Diagnostic and Interventional Imaging (2017) **98**, 253—260

ORIGINAL ARTICLE / *Cancer Imaging*

Evaluation of tumor response to intra-arterial chemoembolization of hepatocellular carcinoma: Comparison of contrast-enhanced ultrasound with multiphase computed tomography

S.B. Paul[a,*], E. Dhamija[a], S.R. Gamanagatti[a], V. Sreenivas[b], D.P. Yadav[c], S. Jain[c], Shalimar[a], S.K. Acharya[c]

[a] *Department of Radiodiagnosis, All India Institute of Medical Sciences (AIIMS), New Delhi 110029, India*
[b] *Department of Biostatistics, All India Institute of Medical Sciences (AIIMS), New Delhi 110029, India*
[c] *Department of Gastroenterology, All India Institute of Medical Sciences (AIIMS), New Delhi 110029, India*

KEYWORDS
Contrast-enhanced ultrasound;
Multiphase computed tomography (CT);
Hepatocellular carcinoma;
Trans-arterial chemoembolization;
Comparative studies

Abstract
Purpose: To compare the diagnostic accuracy of contrast-enhanced ultrasound (CEUS) with that of multiphase computed tomography (CT) in the evaluation of tumor response to transarterial chemoembolization (TACE) of hepatocellular carcinoma (HCC).
Material and methods: Fifty patients (41 men, 9 women; mean age, 53 years ± 12.5 [SD]) with a total of 70 HCCs (mean size, 5 cm ± 3 [SD]) were evaluated. Post-TACE therapeutic assessment of HCC was done at 4 weeks. Patients with TACE done earlier and reporting with suspicion for recurrence were also included. Patients with hepatic masses seen on ultrasound were enrolled and subjected to CEUS, multiphase CT and magnetic resonance imaging (MRI). Hyperenhancing area at the tumor site on arterial phase of CEUS/multiphase CT/MRI was termed as residual disease (RD), the patterns of which were described on CEUS. Diagnostic accuracies of CEUS and MPCT were compared to that of MRI that was used as the reference standard.

* Corresponding author.
E-mail address: shashi.aiims@gmail.com (S.B. Paul).

http://dx.doi.org/10.1016/j.diii.2016.09.002

Results: CEUS detected RD in 43/70 HCCs (61%). RD had a heterogeneous pattern in 22/43 HCCs (51%). Sensitivities of CEUS and multiphase CT were 94% (34/36; 95% CI: 81—99%) and 50% (18/36; 95% CI: 33—67%) respectively. Significant difference in sensitivity was found between CEUS and multiphase CT ($P = 0.0001$). CEUS and multiphase CT had 100% specificity (95% CI: 83—100%).

Conclusion: CEUS is a useful technique for detecting RD in HCC after TACE. For long term surveillance, CEUS should be complemented with multiphase CT/MRI for a comprehensive evaluation.

Transarterial chemoembolization (TACE) is a widely used therapeutic option for unresectable hepatocellular carcinoma (HCC) as a majority of patients with HCC are diagnosed at an advanced stage of the disease [1,2]. TACE involves the use of intra-arterial administration of chemotherapeutic drug emulsion containing iodized oil (Lipiodol®; Laboratoire Guerbet, Roissy-Charles de Gaulle, France) through the tumor feeding artery followed by embolization thus producing cytotoxic damage and ischemic necrosis of the tumor.

Accurate response evaluation following TACE is crucial for the management of patients with HCC. The decision of subsequent therapeutic planning (retreatment or resorting to other modes of therapy) is based on tumor response to TACE. Indicators of successful TACE are in the form of tumor necrosis appearing as early as 1—2 months while the changes of tumor shrinkage invariably takes longer to occur. Estimation of viable tumor tissue following TACE is done by the modified response evaluation criteria in solid tumor (mRECIST criteria) on multiphasic computed tomography (CT) or magnetic resonance imaging (MRI) [3,4]. These imaging modalities have high diagnostic accuracy in evaluating the entire liver during different phases of vascular enhancement [5—9].

However, both techniques have limitations as well. Multiphasic CT involves radiation exposure limiting its repetitive use and the masking effect of the viable tumor by hyperattenuating Lipiodol® used during TACE hinders accurate interpretation of response [4,5,10]. MRI is superior to multiphasic CT as the evaluation by highly sensitive T2 weighted sequences and the multiphasic contrast enhanced sequences are not hampered by the presence of Lipiodol®. This makes MRI a reference imaging modality for post TACE evaluation [11]. But high cost, infrastructure and limited availability poses a constraint in its wide usage. Thus, there emerges a need to explore alternative imaging modalities for therapeutic assessment.

Contrast-enhanced ultrasound (CEUS) can depict tumor vascularity based on the intranodular hemodynamics [12—14]. Earlier studies have focused mainly on the role of CEUS in the diagnosis of HCC and limited literature is available regarding tumor response to TACE [15,16]. Studies comparing CEUS with other imaging techniques are also scarce [17—21].

This study was designed to describe the patterns of residual disease on CEUS and compare the diagnostic accuracy of CEUS with that of multiphasic CT in the evaluation of tumor response to TACE of HCC.

Materials and methods

Study population

From February 2010 to June 2015, patients with HCC presenting to our Liver Clinic after undergoing TACE were included in this prospective study. Patients were of a mix of two types — those who had TACE one month prior and were assessed for the first time for tumor response and patients who had developed complete response to TACE earlier, and were reported on follow up with a clinical suspicion of recurrence such as like deterioration of liver function or raised serum alphafetoprotein (AFP) level. Ethics clearance was obtained from the Institute Ethics committee (IEC/NP-209/2010) and a written informed consent was obtained.

The inclusion criteria were: — Post TACE HCC patients of intermediate stage, Barcelona clinic staging classification (BCLC) B [5] with either a single mass or multinodular HCC (tumor burden < 50% of the liver), entire mass seen on ultrasound, and a mass not larger than 15 cm. Patients with diffuse disease (large mass or multiple nodules involving the entire liver), Child's C cirrhosis, comorbidities (coronary artery disease, cardiac or renal failure) and breast feeding women were excluded.

Enrolled patients underwent CEUS, multiphase CT and MRI in a random order not more than 1 to 2 weeks apart of each other after 4 weeks following TACE. For patients with multinodular HCC, the two largest masses (less than 15 cm) were evaluated. CEUS was tailored to the evaluation of post treatment tumor response indicating complete or partial response (residual/recurrent disease), whereas multiphase CT and MRI provided a comprehensive assessment of the liver. MRI was considered as the gold standard and further management was based on MRI findings. When TACE was repeated following partial response, then a repeat assessment of that patient was done by CEUS, multiphase CT and MRI at one month post-TACE. Each repeat evaluation was considered as a new observation.

TACE procedure

TACE was undertaken through a transfemoral arterial approach. A superior mesenteric artery and celiac axis angiogram were first obtained by using 5F RC1 (reverse curve, Cook, Bloomington, IN, USA) or C1 (Celiac, Cook,) diagnostic catheter and 0.035-inch J-tip guidewire (Terumo; Terumo Corporation, Tokyo, Japan). For approaching

the tumor bed distally, either the 4F slip catheter (VERT slip-cath Beacon Tip® Catheter; Cook,) or 2.7F Progreat® micro-catheter (Terumo Corporation) was used. By superselective cannulation of the feeding artery, a chemotherapeutic emulsion containing a mixture of epirubicin (60 mg), nonionic iodinated contrast material (10 ml) and iodized oil (20 ml, Lipiodol®) was delivered followed by embolization by gelatin sponge slurry made from shaved Gelfoam® (Upjohn Company, Kalamazoo, MI, USA) mixed with iodinated contrast material. Complete absence of opacification of the tumor feeding artery was accomplished with retained Lipiodol®in the tumor bed. Intra-arterial lidocaine (10 mg, Xylocard® 2%, AstraZeneca, Bangalore, India) was given between 10-ml aliquots of chemoembolization to minimize pain.

CEUS examination

CEUS was performed on Siemens S-2000® or Supersonic Imagine® ultrasound machines using second generation ultrasound contrast containing sulphur hexafluoride, SonoVue® (Bracco, Milan, Italy). Antecubital intravenous access with 20 gauge needle catheter and 3-way connector was established. Contrast was prepared in the soluble form within the 5 ml SonoVue® vial by shaking well with saline few minutes prior. Hepatic mass was focused on B-mode ultrasound and then contrast specific mode was put on. A bolus injection of 2.4 ml of SonoVue® followed by flushing with 10 ml of 0.9% normal saline was given and the timer switched on. Continuous cine recording was done while scanning in the arterial phase (10—30 s) and portal venous phase (30—120 s) of the liver followed by intermittent evaluation in delayed phase at 120 s, up to 6 min [10,22]. After TACE procedure, the patient was observed for 30 min. If a second mass needed evaluation, the procedure was repeated after 30 min with another injection of 2.4 ml of SonoVue®. CEUS examination was focused only on the treated target lesion (s). Cine recordings were interpreted and findings noted.

Multiphase CT examination

Multiphase CT of the liver was performed on Somatom Sensation® 40 (Siemens Healthcare, Erlangen, Germany). An initial unenhanced CT acquisition of the liver was acquired. Non-ionic intravenous iodinated contrast material (80 ml, Iohexol, Omnipaque 300, GE Healthcare, Princeton, NJ, USA) was administered using a pressure injector through an antecubital vein access. Liver was scanned at 25 s (arterial phase), 60 s (portal venous phase) and 3 min (delayed phase) at 120 kV and 30—50 mAs with 5-mm slice thickness with reconstruction interval and increment of 1.5-mm. Transverse and coronal sections were obtained.

MRI examination

MRI examinations were performed using a 1.5-Tesla Magnetom Avanto® (Siemens Healthcare, Erlangen, Germany) unit. MRI protocol consisted of two-dimensional T2-weighted turbo spin-echo sequence, TRUFI sequence and T1-weighted (in and opposed phases) sequences, axial and coronal sections of 3D volumetric interpolated breath-hold (VIBE) sequences after intravenous administration of a gadolinium chelate (Gadobenate dimeglumine, Multihance®, Braco, Milan, Italy) at a dose of 0.1 mmol/kg. Post contrast VIBE images were obtained during the arterial phase (18—20 s), portal venous phase (45—60 s) and delayed phase (3 min). Diffusion-weighted sequences were obtained using 3*b* values ($b = 0$, 400, 800 s/mm^2) in the transverse plane.

Study outcome

The study outcome was detection of tumor response in the treated tumor. Complete response (no residual disease) on all three imaging techniques (CEUS, multiphase CT and MRI) was defined as absence of any hyperenhancing area (enhancement more than the adjacent hepatic parenchyma) at the treated tumor site during the arterial phase (Fig. 1).

Partial response (residual or recurrent disease) was defined as the presence of hyperenhancing area at the treated tumor site during the arterial phase with hypoenhancement during the venous or delayed phase. If a HCC had previously showed complete response to TACE and similar findings of hyperenhancing area ring the arterial phase with hypoenhancement during the portal or delayed phase on follow up imaging, this was considered as tumor recurrence.

Based on the location of the residual disease or recurrent disease on the atrial phase CEUS, different patterns were defined (Fig. 2). They consisted of: (a), Peripheral: hyperenhancement at the periphery of the mass depicting an asymmetric focal thickness; (b), Heterogeneous: both hyperenhancing and hypoenhancing areas within the tumor; (c); Homogenous: entire tumor tissue uniformly hyperenhancing; and (d), Central-focal hyperenhancement in the center of the mass.

Image analysis

Image analysis was performed by three independent experienced observers (S. G. for MRI; S. B. P. for CEUS and E.D. for multiphase CT). Each observer was blinded to the findings of the other two modalities of the same patient. In doubtful cases, the final result of that particular investigation was obtained by consensus.

Statistical analysis

Statistical analyses were performed using Stata (version 12). Continuous data were expressed as mean, standard deviation (SD) and categorical data as proportions. Presence of residual/recurrent disease in the target mass was compared between the three imaging modalities. Sensitivity, specificity, negative (NPV) and positive predictive value (PPV) of CEUS and multiphase CT in detecting residual/recurrent disease was estimated taking the results of MRI as the standard of reference and expressed as percentages along with 95% confidence intervals (CI). Differences in sensitivity between CEUS and multiphase CT were searched for using the McNemar test. Statistical difference was considered for a P value < 0.05.

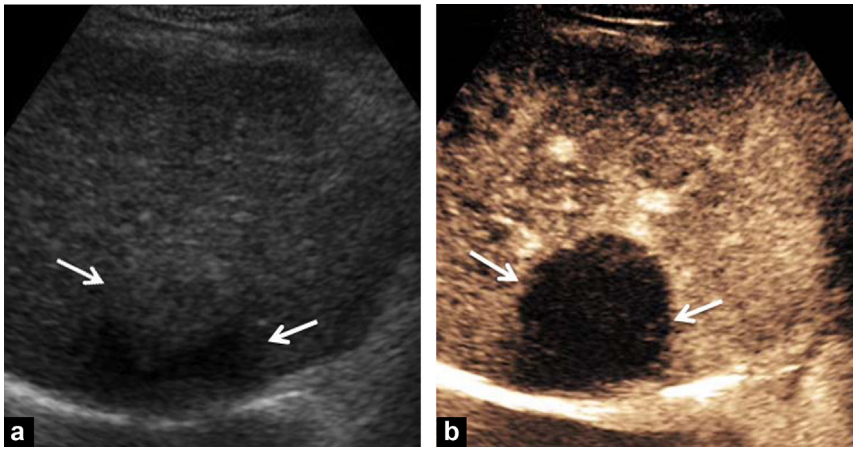

Figure 1. A 42-year-old man with hepatocellular carcinoma treated by transarterial chemoembolization (TACE). (a) Simultaneous display of B mode ultrasound and (b) arterial phase CEUS image shows a large, well-defined, heterogenous mass in segment VII of the liver (arrows in a). On CEUS image obtained at 28 s (arterial phase) following intravenous administration of SonoVue®, the mass does not contain any hyperenhancing area within or at the margin (arrows in b) suggesting complete response to TACE and no residual tumor or recurrence.

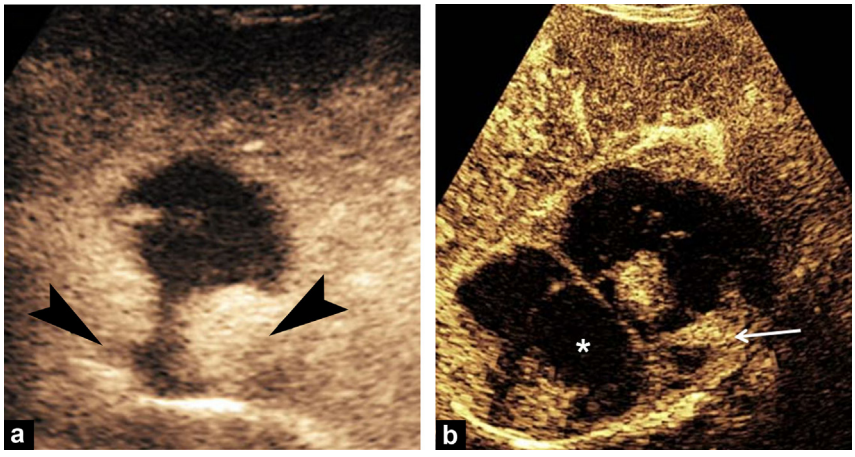

Figure 2. Four patients with hepatocellular carcinoma (HCC) treated with transarterial chemoembolization (TACE) with different patterns of residual disease on arterial phase CEUS images obtained after intravenous administration of SonoVue®. (a) A hyperenhancing tumor tissue is visible at the periphery of a hypoenhancing treated HCC (arrows) corresponding to the peripheral pattern of residual disease. (b) Areas of enhancement (arrow) representing viable tumor and non-enhancing area of necrosis (asterisk) in the mass treated by TACE, corresponding to heterogenous pattern of residual disease. (c) Homogeneous enhancement of the entire mass (arrow) suggesting recurrence at 22 months following TACE. (d) Focal area of enhancement in the center (arrow) of a hypoenhancing treated tumor corresponding to the central pattern of residual disease.

Results

Eighty five HCC patients presented to our liver clinic after TACE (Fig. 3). Of these, 35 patients were excluded for hepatic decompensation ($n = 5$), large tumor size ($n = 8$), co-morbidities illness ($n = 2$), diffuse involvement with multiple masses in liver ($n = 11$), refused evaluation ($n = 3$), no mass seen on ultrasound ($n = 4$) and lost to follow up ($n = 2$). Thus, 50 patients with 70 masses were evaluated by CEUS (single CEUS in 38 and repeat CEUS in 12 patients). Each CEUS evaluation was considered as one observation.

Table 1 illustrates the characteristics of the patients. They were 41 men and 9 women (mean age, 53 years $\pm$ 12.5 [SD]; range; 24—72 years), Child's A cirrhosis was present in 44/50 patients (88%) and Child's B cirrhosis in 6/50 patients (12%). The most common etiology of HCC was hepatitis B in 27/50 patients (54%). Serum AFP was elevated in 24/50 patients (48%). Mean mass size was 5 $\pm$ 3 cm (range 1.0—15 cm). Residual or recurrent disease was detected in 43/70 masses (61%) with different patterns. An heterogeneous pattern was observed in 22/43 masses (51%) (Fig. 4) (Table 1).

Of the 50 patients enrolled, 42 patients with 57 masses could be evaluated on all the three imaging modalities of CEUS, multiphase CT and MRI. Mean time interval between TACE and imaging evaluation was 1.7 months $\pm$ 0.5 (SD) (range: 0.5—3 months) for patients who underwent evaluation post-TACE for the first time ($n = 28$) while for patients being investigated for recurrence ($n = 14$), the mean interval were 11.6 months $\pm$ 11.1 (SD) (range: 3.6—24.2 months). Mean mass size was 5.1 cm $\pm$ 2.67 (SD) (range: 1—15 cm).

The performances of CEUS and multiphase CT in the diagnosis of residual/recurrent disease were compared to the results of MRI (Table 2). Residual/recurrent disease was

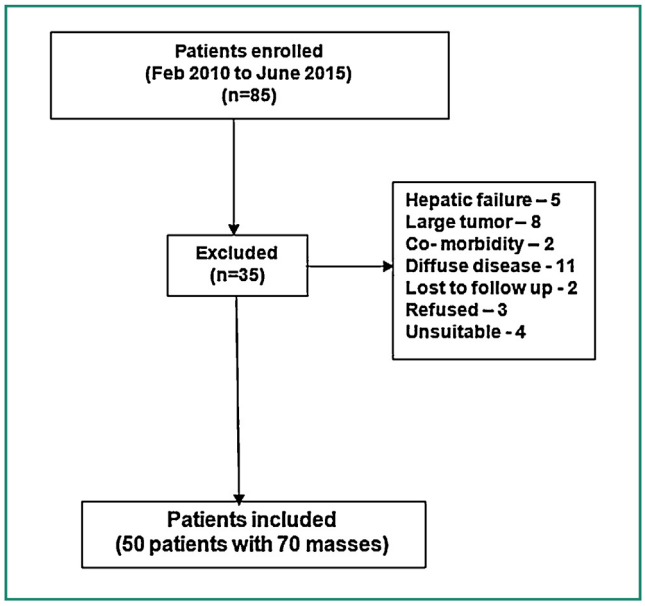

Figure 3. Flow diagram of the study.

deemed present in 36/57 masses on MRI,. Out of these 36 masses, CEUS detected residual/recurrent disease in 34 masses and missed residual/recurrent disease in 2 masses yielding a sensitivity of 94% (34/36; 95% CI: 81—99%). Of the 21 masses with no residual/recurrent disease on MRI, CEUS yielded a specificity of 100% (21/21; 95% CI: 84—100%). The PPV and NPV of CEUS were 100% (34/34; 95% CI: 90—100%) and 91% (21/23; 95% CI: 72—99%), respectively.

Among the 36 masses with residual/recurrent disease on MRI, multiphase CT detected residual/recurrent disease in 18 masses and missed residual/recurrent disease in 18 masses yielding a sensitivity of 50% (18/36; 95% CI: 33—67%) and a specificity of 100% (21/21; 95% CI: 84—100%). The PPV and NPV of multiphase CT were 100% (18/18; 95% CI: 81.5—100%) and 54% (21/39; 95% CI: 37—70%), respectively. The 44% difference in sensitivity for the detection of residual/recurrent disease after TACE between CEUS and multiphase CT was statistically significant ($P = 0.0001$).

Discussion

In our study, marked difference in the diagnostic performance of CEUS and multiphase CT was observed. The sensitivity of CEUS was much higher than that of multiphase CT (94% vs. 50%) whereas the specificities were similar (100%). Lower detection by multiphase CT could be attributed to a number of reasons; of them one can be the masking effect of Lipiodol® used during TACE. Lipiodol®, an ingredient of the chemotherapeutic emulsion, acts as a carrier and remains for long within the tumor and thus enhances

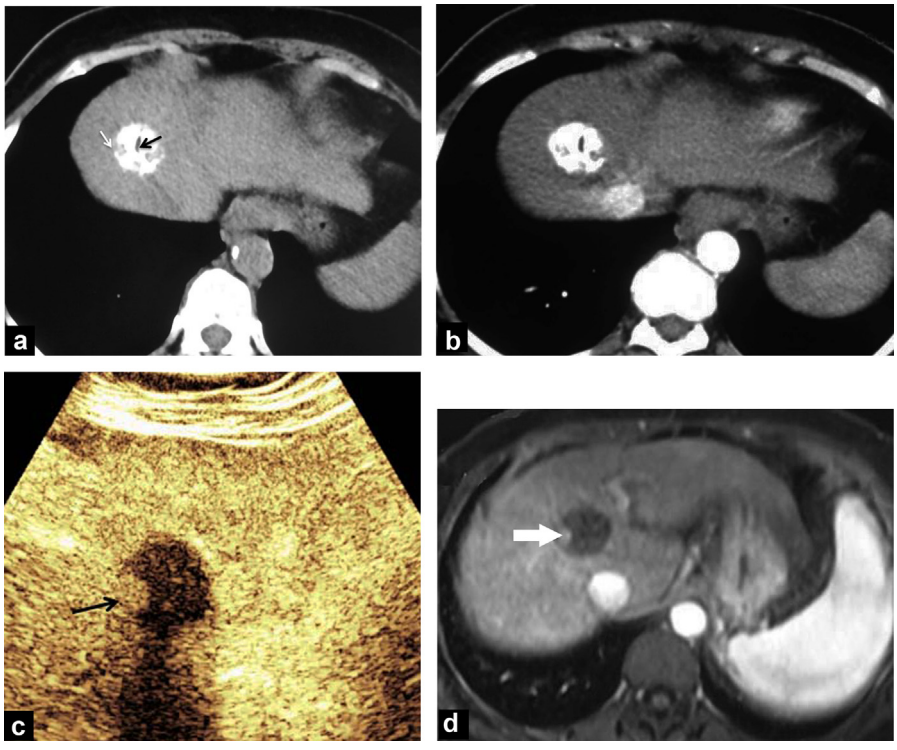

Figure 4. A 61-year-old woman with hepatocellular carcinoma (HCC) treated with transarterial chemoembolization (TACE). This case illustrates the limitation of multiphase CT. (a) Post TACE unenhanced CT image in the transverse plane shows hepatocellular carcinoma in segment IV A of the liver. The lesion is heterogeneous because of uneven distribution of iodized oil (Lipiodol®) at the periphery of the lesion (white arrow) and also in the center (black arrow). (b) CT image obtained during the arterial phase following intravenous administration of iodinated contrast material shows no tumor enhancement. (c) Contrast-enhanced ultrasound image obtained 18 s following intravenous administration of SonoVue® shows focal nodular enhancing lesion (arrow) at the periphery of a treated HCC. (d) 3D VIBE MR image obtained during the arterial phase following intravenous administration of a gadolinium chelate confirms residual disease (arrow) in the segment 4 after TACE.

Table 1 Characteristics of the study population ($n = 50$).

Variable	Patients ($n = 50$)
Age (years)	
Mean (SD)	53.0 ± 12.5
Range	[24–72]
Gender	
Male	41 (82%)
Female	9 (18%)
Child's status	
Child A	44 (88%)
Child B	6 (12%)
Etiology of HCC	
HBV	27 (54%)
HCV	10 (20%)
HVOTO	5 (10%)
NASH	3 (6%)
HBV + HCV	2 (4%)
Cryptogenic	2 (4%)
Alcoholic	1 (2%)
AFP (ng/ml)	
<20	26 (52%)
21–300	12 (24%)
>300	12 (24%)
Number of masses evaluated on CEUS	70
Lesion size (cm)	
Mean size ± SD	4.9 ± 2.9
Range	[1–15]
Mass enhancement on arterial phase	$n = 70$
Hyper enhancement	43 (61%)
No enhancement	27 (39%)
Pattern of arterial phase enhancement	$n = 43$
Heterogenous	22 (51%)
Peripheral	16 (37%)
Homogenous	2 (5%)
Central	3 (7%)

Note: HCC indicates hepatocellular carcinoma; HBV indicates hepatitis B virus; HCV indicates hepatitis C virus; HVOTO indicates hepatic vein outflow tract obstruction; NASH indicates non-alcoholic steato-hepatitis; AFP indicates alpha fetoprotein; CEUS indicates contrast enhanced ultrasound; SD indicates standard deviation.

the antitumoral effect of the chemotherapeutic drugs. Being radiodense, Lipiodol® is seen as a hyperattenuating area in the tumor on multiphase CT and provides information about the extent of tumor necrosis achieved by TACE [23]. Completely Lipiodol® covered tumor on multiphase CT indicates complete response [11]. However, the residual viable tumor also appears hyperattenuating post contrast, quite similar to the dense Lipiodol®. Thus, differentiation between a small viable tumor and hyperattenuating Lipiodol® becomes difficult and the tiny viable tumor if present may get masked by similarly looking Lipiodol® [18,24]. Additionally, Lipiodol® produces beam hardening artifacts on CT, which further obscure the viable tissue [18,25]. Quite frequently, inhomogenous Lipiodol® deposition is visible on post TACE CT. This could result from either the presence of extrahepatic tumor supply or incomplete treatment of TACE because of failed superselective catheterization or inadequate administration of chemotherapeutic drug emulsion. [26]. Lipiodol® devoid areas may either denote tumor necrosis or untreated viable tissue [11]. Therefore, multiphase CT is generally recommended at 4 weeks post TACE so that Lipiodol® can get localized within the tumor [27]. Despite this, assessment with multiphase CT remains challenging.

A newer technique of TACE with drug eluding beads (DEB) does not require the use of Lipiodol® and thus accurate response assessment would be possible due to lack of Lipiodol® hazards. Comparison of outcome of Lipiodol® TACE and DEB-TACE has shown superiority of MRI over multiphase CT in the former and similar outcome in the DEB-TACE group [18]. The role of CEUS in these cases needs further evaluation.

CEUS evaluation is not affected by the presence of Lipiodol®. Small volume of ultrasound contrast agent can delineate even a tiny viable tissue by producing greater arterial enhancement that CT or MRI. [28]. CEUS can accurately assess tumor reponse as early as one week post-TACE [29]. Assessment at 4 weeks post TACE by CEUS has shown superior sensitivity not only than CT (100% vs. 50%) but than MRI as well (100% vs. 50%) [17]. In our study, we were unable to diagnose two masses with residual disease by CEUS. Both masses were small (1 and 1.5 cm) in size and the tiny enhancing viable tissue was missed on CEUS whereas MRI could show the subtle arterial enhancement in both masses.

Few studies about evaluation of tumor response to TACE with CEUS and CT are available in the literature [18–21]. Salvaggio et al. found higher degrees of accuracy for CEUS (100%) by comparison with multiphase CT (92.1%) on

Table 2 Relative performance of multiphasic CT and contrast-enhanced ultrasound in detecting residual disease in hepatocellular carcinoma after post TACE in 42 patients with 57 lesions.

Modalities	Sensitivity	Specificity	PPV	NPV
CEUS	34/36 (94) [81–99]	21/21 (100) [84–100]	34/34 (100) [90–100]	21/23 (91) [72–99]
Multiphase CT	18/36 (50) [33–67]	21/21 (100) [84–100]	18/18 (100) [81–100]	21/39 (55) [37–70]

Note: Numbers are proportions. Numbers in parentheses are percentages. Numbers in brackets are 95% confidence intervals. CEUS indicates contrast enhanced ultrasound. CT indicates computed tomography. PPV indicates positive predictive value; NPV indicates negative predictive value; CI indicates confidence Interval.

evaluating 38 masses post TACE [20]. By comparison with histopathology or angiography, a recent study found superior sensitivity (95.9%) and accuracy (96.2%) for CEUS compared to multiphase CT (sensitivity 76.2%, accuracy 77.7%) and suggested the use of CEUS for therapeutic assessment for HCC patients subjected to TACE [21].

In our study, we used multiphasic MRI as the reference standard. Ideally, histopathology would provide the vital information of cell viability with highest accuracy. However, it is neither feasible nor reasonable to biopsy multiple nodules. Even though both multiphase CT/MRI are recommended modalities [3,11,18,30], MRI is preferred due to its inherent advantages. Despite signal intensity changes by Lipiodol® deposition, accurate interpretation is possible. T2-weighted MRI sequences can reliably help differentiate between necrotic and viable tissue [11]. The necrotic tissue lacks enhancement whereas the viable tissue enhances on post contrast T1-weighted sequences. When atypical features are encountered, additional diffusion weighted sequences (DWI) are done for definitive assessment [31,32]. Our MRI protocol also included DWI to solve these imaging dilemmas.

Different patterns of residual/recurrent were observed on CEUS, which were quite similar to Type I to Type IV Lipiodol® deposition previously described on CT [33]. Heterogenous pattern was the most common one. Of note, two masses with homogenous enhancement were the ones which become viable at 22 months and 12 months post-TACE.

There were few limitations of our study. First, CEUS was targeted only to the treated target lesion(s) and not for detecting fresh lesions. We did not attempt to stage the disease because for this each nodule had to be evaluated with separate CEUS sequences, raising the issue of cost-effectiveness. Additionally, lack of comprehensive evaluation of the entire liver in a short time interval for CEUS is a known limitation leading to inability to stage the disease for which multiphase CT/MRI are recommended [34]. Hence, no attempt for staging by CEUS was done. Second, superficially located, subdiaphragmatic, tiny lesions, patients with obesity or cirrhosis are invariably difficult to visualize on US. We failed to confidently pick up residual disease in tiny, one cm masses which was well elicited on MRI. Finally, we included only masses that were seen entirely on ultrasound because for accurate assessment the complete mass had to be seen during the arterial phase CEUS. Newer CEUS techniques are being investigated to overcome the existent limitations. Dynamic CEUS with quantification is being evaluated to obtain information of microcirculation in treated cases of HCC with encouraging results [35]. The utility of 3D CEUS and fusion techniques are being explored with the aim of generating new evidence for widening the existent clinical indications of CEUS [36,37].

Needless to say, the imaging modality employed for therapeutic assessment should have a high diagnostic accuracy, easy availability, minimum cost and less hazardous side-effects. CEUS fulfills all these attributes [27,38]. Additionally, the relatively inexpensive ultrasound contrast, ultrasound machine coupled with the additional benefit of portability, makes it an attractive imaging technique compared to CT and MRI.

In conclusion, CEUS is a useful alternative technique for evaluating early therapeutic response of HCC following Lipiodol® TACE. For long term surveillance, CEUS should be complemented with CT/MRI for a comprehensive evaluation of the disease.

Funding

This study did not receive any fundings.

Acknowledgements

Authors acknowledge the contribution of the research staff, Mr. Sanjeev Negi, Mr. Bijender Negi and Mr. Dilshad for data handling.

Disclosure of interest

The authors declare they have no competing interest.

References

[1] Paul SB, Manjunatha YC, Acharya SK. Palliative treatment in advanced hepatocellular carcinoma: has it made any difference? Trop Gastroenterol 2009;30:125—34.
[2] Forner A, Reig ME, de Lope CR, Bruix J. Current strategy for staging and treatment: the BCLC update and future prospects. Semin Liver Dis 2010;30:61—74.
[3] Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol 2001;35:421—30.
[4] Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 2010;30:52—60.
[5] Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 1999;19:329—38.
[6] Bartolozzi C, Lencioni R, Caramella D, Falaschi F, Cioni R, DiCoscio G. Hepatocellular carcinoma: CT and MR features after transcatheter arterial embolization and percutaneous ethanol injection. Radiology 1994;191:123—8.
[7] Ito K, Honjo K, Fujita T, Matsui M, Awaya H, Matsumoto T, et al. Therapeutic efficacy of transcatheter arterial chemoembolization for hepatocellular carcinoma: MRI and pathology. J Comput Assist Tomogr 1995;19:198—203.
[8] Lim HK, Han JK. Hepatocellular carcinoma: evaluation of therapeutic response to interventional procedures. Abdom Imaging 2002;27:168—79.
[9] Verslype C, Rosmorduc O, Rougier P. Hepatocellular carcinoma: ESMO—ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23:41—8.
[10] Jang JY, Kim MY, Jeong SW, Kim TY, Kim SU, Lee SH, et al. Current consensus and guidelines of contrast enhanced ultrasound for the characterization of focal liver lesions. Clin Mol Hepatol 2013;19:1—16.
[11] Guan YS, Sun L, Zhou XP, Li X, Zheng XH. Hepatocellular carcinoma treated with interventional procedures: CT and MRI follow-up. World J Gastroenterol 2004;10:3543—8.
[12] Minami Y, Kudo M. Imaging modalities for assessment of treatment response to nonsurgical hepatocellular carcinoma therapy: contrast-enhanced US, CT, and MRI. Liver Cancer 2015;4:106—14.

[13] Claudon M, Dietrich CF, Choi BI, Cosgrove DO, Kudo M, Nolsøe CP, et al. Guidelines and good clinical practice recommendations for Contrast Enhanced Ultrasound (CEUS) in the liver — update 2012: a WFUMB-EFSUMB initiative in cooperation with representatives of AFSUMB, AIUM, ASUM, FLAUS and ICUS. Ultrasound Med Biol 2013;39:187—210.
[14] Shiozawa K, Watanabe M, Takayama R, Takahashi M, Wakui N, Iida K, et al. Evaluation of local recurrence after treatment for hepatocellular carcinoma by contrast-enhanced ultrasonography using Sonazoid: comparison with dynamic computed tomography. J Clin Ultrasound 2010;38:182—9.
[15] Moschouris H, Malagari K, Papadaki MG, Kornezos I, Stamatiou K, Anagnostopoulos A, et al. mRECIST criteria and contrast-enhanced US for the assessment of the response of hepatocellular carcinoma to transarterial chemoembolization. Diagn Interv Radiol 2014;20:136—42.
[16] Sparchez Z, Mocan LT, Radu P, Anton O, Bolog N. Contrast enhanced ultrasonography in assessing the treatment response to transarterial chemoembolization in patients with hepatocellular carcinoma. Med Ultrason 2016;18:96—102.
[17] Cho YZ, Park SY, Choi EH, Baik SK, Kwon SO, Kim YJ, et al. The usefulness of contrast enhanced ultrasonography in the early detection of hepatocellular carcinoma viability after transarterial chemoembolization: pilot study. Clin Mol Hepatol 2015;21:165—74.
[18] Kloeckner R, Otto G, Biesterfeld S, Oberholzer K, Dueber C, Pitton MB, et al. MDCT versus MRI assessment of tumor response after transarterial chemoembolization for the treatment of hepatocellular carcinoma. Cardiovasc Intervent Radiol 2010;33:532—40.
[19] Kaufmann S, Schulze M, Spira D, Horger M. Comparison of volume perfusion computed tomography and contrast-enhanced ultrasound for assessment of therapeutic effect of transarterial chemoembolization in patients with hepatocellular carcinoma: a preliminary report. Acta Radiol 2016;57:8—12.
[20] Salvaggio G, Campisi A, Lo Greco V, Cannella I, Meloni MF, Caruso G. Evaluation of post treatment response of hepatocellular carcinoma: comparison of ultrasonography with second-generation ultrasound contrast agent and multidetector CT. Abdom Imaging 2010;35:447—53.
[21] Liu M, Lin MX, Lu MD, Xu ZF, Zheng KG, Wang W, et al. Comparison of contrast-enhanced ultrasound and contrast-enhanced computed tomography in evaluating the treatment response to transcatheter arterial chemoembolization of hepatocellular carcinoma using modified RECIST. Eur Radiol 2015;25:2502—11.
[22] Xu HX. Contrast-enhanced ultrasound: the evolving applications. World J Radiol 2009;1:15—24.
[23] Takayasu K, Arii S, Matsuo N, Yoshikawa M, Ryu M, Takasaki K, et al. Comparison of CT findings with resected specimens after chemoembolization with iodized oil for hepatocellular carcinoma. AJR Am J Roentgenol 2000;175:699—704.
[24] Saccheri S, Lovaria A, Sangiovanni A, Nicolini A, De Fazio C, Ronchi G, et al. Segmental transcatheter arterial chemoembolization treatment in patients with cirrhosis and inoperable hepatocellular carcinomas. J Vasc Interv Radiol 2002;13:995—9.
[25] Kim KY, Lee JM, Choi B. Assessment of the treatment response of HCC. Abdom Imaging 2011;36:300—14.
[26] Chung JW, Kim HC, Yoon JH, Lee HS, Jae HJ, Lee W, et al. Transcatheter arterial chemoembolization of hepatocellular carcinoma: Prevalence and causative factors of extrahepatic collateral arteries in 479 patients. Korean J Radiol 2006;7:257—66.
[27] Kono Y, Lucidarme O, Choi SH, Rose SC, Hassanein TI, Alpert E, et al. Contrast-enhanced ultrasound as a predictor of treatment efficacy within 2 weeks after transarterial chemoembolization of hepatocellular carcinoma. J Vasc Interv Radiol 2007;18:57—65.
[28] Sugimoto K, Moriyasu F, Shiraishi J, Saito K, Taira J, Saguchi T, Imai Y. Assessment of arterial hypervascularity of hepatocellular carcinoma: comparison of contrast-enhanced US and gadoxetate disodium-enhanced MR imaging. Eur Radiol 2012;22:1205—13.
[29] Xia Y, Kudo M, Minami Y, Hatanaka K, Ueshima K, Chung H, et al. Response evaluation of transcatheter arterial chemoembolization in hepatocellular carcinomas: the usefulness of sonazoid-enhanced harmonic sonography. Oncology 2008;75:99—105.
[30] Kubota K, Hisa N, Nishikawa T, Fujiwara Y, Murata Y, Itoh S, et al. Evaluation of hepatocellular carcinoma after treatment with transcatheter arterial chemoembolization:comparison of Lipiodol-CT, power doppler sonography and dynamic MRI. Abdom Imaging 2001;26:184—90.
[31] Osama RM, Abdelmaksoud AHK, El Tatawy SAM, Nabeel MM, Metwally LIA. Role of dynamic contrast-enhanced and diffusion weighted MRI in evaluation of necrosis of hepatocellular carcinoma after chemoembolization. Egypt J Radiol Nucl Med 2013;44:737—46.
[32] Yuan Z, Li WT, Ye XD, Peng WJ, Xiao XS. Utility of diffusion-weighted imaging to assess hepatocellular carcinoma viability following transarterial chemoembolization. Oncol Lett 2014;8:831—6.
[33] Lim HS, Jeong YY, Kang HK, Kim JK, Park JG. Imaging features of hepatocellular carcinoma after transcatheter arterial chemoembolization and radiofrequency ablation. AJR Am J Roentgenol 2006;187:W341—9.
[34] Zheng SG, Xu HX, Lu MD, Xie XY, Xu ZF, Liu GJ, et al. Role of contrast-enhanced ultrasound in follow-up assessment after ablation for hepatocellular carcinoma. World J Gastroenterol 2013;19:855—65.
[35] Uller W, Wiggermann P, Gössmann H, et al. Evaluation of the microcirculation of hepatocellular carcinomas using contrast-enhanced ultrasound with intraarterial and intravenous contrast application during transarterial chemoembolization with drug-eluting beads (DEB-TACE): preliminary data. Clin Hemorheol Microcirc 2011;49:55—66.
[36] Bartolotta TV, Taibbi A, Matranga D, Midiri M, Lagalla R. 3D versus 2D contrast-enhanced sonography in the evaluation of therapeutic response of hepatocellular carcinoma after Locoregional therapies: preliminary findings. Radiol Med 2015;120:695—704.
[37] Ross CJ, Rennert J, Schacherer D, et al. Image fusion with volume navigation of contrast enhanced ultrasound (CEUS) with computed tomography (CT) or magnetic resonance imaging (MRI) for post-interventional follow-up after transcatheter arterial chemoembolization (TACE) of hepatocellular carcinomas (HCC): Preliminary results. Clin Hemorheol Microcirc 2010;46:101—15.
[38] Morimoto M, Shirato K, Sugimori K, Kokawa A, Tomita N, Saito T, et al. Contrast-enhanced harmonic gray-scale sonographic-histologic correlationof the therapeutic effects of transcatheter arterial chemoembolization in patients with hepatocellular carcinoma. AJR Am J Roentgenol 2003;181:65—9.