% in group B, P=0.018) and lower recurrence rate of 7.7% (16.7% in group B, P=0.016). The result correlated with the sufficient ablation of peripheral tumor infiltration in group A based on CEUS findings, while in group B, ablation was indicated by conventional US findings only. Although the new MLC rate in group A screened by pre-RFA CEUS was a little lower than that in group B (36.1% vs. 41.9%, P>0.05), there was no statistical difference between the two groups.

CEUS is sensitive in detecting small MLC and provides information of tumor features, such as size, number, location, focal infiltration, central necrosis and blood supply. This information is critically helpful in selecting candidates and planning protocol for RFA. Therefore, CEUS may serve as an important auxiliary method for RFA in improving the tumor necrosis outcome and reducing recurrence rate of RFA in MLC.

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