The application of dynamic contrast-enhanced ultrasonography in immediate distinguishing residual tumour from benign periablational enhancement after hepatocellular carcinoma radiofrequency ablation

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Abstract

Aim: This study set out to access the performance of quantitative analysis of contrast-enhanced ultrasound (CEUS) in distinguishing between benign periablational enhancement (BPE) and residual tumor (RT) following radiofrequency ablation (RFA). Materials and methods: 165 tumors from 124 patients with hepatocellular carcinoma between 2021 and 2023 underwent RFA, contrast-enhanced computed tomography (CECT), and CEUS in less than 24 hours. Analysis was done on the quantitative parameters from RT and BPE found by CEUS. Results: Complete ablation was obtained in 89.1% of lesions. When compared to BPE, RT had significantly greater peak intensity (PI), time to peak (TTP), area under the curve (AUC), ratio of PI and base intensity (PI/BI), and enhanced intensity (EI) values (all p<0.05). PI, TTP, AUC, PI/BI, and EI had large areas under the receiver operating (ROC) curves. A binary logistic regression analysis, respectively, demonstrated that PI and PI/BI were independent favorable prognostic variables. Conclusions: Multiple parameters of quantitative analysis of CEUS can aid in distinguishing immediately between RT and BPE lesions. PI and PI/BI may be a more promising parameter. Immediate CEUS evaluation following RFA may allow immediate retreatment of RT during the same operation time, which reduces patients' hospital stays and financial costs.

Keywords: residual tumor; hepatocellular carcinoma; benign periablational enhancement; dynamic contrast-enhanced ultrasonography; radiofrequency ablation

Introduction

Hepatocellular carcinoma (HCC) is responsible for one-third of all cancer-related fatalities globally [1-3]. The incidence of liver cancer is increasing by an estimated 700,000 patients annually worldwide, with over half of all liver cancer fatalities taking place in China [4]. Note that despite improvements in surgical techniques that have reduced perioperative complications, liver resection is still a challenging procedure with high rates of mortality and morbidity [5]. Radiofrequency ablation (RFA) is increasingly utilized to treat HCC due to its low level of discomfort, minimal side effects, and high reproducibility [6-8]. The favorable attributes of RFA have enabled it to be an important option for treatment in early HCC [9,10].

Although RFA has high rate of complete ablation [11], 49-74% of HCC patients treated with RFA experience local recurrence [12], including local tumor progression [13], and distant intrahepatic recurrence [14]. Local tumor progression is linked to a residual tumor (RT), which occurs at the edges of the ablation area and is caused by incomplete ablation. The identification of RT after RFA and the early evaluation of the ablation area is vital in reducing the risk recurrence and improving pa-
tient prognosis. Conventional ultrasound has a poor visualization capability of residual cancers due to its inability to provide information about tumor microperfusion. Contrast-enhanced computed tomography (CECT) and contrast-enhanced magnetic resonance imaging (CEMRI) are routinely used to evaluate therapeutic response. However, CT and MRI still have certain drawbacks, such as the possibility of radiation exposure with CT and the cost and length of time with MRI [15].

Contrast-enhanced ultrasound (CEUS) has been proven to be an alternative method of identification of RT because of its advantage in the real-time observation of dynamic tumor microvascular perfusion and outstanding diagnostic effectiveness similar to CECT [16]. The abnormal high-enhanced area in the peripheral zone of ablation during postprocedural CEUS can be interpreted as a remnant viable tumor [17]. Moreover, CEUS is a promising tool, ultrasound being the most widely imaging technique used in RFA guiding [18], providing the possibility that after RT identification the subsequent re-treatment could be conducted in the same session.

In clinical practice, however, the identification of RT from ablation regions by CEUS interferes with the presence of benign periablational enhancement (BPE). In the early postoperative phase, the surrounding tissue of the lesion undergoes a local inflammatory response due to thermal injury, which manifests as enhancement around the ablation lesion in CEUS cines [19,20]. Since BPE and residual cancer tissue show similar locations and appearances on CEUS, it is difficult to distinguish one from the other in clinical work, which remains a burning question.

Recent literature has proven that dynamic CEUS (DCEUS) can quantitatively analyze tissue blood micro-perfusion with multiple parameters [21-23]. Based on the distinction between residual cancer and BPE with respect to blood perfusion characteristics, we hypothesize that benign and malignant periablational enhancements can be accurately distinguished by multiparameter quantitative DCEUS.

To test this hypothesis, we conducted the present study to verify the usefulness of multiparameter quantitative DCEUS in distinguishing RT from BPE after HCC radiofrequency ablation.

Materials and methods

Study cohort

Retrospective analysis of 165 tumors treated with RFA in 124 patients with HCC at our facility between 2021 and 2023 was done. These patients underwent CECT and CEUS examinations in sequence within 24 hours after RFA. Prior to the procedure, written informed consent was obtained from each subject. Our Ethics Review Committee approved this study.

The criteria for inclusion in the study were defined as follows: the diagnoses of HCC were made using two imaging techniques (CT and MRI) to confirm the typical vascular pattern in HCC cases; biopsy was used when the imaging pattern did not entirely match the HCC diagnostic criteria or there were any findings that could point to a non-HCC tumor [24]; all the tumors were treated by ultrasound-guided percutaneous RFA; a single tumor with a maximum size of 5 cm; several tumors (<3), each tumor with a maximum size of 3 cm; prothrombin time ratio >50% (prothrombin time with international normalized ratio, INR<1.7) [25,26], more than 50,000/ml of platelets without transfusion assistance, absence of extra-hepatic metastases and portal vein thrombosis [13].

Radiofrequency ablation

Based on the patients' performance status, liver function, and tumor profile, a multidisciplinary committee composed of surgeons, radiologists, ultrasonographers, and oncologists determined treatment options for percutaneous ablation. A team of ultrasound specialists with over a decade of hand-on experience in ultrasound-guided interventional treatments performed all RFA procedures. The directions provided by the manufacturer were followed during each ablation treatment. The RFA system that was used in this study was the RITA Model 1500 (RITA Medical System, California, USA). The RFA ablations were carried out through the percutaneous route under ultrasound guidance. Real-time US scanner (Resona 7 expert, Mindray Medical Company, Shenzhen, China) was used to accomplish image-guided ablation, equipped with a 1-6 MHz convex probe. To induce local infiltration anesthesia 10 ml of 2% lidocaine was used. The patient received an intramuscular injection of pethidine (50 mg) before RFA for analgesia. To completely reveal the tumor, the patient had to assume the proper position (supine or lateral). After determining that the lesion was properly centered, the RFA session began as the expandable needle was opened. Overlapping ablations with multiple electrodes were performed in 3–5 cm diameter tumors. The overlapping modes were determined based on mathematic analyses, which was performed to determine how multiple ablation spheres of fixed size could overlap to cover larger tumor most efficiently [27]. Different RFA parameters, including the power, application time, and needle aperture, were adjusted according to the size of the lesion. The growth of gas bubbles was monitored in real time. The deepest sections were first ablated and the surface portions at the end of procedure, to avoid imaging disruptions caused by hyperechogenic gas artifacts produced by boiling tissue. Thermal ablation
aimed to eliminate the target tumor while leaving a safety margin of 5–10 mm of surrounding normal liver tissue [13]. We repeated the RFA if any RT was found.

**One-day CECT**

CECT is the standard reference examination for the assessment of the effects of RFA on HCC in this study [28]. Each patient received a CECT scan within 24 hours after performing RFA (VCT 64; GE Medical Systems, Milwaukee, WI, USA). The voltage of the tube is 120 kV, the current of the tube is 250–300 mAs, the pitch is 1.375, and the layer thickness and layer spacing are 5 mm. Iohexol (300 mgI/ml) was infused into the antecubital vein using a high-pressure syringe at a flow rate of 3 ml/s for 80–100 ml for enhanced scanning. Subsequently, two radiologists with over 10 years of hepatobiliary imaging experience reviewed the reports. If there were differences in opinion between the two radiologists, another expert was invited for consultation, and a final unified opinion was reached through discussion. The patients were divided into two groups according to CT results: RT group (n=18) and BPE group (n=147). Because BPE was present around all the ablated lesions no matter if RT occurred, the cases with both RT and BPE were included in RT group. Patients underwent follow-up CT 1 month and 3 months after RFA.

All of the CT findings below have been taken into account in the determination of whether the ablation was successful: (1) no enhancement of the contrast was found within the tumor or in the surrounding area; (2) the ablation area’s margins were clear and smooth; (3) the tumor’s estimated previously-calculated borders were exceeded by the ablation area [13]; (4) benign periablation enhancement manifested as an enhanced rim of uniform thickness surrounding the ablated lesion, whereas residual HCC manifested as localized and asymmetric peripheral enhancement [29].

**CEUS**

All the enrolled patients were assessed by CEUS prior to RFA treatment, and all tumors were categorized according to the CEUS LI-RADS v. 2017 [30]. After one-day CT, an immediate CEUS was performed. US multiangle scans were taken to reconstruct the same morphologic images that were obtained by CECT. Moreover, by using anatomical landmarks (i.e., portal vein, gallbladder, ligament, hepatic vein, diaphragm, biliary tract), the regions indicated as abnormal by CECT were localized in the ultrasound images [31]. All CEUS tests were carried out with a low mechanical index (0.091) to prevent early microbubble depletion. Sulfur hexafluoride microbubbles (SonoVue, Bracco, Milan, Italy) were injected into the median cubital vein after B-mode and color Doppler imaging, and this was done right before 5-10 ml of 0.9% saline flush. Following the contrast agent injection, cine loops of the CEUS were acquired and recorded for later analysis. No adverse effects were observed during or after the CEUS examinations.

**Qualitative CEUS performance compared to CT**

To evaluate ablation efficacy, cine loops of immediate post-ablation CEUS were qualitatively analyzed by two experienced sonographers independently, who were blind to the CT imaging. When discrepancies were found between the two sonographers, a third, more experienced specialist reevaluated the cines until a consensus was reached. The consistency of ablation efficacy was analyzed between CECT and CEUS.

**Quantitative analysis**

The cine loops were analyzed using the time-signal intensity curves analysis software equipped in the ultrasound scanner (Resona 7 expert, Mindray Medical Company, Shenzhen, China) for perfusion quantification. Two areas of interest (ROIs) were chosen as follows: one was selected within the BPE or RT and the other was delineated in the peripheral normal liver tissue at the same depth (fig 1).

The time-signal intensity curve (TIC) provided quantitative parameters, including peak intensity (PI), defined as the maximum signal intensity; time to peak (TTP), defined as the time it takes to arrive at PI from the start of the enhancement; area under the curve (AUC), defined as the area below the TIC; ascending slope (AS), defined as the slope between the beginning and peak of lesion perfusion on the curve; the ratio of PI to base intensity (PI/
BI), defined as the ratio of the peak intensity to the base intensity of RT or BPE; enhanced intensity (EI), defined as the difference between the PI and BI of RT or BPE.

The CEUS quantitative parameters between the RT and BPE group, as well as the RT and BPE region in cases with both RT and BPE, were compared.

Statistical analysis

The independent samples t-test was conducted to judge significant discrepancies between two groups. The consistency of ablation efficacy between CECT and CEUS was analyzed using kappa coefficient. Binary logistic regression was utilized to identify whether each parameter had independent associations, and the sensitivity and specificity of quantitative parameters for predicting RT were determined by means of receiver operating characteristic curve analysis. The cutoff values for the diagnostic indices were determined when the Youden index reached its maximum. Data analysis was carried out using SPSS 25.0. Statistics were considered significant for p values under 0.05.

Results

The characteristic features of the patients and results of ablation

Table I shows the clinical features of the enrolled HCC patients. The complete ablation rate obtained was of 89.1% (147 of 165 tumors). Table II shows the CEUS spectrum of RT and BPE.

Table III. Comparison of diagnostic results of CECT and CEUS

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
<th>RT (n=18)</th>
<th>BPE (n=147)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>6/12/0</td>
<td>58/73/16</td>
<td></td>
</tr>
<tr>
<td>Thickness of the ring of the annular BPE (mean±SD, mm)</td>
<td>/</td>
<td>9.07±2.02</td>
<td></td>
</tr>
<tr>
<td>Largest diameter (mean±SD, mm)</td>
<td>8.03±1.64</td>
<td>/</td>
<td></td>
</tr>
</tbody>
</table>

RT: Residual Tumor; BPE: Benign Periablational Enhancement.

The RTs were close to the hepatic vein (n=3), portal vein (n=2), hepatic artery (n=3), hepatic capsule (n=5) and diaphragm (n=5) because of thermal convection [32], high position and small ablation safety range. Complications occurred in 18% (22/124) of patients, with 2 biliary fistula instances, 17 cases of abdominal pain, and 4 cases of bleeding.

In comparison with follow-up CT 1 and 3 months after RFA, CT at 24 h predicted the complete treatment of the lesions in 147/147 lesions with accuracy of 100%.

The consistency test of ablation efficacy between CECT and qualitative CEUS

CECT and qualitative CEUS had good consistency (Table III).

CEUS quantitative parameters of RT and BPE region in cases with both RT and BPE

The CEUS parameters of RT and BPE region in cases with both RT and BPE were compared in Table IV. No significant differences were observed between the two groups in AS, whereas the PI, TTP, AUC, PI/BI, EI differed significantly.

CEUS quantitative parameters in RT and BPE group

While AS showed no differences (p=0.107) between the RT and BPE group, significant differences in TTP, PI, AUC, EI, and PI/BI were observed as shown in Figure 2. TTP, PI, AUC, PI/BI, and EI of the RT group were higher than those of the BPE group’s (all p<0.05).

The correlations between CEUS quantitative parameters and RT

Multiple parameter ROC curves are shown in Figure 3. The TTP, PI, AUC, EI, and PI/BI demonstrated good di-
agnostic value in differentiating between RT and BPE. The AUC, cutoff, sensitivity, and specificity of the various parameters are shown in Table V.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>BPE group</th>
<th>RT group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to peak</td>
<td>30.62±16.18</td>
<td>46.67±14.51</td>
<td>0.004</td>
</tr>
<tr>
<td>Peak intensity</td>
<td>43.56±11.23</td>
<td>59.70±12.28</td>
<td>0.000</td>
</tr>
<tr>
<td>Area under curve</td>
<td>1968.65±1046.62</td>
<td>3195.29±757.84</td>
<td>0.000</td>
</tr>
<tr>
<td>PI/BI</td>
<td>7.11±3.49</td>
<td>14.63±10.02</td>
<td>0.005</td>
</tr>
<tr>
<td>EI</td>
<td>30.22±8.29</td>
<td>44.21±12.62</td>
<td>0.000</td>
</tr>
<tr>
<td>Ascending slope</td>
<td>0.92±0.35</td>
<td>0.81±0.54</td>
<td>0.460</td>
</tr>
</tbody>
</table>

RT: Residual Tumor; BPE: Benign Periablational Enhancement; TTP: Time to Peak; PI: Peak Intensity; AUC: Area Under Curve; PI/BI: the ratio of the peak intensity to the base intensity of RT or BPE; EI: peak intensity minus base intensity of RT or BPE.

Values are means±standard deviations.

Fig 2. CEUS perfusion measurements in the residual tumor and benign periablational enhancement groups. Ascending slope (AS) showed no differences between the RT and BPE group (p=0.107), while in the RT group TTP, PI, AUC, PI/BI, and EI were higher compared with the BPE group (all p<0.001).

RT: residual tumor; BPE: benign periablational enhancement group; PI: peak intensity; TTP: time to peak; AUC: area under the curve; PI/BI: the ratio of the peak intensity to the base intensity of RT or BPE; EI: the difference between the PI and BI of RT or BPE.

Fig 3. ROC curves for TTP, PI, AUC and PI/BI. Using receiver operating characteristic curve analysis, TTP, PI, AUC, and PI/BI showed good diagnostic performance in differentiating RT from BPE. TTP, time to peak; PI, peak intensity; AUC, area under the curve; PI/BI, the ratio of the peak intensity to the base intensity of RT or BPE; EI, peak intensity minus base intensity of RT or BPE.

Analysis of binary logistic regression

In order to determine the independent predictive indicators, binary logistic regression analysis was then carried out, which included PI, TTP, AUC, PI/BI, and EI. PI and PI/BI were found to be independent prognostic variables with exp(B) of 1.164 (95%CI, 1.029-1.317; p=0.016) and 1.178 (95%CI, 1.012-1.372; p=0.034), respectively.

Discussion

CEUS was reported to exhibit pretty performance in assessing therapeutic responses to RFA for HCC with a 90% sensitivity and a 100% specificity [33]. Meanwhile, CEUS was proved to be capable of outstanding diagnostic effectiveness similar to CECT, which was in ac-
cording with our consistency test result. Certainly, 24-h CEUS is of more vital clinical significance. If residual tumor is present by 24-h CEUS, re-ablation can be conducted earlier. However, evidence showed that CEUS performed after locoregional therapy had a relatively lower sensitivity within the first 24 h [34]. When CEUS is performed within the first 24 h after RFA, hyperemia develops around the ablated area hindering the diagnostic accuracy [34,35]. Different from qualitative CEUS used in previous studies, multiple parameters of quantitative dynamic CEUS were used in our study, which has better diagnostic capabilities in distinguishing between RT and BPE.

In our study, multiple DCEUS parameters (TTP, PI, AUC, PI/BI and EI) were significantly different between RT and BPE and demonstrated good diagnostic values, highlighting the capacity for differentiating between inflammatory zones following ablation and remaining malignancies. PI and PI/BI might serve as more promising indicators for RT.

Our study demonstrated that the AUC of BPE is lower than that of RT. This may be explained by the fact that in the early stage after radiofrequency ablation, inflammatory cells of BPE around the ablation site did not accumulate in large numbers, and the blood flow volume was lower than that of residual cancer tissue, which is consistent with previous studies [36]. The cancer characteristics of high blood flow perfusion are still present in RT despite the destruction of part of its blood vessels due to heat damage [37], resulting in a higher PI of RT compared to BPE. Additionally, the TTP of RT is higher than that of BPE because of a certain degree of blood vessel destruction mentioned above [38]. EI was established as PI minus BI and is correlated with blood flow volume [8]. RT has a larger blood perfusion volume than BPE, which is in consistence with our study result that the EI of RT is larger than that of BPE.

PI/BI is the ratio of the peak intensity to the base intensity of RT or BPE; EI: peak intensity minus base intensity of RT or BPE.

Table V. Diagnostic performance of CEUS quantitative parameters in residual tumor group and benign periablational enhancement group

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Cut off value</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Area under the ROC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak intensity</td>
<td>55.59</td>
<td>0.78</td>
<td>0.87</td>
<td>0.825</td>
</tr>
<tr>
<td>Time to peak</td>
<td>34.49</td>
<td>0.83</td>
<td>0.66</td>
<td>0.755</td>
</tr>
<tr>
<td>Area under the curve</td>
<td>2166.08</td>
<td>0.94</td>
<td>0.68</td>
<td>0.863</td>
</tr>
<tr>
<td>PI/BI</td>
<td>10.93</td>
<td>0.67</td>
<td>0.93</td>
<td>0.849</td>
</tr>
<tr>
<td>EI</td>
<td>33.44</td>
<td>0.89</td>
<td>0.849</td>
<td>0.830</td>
</tr>
</tbody>
</table>

According to the recommended guidelines, CT is one of the most used modalities for evaluating RFA treatment [29]. It is vital to determine the CT examination time because subsequent actions cannot be determined until the CT evaluation is complete. There is still disagreement about the best time for when patients should have their first CT evaluation. In general, it was recommended that the first follow-up visit be performed at 1 to 2 months after the procedure to evaluate the response [39-41]. However, recent research has suggested that after thermal ablation of liver lesions, CT imaging at 24 hours and 1 month was equally effective in assessing any residual disease [28]. A CECT scan on the same day after RFA can help patients with RT avoid waiting for one to two months for RT retreatment, allowing for complementary treatment at the same hospital time.

In clinical practice, ultrasound guidance is the most popular type of RFA guidance [42]. Using real-time multidimensional scans, ultrasound guidance can pinpoint the puncture location, which is nimble and generally simple to use, to safely penetrate into the tumor, avoiding ligamentous tissues, bile ducts, and major veins [43]. Our study revealed that real-time quantitative CEUS analysis can be performed to accurately identify RT and BPE. This means that the ablation efficacy can be evaluated immediately following RFA, rather than one-day CECT, allowing for immediate retreatment of RT during the same operation time, which greatly benefits the patients by reducing both the time it takes to wait for follow-up results and appropriate interventions and the costs of ablation needles and other operative consumables for reablation.

Our study has several limitations. Firstly, in order to acquire more objective results, future study will include more participants due to the fact that we treated a small number of patients and lesions. Furthermore, RT was diagnosed through typical radiographic imaging [29] with
the absence of histological evidence because it is difficult to obtain pathological tissue after RFA. In the future, animal experiments should be performed, which are feasible for acquiring pathological tissue. Thirdly, single tumor up to 5 cm was included in our clinical study despite there is still controversy regarding the efficacy of RFA therapy in larger tumors measuring 3 to 5 cm. A multi-center study suggested that RFA is usually performed to treat small HCC nodules measuring ≤3cm and surgery or transplantation is suggested for larger tumors measuring >3 cm [44]. However, patients with larger tumors measuring 3 to 5 cm obtained a nice curative effect after RFA therapy in China [42,45]. Therefore, a single tumor with a maximum diameter of 3-5 cm is strongly recommended as a therapy indication in the most recent authoritative Chinese ablation guideline [46]. Additionally, one-day CECT was considered the standard reference for the assessment of treatment efficacy in this study, although CT or MRI 1 or 3 months after treatment is recommended as the gold standard from several guidelines [40,47]. Regrettably, the disappearance or poor visualization of BPE is demonstrated in both CEUS and CECT 1 or 3 months after RFA, by which the feasibility of quantitative evaluation of RT and BPE was negatively affected. Indeed, local inflammation around the ablation lesion attenuates, and the scope of benign periablational enhancement reduces and gradually disappears over time [48]. Several studies found a good correlation between CT or MRI at 24 h and 1-month CT on evaluating treatment efficacy [28,49]. Moreover, we checked if the cases considered BPE at 24 hours were in fact true complete ablations at 1 or 3 months, while the cases considered RT were not inspected because of immediate repeated ablation at 24 hours. In comparison with 1 and 3-months CT respectively, 24-h CT predicted the complete treatment of the lesions in 147/147 lesions with an accuracy of 100%, indicating that CT at 24 h may be of relatively high validity. Finally, CEUS LI-RADS categories were proved to independently predict the outcome for patients with HCC at early stage after initial treatment [50]. Nevertheless, its correlation with post-ablation outcomes in HCC patients was not included in this study because of the short follow-up period, so longer observation periods will be necessary in future analyses.

Conclusions

Multiple parameters of quantitative DCEUS can aid in distinguishing between RT and BPE lesions. PI and PI/BI may be more promising parameters being more accurate and efficient in differentiating between RT and BPE. Immediate CEUS evaluation following RFA may allow immediate retreatment of RT during the same operation time, which reduces patients’ hospital stays and financial costs.

Conflict of interest: none

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