Utility of Contrast-Enhanced Ultrasound for Early Therapeutic Evaluation of Hepatocellular Carcinoma After Transcatheter Arterial Chemoembolization

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Objectives—We aimed to investigate whether contrast-enhanced ultrasound (CEUS) could be useful for early evaluation of the treatment response to transcatheter arterial chemoembolization (TACE) of hepatocellular carcinoma (HCC).

Methods—This study retrospectively selected HCCs in which homogeneous retention of iodized oil was confirmed on non–contrast-enhanced computed tomography performed immediately after TACE. Therapeutic responses of HCCs were evaluated by CEUS 1 to 2 days after TACE and by contrast-enhanced computed tomography (CECT) approximately 4 weeks after TACE. We investigated the noninferiority of CEUS 1 to 2 days after TACE to CECT approximately 4 weeks after TACE in terms of the diagnostic accuracy of the therapeutic response to TACE on HCC.

Results—Eighty-nine HCCs were enrolled in this study between April 2014 and June 2016. A complete response was observed in 57 of 89 nodules (64.0%), and an incomplete response was observed in the remaining 32 nodules (36.0%). The accuracy rates for CEUS 1 to 2 days after TACE and CECT approximately 4 weeks after TACE in the therapeutic effect of TACE on HCCs were 83.1% (95% confidence interval, 73.7%–90.2%) and 83.1% (95% confidence interval, 73.7%–90.2%), respectively. The difference in diagnostic accuracy between methods was 0%, which was below the predetermined noninferiority limit of 15%, and CEUS 1 to 2 days after TACE was noninferior to CECT approximately 4 weeks after TACE.

Conclusions—Our results suggest that CEUS is a useful modality for early therapeutic evaluation of TACE for HCC, and we can thus plan the next treatment strategies for HCC within a few days after TACE.

Key Words—contrast-enhanced computed tomography; contrast-enhanced ultrasound; hepatocellular carcinoma; transcatheter arterial chemoembolization

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Abbreviations

CECT, contrast-enhanced computed tomography; CEUS, contrast-enhanced ultrasound; CI, confidence interval; CT, computed tomography; CTHA, computed tomographic hepatic arteriography; HCC, hepatocellular carcinoma; TACE, transcatheter arterial chemoembolization; US, ultrasound

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Transcatheter arterial chemoembolization (TACE) has been widely used to treat unresectable hepatocellular carcinoma (HCC).[1–4] In conventional TACE procedures, iodized oil is delivered intra-arterially to the liver tumor.[5–8] To improve

survival in patients with HCC who receive TACE, an evaluation of the treatment response and determination of the necessity for additional treatment are important.[9,10]

Contrast-enhanced computed tomography (CECT) is one of the most commonly used modalities for assessing the therapeutic response to TACE.[11] However, after TACE using a mixture of iodized oil, anticancer drugs, and gelatin sponge particles, concentrated iodized oil in the tumor frequently masks local tumor recurrence on CECT.[12,13] As 3 to 4 weeks are usually required for iodized oil to be washed out from the surrounding liver parenchyma after TACE,[14] the therapeutic effects are usually evaluated by CECT several weeks after TACE[15]; thus, CECT is unsuitable for measuring the early therapeutic response of HCC after TACE.

Contrast-enhanced ultrasound (CEUS) offers very high sensitivity to contrast agents and high spatial resolution and, unlike CECT, is less affected by retention of iodized oil. Contrast-enhanced US may therefore have advantages in the early assessment of TACE efficacy in HCC. Several studies have reported that CEUS could detect viable HCC after TACE more sensitively than CECT.[10,16–24] Although many previous studies have reported the usefulness of CEUS performed more than several weeks after TACE, there are few studies that have reported the usefulness of CEUS for the early evaluation of the treatment response of HCC to TACE.[16,23,24] The aim of this study was to investigate the utility of CEUS for early evaluation of the treatment response of HCC to TACE.

Materials and Methods

This study was performed according to the guidelines of the Declaration of Helsinki and was approved by Nihon University Hospital Ethics Committee. Written informed consent for treatment and examination was obtained from all patients.

We retrospectively selected patients with HCC nodules for which homogeneous retention of iodized oil was confirmed by non–contrast-enhanced computed tomography (CT) performed immediately after TACE. Exclusion criteria were as follows: (1) lack of identification of HCC on grayscale ultrasound (US) imaging; and (2) contraindications to iodinated contrast agents or US contrast agents (eg, allergic reactions and impaired renal function). When a patient had multiple HCCs that showed homogeneous retention of iodized oil on non–contrast-enhanced CT performed immediately after TACE, the 2 largest lesions were selected for analysis in this study.

Transcatheter arterial chemoembolization was performed because patients were ineligible for surgical resection and radiofrequency ablation. The diagnosis of HCC was established by at least 2 of the following imaging modalities: CEUS, CECT, and gadolinium-ethoxybenzyl–enhanced magnetic resonance imaging.

Contrast-Enhanced US Examinations

All CEUS studies were performed by the same experienced sonographer (M.O.), who had more than 15 years of experience with CEUS. Contrast-enhanced US examinations were performed with a LOGIQ E9 US scanner (GE Healthcare, Pittsburgh, PA) equipped with a 1–6-MHz convex transducer or a 9.0-MHz linear transducer at a low mechanical index (0.20–0.40). Through a 20- or 22-gauge cannula placed in an antecubital vein, a US contrast agent (Sonazoid; Daiichi Sankyo, Tokyo, Japan) at a dose of 0.5 mL/body was injected manually at a speed of 1 mL/s, followed by a 10-mL normal saline flush. The recommended dose of Sonazoid administered is 0.015 mL/kg of body weight. If tissue harmonic imaging is used, favorable imaging results can be obtained by using half of the recommended volume.[25] Thus, the dose of Sonazoid used in our patients was 0.5 mL, regardless of their body weight. After injection of the contrast agent, the tumor was observed for approximately 2 minutes in the vascular phase. Patients held their breath for a few seconds if necessary. An additional contrast agent injection was administered as needed to confirm tumor vessel flow. Imaging data were recorded to the hard disk of the US device and reviewed by 2 independent experts, 1 of whom was the sonographer who performed the examination. Therapeutic responses were evaluated retrospectively without knowledge of the CECT results. When microbubbles were present nodularly within the tumor, the tumor was defined as showing positive enhancement. When no microbubble signal

was present within the tumor, the tumor was defined as showing negative enhancement.

Contrast-Enhanced CT Examinations

Examinations were performed with a 64- or 320-multidetector row CT scanner (Aquilion CX, Aquilion ONE; Toshiba, Tokyo, Japan) and a tube voltage of 120 kV, tube current of 200 mA, and 0.5-mm collimation. Computed tomographic images were obtained in the pre-enhancement phase and at 30 seconds (arterial phase), 60 seconds (portal phase), and 180 seconds (equilibrium phase) after intravenous injection of the contrast material. A nonionic contrast agent, iomeprol, 350 mg/mL (Iomeron; Eisai, Tokyo, Japan), was administered by a mechanical power injector through a 20-gauge intravenous cannula placed in an antecubital vein at a rate of 4 to 5 mL/s. At least 2 hepatologists specialized in interpreting CT images retrospectively assessed the CT images without any knowledge of the CEUS results. A tumor was defined as showing positive enhancement when it showed identifiable nodular or irregular ringlike enhancement in the arterial phase. A tumor was defined as showing negative enhancement when the tumor did not show identifiable nodular or irregular ringlike enhancement in the arterial phase.

Transcatheter Arterial Chemoembolization Procedure

A 4F catheter (FNSAC IV, Angiomaster; Terumo, Tokyo, Japan) was inserted through the left brachial artery according to the Seldinger method and was navigated to the hepatic artery. In some cases, computed tomographic hepatic arteriography (CTHA) was performed at this time to identify tumor staining and the feeding artery of the tumor. A 1.8F microballoon catheter (Attendant Delta, Attendant Nexus; Terumo; or LOGOS; Piolax, Kanagawa, Japan]) was then advanced through the 4F catheter as close to the tumor as possible, and miriplatin (Miripla; Dainippon-Sumitomo Pharmaceutical, Tokyo, Japan) suspended in iodized oil (Ultra-Fluid; Dainippon-Sumitomo Pharmaceutical) was injected into the hepatic artery under balloon occlusion. Thereafter, 1-mm gelatin sponge particles (Gerpart; Nippon Kayaku, Tokyo, Japan) were injected to completely obstruct the tumor-feeding artery. If several tumor vessels had been identified, a catheter was separately inserted into each vessel, and the treatment was performed.

TACE using miriplatin was approved by the Institutional Review Board of our hospital. Miriplatin was suspended in iodized oil at room temperature at a concentration of 20 mg/mL. The total amount of miriplatin administered was determined according to the size of the tumor. The total amount of miriplatin per session was limited to 120 mg. The 1-mm gelatin sponge particles were mixed with a contrast agent and broken into smaller sizes (150–200 μm in length) by pumping 10 times with two 2.5-mL syringes and a 3-way stopcock.

Follow-up

Conventional non–contrast-enhanced CT was performed immediately after TACE for evaluation of iodized oil accumulation in HCC nodules. Only HCC nodules in which homogeneous retention of iodized oil was confirmed at this time were selected for this study. A CEUS examination was performed 1 to 2 days after TACE to evaluate the effectiveness of TACE. Contrast-enhanced US and CECT examinations were performed on the same day approximately 4 weeks after TACE to reevaluate the effectiveness. When negative enhancement was confirmed by both CEUS and CECT, both modalities were performed again on the same day approximately 16 weeks after TACE. When positive enhancement was not recognized by both CEUS and CECT approximately 16 weeks after TACE, we judged that complete necrosis had been achieved and used those results as the final diagnosis. When residual flow was determined by CEUS, CECT, or both, additional treatment with TACE was performed. In these cases, the diagnosis of residual flow was established again by nodular staining on angiography, CTHA, or both, and these results were used as the final diagnosis. A flowchart of patient examinations and the treatment design is shown in Figure 1.

Statistical Analyses

The main objective of this study was to investigate the noninferiority of CEUS 1 to 2 days after TACE compared to CECT approximately 4 weeks after TACE in terms of the diagnostic accuracy of the response evaluation of TACE for HCC. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (R Foundation for Statistical

Computing, Vienna, Austria). More precisely, EZR is a modified version of R Commander designed to add statistical functions frequently used in biostatistics. The diagnostic accuracy, sensitivity, and specificity of CEUS 1 to 2 days after TACE and CECT approximately 4 weeks after TACE were calculated using the final diagnosis as the reference standard.

The sample size was calculated on the basis of previous studies, which have shown that the diagnostic accuracy of CECT in evaluating the therapeutic effect of TACE for HCC is about 80%.[17,18] Based on projected diagnostic accuracy of 80%, we decided that differences in diagnostic accuracy between CEUS 1 to 2 days after TACE and CECT approximately 4 weeks after TACE of up to 15% would be considered clinically unimportant. To detect this noninferiority margin of 15% with power in excess of 80% and a 1-sided 95% confidence interval (CI), a total of 88 HCCs were required. Statistically significant differences in diagnostic accuracy were tested by the McNemar test, with a level of significance of .05.

Results

From April 2014 to June 2016, we performed TACE selectively for 198 HCC nodules. Homogeneous retention of iodized oil was confirmed in 128 HCC nodules by non–contrast-enhanced CT performed immediately after TACE. Of these, 39 nodules were excluded because no masses were seen with US (n = 4), loss to follow up (n = 4), contraindications to iodinated contrast agents (n = 3), lack of a reference standard (n = 25), and the presence of more than 3 nodules with homogeneous retention of iodized oil in a single patient (n = 3). Thus, a total of 70 patients (43 men and 27 women; age range, 44–87 years; mean age ± SD, 72.0 ± 9.5 years) with 89 HCC nodules were enrolled in this study. The baseline characteristics of the patients are shown in Table 1.

Overall, a complete response was observed in 57 of 89 nodules (64.0%; Figure 2). The remaining 32 nodules (36.0%) showed an incomplete response

Figure 1. Flowchart for this study.

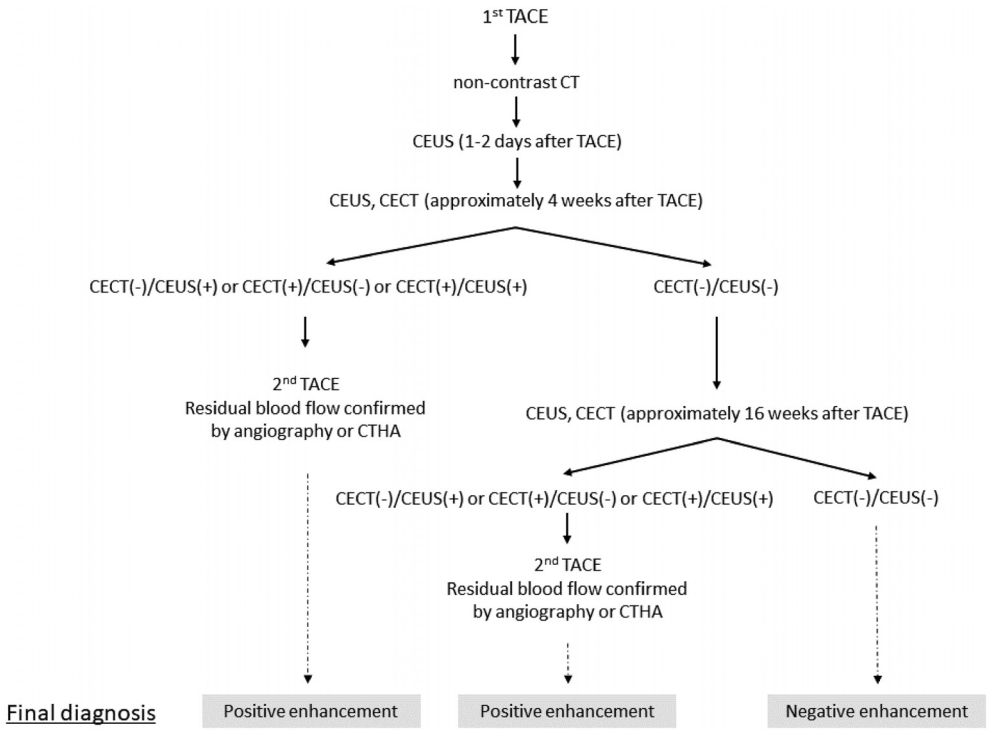


Table 1. Baseline Clinical Characteristics of the Patients

Characteristic	Value
Age, y	72.0 ± 9.5
Male/female	43/27
Etiology of liver disease: HCV/HBV/alcohol/unknown	45/11/10/4
Child-Pugh score: A/B/C	55/15/0
BCLC stage: A/B/C/D	46/24/0/0
No. of tumors: 1/2/≥3	32/22/16
Size of target tumors, mm	18.1 ± 10.5

Data are presented as mean ± SD where applicable. BCLC indicates Barcelona Clinic Liver Cancer Classification; HBV, hepatitis B virus; and HCV, hepatitis C virus.

(Figure 3). All incomplete responses were confirmed by angiography or CTHA. Contrast-enhanced US 1 to 2 days after TACE detected 22 of the 32 incomplete responses. There were 5 false-positive findings with CEUS 1 to 2 days after TACE. These 5 nodules showed negative enhancement on the CEUS examinations and CECT approximately 4 weeks after TACE (Figure 4).

The accuracies of CEUS 1 to 2 days after TACE and CECT 4 weeks after TACE in evaluating the therapeutic effect of TACE for HCC were 83.1% (95% CI, 73.7%–90.2%) and 83.1% (95% CI, 73.7%–90.2%), respectively; the sensitivities were 68.0% (95% CI, 50.0%–83.9%) and 53.1% (95% CI, 34.7%–60.9%); and the specificities were 91.2% (95% CI, 80.7%–97.1%) and 100% (95% CI, 72.7%–100%), respectively (Tables 2 and 3). As the difference in accuracy between CEUS 1 to 2 days after TACE and CECT approximately 4 weeks after TACE was 0%, and therefore less than 15%, CEUS 1 to 2 days after TACE was considered noninferior to CECT approximately 4 weeks after TACE. No significant differences in diagnostic accuracy were seen between

Figure 2. Images from a 77-year-old woman with HCC treated with TACE. **A**, Non–contrast-enhanced CT performed immediately after TACE shows homogeneous retention of iodized oil in the tumor (arrows). **B**, Contrast-enhanced US examination performed 1 day after TACE shows no residual blood flow in the tumor. **C**, Contrast-enhanced CT performed 4 weeks after TACE shows no wash-out of iodized oil and no enhancement in the tumor.

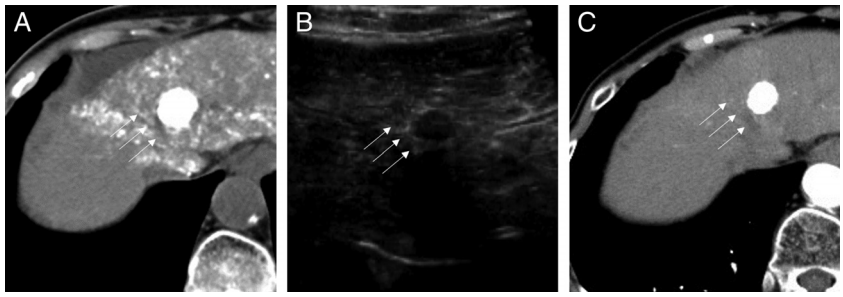
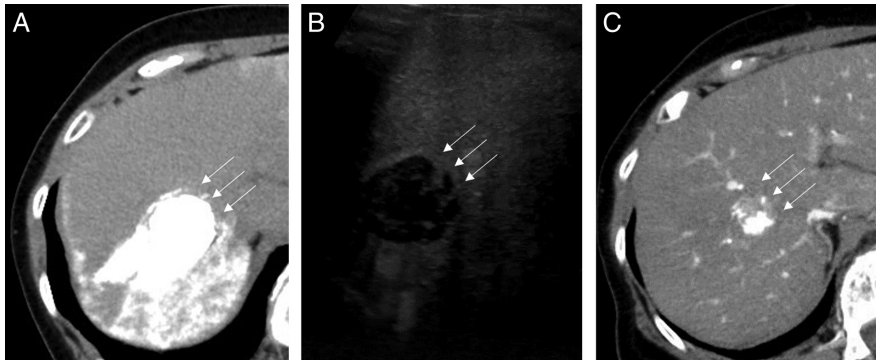


Figure 3. Images from a 71-year-old woman with HCC treated with TACE. **A**, Non–contrast-enhanced CT performed immediately after TACE shows homogeneous retention of iodized oil in the tumor (arrows). **B**, Contrast-enhanced US examination performed 1 day after TACE shows residual blood flow in the tumor. **C**, In the arterial phase of CECT performed 4 weeks after TACE, most iodized oil has been washed out, and hyperenhancement within the tumor is confirmed.



CEUS 1 to 2 days after TACE and CECT approximately 4 weeks after TACE ($P > .99$).

Discussion

This study investigated the utility of CEUS in evaluating the early therapeutic response to TACE in patients with HCC. This study selected only patients with HCC nodules that showed homogeneous retention of iodized oil on non–contrast-enhanced CT performed immediately after TACE. We excluded all other patients because residual blood flow is generally observed when retention of iodized oil in nodules is insufficient after TACE. The utility of intra-arterial CEUS has recently been reported in TACE using

Figure 4. Images from an 81-year-old woman with HCC treated with TACE. **A**, Non–contrast-enhanced CT performed immediately after TACE shows complete retention of iodized oil in the tumor (arrows). **B**, Contrast-enhanced US examination performed 1 day after TACE shows residual blood flow in the tumor. **C**, Contrast-enhanced US examination performed 4 weeks after TACE shows no enhancement in the tumor. **D**, Contrast-enhanced CT performed 4 weeks after TACE shows no wash-out of iodized oil and no enhancement in the tumor.

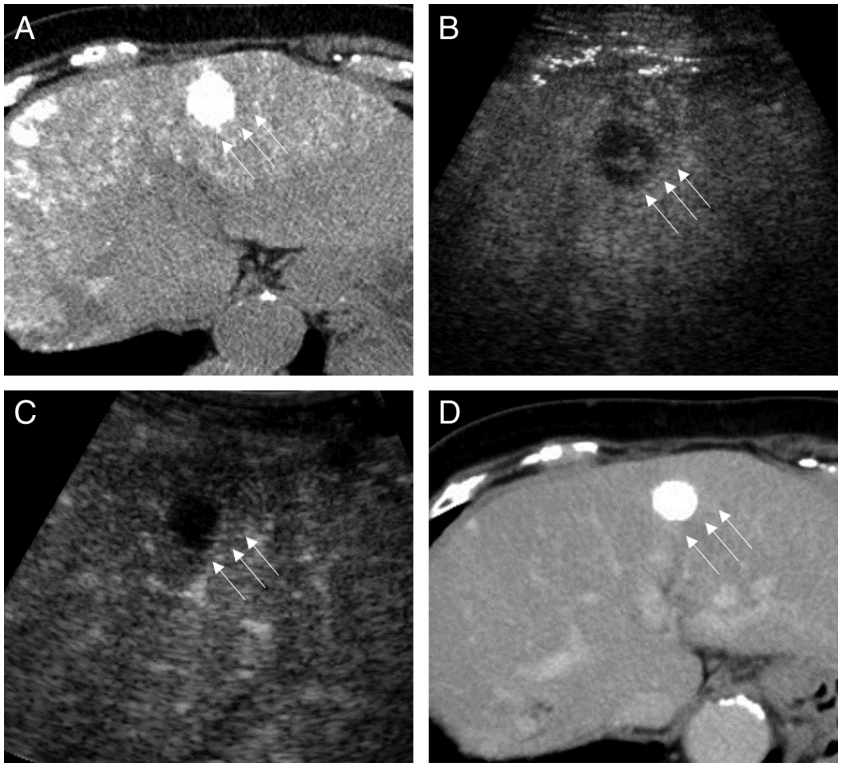


Table 2. Comparison of CEUS Findings 1 to 2 Days After Treatment With Final Diagnosis

	Final Diagnosis		
CEUS Findings	**Positive Enhancement**	**Negative Enhancement**	**Total**
Positive enhancement	22	5	27
Negative enhancement	10	52	62
Total	32	57	89

Table 3. Comparison of CECT Findings Approximately 4 Weeks After Treatment With Final Diagnosis

	Final Diagnosis		
CECT Findings	**Positive Enhancement**	**Negative Enhancement**	**Total**
Positive enhancement	17	0	17
Negative enhancement	15	57	72
Total	32	57	89

drug-eluting beads.[26–28] However, intra-arterial administration of Sonazoid is contraindicated, and in the case of TACE using iodized oil and gelatin sponge particles, as artifacts appear due to air mixed in during the procedure and the entire tumor may be observed as a strongly hyperechoic lesion with acoustic shadow on US images immediately after TACE, it becomes difficult to judge the detailed treatment effect. Therefore, we performed CEUS examinations 1 to 2 days after TACE in this study. In the CEUS evaluation 1 to 2 days after TACE, the artifacts disappeared, and we could perform a detailed evaluation.

The therapeutic effect 1 to 2 days after TACE mainly reflects the embolic effect and does not reflect the effect of the anticancer drug so much. However, the main tissue change in HCC after TACE is coagulation necrosis due to ischemia, and the therapeutic effect of TACE is largely affected by the embolic effect. The efficacy of TACE's anticancer drug was compared to hepatic artery embolization without the anticancer drug in previous studies, but no difference in the survival prognosis was not observed between the treatments.[29,30] Takayasu et al[31] reported that there was no significant difference in the therapeutic effect of TACE with or without the anticancer drug. Although we believe that there are potential effects of the local chemotherapy that is part of the TACE procedure, the main therapeutic effect of TACE is the embolic effect. Therefore, we considered that the therapeutic effect of TACE could be evaluated even after 1 or 2 days. The results showed the high diagnostic accuracy of CEUS in the assessment of the therapeutic response to TACE after 1 to 2 days, and CEUS 1 to 2 days after TACE was noninferior to CECT approximately 4 weeks after TACE.

A previous study showed that the rates of detection of residual blood flow after TACE using CEUS were markedly superior to those using CECT because tumor depiction by CEUS is less affected by retention of iodized oil.[16–22] Although a previous study reported that dual-energy CT and iodine mapping could discriminate contrast-enhanced lesions from compact iodized oil accumulations and help identify viable lesions around the HCC after TACE,[32] dual-energy CT and iodine mapping are not yet widely used in clinical practice, and further accumulation of studies is desired. A recent retrospective study comparing CEUS to CECT performed 0.5 to 2 months after TACE for evaluating the treatment response reported that the sensitivities, specificities, and accuracies of CEUS versus CECT were 95.9% versus 76%, 100% versus 100%, and 96.2% versus 77.7%, respectively.[17] Thus, many previous studies have reported the usefulness of CEUS by comparing CEUS to CECT, but the therapeutic evaluation was performed several weeks after TACE in almost all of the studies, and there were few studies in which the therapeutic evaluation was performed within a week after TACE.[33] Our study focused on the utility of CEUS for the very early evaluation of the therapeutic response to TACE. It is well known that early HCC diagnosis offers better outcomes. Therefore, we can assume that an earlier evaluation of incomplete necrosis and judgment of the need for additional treatment increase the overall survival.

Currently, no consensus has been reached regarding the optimal interval for performing a CEUS examination after TACE.[21] Our study suggested that a CEUS examination should be performed early after TACE for the therapeutic evaluation. Contrast-enhanced US is a noninvasive modality, does not need an iodinated contrast agent, and has no risk of radiation exposure, unlike CECT. Therefore, a CEUS examination can be safely performed even the day after TACE. The biggest advantage of an early therapeutic evaluation is the ability to plan further treatment within a few days after TACE. For example, we can plan to perform TACE again at a close interval (about 4 weeks after previous TACE) or decide to switch to a different treatment, such as molecularly targeted drugs, without delay. In addition, since the therapeutic evaluation can be performed while the patient is still in the hospital for TACE, it is not necessary for patients to return to the hospital for the therapeutic evaluation, and the physical burden of patients is reduced. Previous studies reported the utility of TACE as a bridging therapy for liver transplantation, in which a pretransplant treatment with TACE resulted in delayed HCC progression during the waiting list time and lowered tumor recurrence after liver transplantation.[34–36] The response to TACE provides important information for the prognosis. An early evaluation of the responsiveness to TACE may help guide patient prioritization in the waiting list, which may help improve the prognosis of patients listed for liver transplantation.

In this study, 5 false-positive cases were encountered in the CEUS assessment 1 to 2 days after TACE. Three of these 5 false-positive cases were due to evaluations of nontumor vessels around posttreatment nodules as residual tumor vessels. Hypervascularity around posttreatment nodules could occur because of inflammation generated by TACE. It is important not to assess this hypervascularity as residual tumor vessels in the early therapeutic response evaluation of TACE. In 2 of the 5 false-positive cases, even though residual flow was clearly recognized within the nodule in the assessment by CEUS 1 to 2 days after TACE, it had disappeared in the CEUS assessment approximately 4 weeks after TACE. This may have been due to the sustained-release effects of miriplatin. In an animal experiment, a slower decrease in the concentrations of platinum compounds was observed among tumors administered miriplatin suspended in iodized oil than in those administered cisplatin, a water-soluble platinum compound, suspended in iodized oil.[37] Although sustained-release effects were only recognized in 2 of the 89 cases (2.2%) in this study, sustained-release effects should be taken into consideration when using miriplatin in TACE. We evaluated these 2 cases as false-positive cases in this study. However, if the sustained-release effects of miriplatin are proved, these 2 cases should not be regarded as real false-positive cases and should be taken as a result of the sensitivity of CEUS in detecting vascularity early after TACE. Further accumulation of data on sustained-release effects is needed.

Our study had some limitations that must be considered when interpreting the results. First, this study was retrospective, which essentially decreased the statistical strength. Prospective studies are therefore needed. Second, CEUS is an operator-dependent imaging technology[38] and is not very suitable in patients with a poor acoustic window.[39,40] Several studies have reported that the tumor location limits the visualization of lesions by CEUS. In this study, we selected nodules detectable with grayscale US, and this limitation could have led to some patient selection bias.

In conclusion, the diagnostic accuracy of CEUS in assessing the therapeutic response to TACE after 1 to 2 days was found to be noninferior to that of CECT after approximately 4 weeks. This result suggests that CEUS could allow early therapeutic evaluation of TACE, permitting planning of the next treatment strategy within a few days after TACE. Further studies are needed to validate these findings.

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Utility of Contrast-Enhanced Ultrasound for Early Therapeutic Evaluation of Hepatocellular Carcinoma After Transcatheter Arterial Chemoembolization
（肝細胞癌の TACE 後早期治療効果判定における、造影超音波検査の有用性）

【目的】　肝動脈化学塞栓療法（transcatheter arterial chemoembolization: TACE）は切除適応外の肝細胞癌に対して広く施行されている。TACE の治療効果判定として造影 CT 検査を用いるのが一般的であるが、造影 CT 検査では腫瘍内に集積したリピオドールの影響で腫瘍内に残存した血流を正しく評価できないことが多々ある。また、腫瘍周囲の正常肝組織に集積したリピオドールが消失されるのには約 4 週間かかるとされているため、造影 CT 検査で TACE 後の治療評価を行う場合は治療後 1 ヵ月以上経過してから行うことが標準となっている。造影超音波検査は空間・時間分解能に優れており、リピオドールにあまり影響されることなく詳細な血流の評価が可能なモダリティである。過去にも TACE 後の肝細胞癌の残存血流の診断においては造影 CT 検査より優れているという報告は多く認めているが、造影超音波検査の TACE 後早期治療効果判定における有用性についての報告は少ない。今回、我々は肝細胞癌の TACE 後早期治療効果判定における造影超音波検査の有用性を検討した。

【対象と方法】　TACE を施行した肝細胞癌のうち、治療終了直後に撮影した単純 CT 検査において腫瘍内にリピオドールの均一な集積を認めた肝細胞癌を本研究の対象とした。TACE 後の残存血流評価において、TACE 後 1～2 日に施行した造影超音波検の正診率と TACE 後約 4 週に施行した造影 CT 検査の正診率を比較し、TACE 後約 4 週の造影 CT 検査に対する TACE 後 1～2 日の造影超音波検査の非劣性を検討した。

造影超音波検査は超音波造影剤としてソナゾイド（ペルフルブタン：水素添加卵黄ホスファチジルセリンナトリウム）を用い、TACE 後結節内に血流信号を認めた場合を残存血流あり（positive enhancement）、血流信号を全く認めなかった場合を残存血流なし（negative enhancement）と評価した。造影 CT 検査では、TACE 後結節内部および辺縁に濃染を認めた場合を残存血流あり、濃染を全く認めなかった場合を残存血流なしと評価した。造影超音波検査の評価は超音波専門医 2 名、造影 CT 検査の評価は肝臓専門医 2 名で行った。TACE の際には全例で抗がん剤はミリプラチン、塞栓物質は多孔性ゼラチン粒を用いた。

過去の論文を基に TACE 後約 4 週の造影 CT 検査の正診率を 80％と設定し、予測される TACE 後 1～2 日の造影超音波検査の正診率を 80％とした。非劣性マージンを 15％に設定し、この差を片側 5％の有意水準と 80％の検出力で検出するための目標結節数を 88 とした。尚、本研究はヘルシンキ宣言に則り行われ、日本大学病院臨床研究審査委員会の承認を得た（承認番号 2017-0905）。

【結果】　2014 年 4 月 1 日～2016 年 6 月 30 日の期間において、TACE を施行した 70 症例 89 結節（男女比 43:27、平均年齢 72 歳、平均腫瘍径 18.1mm）が本研究の対象となった。89 結節のうち 57 結節（64.0%）で TACE 後に完全壊死が観察され、残りの 32 結節（36.0%）で不完全壊死が観察された。治療効果判定における TACE 後 1～2 日の造影超音波検査および TACE 後約 4 週の造影 CT 検査の正診率は、83.1%（95%信頼区間（CI）、73.7-90.2%）および 83.1%（95%CI、73.7-90.2%）であった。両検査の正診率の差は 0%であり、事前に設定した 15%の非劣性マージンを下回り、TACE 後 1-2 日の造影超音波検査は TACE 後約 4 週の造影 CT 検査に対する非劣性を示した。

【考察】　TACE 後に腫瘍内の造影効果が消失した部位は組織学的に凝固壊死することが報告されている。腫瘍内の血流の残存（positive enhancement）は腫瘍の残存を意味することから、TACE 後の治療効果判定は残存血流の評価が重要となる。本研究はリピオドールの影響をあまり受けずに微細血流の評価が可能な造影超音波検査が、TACE 後の早期治療効果判定に有用な手法であることを示した。早期治療効果判定を行うことで、同一入院内に追加 RFA を施行する、短い間隔で追加 TACE を行う、分子標的薬に切り替えるなど、早期に治療計画を立案することが可能となり、早い段階での追加治療が肝細胞癌患者の予後延長につながる可能性がある。

本研究では TACE 後 1～2 日の造影超音波検査で、5 例の擬陽性、10 例の偽陰性を認めた。擬陽性例のうち 3 例は TACE 後に生じた炎症性変化を腫瘍の残存血流として捉えた可能性が、残りの 2 例はミリプラチンの徐放効果により腫瘍が経過ともに壊死に陥った可能性が考えられた。偽陰性症例を認めた原因については、腫瘍の位置や被検者の体格によっては造影超音波検査の血流感度が低下したこと、ミリプラチンの腫瘍内への密な集積のため結節全体が強く高エコー化したことで微細な血流信号を正確に捉えることができなかったことが考えられた。

本研究は後方視的研究であり、造影超音波検査による TACE 後早期治療効果判定の更なるエビデンスの確立を行うためには、症例数の蓄積及び、多施設共同の前方視的研究が必要と考える。

【結論】　今回の研究は、肝細胞癌における TACE 後治療効果判定において、TACE 後 1～2 日の造影超音波検査は高い診断精度を有し、TACE 後約 4 週の造影 CT 検査に対する非劣性を示した。この結果により、造影超音波検査が TACE の早期治療評価に有用であることが示された。TACE 後に造影超音波検査による早期治療効果判定を行うことで、TACE 後数日以内に次の治療計画の立案が可能となることが示唆された。

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