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Original Article

The usefulness of contrast-enhanced ultrasonography in the early detection of hepatocellular carcinoma viability after transarterial chemoembolization: pilot study

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Background/Aims: The therapeutic effect of transarterial chemoembolization (TACE) against hepatocellular carcinoma (HCC) is usually assessed using multidetector computed tomography (MDCT). However, dense lipiodol depositions can mask the enhancement of viable HCC tissue in MDCT. Contrast-enhanced ultrasonography (CEUS) could be effective in detecting small areas of viability and patency in vessels. We investigated whether arterial enhancement in CEUS after treatment with TACE can be used to detect HCC viability earlier than when using MDCT.

Methods: Twelve patients received CEUS, MDCT, and gadoxetic-acid-enhanced dynamic magnetic resonance imaging (MRI) at baseline and 4 and 12 weeks after TACE. The definition of viable HCC was defined as MRI positivity after 4 or 12 weeks.

Results: Eight of the 12 patients showed MRI positivity at 4 or 12 weeks. All patients with positive CEUS findings at 4 weeks (n=8) showed MRI positivity and residual viable HCC at 4 or 12 weeks. Five of the eight patients with positive CEUS findings at 4 weeks had negative results on the 4-week MDCT scan. Four (50%) of these eight patients did not have MRI positivity at 4 weeks and were ultimately confirmed as having residual HCC tissue at the 12-week MRI. Kappa statistics revealed near-perfect agreement between CEUS and MRI (κ=1.00) and substantial agreement between MDCT and MRI (κ=0.67).

Conclusions: In the assessment of the response to TACE, CEUS at 4 weeks showed excellent results for detecting residual viable HCC, which suggests that CEUS can be used as an early additive diagnosis tool when deciding early additional treatment with TACE. **(Clin Mol Hepatol 2015;21:165-174)**

Keywords: Hepatocellular carcinoma; Transarterial chemoembolization; Contrast-enhanced ultrasonography; Computed tomography; Magnetic resonance imaging

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INTRODUCTION

Hepatocellular carcinoma (HCC) accounts for more than 5% of all cancers worldwide and has an increasing incidence.[1] HCC is the second-leading cause of cancer-related death worldwide.[2] The long-term prognosis of HCC remains poor due to a high incidence of recurrence (68-96%); thus, effective therapeutic strategies aimed at controlling tumor recurrence are critical for prolonging survival after HCC treatment.[3,4] When HCC is diagnosed at an early stage, patients may undergo surgical resection and liver transplantation. These are considered potentially curative options; however, fewer than 30% of patients are surgical candidates at the time of diagnosis due to advanced tumor stage, difficult resection due to lesion location, underlying liver cirrhosis, multifocal disease or co-morbid conditions.[5] Nonsurgical treatments such as radiofrequency ablation (RFA), transarterial chemoembolization (TACE), percutaneous ethanol injection, and others should be considered for many patients with HCC.[1]

TACE has been widely used as an effective treatment in cases of inoperable HCC.[6] Accuracy in assessing treatment response is crucial both to guarantee the complete necrosis of the tumor tissue and to assess the need for additional therapy.[7] In addition, not only a reduction in overall tumor load, but also a reduction in viable tumor is important point in imaging assessment after treatment. Multidetector computer tomography (MDCT) is one of the most commonly used modalities for assessing the therapeutic response of TACE.[8-10] In general, a compact dense deposition of lipiodol is accepted as a sign of successful TACE. However, dense lipiodol deposition could also mask the enhancement of viable HCC tissue via MDCT, especially in the period immediately following TACE treatment.

The recent advance in magnetic resonance imaging (MRI) makes faster sequences with high-quality imaging of the entire liver with high intrinsic soft-tissue contrast possible, so MRI provides better contrast between the different soft tissues and higher spatial resolution than that of CT. Enhanced areas in the embolization site on gadolinium-enhanced MRI presumably represent viable tumor with high sensitivity but low specificity.[6]

Contrast-enhanced ultrasonography (CEUS) using 2nd-generation microbubble ultrasonography contrast agent (UCA) has advantages for detecting the viability of cells and the patency of vessels because the size of the UCA is smaller than a red blood cell at approximately 2.4-8 μm.[11,12] Several studies have used CEUS in cases of HCC to evaluate the therapeutic response to target agents such as sorafenib.[7,13-15] CEUS using 2nd-generation UCA may have an advantage in the early assessment of viable HCC following TACE due to no interference in lipiodol deposition. However, evidence for the effectiveness of CEUS for therapeutic response prediction following TACE is insufficient. Therefore, in this preliminary study, we investigated whether the arterial enhancement from CEUS following TACE can accurately assess or predict HCC viability at an earlier stage than that needed for MDCT.

MATERIALS AND METHODS

Study population

From November 2011 to November 2012, 12 consecutive patients with HCC were included in this study. HCC was diagnosed based on the typical dynamic pattern hyper-enhancement on the arterial phase and washout on the portal/delay phase of the tumor on MDCT or Gadoxetic acid-enhanced dynamic MRI and elevated alpha-fetoprotein.[16-18] All patients were deemed ineligible for liver transplantation, surgery or radiofrequency ablation, and TACE was thus the most appropriate treatment. Exclusion criteria were as follows: (1) the lack of identification of HCC in gray-scale sonography; (2) a history of multiple treatments (≥ 2) with TACE; (3) a history of therapy with anti-angiogenic agents; (4) massive (≥ 10 cm)/diffuse hepatocellular carcinoma; (5) severe hepatic dysfunction or hepatic failure (The Barcelona Clinic Liver Cancer Classification stage D with Child-Pugh C, performance status 3-4); (6) the presence of a portosystemic shunt; (7) hepatofugal blood flow; (8) thrombus within the main portal vein; (9) contraindication to iodinated contrast agents (allergic reactions or impaired renal function); and (10) contraindication to MRI (implanted metallic devices, cardiac pacemaker, renal insufficiency, claustrophobia, non-cooperation, etc.).

This study was approved by the institutional review board for human research at the Yonsei University Wonju Severance Christian Hospital (CR 311052) with the latest version of the Helsinki Declaration, and written informed consent for treatment and examination was obtained from all patients.

Study design

The baseline evaluation of the patients included CEUS, MDCT and Gadoxetic acid-enhanced dynamic MRI examination. All patients were treated with TACE within 7 days of the baseline study. To assess the effectiveness of TACE, all patients underwent CEUS,
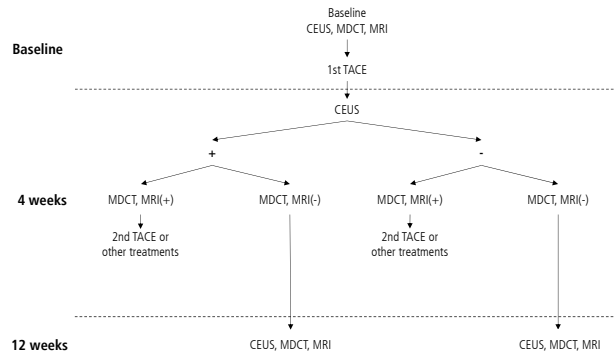
MDCT and MRI evaluation at 4 and 12 weeks after receiving TACE. MRI was used as a standard method of diagnosis, and the

Figure 1. Flow chart of the study. CEUS, contrast-enhanced ultrasonography; MDCT, multidetector computer tomography; MRI, magnetic resonance imaging; TACE, transarterial chemoembolization.

definition of residual or recurrent viable HCC was defined as MRI positivity at 4 or 12 weeks. At 4 weeks, patients with MRI positivity immediately underwent additional treatment with TACE or another agent. In patients with MRI negativity at 4 weeks, CEUS, MDCT and MRI were repeated at 12 weeks. A flow diagram of patient examinations and the treatment design is shown in Figure 1.
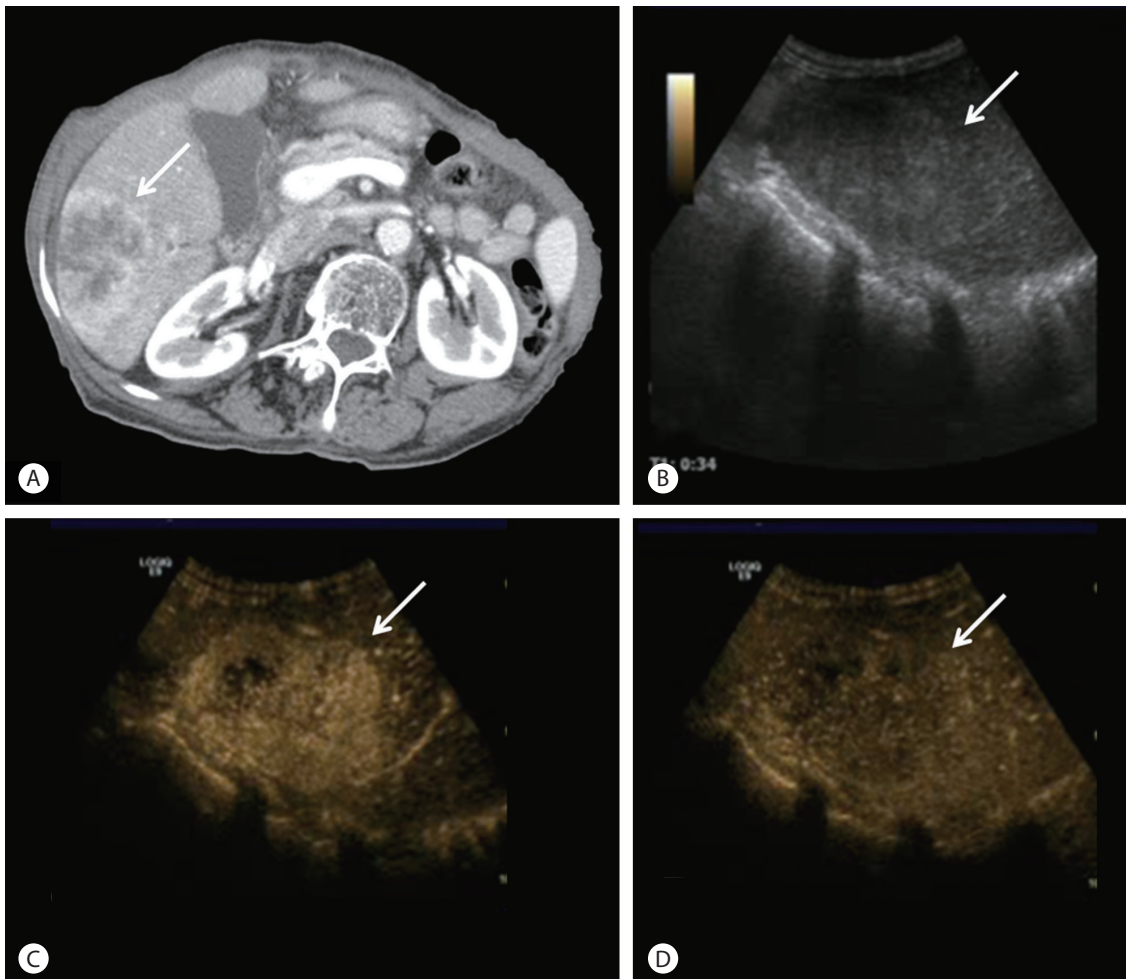
The primary end point was the diagnostic value of CEUS compared with that of MDCT at 4 weeks following TACE for the early prediction of viable HCC.

CEUS examination

One tumor was selected as the target lesion for the subsequent CEUS study. In cases with multifocal lesions, the target lesion was that with the largest diameter among the lesions with a baseline

Figure 2. A typical hepatocellular carcinoma showing the characteristic arterial-phase hypervascularity and late-phase washout. (A) multidetector computed tomography (MDCT) finding, arterial phase (B) grey-scale ultrasonography, (C) contrast-enhanced ultrasonography (CEUS), arterial phase, (D) CEUS, late phase.

necrosis of <50% and a well-delineated margin and superficial location. All target lesions were suitable for detailed and reproducible sonography study. The largest diameter of the target tumors ranged from 1.5 to 5 cm. In general, the characteristics used to identify HCC via CEUS are similar to those via MDCT. HCC shows hyperenhancement in the arterial phase and a washout pattern in the portal and late phases.[19,20]

All CEUS studies were performed by an expert (M.Y.K.) with 7 years of experience using CEUS. First, in all patients, B-mode sonography of the liver was performed to identify the target lesion and define the best position for the probe and the patient. The patients were scanned using a LOGIQ E9 (GE Healthcare, Milwaukee, WI, USA) with a convex array probe (4 MHz) at a low mechanical index (MI=0.09).

CEUS was performed using a second-generation sulfur hexafluoride microbubbles-based ultrasonography contrast agent (SonoVue®, Bracco, Milan, Italy). A 2.4-mL bolus injection of SonoVue® was administered for 1 second and was immediately followed by a rapid flush of normal saline (5 mL) through a three-way tap for 2 seconds through a 20-gauge intravenous catheter that had been inserted into the cubital vein at the level of the left antecubital fossa. After the SonoVue® injection, the enhancement pattern of the tumor was scanned for 240 sec. Patients held their breath for a few seconds if necessary (observation of the arterial, portal, and late phases). Each of the 12 patients underwent this CEUS examination using the same imaging plane within 7 days prior to receiving TACE, as well as at 4 weeks and 12 weeks after TACE (Fig. 2). The imaging data were recorded on the hard drive of the ultrasonography device and reviewed by the same expert. In each stage, all CEUS examinations were performed prior to MDCT and MRI, and the CEUS exam was performed and interpreted without any information regarding the MDCT or MRI results. At the examinations at 4 and 12 weeks, no enhancement was interpreted as complete tumor necrosis (CEUS-negative, complete response). The lesions were considered to have viable and non-necrotized tissue when they showed partial or entire enhancement behavior characteristic of the baseline mass (CEUS-positive, incomplete response).

MDCT examination

The examinations were performed with a 64-slice CT scanner (Philips Brilliance, Best, The Netherlands) using the following parameters: matrix, 512×512; slice thickness, 2.0-2.5 mm; reconstruction index, 1.0-1.25 mm; gantry rotation speed, 0.75 sec-

onds; pitch, 0.935:1; tube voltage, 120 kVp; and automatic tube current (mA). CT scans were obtained at the pre-enhancement phase, at 30-35 s (arterial phase), at 70-75 s (portal phase), and at 180 s (late phase) after intravenous injection of the contrast material. An iodine contrast agent material, 370 mg/dL of iopromide (Ultravist 370, Schering, Berlin, Germany), was administered via a mechanical power injector using a 20-gauge intravenous cannula placed in the antecubital vein at a rate of 3-4 mL/s. Injection of contrast media was followed by a saline chaser administered at the same flow rate as the contrast medium. One radiologist (S.H.C) with more than 10 years of experience in evaluating liver tumors interpreted the findings of the MDCT without any knowledge of the CEUS results. Evaluation criteria of the treatment response using MDCT were as follows: a complete response was diagnosed when a complete homogeneous retention of iodized oil was present; incomplete response was diagnosed when an incomplete retention of iodized oil with areas of non-retention were present or when there was enhancement in the arterial phase and wash-out in the delay phase.

Gadoxetic acid-enhanced dynamic MRI: Reference standard

Gadoxetic acid-enhanced dynamic MRI was performed as the reference standard using a 3.0T MR scanner (Achieva TX, Philips, Best, the Netherlands). The MRI protocol consisted of a dual-echo T1-weighted gradient-echo sequence, a respiratory-triggered fast spin T2-weighted sequence, and a contrast-enhanced dynamic sequence. Gadoxetic acid was administered at a dosage of 0.025 mmol/Kg with 1 mL per second followed by a 20-mL saline flush. After administering the contrast, early arterial phase (25-30 s), portal venous phase (70 s), equilibrium phase (5 min), and additional hepatobiliary phase (after 20 min) images were obtained. Complete tumor response was diagnosed when the lesion failed to enhance throughout the MRI study. Incomplete tumor response was diagnosed when enhanced areas were observed within the tumor after contrast material administration at MRI.

Transarterial chemoembolization

All TACE procedures were performed by an interventional radiologist (Y.J.K) with more than 25 years of experience in interventional radiology. TACE was performed as an inpatient procedure in all patients. Prior to TACE, angiography of the hepatic and mesenteric artery was performed to map the liver vascular anato-

my, to check for arteriovenous shunt, and to identify arterial feeders of the tumor. Feeding arteries were super-selectively catheterized with a microcatheter (2.0F or 2.7F Progreat; Terumo, Europe N.V, Leuven, Belgium). Emulsions of doxorubicin (Adriamycin RDF; Ildong Pharmaceutical, Seoul, Korea) and lipiodol (Laboratoire Guerbet, Aulnay-sous-Bois, France) followed by particle embolization (gelatin sponges; Gelfoam; Upjohn, Kalamazoo, MI, USA) were administered by means of a transcatheter technique and injected with fluoroscopic guidance. After embolization, angiography was performed to determine the extent of the vascular occlusion and the presence of any residual tumor staining. After TACE, the patients were maintained under close observation for 24 hours and were discharged if no complications were observed. Liver function and complete blood counts tests were performed within 24 hours following the procedure.

Statistical analysis

Categorical variables are expressed as proportions. Continuous variables are expressed as the mean ± standard deviation (SD). Agreement was measured using the Kappa statistic. A K statistic value of 0.61 to 0.80 indicates substantial agreement, and 0.81 to 1.00 indicates nearly perfect agreement.[21] The statistical analysis was performed with IBM SPSS Statistics 20 (SPSS, Chicago, IL, USA) and SAS version 9.3 (SAS Institute, Cary, NC, USA).

RESULTS

The baseline characteristics of the patients are presented in Table 1. All 12 patients (10 men and 2 women, age range 21-81 years, mean age 63.9±15.3 years) had cirrhosis (alcohol n=3, CHB n=2, alcohol and CHB n=6, CHC n=1). Eleven patients had a Child-Pugh score of A, and one patient had a score of B. One patient had a Union for International Cancer Control stage of I, 7 patients had stage II, and 4 patients had stage III. All patients were deemed ineligible for surgery or radiofrequency ablation. Seven patients had solitary lesions, and 5 patients had multifocal involvement.

None of the patients experienced side effects from the contrast agent. Patients with viable HCC at the 4- and 12-week MRI immediately received proper management (additional TACE in 5 patients, RFA in 1 patient, and conservative care in 2 patients with high Eastern Cooperative Oncology Group performance status).

Table 1. Baseline characteristics of the 12 patients

Age (years)	63.9±15.3
Sex (male/female)	10 (83)/2 (17)
Underlying liver disease	
Alcohol	3 (25)
Hepatitis B	2 (17)
Alcohol and hepatitis B	6 (50)
Hepatitis C	1 (8)
ALT (IU/L)	28.0±31.6
Total bilirubin (mg/dL)	0.96±0.85
Albumin (g/dL)	4.0±0.41
PT (INR)	1.1±0.17
Child-Pugh score	
A/B/C	11 (92)/1 (8)/0
AFP (ng/mL)	63.9±15.3
Tumor diameter (cm)	3.2±1.1
Number of tumors	
1	7 (58)
2	2 (17)
≥3	3 (25)
Modified UICC stage	
I/II/III/IV	1 (8)/7 (58)/4 (34)/0
BCLC stage	
A/B/C/D	9 (75)/3 (25)/0/0

Values are presented as mean±SD or n (%).
ALT, alanine transaminase; PT, prothrombin time; INR, international normalized ratio; AFP, alpha-fetoprotein; UICC, Union for International Cancer Control; BCLC, The Barcelona Clinic Liver Cancer Classification.

The first step: post-TACE follow-up at 4 weeks

Among 12 patients, 8 (75%) had positive findings for HCC viability after TACE (MRI positive at 4 weeks or 12 weeks). Four patients (33.3%) were diagnosed as positive at the 4-week MRI and discontinued the study to undergo additional treatment. The 8 patients who were negative at the 4-week MRI proceeded to the 12-week follow-up. At 4 weeks, CEUS and MDCT showed positivity in 8 (66.7%) and 3 (25%) patients, respectively.

The second step: post-TACE follow-up at 12 weeks

Among the 8 patients who continued the study, 4 patients (50%) were newly diagnosed as having viable residual HCC at the 12-week MRI. CEUS and MDCT also showed positive findings in 4
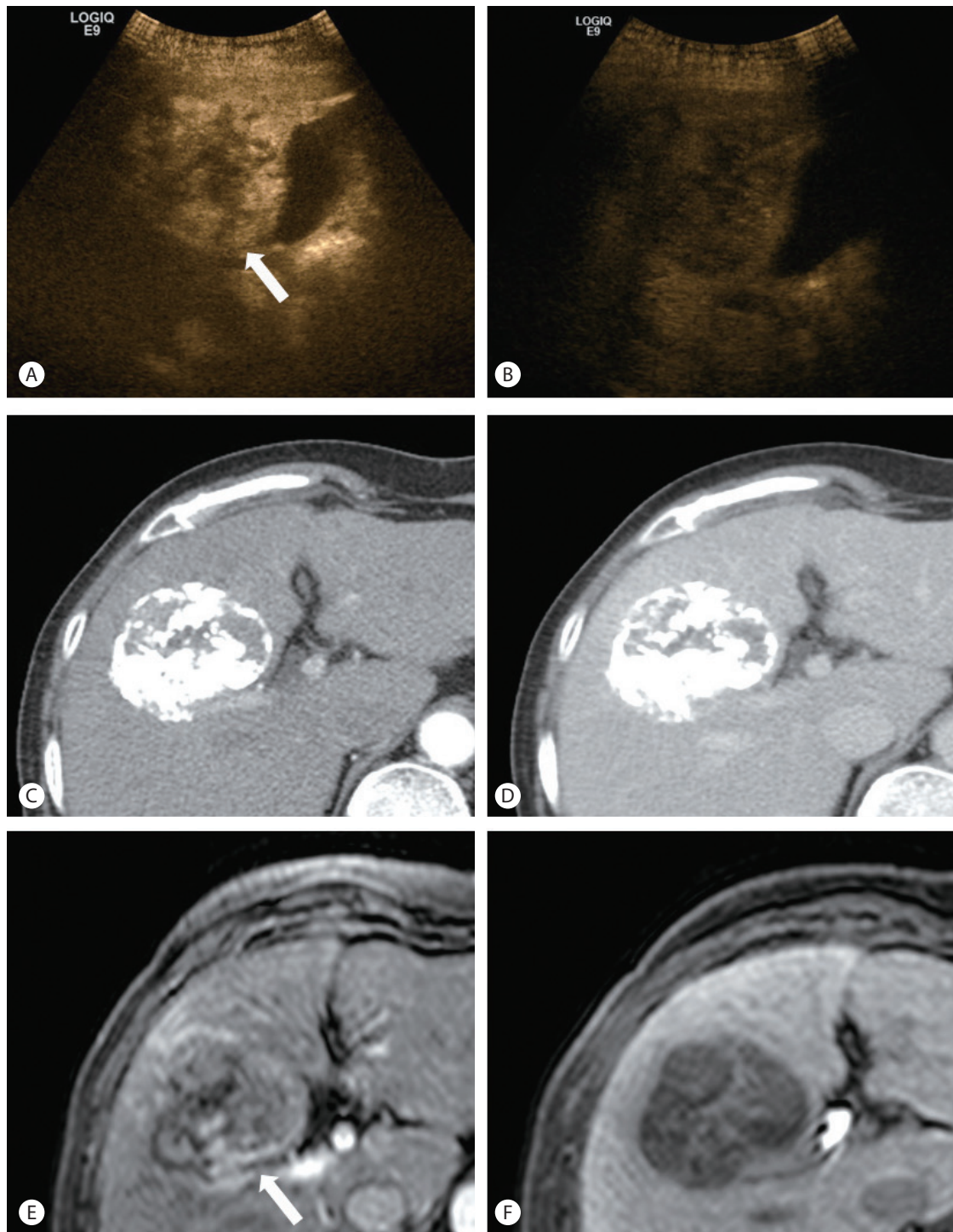
Figure 3. A 76-year-old patient with an hepatocellular carcinoma (HCC) on segment 5 at 4 weeks after transarterial chemoemboliza-tion (TACE). The image shows positivity for viable tissue in contrast-enhanced ultrasonography (CEUS) and gadoxetic-acid-enhanced dynamic magnetic resonance imaging (MRI) without evidence of viable tissue on multidetector computed tomography (MDCT). (A) Arterial phase and (B) late phase of CEUS. These showed slight enhancements (arrow) of peripheral portions of HCC in the arterial phase and wash-out in the late phase of CEUS. (C) Arterial and (D) delayed phase of MDCT. These showed compact lipiodol retention without viable tissue. (E) Arterial phase and (F) hepatobiliary phase of T1 weighted-MRI. The MRI shows intratumoral enhancement in the posterior aspect of the lesion (arrow: same aspect of CEUS enhancements) in the arterial phase and more definite hypointensity in the hepatobiliary phase image, which suggests an incomplete tumor response.

Table 2. The positivity of each imaging modality test after transarterial chemoembolization

Patient No.	CEUS 4 weeks	CT 4 weeks	MRI 4 weeks	CEUS 12 weeks	CT 12 weeks	MRI 12 weeks
1	+	-	-	+	+	Θ
2	+	-	-	+	+	Θ
3	+	+	Θ	Stop		
4	-	-	-	-	-	-
5	-	-	-	-	-	-
6	+	+	Θ	Stop		
7	-	-	-	-	-	-
8	+	-	Θ	Stop		
9	+	+	Θ	Stop		
10	+	-	-	+	+	Θ
11	-	-	-	-	-	-
12	+	-	-	+	-	Θ

+, positive result for residual hepatocellular carcinoma; -, negative result for residual hepatocellular carcinoma; Θ, confirmation of primary end-point (diagnosis of residual hepatocellular carcinoma on MRI).
Stop, confirmation of residual hepatocellular carcinoma and withdrawal from the study to obtain additional therapy. CEUS, contrast-enhanced ultrasonography; CT, computed tomography; MRI, magnetic resonance imaging; CEUS, contrast-enhanced ultrasonography.

(50%) and 3 patients (37.5%), respectively.

CEUS, MDCT diagnostic value compared with MRI

All patients who had positive findings at the 4-week CEUS (n=8) showed MRI positivity (residual viable HCC) at 4 or 12 weeks. Among them, 4 patients (50%) showed positivity in only the 4-week CEUS but not in the MRI; all showed positivity in the CEUS at 12 weeks, and the 12-week MRI confirmed that they all had residual HCC tissue.

Among the 8 patients who were confirmed via MRI as having residual HCC viability, 5 had negative findings on the 4-week MDCT scan. Of these 5 patients, 1 who showed positivity in both the CEUS and MRI at 4 weeks discontinued the study to receive additional treatment (Fig. 3). Three patients showed positivity at the 12-week MDCT, but 1 patient could not be confirmed to have viable HCC at 12 weeks (Table 2).

Comparison of CEUS *vs.* MDCT

At 4 week, 4 patients who showed positivity in CEUS did not showed positivity in MRI (they finally showed positivity at 12 weeks), so K statistic calculations at 4 weeks were lower as 0.40 between CEUS and MRI than 0.80 between MDCT and MRI. However it finally revealed near-perfect agreement between CEUS

and MRI (K=1.00) and substantial agreement between MDCT and MRI (K=0.67) at 12 weeks.

DISCUSSION

TACE is considered to be an effective means of treating HCC when curative loco-regional therapy is not possible, and it is the most commonly used therapeutic approach for HCC.[22] However, it is difficult to achieve complete tumor necrosis with TACE alone.[23,24] Accuracy and timing in assessing the treatment response are essential in determining the need for additional therapy. Intratumoral vascularity following TACE has been shown to be correlated with tumor viability and has been used as the primary criterion for additional treatment.[25] Therefore, many studies have used various imaging modalities to evaluate the vascularity of HCCs treated with TACE.[26-28]

The therapeutic effect of TACE is usually assessed via MDCT several weeks after treatment.[29,30] MDCT is often limited in early the detection of post-TACE tumor vascularity because the homogenous retention of embolic material (iodized oil) may obscure the enhanced area within the tumor. Moreover, it usually takes 3 to 4 weeks for iodized oil to be washed out from the surrounding liver parenchyma after TACE,[27] and the detection of small nodules and hypovascularized tumors may be limited.[31] Additionally, radiation hazard and renal iodine contrast toxicity often limit the possibility

of repeated applications of MDCT among patients with HCC.

Gadoxetic acid-enhanced dynamic MRI is considered the most accurate diagnostic tool for HCC and has been increasingly used in diagnosis and follow-up evaluations after HCC treatments such as TACE.[6,32] MRI has specific advantages over MDCT due to its minimal influence of the intratumoral retention of iodized oil, therefore, MRI was used as the reference standard in the present study. However, MRI also have some limitations to the application including the cost of the examination and breath holding related artifacts or examination failure.[33]

The effectiveness of CEUS in assessing the therapeutic response of HCC has been advocated in several previous studies.[31,34] Previous studies reported that the sensitivity and specificity of CEUS were 88.0-93.3% and 100%, respectively, in evaluating the tumoral vascularity of HCCs treated with TACE when MDCT or gadoxetic acid-enhanced dynamic MRI was used as the reference standard.[6,35] Those studies used a first-generation air-based UCA (Levovist®) with a mean microbubble diameter of 2-5 μm. However, there were some limitations for CEUS using Levovist® because it could not obtain real-time images and because it requires a high mechanical index that destroys the microbubbles and results in image artifacts.[19]

Recently, applications of new 2nd-generation contrast agents, such as SonoVue®, as well as new software for analyzing sonographic images, have created new prospects for characterizing liver lesions and evaluating treatment responses.[20] We used SonoVue® in the present study to obtain real-time and continuous CEUS images. CEUS evaluations have several advantages in assessing treatment response among patients with HCC. CEUS is non-invasive and less expensive than MDCT or MRI and can be performed repeatedly at bedside. In patients with impaired renal function, which is a frequent complication of advanced liver cirrhosis, sonography avoids the use of iodinated contrast agent. Additionally, CEUS can visualize serial enhancement patterns of HCCs, and the interpretation is not disturbed by iodized oil. Therefore, CEUS has advantages in the early detection of tumor recurrence or in incomplete treatment, as shown in the present study.

In the present study, MDCT was less sensitive than CEUS in detecting residual vascular enhancement in HCC nodules after TACE. CEUS accurately revealed the enhancement from the residual viable portion (incomplete response) in all cases of residual or recurrent viable HCC at 4 weeks after TACE. Compared with MRI, MDCT and CEUS showed sensitivities of 75% and 100%, respectively, in identifying the presence of residual tumor at 4 weeks. Post-chemoembolization intratumoral blood flow detection rates

using CEUS were superior to those using MDCT because tumor visualization via CEUS was less affected by iodized oil retention.

Both CEUS and MRI identified 8 patients with viable HCC at the 12-week follow-up. CEUS identified all 8 patients with viable HCC at 4 weeks, whereas MRI detected 4 patients at 4 weeks and 4 patients at 8 weeks. There was no statistical difference in the clinical characteristics including tumor size, number, tumor area between patients whose HCC recurrence were detected at 4 weeks and 12 weeks with MRI. It is also difficult to interpret the clinical meaning of 4 patients who showed early positivity in CEUS without MRI enhancement. The small number of included patients in this study might make an accurate statistical analysis impossible. However, CEUS with SonoVue® is considered to have the benefit of being able to detect smaller areas of viable HCC and the patency of smaller vessels in early stage of post-treatment and it makes CEUS be more capable than MRI in detecting small areas of HCC viability in earlier time. More well designed and large numbers of prospective study is needed to validate and clarify this finding.

There are a few limitations to this study. First, as mentioned above, a small number of patients decreased the statistical power of our observations. However, this study can be a good reference as a pilot study for future well-designed randomized trials. Second, CEUS was not performed in patients with a poor acoustic window, obesity or incorporation. Several studies have shown that tumor location limits the visualization of lesions using CEUS.[7,36] Several factors (deep-seated target lesion, poor echo window, and the administration of bland embolic agents) could be responsible for the variability in results. Finally, CEUS was performed by a single expert, and the diagnosis accuracy is influenced by the skill of the CEUS examiner and the analysis experience of the CEUS images.

In conclusion, 4-week-early CEUS showed excellent results in the diagnosis and prediction of residual viable HCC for the assessment of the therapeutic response of TACE. This finding suggests that CEUS may be used to obtain early additive diagnostic information when deciding whether TACE treatment should be repeated. However, this result was derived from a small number of patients and must be confirmed in a well-designed study with a large population.

Acknowledgements

Conflicts of Interest

The authors have no conflicts to disclose.

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