Radiology

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Contrast-enhanced US Evaluation of Hepatocellular Carcinoma Response to Chemoembolization: A Prospective Multicenter Trial

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Background: Contrast-enhanced (CE) US has been studied for use in the detection of residual viable hepatocellular carcinoma (HCC) after locoregional therapy, but multicenter data are lacking.

Purpose: To compare two-dimensional (2D) and three-dimensional (3D) CE US diagnostic performance with that of CE MRI or CT, the current clinical standard, in the detection of residual viable HCC after transarterial chemoembolization (TACE) in a prospective multicenter trial.

Materials and Methods: Participants aged at least 21 years with US-visible HCC scheduled for TACE were consecutively enrolled at one of three participating academic medical centers from May 2016 to March 2022. Each underwent baseline 2D and 3D CE US before TACE, 2D and 3D CE US 1–2 weeks and/or 4–6 weeks after TACE, and CE MRI or CT 4–6 weeks after TACE. CE US and CE MRI or CT were evaluated by three fellowship-trained radiologists for the presence or absence of viable tumors and were compared with reference standards of pathology (18%), angiography on re-treatment after identification of residual disease at 1–2-month follow-up imaging (31%), 4–8-month CE MRI or CT (42%), or short-term (approximately 1–2 months) CE MRI or CT if clinically decompensated and estimated viability was greater than 50% at imaging (9%). Diagnostic performance criteria, including sensitivity and specificity, were obtained for each modality and time point with generalized estimating equation analysis.

Results: A total of 132 participants were included (mean age, 64 years ± 7 [SD], 87 male). Sensitivity of 2D CE US 4–6 weeks after TACE was 91% (95% CI: 84, 95), which was higher than that of CE MRI or CT (68%; 95% CI: 58, 76; $P < .001$). Sensitivity of 3D CE US 4–6 weeks after TACE was 89% (95% CI: 81, 94), which was higher than that of CE MRI or CT ($P < .001$), with no evidence of a difference from 2D CE US ($P = .22$). CE MRI or CT had 85% (95% CI: 76, 91) specificity, higher than that of 4–6-week 2D and 3D CE US (70% [95% CI: 56, 80] and 67% [95% CI: 53, 78], respectively; $P = .046$ and $P = .023$, respectively). No evidence of differences in any diagnostic criteria were observed between 1–2-week and 4–6-week 2D CE US ($P > .21$).

Conclusion: The 2D and 3D CE US examinations 4–6 weeks after TACE revealed higher sensitivity in the detection of residual HCC than CE MRI or CT, albeit with lower specificity. Importantly, CE US performance was independent of follow-up time.

Clinical trial registration no. NCT02764801

Supplemental material is available for this article.

Hepatocellular carcinoma (HCC), the most prevalent liver cancer worldwide, comprises 75%–85% of primary liver cancer cases (1). Local-regional therapies are integral for HCC treatment in patients ineligible for surgical resection or liver transplantation and bridges patients eligible for liver transplantation (2). Transarterial chemoembolization (TACE) is a catheter-based intra-arterial therapy that delivers embolic material and chemotherapeutic agents through the tumor arterial supply to induce ischemic necrosis (3).

Currently, the clinical standard imaging protocol used to assess HCC response to TACE is contrast-enhanced (CE) MRI or triphasic CE CT. The Society of Interventional Radiology recommends CE MRI or CT follow-up 4–6 weeks after TACE to enable differentiation between viable tumors and posttreatment inflammation (4,5). On images obtained earlier, posttreatment inflammatory changes typically demonstrate arterial phase enhancement, mimicking or obscuring residual viable tumors

Abbreviations

CE = contrast enhanced, HCC = hepatocellular carcinoma, TACE = transarterial chemoembolization, 3D = three-dimensional, 2D = two-dimensional

Summary

Contrast-enhanced US evaluations of hepatocellular carcinoma response to transarterial chemoembolization demonstrated high sensitivity in the detection of residual viable tumor yet lower specificity when compared with the current 4–6-week recommended follow-up.

Key Results

- In a prospective multicenter trial of 132 participants with hepatocellular carcinoma, two-dimensional (2D) and three-dimensional (3D) contrast-enhanced US (CE US) depicted response to transarterial chemoembolization (TACE) with higher sensitivity 4–6 weeks after TACE (2D CE US, 91%; 3D CE US, 89%) than CE MRI or CT (68%, $P < .001$).
- CE MRI or CT (86%) had higher specificity than 4–6-week 2D and 3D CE US (70% and 67%, respectively, $P < .046$).
- There was no evidence of differences in diagnostic performance between 2D CE US performed 1–2 weeks and 4–6 weeks after TACE ($P > .21$).

(6). Phase II efficacy and pharmacokinetic studies in the literature show that liver function is restored within 7 days after TACE (6). Thus, approximately one-half to two-thirds of patients who require re-treatment could potentially undergo subsequent therapy earlier if a modality could enable earlier detection of residual viable tumor (7–9).

Previous research has shown the efficacy of CE US in the detection of residual HCC after TACE (10–12). CE US uses US contrast agents, which are inert gas-filled microbubbles 1–8 μm in diameter (13,14). These contrast agents are approved for a variety of clinical uses and permit real-time visualization of HCC enhancement patterns with high spatial and temporal resolution, with frame rates greater than 30 Hz (15–17). Unlike CE MRI or CT, CE US lacks nephrotoxicity, exposure to ionizing radiation, and radiopacity–obscuring tumor enhancement with ethiodized oil (Lipiodol; Guerbet); it is portable, cost-efficient, enables repeat injections, and is relatively insensitive to breathing (11,18). The disadvantages of CE US include operator dependence and visualization difficulties in patients with multiple HCC treatments, cirrhotic livers, or tumor in the liver dome or adjacent to the ribs.

Single-arm studies suggested that CE US can be used to assess HCC response to TACE earlier than CE MRI or CT (8,10). However, to our knowledge, data from prospective multicenter clinical trials on two-dimensional (2D) or three-dimensional (3D) CE US assessing HCC response to TACE are lacking. Few studies have used long-term imaging surveillance, which was limited to comparisons with CE MRI or CT at 1 month. Furthermore, data on the clinical utility of 3D CE US are limited. Thus, the hypothesis in this study was that CE US may enable sensitive and accurate evaluation of residual HCC after TACE. Consequently, the purpose of this study was to compare the diagnostic performances of 2D and 3D CE US with the performance of the current clinical standard, CE MRI or CT, in the detection of residual viable HCC after TACE in a prospective multicenter trial.

Materials and Methods

The protocol for this prospective multicenter clinical study (NCT02764801) was approved by the institutional review boards of the three participating academic medical centers and performed with approval of the Food and Drug Administration (investigational new drug application no. 115,094). All participants provided written informed consent. GE HealthCare provided equipment for CE US, and Lantheus Medical Imaging provided contrast agents; however, authors had sole control of the data and information submitted for publication.

Study Participants

Individuals with HCC scheduled for TACE were consecutively enrolled at one of three participating academic medical centers between May 2016 and March 2022 (Fig 1). Self-reported race was collected per National Institutes of Health requirements. Previously, portions of data from the current study were used in tangential studies independent of the current study for quantitative and image analysis, investigations into re-treatment vessel mapping, and identification of HCC imaging hallmarks after partial treatment (19–22).

Included participants were scheduled for TACE if they had Liver Imaging Reporting and Data Systems (LI-RADS) category 4 or 5 lesions, had HCC visible at US, were not pregnant (verified with a pregnancy test), and were aged at least 21 years. Participants undergoing combination or systemic therapy, participants with cardiopulmonary conditions, participants who were medically unstable, participants with poor venous access, and participants who were not able to participate (ie, excluded participants either had COVID-19 or were unable to return to the hospital for research imaging due to COVID-19 hospital protocols during the pandemic) were excluded. On the basis of the enrollment criteria of a visualized HCC, all enrolled participants had LI-RADS US category 3 lesions with an A or B visualization score.

TACE

TACE was performed by fellowship-trained interventional radiologists (C.M.S., A.T., K.A., S.S.N., S.H., M.C.S.; 6–22 years of experience). Conventional TACE or drug-eluting bead TACE were performed, and the protocols are outlined in Appendix S1 (23).

CE US

US examinations were performed before TACE, 1–2 weeks after TACE, and 4–6 weeks after TACE by an accredited sonographer or trained physician (C.E.W., J.B.L., S.S., Y.K.; >5 years of experience) using a Logiq E9 scanner (GE HealthCare). Baseline B-mode images were acquired to visualize the tumor. If multiple tumors were treated, the largest visible treated tumor was studied (one per participant). CE US LI-RADS imaging protocol was followed (24). The protocols used for both 2D and 3D CE US examinations are highlighted in Appendix S1.

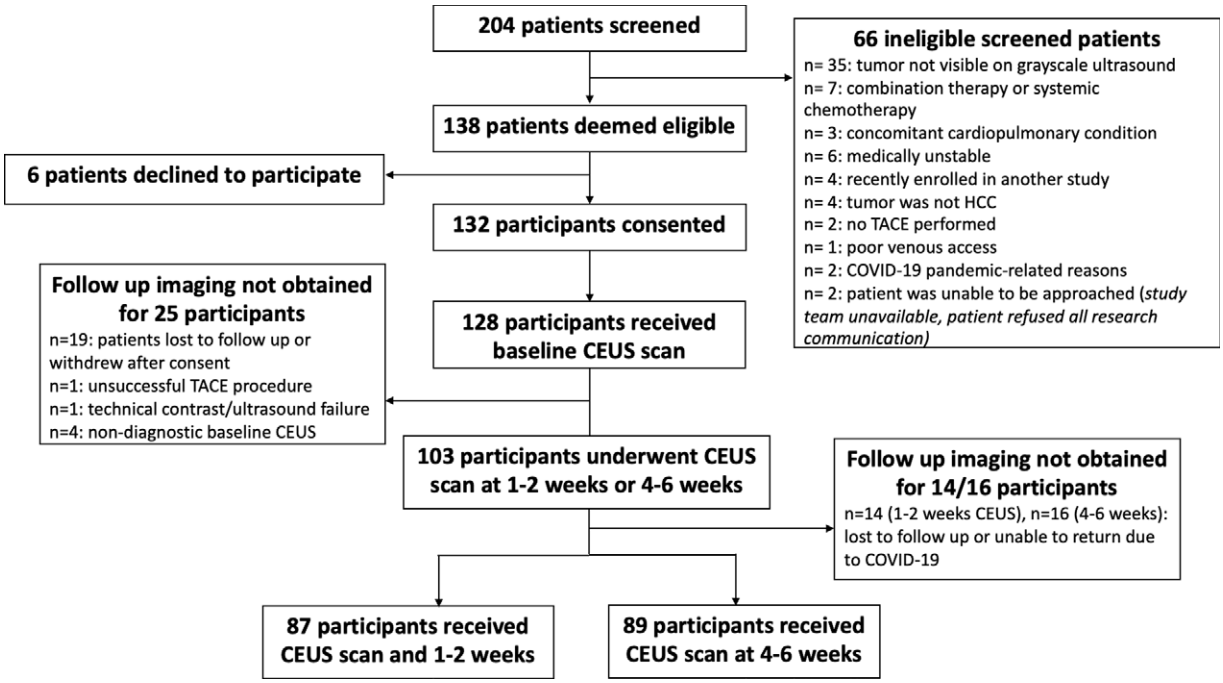

Figure 1: Participant enrollment flowchart. CE = contrast enhanced, HCC = hepatocellular carcinoma, TACE = transarterial chemoembolization.

CE MRI or CT

CE MRI or CT was performed 4–6 weeks after TACE. The protocol details for CE MRI or CT are outlined in Appendix S1.

Image Interpretation

Posttreatment CE US and CE MRI or CT images were compared with pretreatment images using a Radiant Digital Imaging and Communications in Medicine viewer (version 2020.2.3; Medixant). The 3D CE US images were evaluated in 4DView (version 14, ext 0; GE HealthCare) to visualize individual sections. Interpretations were compared with the following reference standards in order of preference: pathologic analysis of liver explant, confirmed tumor enhancement at retreatment angiography after identification of viability on CE MRI or CT images obtained 1–2 months after TACE, on CE MRI or CT images obtained at 4–8 month follow-up, or on short-term CE MRI or CT images (median, 1.1 months after TACE) if clinically decompensated and the tumor seen at imaging is more than 50% viable.

CE US images were read by three board-certified radiologists (A.L., P.O., R.F.M.; >20 years of experience). CE MRI or CT images were read by three additional fellowship-trained body radiologists (H.N., R.B., C.G.R.; >12 years of experience). Radiologists were blinded to the reference standard for the presence or absence of residual viable tumor, and there was at least 1 month between readout sessions for CE US images of the same participant.

Pretreatment images were read first followed by post-TACE images in a single-blinded randomized independent manner to determine the presence of residual viable tumor. Viability was defined as persistent arterial phase hyper- or isoenhancing areas within the tumor (including nodular peripheral enhancement). Nonviability was defined as no arterial phase enhancement or minimal hypoenhancement within the treated lesion (including posttreatment inflammatory rim enhancement). The readers rated their confidence level from 1 to 5 (lowest to highest). Instead of consensus reading, a majority reading analysis was conducted after completion of individual radiologists' CE US and CE MRI or CT reads. In the event of disagreement between the three radiologists' reads in the detection of residual viable tumor after TACE, the conclusion reached by the majority of readers (at least two of three radiologists in agreement) was used.

Statistical Analyses

Statistical analyses were performed with SAS software (version 9.4; SAS Institute) by the project biostatistician (S.W.K., 19 years of experience). Power and sample size considerations (minimum observational group of 87 participants was expected to provide lower 95% CI limits of 92% and 85% for sensitivity and specificity, respectively) are detailed in Appendix S2. Diagnostic performance criteria included sensitivity, specificity, positive and negative predictive values, and accuracy for each modality and time point. Since the repeated diagnoses of a participant by multiple readers were expected to be correlated, we used a generalized estimating equation modeling approach to logistic regression estimation of diagnostic performance criteria for robust error variance estimation and 95% CIs based on methods described in the literature (25,26) (complete details in Appendix S2). To compare modalities and time points, we used generalized estimating equations to estimate 95% CIs and *P* values. The majority (where at least two of three radiologists agree) were quantified to represent secondary or multidisciplinary tumor board

Table 1: Participant and Tumor Characteristics

Parameter	No. of Participants (n = 103)
Participant characteristic	
Sex	
Male	87 (85)
Female	16 (16)
Age (y)*	64.2 ± 7.0 (43–82)
Race and ethnicity	
Black	10 (10)
Asian	14 (14)
White	63 (61)
Hispanic	16 (16)
Body mass index (kg/m^2)*	29.0 ± 5.6
Treated tumor diameter (cm)*	3.8 ± 2.5
Residual viable tumor 4–8 months after TACE	62 (60)
Total HCC lesions per participant*	2.6 ± 1.5
TACE method	
Conventional TACE	58 (56)
Drug-eluting bead TACE	46 (44)
Child-Pugh score*	6.3 ± 1.2
Reference standard	
Pathologic analysis of liver explant	19 (18)
Re-treatment angiography after identification of residual disease on images 1–2 months after TACE	32 (31)
4–8-month follow-up CE MRI or CT	43 (42)
Short-term imaging if clinically decompensated	9 (9)

Note.—Except where indicated, data are numbers of participants, with percentages in parentheses. CE = contrast enhanced, HCC = hepatocellular carcinoma, TACE = transarterial chemoembolization.

* Data are means ± SDs. Data in parentheses are ranges.

reading. Interrater agreement was assessed with the Cohen κ coefficient. Differences in means of confidence and κ scores were compared using generalized estimating equation regression. No adjustments were made for multiple testing. A nominal α = .05 level and $P < .05$ were used to judge significance.

Results

Participant Characteristics

A total of 132 participants with HCC were enrolled (Fig 1), and 103 were included in the study (lost to follow-up or withdrew after consent, n = 25; unsuccessful TACE, n = 1; technical US or contrast agent failure, n = 1; nondiagnostic baseline CE US findings, n = 4). Demographic details are summarized in Table 1. Mean age was 64 years ± 7 [SD], and 87 of 103 participants (85%) were male. Of 608 total contrast material injections, there were eight adverse events (four major, four minor) unrelated to the study intervention (ie, the US contrast agent) as per the data and safety monitoring board. The four major adverse events included shortness of breath, episodic atrial fibrillation, esophageal variceal bleeding, and dyspnea. The four minor adverse events were nausea or vomiting, intravenous infiltration, and postembolization syndrome in two participants.

Reference standard use included pathologic analysis of a liver explant (19 of 103 participants, 18%) with 100% tumor necrosis (median, 9.3 months after TACE), consistent with prior stratification in the literature (27); re-treatment angiography approximately 1.5–3.0 months after TACE after viability was found on 1–2-month follow-up CE MRI or CT images (32 of 103 participants [31%]); 4–8-month follow-up CE MRI or CT (43 of 103 participants [42%]); and short-term imaging in the event of clinical decompensation and an estimated viable tumor of more than 50% on imaging (nine of 103 participants [9%]).

Diagnostic Performance Criteria

On the basis of the composite reference standard summarized in Table 1, 60% of participants (62 of 103 participants) had residual viable tumors after TACE. Diagnostic performance criteria for both modalities (2D or 3D CE US, CE MRI or CT) and time points (1–2 weeks and 4–6 weeks after TACE) are summarized in Table 2.

An example of CE US and CE MRI concordance is shown in Figure 2. Examples of discordance between CE US and CE MRI findings are shown in Figures 3 and 4.

Details of diagnostic performance criteria regarding 2D and 3D CE US 4–6 weeks after TACE, CE MRI or CT 4–6 weeks after TACE, and 2D and 3D CE US 1–2 weeks after TACE are detailed in Appendix S3 and Tables S1 and S2.

Majority Reads

Majority reads (at least two of three radiologists in agreement) for all modalities and time periods were used to calculate diagnostic performance (Table 3). The 2D CE US study 4–6 weeks after TACE had 94% sensitivity (95% CI: 85, 99), 74% specificity (95% CI: 56, 87), and 86% accuracy (95% CI: 77, 93). The 3D CE US study 4–6 weeks after TACE had 94% sensitivity (95% CI: 84, 99), 75% specificity (95% CI: 57, 89), and 87% accuracy (95% CI: 78, 93). CE MRI or CT 4–6 weeks after TACE had 72% sensitivity (95% CI: 59, 83), 93% specificity (95% CI: 81, 99), and 81% accuracy (95% CI: 72, 88).

Comparisons between Groups and Time Periods

Two-dimensional CE US versus 3D CE US.—No evidence of a difference in diagnostic performance criteria was observed between 2D and 3D CE US, respectively, 4–6 weeks after TACE (sensitivity, 91% [95% CI: 84, 95] vs 89% [95% CI: 81, 94]; P = .22; specificity, 70% [95% CI: 56, 80] vs 67% [95% CI: 53, 78]; P = .20; overall $P > .11$ for all diagnostic performance criteria). The averages of the three CE US readers' confidence levels were 4.3 ± 0.1 and 4.2 ± 0.1 for 2D CE US 1–2 weeks and 4–6 weeks after TACE, respectively, and 3.8 ± 0.1 and 3.7 ± 0.1 for 3D CE US 1–2 weeks and 4–6 weeks after TACE, respectively (2D CE US vs 3D CE US, $P < .001$; 2D CE US 1–2 weeks after TACE vs 4–6 weeks after TACE, $P > .37$). At both time points, reader confidence was higher for 2D CE US

Table 2: Summary of Diagnostic Performance Criteria

Performance Measure	2D CE US 1–2 Weeks after TACE	3D CE US 1–2 Weeks after TACE	2D CE US 4–6 Weeks after TACE	3D CE US 4–6 Weeks after TACE	CE MRI or CT 4–6 Weeks after TACE
Sensitivity (%)	94 (49 of 52) [88, 97]	96 (49 of 51) [91, 98]	91 (49 of 54) [84, 95] {*P* < .001}	89 (46 of 52) [81, 94] {*P* < .001}	68 (39 of 58) [58, 76]
Specificity (%)	70 (24 of 35) [58, 79]	64 (22 of 34) [53, 74]	70 (24 of 34) [56, 80] {*P* = .046}	67 (21 of 32) [53, 78] {*P* = .02}	85 (37 of 43) [76, 91]
PPV (%)	82 (49 of 60) [73, 89]	80 (49 of 61) [70, 87]	83 (49 of 59) [72, 90] {*P* = .42}	81 (46 of 57) [71, 89] {*P* = .28}	86 (39 of 45) [76, 92]
NPV (%)	89 (24 of 27) [77, 95]	92 (22 of 24) [80, 97]	83 (24 of 29) [69, 91] {*P* = .004}	79 (21 of 27) [64, 89] {*P* = .03}	66 (37 of 56) [54, 76]
Accuracy (%)	84 (73 of 87) [78, 89]	83 (71 of 85) [77, 88]	83 (73 of 88) [76, 88] {*P* = .09}	81 (67 of 84) [73, 86] {*P* = .24}	75 (76 of 101) [68, 81]

Note.—Data in parentheses are numbers of reads. Data in brackets are 95% CIs. Data in fences are *P* values and are relative to CE MRI or CT 4–6 weeks after TACE. Diagnostic performance criteria are estimated with generalized estimating equations logistic regression. CE = contrast enhanced, NPV = negative predictive value, PPV = positive predictive value, TACE = transarterial chemoembolization, 3D = three-dimensional, 2D = two-dimensional.

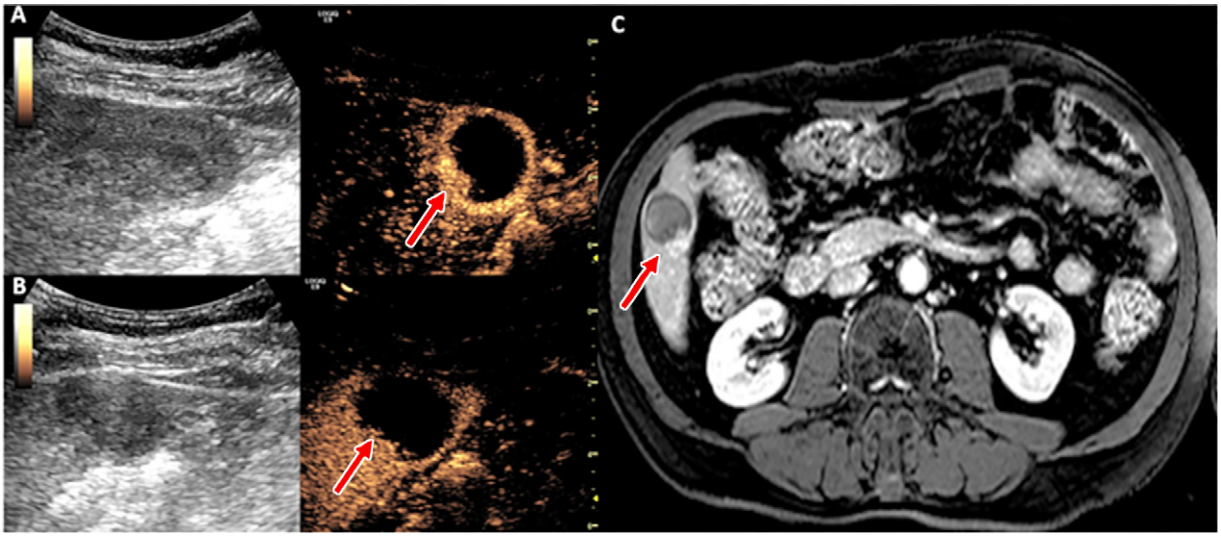

Figure 2: Example of two-dimensional (2D) contrast-enhanced (CE) US and CE MRI concordance. **(A)** Transverse 2D dual B-mode (left) and CE US (right) images obtained 1–2 weeks after transarterial chemoembolization (TACE). **(B)** Transverse 2D dual B-mode (left) and CE US (right) images obtained 4–6 weeks after TACE. **(C)** Axial CE MRI scan obtained 4–6 weeks after TACE. All images were obtained in a 67-year-old male participant with a 2.8-cm hepatocellular carcinoma in segment VI of the liver that was incompletely treated with TACE and that was confirmed when residual viability was present on the 4–8-month follow-up CE MRI scan (reference standard). Peripheral enhancement visible on **C** suggests residual tumor after TACE, which parallels the enhancement within the tumor on the CE US scan. This example shows 2D CE US and CE MRI diagnostic concordance, where readers for both modalities deemed this lesion incompletely treated based on arterial phase hyperenhancement (arrows). Here, CE US was used effectively to determine post-TACE viability earlier than with CE MRI, which ultimately yielded the same result.

than for 3D CE US but showed no evidence of difference over time for either mode. An example of 2D and 3D CE US in tandem is shown in Figure 5.

Two-dimensional and 3D CE US versus CE MRI or CT.—The 2D CE US study 4–6 weeks after TACE had higher sensitivity (91%; 95% CI: 84, 95) than CE MRI or CT (68%; 95% CI: 58, 76; *P* < .001). The negative predictive value of 2D CE US was also higher than that of CE MRI or CT 4–6 weeks after treatment (83% [95% CI: 69, 91] vs 66% [95% CI: 54, 76], *P* = .004). There was no evidence of a difference in accuracy between 2D CE US and CE MRI or CT (83% [95% CI: 76, 88] vs 75% [95% CI: 68, 81], *P* = .09). CE MRI or CT resulted in a higher specificity relative to 2D CE US 4–6 weeks after treatment (85% [95% CI: 76, 91] vs 70% [95% CI: 56, 80], *P* = .046). There was no evidence of a difference in positive predictive value (*P* = .42) between 2D CE US (83%; 95% CI: 72, 90) and CE MRI or CT (86%; 95% CI: 76, 92) 4–6 weeks after treatment.

Similar to 2D findings, 3D CE US 4–6 weeks after TACE achieved a higher sensitivity than CE MRI or CT (89% [95% CI: 81, 94] vs 68% [95% CI: 58, 76], *P* < .001) and higher negative predictive value (79% [95% CI: 64, 89] vs 66% [95% CI: 54, 76], *P* = .03). However, CE MRI or CT provided higher specificity relative to 3D CE US at 4–6 weeks after treatment

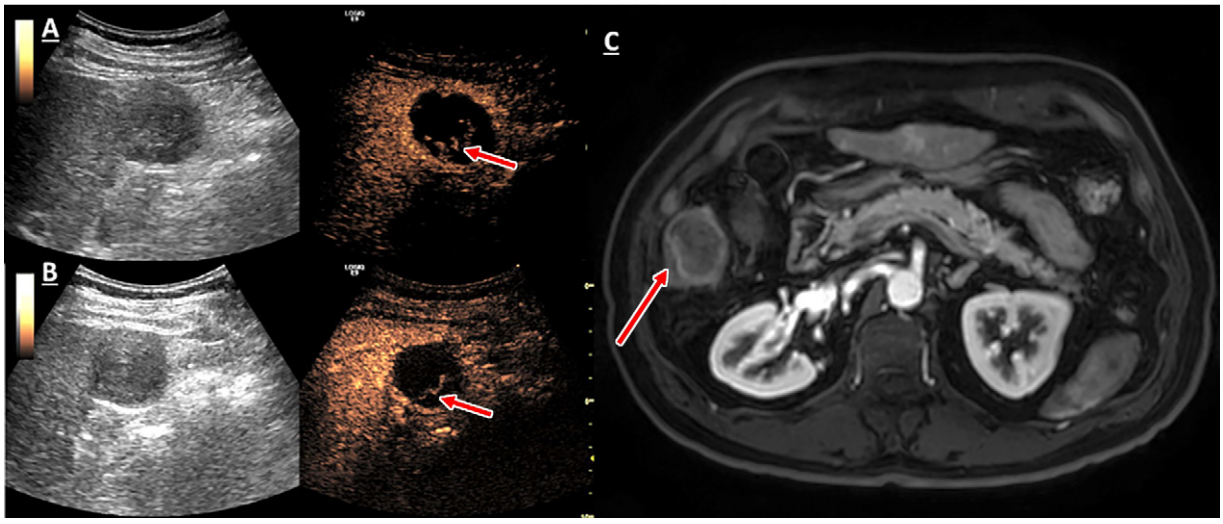

Figure 3: Example of two-dimensional (2D) contrast-enhanced (CE) US and CE MRI discordance. **(A)** Transverse 2D dual B-mode (left) and CE US (right) images obtained 1–2 weeks after transarterial chemoembolization (TACE). **(B)** Transverse 2D dual B-mode (left) and CE US (right) images obtained 4–6 weeks after TACE. **(C)** Axial CE MRI scan obtained 4–6 weeks after TACE. All images were obtained in a 62-year-old male participant with a 5.5-cm hepatocellular carcinoma in segment V of the liver that had residual tumor after TACE, confirmed with re-treatment angiography (reference standard) after identification of residual disease at imaging 1–2 months after TACE. This example shows CE US and CE MRI discordance, with CE US readers correctly identifying this lesion as incompletely treated, while CE MRI readers incorrectly deemed this treatment complete based on posttreatment inflammatory rim enhancement (arrows). Here, CE US revealed the success of TACE earlier and more accurately than CE MRI, with this series demonstrating the high sensitivity of CE US.

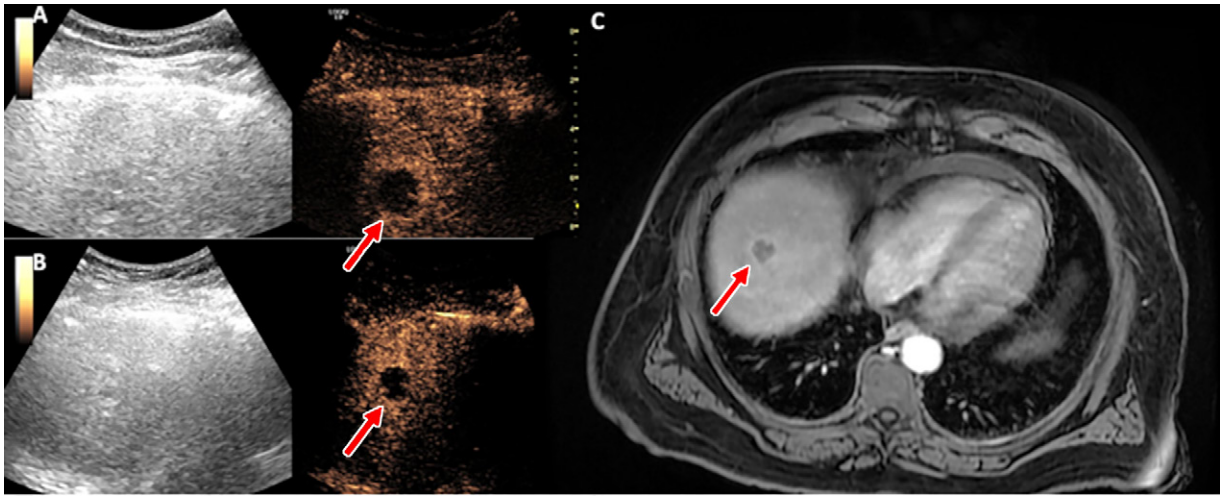

Figure 4: Example of two-dimensional (2D) contrast-enhanced (CE) US and CE MRI discordance. **(A)** Transverse 2D dual B-mode (left) and CE US (right) image obtained 1–2 weeks after transarterial chemoembolization (TACE). **(B)** Transverse 2D dual B-mode (left) and CE US (right) images obtained 4–6 weeks after TACE. **(C)** Axial CE MRI scan 4–6 weeks after TACE. All images were obtained in a 63-year-old male participant with a 2.4-cm hepatocellular carcinoma in segment VIII of the liver who underwent successful TACE with no residual tumor, as confirmed with 4–8-month follow-up CE MRI (reference standard). This is an example of CE US and CE MRI discordance. CE MRI reads correctly noted that this tumor was completely treated, whereas CE US reads incorrectly deemed this lesion incompletely treated based on arterial phase hyperenhancement (arrows). Here, we show the high specificity of CE MRI and CE CT.

(85% [95% CI: 76, 91] vs 67% [95% CI: 53, 78], $P = .02$). There was no evidence of a difference in accuracy between 3D CE US and CE MRI or CT (81% [95% CI: 73, 86] vs 75% [95% CI: 68, 81], $P = .24$). There was no evidence in positive predictive value ($P = .28$) between 3D CE US (81% [95% CI: 71, 89]) and CE MRI or CT (86% [95% CI: 76, 92]).

CE US 1–2 weeks after TACE versus 4–6 weeks after TACE.—There was no evidence of differences in diagnostic performance criteria between 2D CE US 1–2 weeks after TACE and 4–6 weeks after TACE (sensitivity, 94% [95% CI: 88, 97] vs 91% [95% CI: 84, 95], $P = .23$; specificity, 70% [95% CI: 58, 79] vs 70% [95% CI: 56, 80]; $P = .99$; overall $P > .21$ for all diagnostic performance criteria). Interestingly, 3D CE US sensitivity ($P = .02$) and negative predictive value ($P = .03$) were higher 1–2 weeks after TACE than 4–6 weeks after TACE, while all other diagnostic criteria remained indistinguishable ($P > .46$).

Table 3: Majority Radiologist Reads (At Least Two of Three Radiologists in Agreement) CE US and CE MRI or CT Diagnostic Performance Criteria Summaries

Performance Measure	2D CE US 1–2 Weeks after TACE	3D CE US 1–2 Weeks after TACE	2D CE US 4–6 Weeks after TACE	3D CE US 4–6 Weeks after TACE	CE MRI or CT 4–6 Weeks after TACE
Sensitivity (%)	96 (50 of 52 reads) [87, 100]	98 (50 of 51) [90, 100]	94 (51 of 54) [85, 99]	94 (49 of 52) [84, 99]	72 (42 of 58) [59, 83]
Specificity (%)	80 (28 of 35) [63, 92]	74 (25 of 34) [56, 87]	74 (25 of 34) [56, 87]	75 (24 of 32) [57, 89]	93 (40 of 43) [81, 99]
PPV (%)	88 (50 of 57) [79, 93]	85 (50 of 59) [76, 91]	85 (51 of 60) [76, 91]	86 (49 of 57) [77, 92]	93 (42 of 45) [82, 98]
NPV (%)	93 (28 of 30) [78, 98]	96 (25 of 26) [78, 99]	89 (25 of 28) [73, 96]	89 (24 of 27) [72, 96]	71 (40 of 56) [62, 79]
Accuracy (%)	90 (78 of 87) [81, 95]	88 (75 of 85) [79, 94]	86 (76 of 88) [77, 93]	87 (73 of 84) [78, 93]	81 (82 of 101) [72, 88]

Note.—Data in parentheses are numbers of reads. Data in brackets are 95% CIs. CE = contrast enhanced, NPV = negative predictive value, PPV = positive predictive value, TACE = transarterial chemoembolization, 3D = three-dimensional, 2D = two-dimensional.

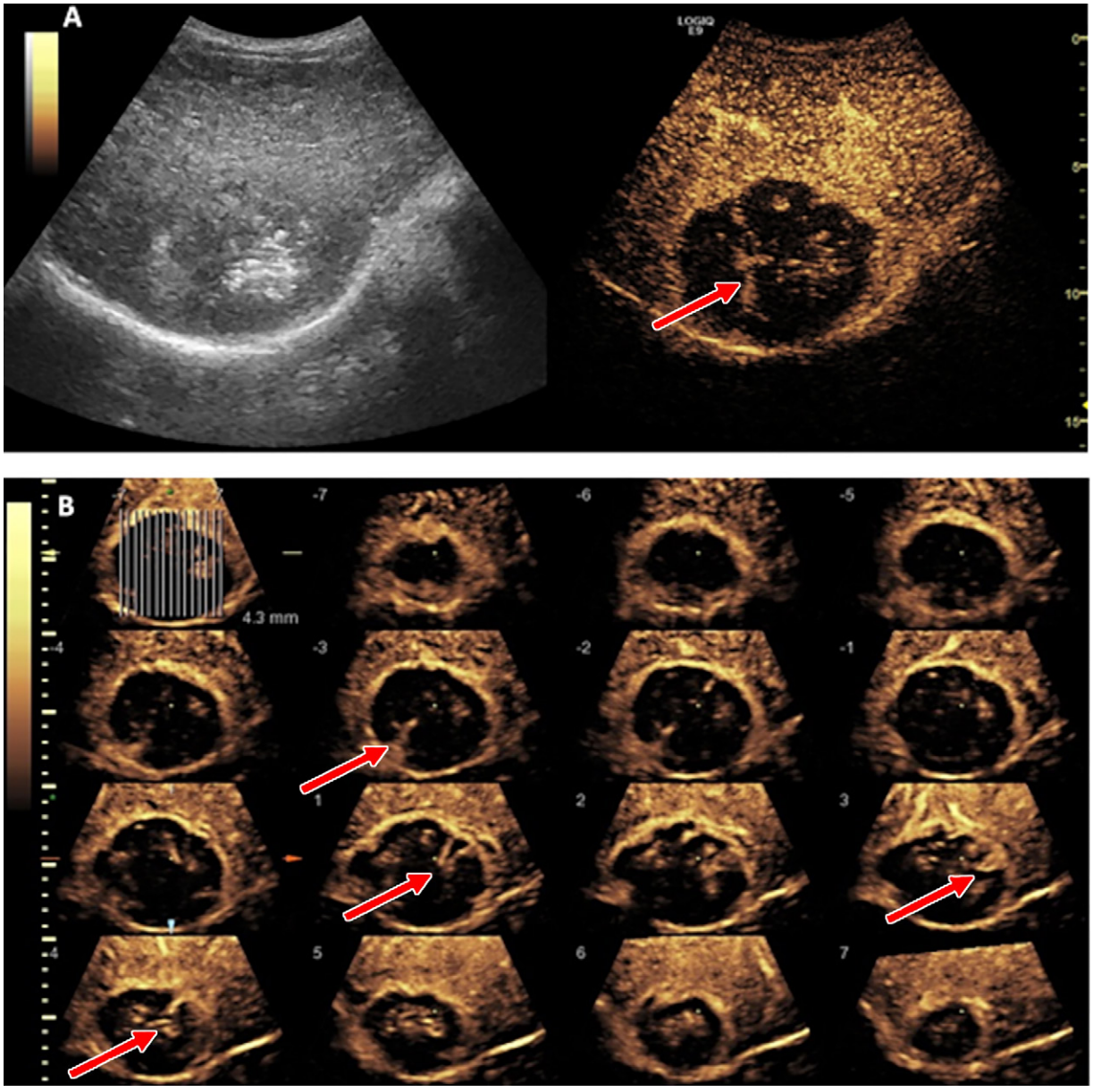

Figure 5: Transverse **(A)** two-dimensional dual B-mode (left) and contrast-enhanced (CE) US (right) images and corresponding **(B)** three-dimensional (3D) CE US images in a 71-year-old male participant 11 days after transarterial chemoembolization (TACE) for a 7.1-cm hepatocellular carcinoma in segment VII of the liver. In **A**, large areas of residual enhancement and peripheral nodularity (arrow) are appreciated in the arterial phase, indicative of a viable residual tumor. In **B**, 3D CE US enables visualization across multiple sections (4.3-mm thickness, as shown in the top left panel), enabling visualization of various enhancing internal components (arrows).

Table 4: Summary of κ Coefficients for Interrater Reliability Results

Readers*	2D CE US 1–2 Weeks after TACE	3D CE US 1–2 Weeks after TACE	2D CE US 4–6 Weeks after TACE	3D CE US 4–6 Weeks after TACE	CE MRI or CT 4–6 Weeks after TACE
1 and 2	0.63 (0.46, 0.80)	0.62 (0.44, 0.79)	0.77 (0.63, 0.91)	0.78 (0.63, 0.93)	0.48 (0.31, 0.65)
1 and 3	0.62 (0.44, 0.79)	0.52 (0.33, 0.71)	0.55 (0.36, 0.74)	0.53 (0.34, 0.73)	0.66 (0.52, 0.81)
2 and 3	0.48 (0.27, 0.68)	0.39 (0.17, 0.62)	0.54 (0.35, 0.73)	0.49 (0.29, 0.69)	0.46 (0.29, 0.64)
Mean†	0.57 (0.49, 0.65)	0.50 (0.39, 0.61)	0.61 (0.50, 0.71)	0.58 (0.45, 0.72)	0.51 (0.42, 0.61)

Note.— Data are coefficients, and data in parentheses are 95% CIs. CE = contrast enhanced, TACE = transarterial chemoembolization, 3D = three-dimensional, 2D = two-dimensional.

* Readers 1, 2, and 3 are unique for CE US and CE MRI or CT (total of six readers in the study).

† Mean was estimated with an inverse variance-weighted generalized estimating equation regression model.

Interrater Reliability

Cohen κ coefficient for each reader pair is summarized in Table 4. No evidence of differences in κ coefficients was observed between any CE US time point compared with CE MRI or CT 4–6 weeks after TACE (2D CE US 4–6 weeks after TACE: range, 0.54–0.77; 3D CE US 4–6 weeks after TACE: range, 0.49–0.78; CE MRI or CT: range, 0.46–0.66; $P > .20$).

Discussion

This study aimed to compare contrast-enhanced (CE) US and CE MRI or CT in the detection of residual viable hepatocellular carcinoma (HCC) after transarterial chemoembolization (TACE), addressing the lack of prospective multicenter trials with long-term reference standards in the literature. In our study, 60% (62 of 103 participants) had residual viable tumors after TACE (4–8 months imaging [31% of participants], 1–2 months imaging [69% of participants] with pathology, re-treatment angiography, or imaging). Our results showed two-dimensional (2D) and three-dimensional (3D) CE US at 4–6 weeks after TACE had higher sensitivity (2D CE US, 91% [95% CI: 84, 95]; 3D CE US, 89% [95% CI: 81, 94]) than CE MRI or CT (68%; 95% CI: 58, 76; $P < .001$). Importantly, CE MRI or CT had higher specificity (85%; 95% CI: 76, 91) than CE US 4–6 weeks after treatment (2D CE US, 70%; 95% CI: 56, 80; 3D CE US, 67%; 95% CI: 53, 78; $P = .046$ and $P = .023$, respectively). There was no evidence of differences in accuracy between 2D CE US (83%; 95% CI: 76, 88) or 3D CE US (81%; 95% CI: 73, 86) 4–6 weeks after TACE and CE MRI or CT (75%; 95% CI: 68, 81; $P = .09$ and $P = .24$, respectively). There was no evidence of differences between 2D and 3D CE US for diagnostic performance criteria (ie, sensitivity, 91% for 2D CE US vs 89% for 3D CE US; $P > 0.10$). No evidence of differences in diagnostic performance between 2D CE US 1–2 weeks and 4–6 weeks after treatment was found (ie, sensitivity, 94% [95% CI: 88, 97] 1–2 weeks after treatment vs 91% [95% CI: 84, 95] 4–6 weeks after treatment; $P > .21$). Majority reads sensitivity was 94% (for both 2D and 3D CE US) and 72% (for CE MRI or CT); specificity was 74% (for 2D CE US), 75% (for 3D CE US), and 93% (for CE MRI or CT).

CE US has been studied as an alternative to CE MRI and CE CT in the evaluation of local-regional therapy efficacy as early as 1 day after TACE. Several single-center studies have corroborated the high sensitivity, specificity, and accuracy of CE US compared with CE MRI or CT in post-TACE monitoring, from 1 day to 4 weeks (ie, accuracy: CE US, 96%; CE CT, 79%; $P < .05$ [26]) (10,28–31).

CE US is unaffected by Lipiodol retention or inflammatory infiltrate obscuring differentiation from residual tumor after treatment (4,32). Its high spatial and high temporal resolution and ability for repeat contrast material injection enable real-time arterial phase enhancement visualization to detect viable tumors. However, CE US is operator dependent, with visualization difficulties in the liver dome and with cirrhotic livers.

Our study highlights the advantages of CE US, given its higher sensitivity compared with CE MRI or CT despite its drawback of lower specificity. This tradeoff was reflected by an insignificant difference in accuracy between 2D or 3D CE US 4–6 weeks after TACE and CE MRI or CT. We found no evidence of a statistical difference between 2D and 3D CE US. Our results indicate improved sensitivity of CE US in the detection of residual disease relative to the current clinical standard (CE MRI or CT), suggesting an ideal follow-up approach using both techniques.

The diagnostic performance criteria for majority reads (at least two of three radiologists in agreement) mirrored the aforementioned results, albeit with slightly higher performance. This method mimics multidisciplinary tumor board or secondary reads. Importantly, we found no evidence of differences in diagnostic performance between 2D CE US 1–2 weeks and 4–6 weeks after treatment. As 60% of participants had residual viable tumors after TACE, CE US may allow for earlier selection of patients who could benefit from subsequent therapy. Additionally, CE US may provide practical advantages as an alternative in patients for whom CE MRI or CT is contraindicated. In this study, radiologists' reads relied on arterial phase hyperenhancement and isoenhancement, which is supported by a study showing that arterial phase hyperenhancement more aptly identifies residual HCC after TACE than washout (22).

Our study had several limitations. First, it showed a lower overall CE US performance than smaller single-center trials and retrospective meta-analyses (10,30,33,34) due to enrollment at

sites with a variety of CE US volumes and longer-term reference standard use. Second, our institutions frequently treat smaller well-visualized lesions on US images with ablation and larger tumors (which frequently result in large residual viable tumor) with radioembolization. Exclusion of these populations may decrease the reported CE US performance. Third, the study sample was limited to lesions well visualized on US images, excluding lesions in the liver dome. Fourth, different US contrast agents (Lumason [Bracco Diagnostics], known as SonoVue [Bracco] outside the United States) are used worldwide compared with our study (Definity [Lantheus Medical Imaging]). Fifth, volumetric or 3D CE US failed to improve performance, unlike prior quantitative work assessing HCC response to systemic therapy (35), potentially limited by technologic failure to incorporate tumor margins with accompanying B-mode US. Lastly, the use of a composite reference standard undermines the inherent differences among each. In our study, participants underwent re-treatment angiography or pathologic analysis of liver explant at CE MRI or CT, mirroring current clinical practice, but also introducing bias against positive CE US examinations.

In conclusion, two-dimensional (2D) or three-dimensional contrast-enhanced (CE) US 4–6 weeks after transarterial chemoembolization (TACE) demonstrated higher sensitivity in the detection of residual hepatocellular carcinoma (HCC) than CE MRI or CT, albeit with lower specificity. This renders CE US a promising addition to CE MRI or CT in the detection of residual viable HCC as early as 1–2 weeks after TACE (for 2D CE US), potentially enabling earlier re-treatment. Including non-US visible lesions would allow for optimal consideration of each modality. Next, the inclusion of multiple HCCs per patient with repeat contrast material injections would enhance real-world applicability in a population that often has multiple lesions. Lastly, a larger study assessing the morbidity and mortality of earlier re-treatment after viable tumor detection with CE US would elucidate the benefit of an earlier diagnosis after TACE. Ultimately, given the high sensitivity of CE US and the high specificity of CE MRI or CT, an ideal follow-up protocol may require multimodality imaging.

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