

Hepatocellular carcinoma after ablation: The imaging follow-up scheme

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Abstract

Percutaneous ablation using thermal or chemical methods has been widely used in the treatment of hepatocellular carcinoma (HCC). Nowadays, contrast-enhanced imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), and contrast-enhanced ultrasound (CEUS) are widely used to evaluate local treatment response after ablation therapies. CEUS is gaining increasing attention due to its characteristics including real-time scanning, easy performance, lack of radiation, wide availability, and lack of allergy reactions. Several studies have documented that CEUS is comparable to CT or MRI in evaluating local treatment efficacy within 1 mo of treatment. However, little information is available regarding the role of CEUS in the follow-up assessment after first successful ablation treatment. Zheng *et al*^[1] found that in comparison with contrast-enhanced computed tomography (CECT), the sensitivity,

specificity, positive predictive value, negative predictive value and overall accuracy of CEUS in detecting local tumor progression (LTP) were 67.5%, 97.4%, 81.8%, 94.4% and 92.3%, respectively, and were 77.7%, 92.0%, 92.4%, 76.7% and 84.0%, respectively for the detection of new intrahepatic recurrence. They concluded that the sensitivity of CEUS in detecting LTP and new intrahepatic recurrence after ablation is relatively low in comparison with CECT, and CEUS cannot replace CECT in the follow-up assessment after percutaneous ablation for HCC. These results are meaningful and instructive, and indicated that in the follow-up period, the use of CEUS alone is not sufficient. In this commentary, we discuss the discordance between CT and CEUS, as well as the underlying mechanisms involved. We propose the combined use of CT and CEUS which will reduce false positive and negative results in both modalities. We also discuss future issues, such as an evidence-based ideal imaging follow-up scheme, and a cost-effectiveness analysis of this imaging follow-up scheme.

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Key words: Hepatocellular carcinoma; Radiofrequency ablation; Ethanol ablation; Contrast-enhanced ultrasound; Follow-up; Treatment response; Computed tomography

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COMMENTARY ON HOT TOPICS

We read with great interest the recent article by Zheng *et al*^[1] evaluating the usefulness of contrast-enhanced ultrasound (CEUS) in the follow-up of patients with he-

patocellular carcinoma (HCC) who had undergone local ablation therapies.

As a minimal invasive and safe treatment method, percutaneous ablation using thermal or chemical methods has been widely used in the treatment of early HCC, recurrent HCC, and even advanced HCC^[2-11]. Percutaneous ablation such as radiofrequency ablation (RFA), microwave ablation and ethanol ablation (EA), is regarded as the curative treatment method for early HCC^[12,13]. In contrast to surgical resection where the tumor is removed, the tumor is not eradicated from the body but is deactivated by ablation therapy, therefore, it is of paramount importance to evaluate the efficacy of this treatment to determine follow-up treatment and strategy. Currently, the use of contrast-enhanced imaging to detect residual viable tumor or recurrent HCC is widely accepted^[14-19]. The underlying mechanism of this imaging method relates to the fact that viable tumor tissue shows arterial hypervascularity (*i.e.*, hyper-enhancement), whereas destroyed tumor shows absence of vascularity (*i.e.*, non-enhancement), thus the distinction between them is achievable. However, this method is not ideal as imaging studies may fail to detect tiny viable tumor tissue, especially when neoangiogenesis is not obvious. Percutaneous biopsy may be another option, however, this technique has significant sample error and it is not ethical and practical to sample all the lesion after ablation. Consequently, contrast-enhanced imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), and CEUS are currently widely used to evaluate local treatment response after ablation therapies. Although CT and MRI are accepted as the reference standards, the newly introduced CEUS is also gaining increasing attention due to its characteristics including real-time scanning, easy performance, lack of radiation, wide availability, and lack of allergic reactions^[20-38]. Several studies have documented that CEUS is comparable to CT or MRI in evaluating local treatment efficacy within one mo of treatment (Table 1)^[18,39-41]. Kim *et al.*^[42] also reported that they were in favor of CEUS as it had the advantage of being able to detect lesions < 2 cm; therefore, CEUS has been used effectively in diagnostic algorithms for small 1-2 cm newly detected nodules in HCC patients. However, little information is available regarding the role of CEUS in the follow-up assessment after first successful ablation treatment. In the follow-up period, the patient may develop local tumor progression (LTP) or new intrahepatic recurrence, and imaging modalities are used to successfully detect these lesions.

In the study by Zheng *et al.*^[1], 141 patients with HCCs who underwent percutaneous ablation therapy were assessed by paired follow-up CEUS and contrast-enhanced computed tomography (CECT). Using CECT as the reference standard, the ability of CEUS to detect LTP or new intrahepatic recurrence during follow-up was evaluated. They found that 33 LTP and 131 new intrahepatic recurrent foci were detected on CEUS, whereas 40 and 183 were detected on CECT, respectively (both $P < 0.05$).

Compared with CECT, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and overall accuracy of CEUS in detecting LTP were 67.5%, 97.4%, 81.8%, 94.4% and 92.3%, respectively, and were 77.7%, 92.0%, 92.4%, 76.7% and 84.0%, respectively for the detection of new intrahepatic recurrence. They concluded that the sensitivity of CEUS in detecting LTP and new intrahepatic recurrence after ablation was relatively low compared with CECT, and that CEUS can not replace CECT in the follow-up assessment after percutaneous ablation for HCC. Their results are interesting and meaningful, and we agree with the authors regarding the role of CEUS in the follow-up of HCC patients after ablation therapy.

The discordance in imaging features between CT and CEUS is well recognized, and is largely due to the difference in pharmacokinetics between CT contrast medium and ultrasound contrast agent^[35,43]. The CT contrast medium diffuses into the interstitial space, while the ultrasound contrast agent is a pure blood pool tracer. The CEUS characteristic of real-time scanning is helpful in detecting subtle lesions with transient arterial hyper-enhancement which is hard to visualize on CT. Some lesions may show arterial iso-enhancement on CT and hyper-enhancement on CEUS due to the limited time window in CT scanning^[44-49]. On the other hand, CEUS also has its shortcomings as shown by Zheng *et al.*^[1] who found that image quality was affected by lesions located near the liver dome, and obscuration due to gas from the lung or intestine. The development of new foci may be located in different lobes of the liver, and the arterial hyper-enhancement on CEUS only lasts for several seconds, thus it is difficult to detect all hypervascular lesions in one scanning procedure. Most importantly, in comparison with CT/MRI, there is universal bias in readers' minds with regards to ultrasound images. The quality of the procedure and subsequent results are largely operator-dependent, thus less uniformity is encountered in clinical practice (Table 2).

The data in the above-mentioned article are detailed and reasonable results have been obtained. However, there is still controversy over the role of CEUS *vs* CECT in the diagnosis of HCC after ablation, which is largely dependent on individual opinion and familiarity with the techniques. Frieser *et al.*^[39] concluded that CEUS is equal to CECT in evaluating treatment response. Gallotti *et al.*^[46] found that CEUS was excellent in evaluating treatment response after RFA, whereas it was inadequate for evaluating treatment response after EA. It should be noted that despite the vast number of published studies on the subject, a unanimous consensus has not been achieved.

There are a number of unsolved issues regarding the use of CEUS and CECT including the following: (1) The authors should recommend the combined use of CT and CEUS in clinical practice when CEUS is available, which will reduce the number of false positive and negative findings in both modalities^[50]. In a study of liver lesion characterization, although no follow-up assessment after

Table 1 Diagnostic values of contrast-enhanced imaging in evaluating treatment response after ablation for liver cancer

Ref.	n	Imaging	Accuracy	Sen	Spe	PPV	NPV
¹ Lu <i>et al.</i> ^[18]	151 patients	CEUS	96.6%	-	98.20%	-	-
Frieser <i>et al.</i> ^[39]	76 patients 118 nodules	CEUS	93.8%	-	-	-	-
		CECT	86.2%	-	-	-	-
		CEUS	100%	-	-	-	-
		CEMRI	88.4%	-	-	-	-
² Ricci <i>et al.</i> ^[40]	100 patients	CEUS	-	92.3%	100%	100%	97.4%
² Salvaggio <i>et al.</i> ^[41]	100 nodules						
	148 nodules	CEUS	97%	83.3%	100%	-	-

¹In comparison with contrast-enhanced computed tomography (CECT) or contrast-enhanced magnetic resonance imaging (CEMRI); ²In comparison with CECT. -: Not applicable. Sen: Sensitivity; Spe: Specificity; PPV: Positive predictive value; NPV: Negative predictive value; CEUS: Contrast-enhanced ultrasound.

Table 2 Comparison between contrast-enhanced ultrasound and contrast-enhanced computed tomography in the follow-up scheme after liver cancer ablation

	CEUS	CECT
Pharmacokinetics of the contrast	Early vascular phase; followed by diffusion into the interstitial space	Pure blood pool tracer; without diffusion into the interstitial space
Strong points	Real-time scanning, easy to perform, no radiation, wide availability, and no allergic reactions	High image quality; operator-independent; panoramic imaging; easy to interpret
Weak points	Image quality is apt to be affected by lesions located near the liver dome, and obscuration by gas from the lung or intestine; Inability to imaging multiple lesions in one procedure; operator-dependent	Inferior temporal resolution; allergic reaction to the contrast-medium; unsuitable for patients with kidney function impairment; radiation; inferior availability

CEUS: Contrast-enhanced ultrasound; CECT: Contrast-enhanced computed tomography.

ablation was carried out, the authors found that combined assessment using CEUS/CT provided higher sensitivity (97%, both readers) than separate assessment using CEUS (88% reader 1; 87% reader 2) and CT (74% reader 1; 71% reader 2; $P < 0.05$), while no change in specificity was observed using the combined analysis. The combined assessment of hepatocellular nodule vascularity using CT and CEUS improved diagnostic sensitivity of malignancy in patients with liver cirrhosis^[50]. However, the study by Zheng *et al.*^[1] was retrospective, thus it is difficult to assess the value of the combined diagnostic procedures in clinical practice, which has prompted a future prospective study to evaluate this issue. Fusion imaging may be another solution which combines the virtues of both modalities^[51]; (2) The ideal imaging follow-up scheme is not yet available. Future evidence-based studies are necessary to establish this scheme. Every practicing clinician must make a decision on the most accurate, cost-effective radiologic test to be used in the follow-up of liver lesions

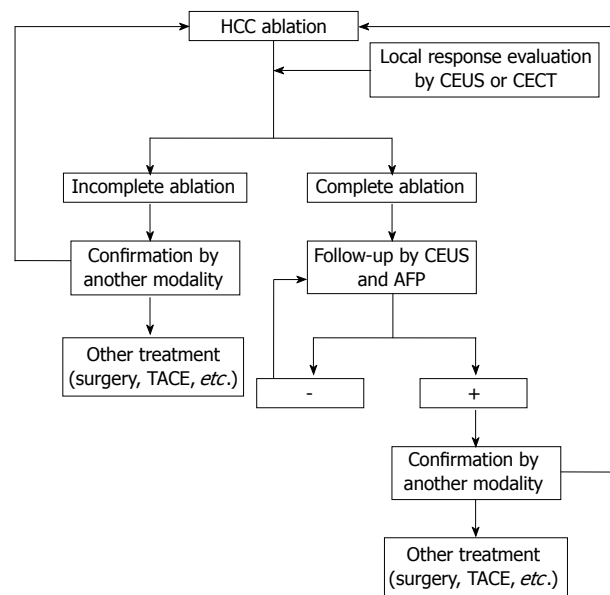


Figure 1 The proposed algorithm combining the strengths of the radiologic techniques of contrast-enhanced ultrasound and contrast-enhanced computed tomography. HCC: Hepatocellular carcinoma; CEUS: Contrast-enhanced ultrasound; CECT: Contrast-enhanced computed tomography; AFP: α fetoprotein; TACE: Transarterial chemoembolization; -: Negative finding; +: Positive finding.

after local treatment. A reasonable algorithm is proposed and is shown in Figure 1, however, further study is mandatory to evaluate its efficacy; (3) A cost-effectiveness analysis should be performed to select the best imaging follow-up scheme; and (4) Long-term follow-up studies are needed to help guide our approach and therapy.

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