Is Contrast-Enhanced US Alternative to Spiral CT in the Assessment of Treatment Outcome of Radiofrequency Ablation in Hepatocellular Carcinoma?

Kontrastmittelsonografie als Alternative zum Spiral-CT bei der Beurteilung des Therapieerfolg nach Radiofrequenzablation des hepatozellulären Karzinoms?

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Key words
- neoplasms
- abdomen
- CT
- ultrasound
- radiofrequency

Zusammenfassung

Ziel: Die vorliegende Studie diente dem Ziel, die Wertigkeit der Kontrastmittelsonografie mit niedrigem mechanischem Index bei der Beurteilung des Therapieerfolgs der perkutanen Radiofrequenzablation des hepatozellulären Karzinoms im Vergleich mit dem 4-zeiligen Spiral-CT zu ermitteln.

Material und Methoden: 100 aufeinanderfolgend vorgestellte Patienten (65 Männer und 35 Frauen, Alter: 62 – 76 Jahre) mit hepatozellulärem Karzinom (mittlere Tumorgröße 3,7 ± 1,1 cm SD) wurden mit gekühlter Radiofrequenzablation behandelt. Das Behandlungsergebnis wurde einen Monat nach dem Eingriff mit kontrastmittelgestütztem Dreiphasen-Spiral-CT sowie der Kontrastmittelsonografie mit niedrigem mechanischem Index nach Injektion eines Bolus von 2,4 ml SonoVue (Bracco, Mailand) untersucht. 60 von 100 Patienten wurden 3 Monate später nachuntersucht. Die kontrastgestützten Sonografieaufnahmen wurden von zwei verblindeten Radiologen zusammen begutachtet. Sensitivität, Spezifität, NPV und PPV der Kontrastmittelsonografie wurden ermittelt.

Ergebnisse: Nach der Behandlung stellte die Kontrastmittelsonografie eine persistierende Signalverstärkung bei 24 Patienten dar (24%), wohingegen bei den übrigen 76 Patienten (76%) keine Anreicherung innerhalb des Tumors festgestellt werden konnte. Im Vergleich mit dem CT als Goldstandard lagen Sensitivität, Spezifität, NPV, and PPV der Kontrastmittelsonografie bei 92,3% (95% CI = 75,9 – 97,9%), 100% (95% CI = 95,2 – 100%), 97,4% (95% CI = 91,1 – 99,3%) und 100% (95% CI = 86,2 – 100%).

Schlussfolgerung: Die Kontrastmittelsonografie mit niedrigem mechanischem Index und der Anwendung von SonoVue stellt ein brauchbares Instrument für die Bewertung des Therapieerfolgs der Radiofrequenzablation beim hepatozellulären Karzinom dar mit einer Genauigkeit, die der des 4-zeiligen Spiral-CT vergleichbar ist.

Abstract

Purpose: The present study was conducted to assess the efficacy of contrast-enhanced ultrasound with low mechanical index in evaluating the response of percutaneous radiofrequency ablation treatment of hepatocellular carcinoma by comparing it with 4-row spiral computed tomography.

Materials and Methods: 100 consecutive patients (65 men and 35 women; age range: 62 – 76 years) with solitary hepatocellular carcinomas (mean lesion diameter: 3.7 cm ± 1.1 cm SD) underwent internally cooled radiofrequency ablation. Therapeutic response was evaluated at one month after the treatment with triple-phasic contrast-enhanced spiral CT and low-mechanical index contrast-enhanced ultrasound following bolus injection of 2.4 ml of Sonovue (Bracco, Milan). 60 out of 100 patients were followed up for another 3 months. Contrast-enhanced sonographic studies were reviewed by two blinded radiologists in consensus. Sensitivity, specificity, NPV and PPV of contrast-enhanced ultrasound examination were determined.

Results: After treatment, contrast-enhanced ultrasound identified persistent signal enhancement in 24 patients (24%), whereas no intratumoral enhancement was detected in the remaining 76 patients (76%). Using CT imaging as gold standard, the sensitivity, specificity, NPV, and PPV of contrast enhanced ultrasound were 92.3% (95% CI = 75.9 – 97.9%), 100% (95% CI = 95.2 – 100%), 97.4% (95% CI = 91.1 – 99.3%), and 100% (95% CI = 86.2 – 100%).

Conclusion: Contrast-enhanced ultrasound with low mechanical index using Sonovue is a feasible tool in evaluating the response of hepatocellular carcinoma to radiofrequency ablation. Accuracy is comparable to 4-row spiral CT.

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary hepatic malignancy and one of the most prevalent visceral malignancies worldwide with an estimated annual number of cases of more than 500000 [1]. Surgical resection has long been considered the only treatment providing the greatest potential for cure in patients with HCC. Unfortunately, most patients with HCC are not candidates for surgery because of large tumour size, location of lesions making resection difficult, multifocal disease, inadequate liver reserve, or co-morbid medical conditions precluding a safe operation [2].

The development of non-surgical local ablative techniques has provided a new therapeutic option, which aims to eradicate the tumour completely. Radiofrequency thermal ablation has proved to be safe and effective for the treatment of hepatic tumours in patients considered unsuitable for surgical interventions, and the method has gained tremendous popularity all over the world over the past 5 years [3 – 6]. Close follow-up of radiofrequency thermal (RF) ablation by imaging, however, is crucial both to guarantee that the tumour tissue is completely ablated and to detect early recurrences which may be treated with repeated ablation. Therefore, post-treatment follow-up is currently performed with more expensive tools such as contrast enhanced CT or MRI [1]. More specifically, multiphasic helical CT at least 4 weeks after treatment is currently accepted as the standard imaging modality in this setting [7]. Since radiofrequency ablation is generally performed under US-guidance, however, it would be preferable to assess the treatment response using sonographic techniques.

Today, the development of new sonographic technologies, and the introduction of second generation sonographic contrast media such as Sonovue™ (Bracco, Milan, Italy) have opened new prospects in the evaluation of the therapeutic response to ablation therapy [8, 9].

The purpose of our study is to assess the reliability of CEUS in the evaluation of the response to RF ablation therapy in patients with HCC using 4-row helical CT as the gold standard imaging modality.

Materials and methods

Patients

From January 2001 and May 2004, 100 consecutive patients (65 men and 35 women; age range: 62 – 76 years) with HCC underwent radiofrequency thermal ablation therapy. Eighty patients had cirrhosis (50 with Child A and 30 with Child B), and 20 patients had chronic hepatitis. All patients were deemed ineligible for surgery by the referring surgeon [2].

All patients presented with a solitary lesion measuring 3.7 ± 1.1 cm (2.6 – 4.8 median 3.4 cm). The pre-treatment work-up of the patients included continuous, real time contrast-enhanced examination at low-mechanical index (MI) with and without Sonovue, triple phase helical CT, measurement of α-fetoprotein (NV: < 200 mg/ml) and bilirubine (NV: < 1.0 mg/dl) levels. Biopsy confirmation was obtained in 20 patients because their α-fetoprotein levels were less than 200 mg/ml (range: 30 – 180 nm/ml) and their CT findings were equivocal. In the remaining patients, helical CT demonstrated contrast enhancement patterns typical of HCC and the α-fetoprotein level was higher than 200 ng/ml (200 – 800 ng/ml).

Radiofrequency Ablation Technique

Written investigational review board approval was obtained before initiation of the study, and written informed consent for the treatment was obtained in all patients.

The ablation procedures were performed with a 2 – 5 MHz convex-array transducer under real-time sonographic guidance (Technos Mpx; Esaote, Genova, Italy; Toshiba Aplio VX, Osaka, Japan; Acuson Sequoia, Siemens Erlangen, Germany), by using the free-hand technique. The patient was monitored continuously before, during and after the procedure.

RF ablation was performed as an inpatient procedure in all patients. Local anaesthetic (Lidocaine) was injected along the predetermined needle insertion route from the skin to the hepatic capsule. In 82 patients, the RF ablation procedure was performed with intravenous sedation consisting of 2 – 5 mg of midazolam and 100 – 300 µg of fentanyl while the cardiovascular and respiratory systems were continuously monitored. In 18 patients, a potentially more painful procedure was anticipated because of tumour location very close to the liver capsule or close to the diaphragm. These patients were treated under deep sedation with propofol, with the assistance of an anaesthesiologist.

Coagulation status was checked before the procedure in every patient. After the patient's skin was cleansed with iodised alcohol, the most appropriate approach to target the lesion was chosen. Then, a 20-cm long, 18 gauge internally cooled radiofrequency electrode (Radionics, Burlington, MA) with 2 – 3 cm of exposed metallic tip was used to deliver the radiofrequency to the tissue. Seventy lesions were treated using just a single electrode, and 30 larger lesions (≥ 4 cm) were treated with triple-cluster electrodes. Grounding was achieved by attaching a dispersive pad with a surface area greater than 400 cm^2 to each of the patient's thighs. The electrode was then attached to a 500-kHz, 200-W radiofrequency generator (Radionics, Burlington, MA). During lesion ablation, a thermocouple embedded in the electrode tip continuously measured the local temperature. Tissue impedance was monitored continuously by means of circuitry incorporated in the generator. For lesions measuring less than 3 cm, one application was sufficient; for larger lesions, up to three insertions were required during the same session. The mean total procedure time was approximately 40 min per session. Before taking out the probe, the ablation of the puncture line was performed to prevent tumour cell metastasis.

After RF ablation, patients were kept under close observation for 48 hours and were then discharged if no complications had been observed. Liver function and complete blood counts tests were performed within 24 hours after the procedure.

Follow-up of the patients

To assess the effectiveness of the radiofrequency ablation therapy, all patients underwent low-mechanical index US examination with Sonovue (Bracco, Milan, Italy) and contrast-enhanced 4-row spiral CT, 1 month after the procedure.

Lack of enhancement throughout the entire lesion during the contrast-enhanced sonographic examination was considered the hallmark of complete necrosis. Another important criterion for complete ablation was the evolution over time of the size of the defect. Therefore, if size remained stable or decreased, without signs of contrast-enhancement, the lesion was considered completely ablated. The lesions were considered partially necrotic when the margins were ill-defined and the peripheral viable tumour tissue maintained the characteristic enhance-

ment behaviour of native nodules; these patients underwent a second radiofrequency treatment session. All patients were re-evaluated with CT 3 – 6 months later (i. e., at 8 – 10 months). Biopsies were not performed.

Follow-up evaluation

Patients were examined using the same US equipment previously indicated. For each session, the sonographic examinations consisted of conventional grey-scale imaging to identify anatomic landmarks; then one real-time continuous examination with at low MI examination, after administration of one bolus of SonoVue. SonoVue was administered as an intravenous hand-injected fast bolus of 2.4 ml, followed by 3 cc of saline flush. Technical parameters (Toshiba Aplio XV, CHI Contrast; Technos MPX, Contrast Tuned Imaging; Acuson Sequoia, Cadence Contrast Pulse Sequencing) for contrast-specific technique were: low transmit power (0.09 – 0.14); dynamic range (65 – 90 dB); temporal resolution between frames, 75 – 100 milliseconds (10 – 20 frames/sec); echo-signal gain below noise visibility; signal persistence turned off and one focus below the level of the tumour.

SonoVue was administered as intravenous hand-injected fast bolus of 2.4 ml, followed by 3 cc of saline flush. After injection of Sonovue, and when the first microbubble signal intensity appeared in the liver parenchyma, the patient was instructed to hold his or her breath so as to minimize any significant change in the position of lesion. Images in the ideal scanning plane were displayed in a real-time fashion by slightly changing the scanning plane to portray the whole area of the nodule.

The true subtraction effect can be obtained only with lower MI (0.04 – 0.2); this is the reason why this technique is called "Very Low Mechanical Index (VLMI). This technique is based on signal amplitude subtraction (and not only frequency subtraction), and it is possible because two different components are combined: the harmonic signal coming from SonoVue™, and the dynamic threshold of low amplitude signals which suppress the low amplitude signals returning to the transducer. During contrast-enhanced evaluations, the entire vascular phase was studied continuously, consisting of an arterial phase (15 – 45 sec after the injection), a portal venous phase (50 – 90 sec), and a late phase (90 sec to 4 – 5 min). Our scanning technique was stationary in the region of the lesion, allowing the visualisation of macro- and microcirculation of the lesion, as a result of the blood pool characteristics of SonoVue. A second injection of contrast medium was given about 10 minutes later and was performed in order to evaluate the remaining liver parenchyma to assess any other lesions.

The entire examination was recorded on video home system (VHS) tapes, with still images recorded on the optic disk. These images were subsequently reviewed on a frame-by-frame basis. Subsequently, all patients underwent a triple phase contrast-enhanced spiral CT examination with a 4-row spiral scanner (Somatom Plus 4 Volume Zoom, Siemens, Erlangen, Germany) within one week from the day of the contrast-enhanced examination. CT was performed using a helical technique (pre-contrast acquisition parameters: 5 mm-thick sections, 5 mm collimation, 1:1.4 pitch, 120 – 140 kVp, 220 – 280 mA; arterial phase parameters acquisitions: 1 mm-thick sections, 1-mm collimation; portal phase: 1-mm collimation; 1-mm thick sections). Unenhanced images were acquired first and were followed by dual-phase contrast enhancement during the power injection of 130 – 150 mL of iopamidol (Iopamiro; Bracco, Milan, Italy) at the rate of 3 – 4 mL/sec. The entire liver was scanned twice: first at 22 ± 5 sec, and then at 60 – 70 sec (portal phase) after the initiation of contrast injection.

Image analysis

Complete response was defined as the absence of enhanced tumoural areas reflecting complete tissue necrosis. Treatment failure was defined as the persistence of contrast enhancement within the tumoural area after completing treatment [1, 7, 10 – 12]. The videos were analysed off-side by two experienced observers in a consensus fashion, blinded to clinical and other imaging data, both experienced in contrast ultrasound imaging of the liver.

Results were tabulated, and positive findings were compared. Sensitivity, specificity, positive and negative predictive value of low MI contrast-enhanced sonography were calculated along with 95% confidence intervals by accepting CT imaging evaluated by two experienced radiologists as gold standard.

Results

One month after effective treatment, well-demarcated areas of low attenuation with no enhancement of tumour vessels or tumour parenchymal flow, representing complete therapeutic success, were demonstrated by spiral CT in 74 in patients (74%). This result was thereafter confirmed in all but 5 patients, by re-evaluation at 3 – 6 months (**Fig. 1a–d**). Areas of enhancement at the tumour periphery suggesting residual viable tumour were identified in 26 patients (26%) (**Fig. 2a–d**). All patients with viable residual tumour tissue underwent a second radiofrequency ablation, and all but one (who developed multiple lesions) had no evidence of local tumour recurrence 3 months after the second treatment. Thus, a complete treatment was achieved in 99/100 (99%) of the patients recruited in this study, with an average of 1.4 therapy sessions per patient. Regarding tumour size measurements, the lesions measured 4.8 ± 1.1 cm at CEUS and 4.9 ± 1.1 cm at CT, and at 3 months, 4.6 ± 1.1 cm and 4.5 ± 1.1 cm at CEUS and CT, respectively. In 53 out of 80 patients in whom pre-treatment values of α-fetoprotein were more than 200 mg/ml, the α-fetoprotein levels decreased, whereas in the remaining patients the α-fetoprotein levels ranged between200 and 400 mg/ml. Treatment monitoring with CEUS allowed detection of residual tumour enhancement in 24 (24%) of the 100 lesions. The residual viable tumour appeared during the dynamic continuous observations as: 1. enhancing foci during the early arterial phase (20 – 38 sec), with subsequent washout during the portal phase (50 – 70 sec) and thus becoming indistinguishable from the treated tumour. Morphology and dimensions of these persistent foci on US were identical to their appearance on CT imaging in all 24 patients (100%). Contrast-enhanced sonographic examination did not show any signs of enhancement in the remaining 76 lesions (76%). In summary, with CT as the reference imaging modality, the resulting sensitivity, specificity, negative predictive value, and positive predictive value of contrast enhanced sonographic examination were 92.3% (95% CI = 75.9 – 97.9%), 100% (95% CI = 95.2 – 100%), 97.4% (95% CI = 91.1 – 99.3%), and 100% (95% CI = 86.2 – 100%), respectively (**Table 1**). At 3 months' follow-up, 5 patients showed recurrence of tumour elsewhere within the liver parenchyma, clearly detected by both contrast-enhanced sonography and spiral CT.

None of the patients experienced side effects of contrast agent application, and the contrast-enhanced studies were considered of sufficient diagnostic quality in all patients.

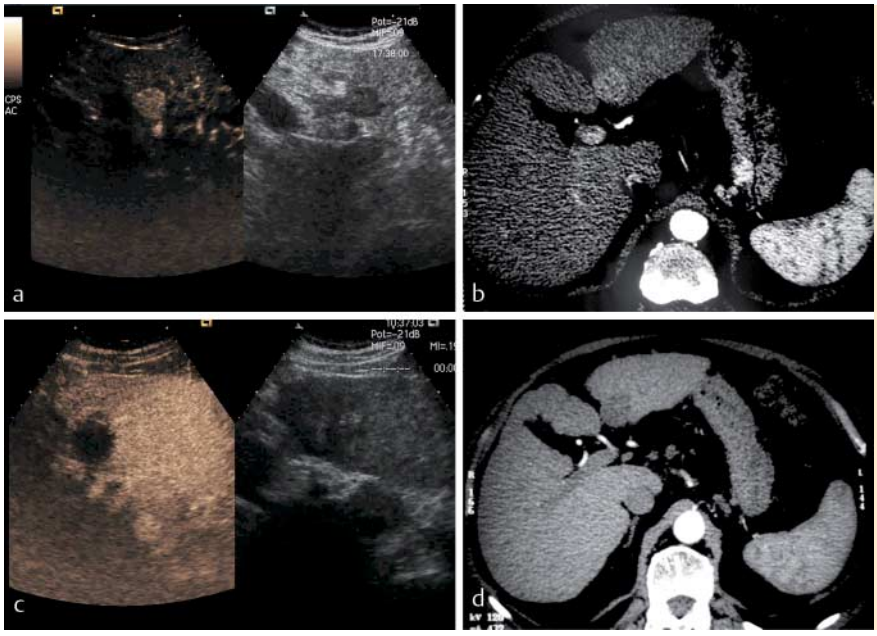

Fig. 1 **a** Pre-RF treatment: hypoechoic lesion at baseline US (right side) which shows strong arterial enhancement at CEUS (left side). **b** Pre-RF treatment RF: arterial phase at CECT confirms strong enhancement. **c** After RF ablation: no contrast uptake in arterial phase at CEUS. **d** After RF ablation: no enhancement in the arterial phase at CECT.

Abb. 1 **a** Vor RF-Behandlung: Echoarmer Tumor im Nativultraschall, der bei der Kontrastmitteluntersuchung eine starke arterielle Kontrastverstärkung zeigt (links). **b** Vor RF-Behandlung: Die arterielle Phase im Kontrastmittel-CT bestätigt die starke Kontrastanreicherung. **c** Nach RF-Ablation: Keine Kontrastmittelaufnahme in der Kontrastmittelsonografie. **d** Nach RF-Ablation: keine Anreicherung in der arteriellen Phase im Kontrast-CT.

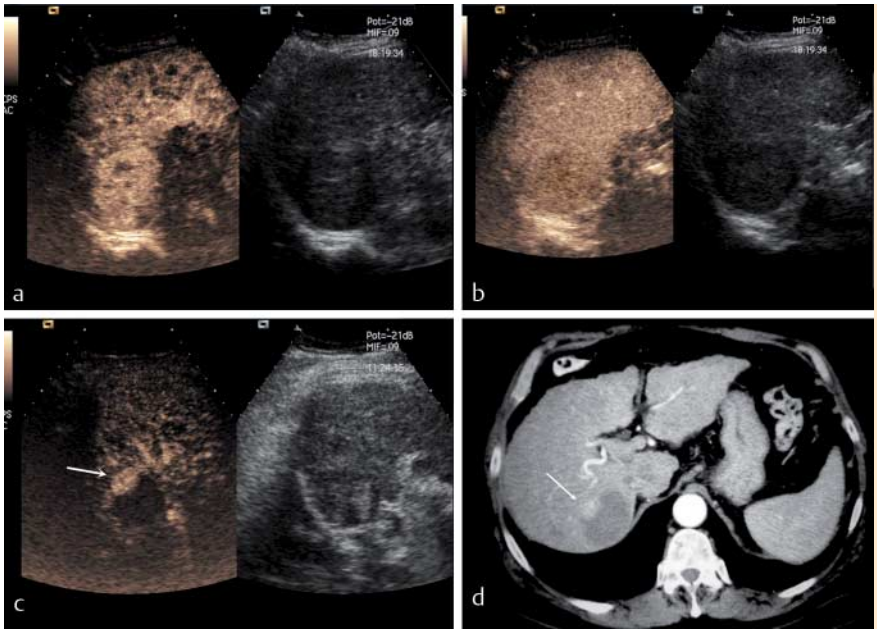

Fig. 2 **a** Pre-RF ablation: CEUS shows an hypervascular hepatic lesion during the arterial phase. **b** Pre-RF ablation: almost complete wash-out during the portal phase. **c** Post-RF treatment: arterial phase of CEUS shows the presence of local recurrence (arrow). **d** After RF treatment: arterial phase of CT (arrow indicates recurrence).

Abb. 2 **a** Vor RF-Ablation: Die Kontrastmittelsonografie zeigt einen hypervaskularisierten Leberherd während der arteriellen Phase. **b** Vor RF-Ablation: fast vollständiges Auswaschen während der portalen Phase. **c** Nach der RF-Ablation: Die arterielle Phase des Kontrastmittelultraschalls zeigt ein Lokalrezidiv (Pfeil). **d** Nach RF-Ablation: die arterielle Phase im CT (der Pfeil markiert das Rezidiv).

Table 1 Complete response according to CT at 1 month.

CT at 1 month	CEUS at 1 month
CR[1]	
n = 74	n = 76
n = 26	n = 24
sensitivity (%)	92.3%
specificity (%)	100%
PPV (%)	100%
NPV (%)	97.4%

[1] CR = Complete Response.

Minor complications were observed in 18 patients and included mild pain, lasting between 3 and 9 hours after the procedures (n = 12) and moderate fever (temperature below 38 °C) (n = 5), which were treated with non-steroidal anti-inflammatory drugs. One patient, with a lesion close to the diaphragm, developed moderate right pleural effusion which caused mild chest pain; the effusion required no treatment and resolved within three weeks while the pain slowly resolved in 48 hours. No major complications were observed.

Discussion

Regarding HCC, minimally invasive therapeutic techniques are selected on the basis of the size, position and number of the lesions, patient's general condition, and clinical stage of the disease [13, 14]. As an alternative to surgical resection, radiofrequency ablation induces in situ thermal coagulation necrosis through the delivery of high-frequency alternating current to the tissue. Accuracy in assessing treatment response is essential for determining the necessity of additional therapy to complete the treatment. To date, computed tomography (CT) has been used most frequently to assess the effectiveness of tumour treatment and to identify early recurrences which might

benefit from re-ablation. Complete ablation creates an area of necrosis which, at CT, shows low attenuation compared with the surrounding liver tissue, is often homogeneous, and has smooth margins. The most important features to be considered are the size of the necrotic defect, which, immediately after treatment, should be larger than the pre-treatment tumour, and the sharpness of the margins, which indicates an abrupt change in attenuation between necrotic and surrounding tissue. Over time, the size of the defect remains stable or decreases, whereas any variation from these general patterns is suggestive of incomplete ablation or recurrence.

Colour-Doppler US has long been employed to assess liver tumour vascularity [15]; despite the improved results achieved with the use of newer Doppler US technologies, such as power Doppler imaging, however, reliable assessment of intra-tumoural blood flow was not possible, particularly when the lesions were too small, located deep down in the liver parenchyma, or located in the left lobe because of motion artefacts from cardiac pulsation [16, 17]. Recently, the combination of ultrasound contrast agents with harmonic imaging has been shown to be useful in reducing flash artefacts of power Doppler imaging and for increasing the sensitivity for detection of small, tumour vessels with low-velocity [18, 19]. Nevertheless, previous reports on conventional contrast enhanced power Doppler sonography to assess the efficacy of RF treatment of HCC showed no encouraging results [20].

Phase-inversion or pulse inversion harmonic US imaging technique is a microbubble-specific approach which overcomes the conflicts between the requirements of contrast and spatial resolution in harmonic imaging and thus provides greater image clarity [21 – 24].

Meloni et al. [12] demonstrated that this sonographic technique increased the sensitivity of sonographic detection of residual tumour tissue by 50%, from 33.3 to 83.3%. Recently, real-time grey-scale harmonic US imaging has become available owing to the recent development of the coded excitation mode [21] in which phase-inversion harmonic US imaging is combined with coded technology. Wen et al. [25] compared contrast-enhanced US and spiral CT in the evaluation of radiofrequency ablation of HCC. In their study, the two imaging modalities achieved roughly comparable results in the detection of residual tumour tissue. Ding et al. [21] reported their experience with Coded harmonic angiographic study reaching a sensitivity of 92% in detecting tumoural recurrence. Actually, with the introduction of new contrast agents, such as Sonovue, and new software for analysing sonographic images, new prospects were opened regarding the characterisation of liver lesions and evaluation of response HCC to treatment with RF ablation.

Sonovue is a new blood pool ultrasound contrast agent, which consists of a stabilised aqueous suspension of sulphur hexafluoride microbubbles with a phospholipidic shell. The mean diameter of Sonovue bubbles is 2.5 mm, allowing for both transpulmonary and transinusoidal passage. These bubbles have a strong wideband harmonic response at low mechanical index (MI), which is ideal for vascular phase imaging. Contrast-enhanced sonography with low MI and non-destructive method using a second generation contrast agent like Sonovue allows performance of moving scans of the whole liver for 4-5 minutes avoiding the destruction of microbubbles and maximising the harmonic signals generated by microbubbles. This gas has a low solubility in blood (unlike air), and it provides microbubbles with high resistance to pressure, allowing them to reach the capillary network. This property, in addition to the high echogenicity of the microbubbles, makes Sonovue a 2nd generation contrast agent suited to the newest real time contrast specific modalities, which can display dynamic specific enhancement useful for liver lesion characterisation and detect residual enhancement suitable for treatment evaluation [8].

In the present study, we found that CEUS with Sonovue was very effective in the detection of residual viable neoplastic tissue in HCC lesions after treatment with RF with a sensitivity, specificity, NPV, and PPV of 92.3%, 100%, 97.4%, and 100%, respectively. In the 24 cases with incomplete tumour response, the portion of the tumour in which enhancement was still detected with contrast-enhanced sonography closely matched the enhancing areas on CT. Parallel to our results, Vilana et al. reported an accuracy of 95% for contrast-enhanced US with Sonovue in the evaluation of tumour response to percutaneous treatment (either ethanol injection or RF ablation) in their study of patients with HCC [9]. Likewise, Kim et al. [26] reported that contrast-enhanced sonography had a higher sensitivity (93%) than tri-phasic CT (64%) in assessing the therapeutic response of HCCs treated with transcatheter arterial chemo-embolisation [26].

Unfortunately, the absence of contrast enhancement within the ablated lesions at short-term follow-up within 3 months after treatment does not always indicate successful treatment, as later follow-up studies can demonstrate tumour regrowth at the periphery of the ablated lesions [27]. In our study, 5 of the 37 ablated lesions which were interpreted as completely ablated showed tumour recurrence at the peripheral margin of the treated lesions at later follow-up studies performed both with spiral CT and enhanced contrast sonography. Regarding this fact, patients should be regularly assessed with either CT or US to detect early recurrences. According to our results and to the previously reported series [8, 9], low-MI real-time contrast-enhanced sonography may be considered an accurate alternative to 4-row spiral CT in the assessment of local reactivation, meaning treatment failure of the patients with HCC treated with RF ablation. In our study, no false positive were found with CEUS, achieving a specificity of 100%. The sensitivity was 92.3%, owing to two false negatives, which were located in the subphrenic position (deeply located lesion). In fact, as previously reported by other authors, the lesions located deeper than 10 cm from the skin, especially the posterior deep-lying lesions are difficult to be evaluated with US and CEUS because of the decreasing power of the ultrasound beam [28 – 30].

As an imaging modality, however, contrast-enhanced sonographic evaluation has several advantages in the follow-up of treatment response in this patient population. It is non-invasive and less expensive than CT and MR imaging and can be performed numerous times. In patients with impaired renal function, a frequent complication of liver cirrhosis, sonography avoids the use of iodinated contrast agents. Another advantage is the ability to perform continuous evaluation of the target lesion, thus avoiding the risk of missing the optimal contrast enhancement phase; as it is well known, optimisation of scan timing represents one of the major challenges for the optimisation of contrast-enhanced CT protocols [31]. However, this technique could be less than optimal for screening the rest of the liver, where a large proportion of recurrences appear. Screening the whole liver by CEUS would require repeated injections of the contrast agent to allow proper examination of all segments, and for this reason, it is clearly more cost-effective to use CT scan [32]. In addition, CEUS

technique requires a high level of operator skill and is difficult to perform for inexperienced examiners. Operator dependency is a well known general and intrinsic limitation of ultrasound, however.

Nevertheless, our study has some limitations. One limitation is that we have evaluated only the axial images of both CEUS and CT, but not the MPR reconstruction. As reported by Imai et al., this technique, although providing high accuracy in revealing residual tumour, is less valuable than 3-D image reconstructions by using CT-MPR in the evaluation of safety margin [22, 23]. In our study, however, follow-up confirmed the results of CEUS and CT, thus not revealing false positives, and reducing the negative effects on the clinical value of our study. Another limitation of our study is that we had no pathological proof of the ablated lesions. However, as postulated by other authors [33 – 35], the use of needle biopsy is limited in depicting residual viable tumours after RF ablation because of sampling errors. Therefore, negative biopsy results do not guarantee complete necrosis of the tumour. Furthermore, percutaneous biopsy is an invasive procedure, and patients with hepatic cirrhosis may need longer hospitalisation owing to possible bleeding. Therefore, to date, most investigators rely on long-term follow-up to assess the therapeutic response by imaging methods. The only possibility to clearly establish the effectiveness of this new mini-invasive technique could be a longer follow-up, which is, however, limited by the fact that these patients do not survive long enough to establish the true long-term local recurrence rate.

In conclusion, real-time low MI contrast-enhanced sonography should be considered a useful tool in the evaluation of response to thermal ablation of HCC, thus providing accuracy roughly comparable to that of 4-row spiral CT in the detection or residual tumoural tissue. By diminishing the number of CT sessions, the cost of treatment and exposure to radiation decreases, while safety and convenience increase. Indeed, when indicated in these cases, the US examination should be performed with second generation contrast media and new technologies. Although spiral CT was able to detect residual tumoural tissue in two patients missed by contrast-enhanced US, because of the rapid development of real-time contrast imaging technologies and the imminent marketing of new products, the use of 3-D image reconstructions, it is believed that in the next decade, contrast ultrasound will significantly extend the role of the most cost-effective, accessible and safest diagnostic imaging modality. This is in fact a cost-effective technique with further possible margins of improvement. Further evaluations, including multi-center trials are needed to confirm our encouraging results.

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