Advancements in minimally invasive image-guided liver therapies

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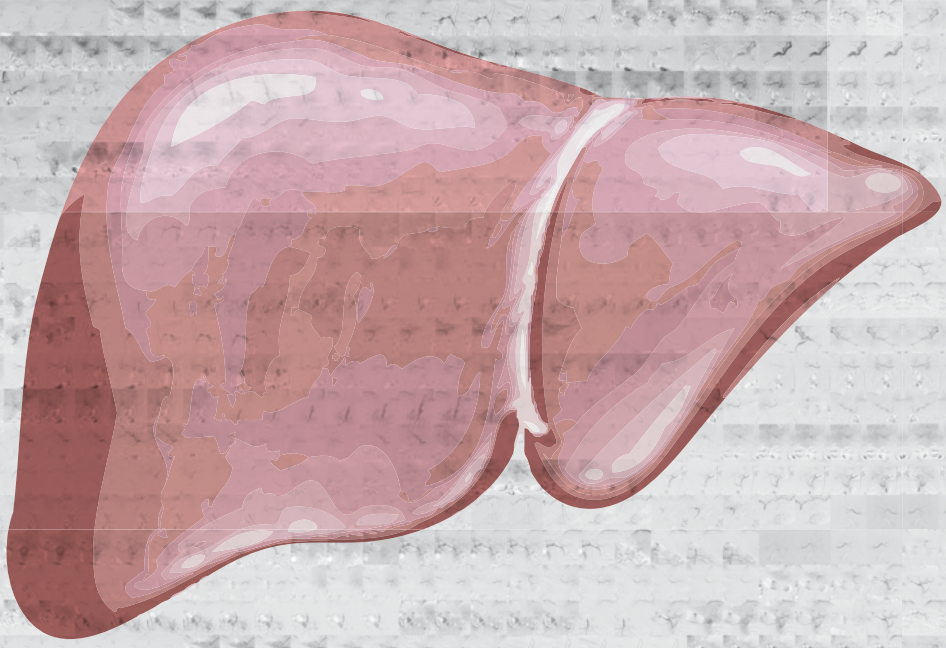
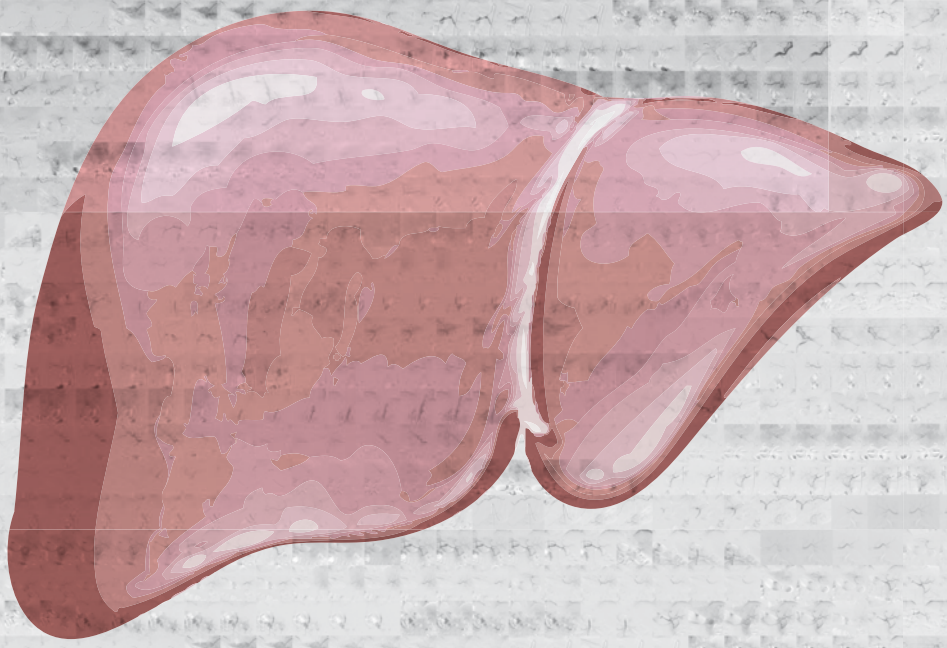
PART II

TRANSARTERIAL LIVER THERAPIES



Chapter 5

Pilot study evaluating catheter-directed contrast-enhanced ultrasound compared to catheter-directed computed tomography hepatic arteriography as adjuncts to digital subtraction angiography to guide transarterial chemoembolization



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ABSTRACT

Purpose

To investigate the feasibility and procedural value of catheter-directed contrast-enhanced ultrasound (CCEUS) compared with catheter-directed computed tomography hepatic arteriography (CTHA) in patients undergoing transarterial chemoembolization (TACE) guided by digital subtraction angiography (DSA).

Methods

From December 2010 to December 2011, a pilot study was conducted including 9 patients (mean age 66.6 years; SD 8.3 years; seven men) undergoing TACE with drug-eluting beads for unresectable hepatocellular carcinoma (HCC). Both CCEUS and CTHA were performed in addition to DSA. Alterations of treatment plan based on CCEUS were recorded and compared with CTHA.

Results

CCEUS provided additional information to DSA altering the treatment plan in 4 out of 9 patients (44.4%). In these four patients, CCEUS helped to identify additional tumor feeders (n=2) or led to a change in catheter position (n=2). The information provided by CCEUS was similar to that provided by CTHA.

Conclusion

CCEUS is a potentially valuable imaging tool in adjunction to DSA when performing TACE and may provide similar information as CTHA.

INTRODUCTION

Transarterial chemoembolization (TACE) improves survival in patients with intermediate stage hepatocellular carcinoma (HCC) (1-3). Traditionally, TACE is guided by digital subtraction angiography (DSA). Yet the information obtained with DSA is limited as DSA only allows two-dimensional imaging. Different studies have shown the value of catheter-directed computed tomography hepatic arteriography (CTHA) and cone-beam computed tomography (CBCT) when performing transarterial liver therapies (4-8). These techniques allow accurate multi-planar visualization of tumor enhancement and improve identification of tumor-feeding arteries. The image quality of CTHA is superior to CBCT as a result of higher soft tissue contrast resolution and CTHA allows imaging with a larger field of view (9).

Contrast-enhanced ultrasound with catheter-directed intra-arterial injection (CCEUS) may potentially be a good alternative to CTHA or CBCT. CCEUS enables real-time visualization of tumor enhancement in multiple directions. Moreover, it is widely available and does not expose the patient to radiation. The aim of this prospective pilot study was to evaluate the procedural impact of CCEUS when used in addition to DSA to guide TACE with drug-eluting beads (DEB-TACE) in patients with intermediate stage HCC and to compare CCEUS with CTHA.

METHODS

Patients

The study was approved by the local ethics committee. Informed consent was obtained for all study patients. From December 2010 to December 2011, nine consecutive patients with HCC were included in the study (mean age 66.6 years; SD 8.3 years; seven men). Inclusion criteria for the study were: unresectable HCC, Child-Pugh A or B and ECOG performance status <2. The diagnosis of HCC was confirmed according to American Association for the Study of Liver Diseases (AASLD) practice guidelines criteria (10). Exclusion criteria were age < 18 years, diffuse HCC or more than 5 lesions, previous treatment with TACE or radioembolization, advanced stage disease according to Barcelona Clinic Liver Cancer (BCLC) criteria (11), total bilirubin >3 mg/dL, uncorrectable coagulopathy, end-stage renal failure, any contra-indication for doxorubicin, known hypersensitivity to sulphur hexafluoride (SF6) micro-bubbles, known right-to-left intra-cardiac shunts, severe pulmonary hypertension, pregnancy.

All patients provided written informed consent. The study was performed in accordance with the Declaration of Helsinki, the International Conference on Harmonization Guideline on Good Clinical Practice and relevant local laws and regulations.

Design and procedures

All patients enrolled in the study underwent grey-scale ultrasonography in the angiography room prior to TACE. In addition to this, contrast enhanced ultrasound was performed with injection of 2.4ml SF6 microbubbles (SonoVue, Bracco International, Amsterdam, The Netherlands) through a cannula in the median cubital vein (IVCEUS). Additional boluses of 2.4ml of microbubbles were given, if the distance between different tumors was such that the enhancement of each tumor could not be analyzed optimally during a single injection. Sufficient time was allowed in between injections for the first bolus of microbubbles to be cleared from the body.

The right groin and upper abdomen were cleansed with iodine and the patient was draped under sterile cloths with exposure of the right groin and upper abdomen. Vascular access was created through the right common femoral artery using a 6F vascular sheath. Using a 5F C2 catheter (Terumo, Tokyo, Japan) selective DSA from the celiac axis (CA), common hepatic artery (CHA) and proper hepatic artery (PHA) was performed with pump injection of a contrast agent (Omnipaque 300; GE Healthcare, Shanghai, China). Angiography from the superior mesenteric artery (SMA) was performed in individual cases when hepatic tumor supply from an aberrant right hepatic artery or other SMA branches was expected based on pre-procedural CT or magnetic resonance imaging (MRI). Immediately after DSA from the PHA and using the same catheter position, CCEUS was performed followed by CTHA. A 2.2F or 2.7F Progreat catheter (Terumo, Tokyo, Japan) was then used to catheterize the lobar artery of the tumor bearing lobe(s) and selective DSA was performed. Again, this was followed by CCEUS and then CTHA with the micro-catheter in the same position. Finally, the (sub)segmental arteries were catheterized using the micro-catheter and sequential DSA, CCEUS and CTHA were performed. In patients with bilobar disease, imaging at a lobar and (sub)segmental level was first performed on one side followed by TACE of the tumors in that lobe. After that, images were obtained at a lobar and (sub)segmental level on the other side and the tumors in the other lobe were treated.

DSA images were obtained with breath-hold, 3 frames/sec and 50mAs/120kV for anteroposterior projections. Using a Mark V ProVis injector (Medrad Inc, Warrendale, PA, USA), contrast medium was injected at 6ml/sec for 25ml for the CA, 5ml/sec for 15ml for the PHA, 3ml/sec for 12ml for lobar injections and 1-2ml/sec for 6-10 ml for (sub)segmental injections. CCEUS was performed using contrast harmonic imaging on a high-perfor-

mance processor (Aplio, Toshiba Medical Systems, Tokyo, Japan) with a multifrequency curved-array probe (2–5 MHz). SF6 micro-bubbles were slowly hand-injected. Injections of 1ml were used for the PHA, 0.5ml for the lobar artery and 0.3-0.5ml for (sub)segmental arteries. During the injection, the entire tumor volume was scanned to assess the presence of unenhancing areas. CTHA was performed using a hybrid 16-slice Aquilion CT/ Infinix VC-1 angiography system (Toshiba Medical Systems, Tokyo, Japan). Pump-injections were used with an injection rate similar to that used for DSA. The injected contrast volume for CTHA was calculated using the equation:

volume = (scan delay + scan time) x flow rate

with the scan delay being the time between the start of injection and enhancement of the region of interest at DSA. CTHA images were acquired using the following parameters: collimation 16x1.0, pitch factor 15, helical pitch 0.938, 120kV and 160 effective mAs. The radiation dose used to perform CTHA was recorded as dose length product (DLP) per patient.

All patients underwent super-selective TACE with the micro-catheter placed as selectively as possible. TACE was performed with DC-Bead (Biocompatibles, Surrey, UK). First 1 vial of 100-300 µm beads was injected, followed by 1 vial of 300-500 µm beads. The beads were loaded with a total of 150mg of doxorubicin (75mg per vial) and mixed with contrast medium prior to injection.

All patients underwent repeated IVCEUS immediately after TACE. Both IVCEUS and CCEUS were performed by the interventional radiologist performing the procedure. All IVCEUS and CCEUS images were archived digitally for review as cine loops in Windows Media Videos (Microsoft, Redmont, WA, USA).

Imaging analysis

At the time of the procedure, DSA images were analyzed by the interventional radiologist performing the procedure and a treatment plan was formulated. Then CCEUS images were analyzed to see if CCEUS provided additional information to DSA. CCEUS images were compared to pre-procedural IVCEUS images. If incomplete tumor enhancement was seen at CCEUS from the hepatic arteries, this prompted a search for extra-hepatic feeding arteries. If tumor enhancement was incomplete upon CCEUS from a lobar or (sub)segmental artery, but not upon CCEUS from a more proximal hepatic artery injection, the catheter was repositioned more proximally prior to injection of DC-Bead. The information obtained with CCEUS was classified into three categories: 1. no change in treatment plan; 2. identification of additional tumor feeding arteries; 3. alteration in

location of injection of the drug-eluting beads. After this, CTHA images were analyzed to see if CTHA provided information not evident on DSA and CCEUS.

IVCEUS images obtained before and after TACE were retrospectively compared to see if complete devascularization of tumors was achieved.

RESULTS

Patient and tumor characteristics are summarized in Table 1. Nineteen HCCs were identified on pre-procedural cross-sectional imaging (CT and/or MRI) with an average of 2.1 (range 1-5) tumor per patient. The mean maximal tumor size was 45.3 mm (range 10-145 mm).

Table 1. Baseline patient and tumor characteristics.

Patient and tumor characteristics	Value
Age	Mean age 67 years
	Range 58-79 years
Sex	M=7
Performance status (n=9)	
0	8 (88.9)
1	1 (11.1)
Cause of cirrhosis (n=9)	
Hepatitis B	6 (66.7)
Alcohol	2 (22.2)
NASH	1 (11.1)
Child Pugh score (n=9)	
A	8 (88.9)
B	1 (11.1)
Tumor burden (n=9)	
Unilobar	6 (66.7)
Bilobar	3 (33.3)
No. nodules (n=9)	
1-3	8 (88.9)
>3	1 (11.1)
Tumor diameter (n=19)	
1-3cm	10 (52.6)
3-5cm	2 (10.5)
5-10cm	3 (15.8)
>10cm	4 (21.1)

In four patients (44.4%), the information provided by CCEUS was not evident at DSA and led to a change of treatment plan. In two of these four patients (22.2% of total) CCEUS led to identification of additional tumor feeding arteries. Both patients had a right liver lobe tumor with a dominant vascular supply from the right hepatic artery. At DSA from the right hepatic artery, incomplete tumor enhancement was not evident. Yet, at CCEUS, there was incomplete enhancement of the tumor and this eventually helped in identifying additional tumor supply from the middle hepatic artery (Figure 1). In the two other patients (22.2%), CCEUS provided information that led to a change in the decision on where to inject the DC Bead. In these cases CCEUS allowed a more selective chemoembolization while ensuring that the entire tumor was accurately targeted (Figure 2).

In four patients where CCEUS provided information that led to a change in treatment, CTHA provided the same information (Figure 1 and 2). CTHA did not provide additional information that led to a change in treatment plan.

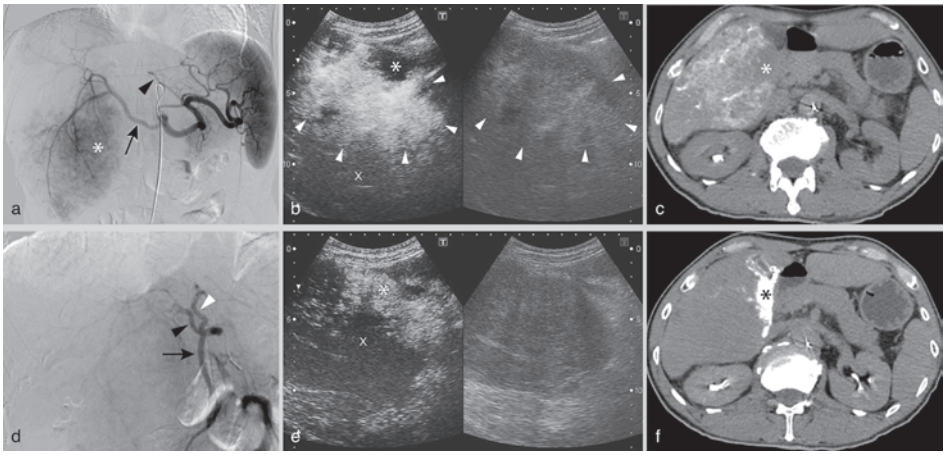

Figure 1. 58-yearr-old male with right liver lobe HCC with a maximal diameter of 12 cm. (a) DSA from the celiac axis (CA) shows tumor enhancement (asterix) through the right hepatic artery (RHA) (arrow). There is a left hepatic artery (LHA) that originates from the left gastric artery (arrowhead). No middle hepatic artery (MHA) is seen. (b) CCEUS (left) and B-mode (right) image during injection of SF6 microbubbles into the RHA. Marked arterial enhancement of the tumor (arrowheads) is seen compared to the non-tumorous liver parenchyma (cross-mark). Absent enhancement is seen in part of the tumor (asterix) (c) CTHA from the RHA also shows absent enhancement in part of the tumor (asterix). (d) DSA from the superior mesenteric artery shows retrograde flow through the gastroduodenal artery (GDA) (arrow) and opacification of the MHA (black arrowhead) and a second LHA (white arrowhead). This MHA and LHA have an origin from the CA that was not opacified at DSA from the CA due to the reversed flow through the GDA. (e) CCEUS (left image) from the MHA shows tumor supply (asterix) through the MHA with absent enhancement in the rest of the tumor (cross-mark). (f) CTHA from the MHA also shows enhancement of part of the tumor through the MHA.

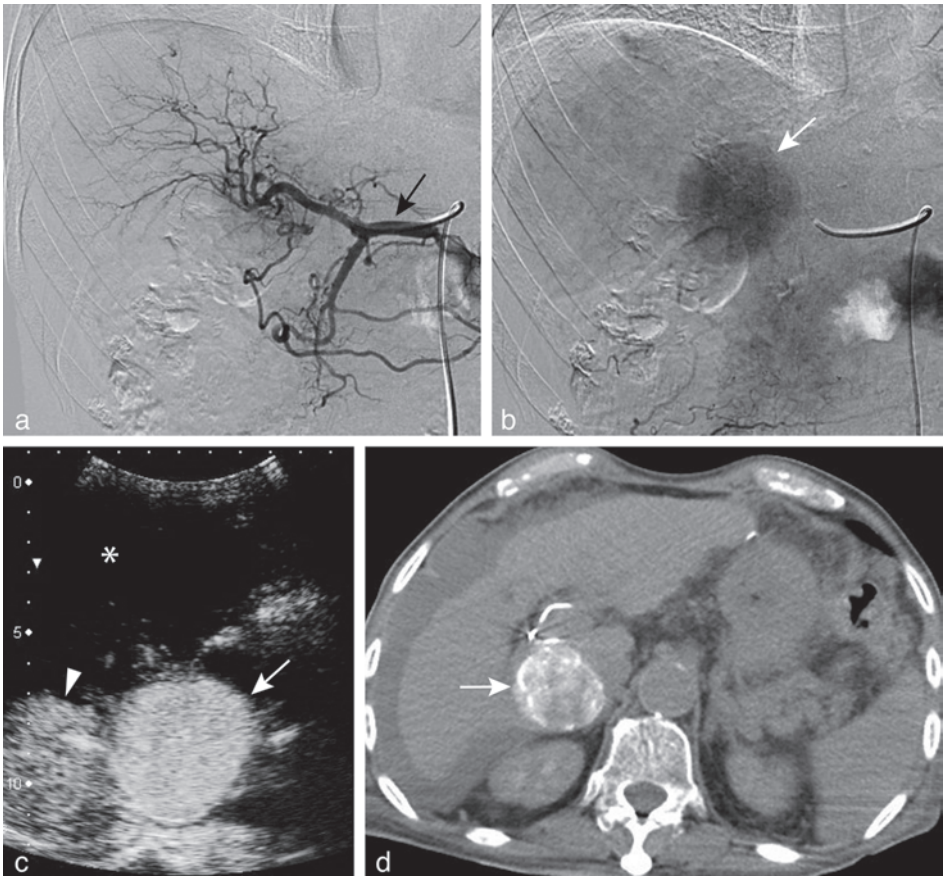

Figure 2. 79-year-old man with a 4.5 cm HCC at the border of segment 6 and the caudate lobe. (a-b) DSA from the common hepatic artery (black arrow) in arterial (a) and parenchymal (b) phase with opacification of the tumor (white arrow). (c) CCEUS from the subsegmental artery showed complete tumor enhancement (white arrow) with enhancement of a small portion of non-tumorous liver parenchyma (arrowhead) and no enhancement of most of the right liver lobe (asterisk). (d) CTHA confirmed enhancement of the entire tumor upon injection of contrast into the subsegmental artery. CCEUS and CTHA thus ensured complete tumor targeting by injection of drug-eluting beads into the subsegmental artery. IVCEUS directly after treatment and CT at 6 weeks showed complete devascularization of the tumor (not shown).

The use of CTHA did result in additional information on extra-hepatic enhancement that was not provided by DSA and CCEUS. In four patients (44.4%), CTHA revealed enhancement of the gallbladder (GB) (n=1), the hepatic falciform artery (HFA) (n=2) or both the GB and HFA (n=1) when contrast was injected from the intended location of release of the drug-eluting beads. This information did not alter the treatment plan. None of these 4 patients developed complications related to injection of drug-eluting beads into the cystic artery or HFA.

IVCEUS immediately after TACE showed complete devascularization of liver tumors in 5 patients (55.6%). The 4 patients with residual enhancement at IVCEUS all had large liver tumors (>10cm). In these patients, vascular stasis was not achieved after delivery of the full dose of drug-eluting beads and the decision was made to treat the remaining viable tumor during a second TACE procedure. The area of residual enhancement on IVCEUS corresponded to the vascular territory of the supplying artery that was not completely embolized, indicating that residual enhancement was not a result of failure to detect additional tumor feeding arteries.

The mean DLP per patient was 921.5 mGy•cm (SD 371.7 mGy•cm)

DISCUSSION

The objective of TACE is to accurately target the entire tumor while preserving the non-tumorous liver parenchyma and extra-hepatic organs. To achieve this, it is generally recommended to deliver the beads as selective as possible (12). Super-selective injection, i.e. into the segmental or sub-segmental arteries, is associated with better treatment outcomes compared to lobar or whole liver chemo-embolization (13).

DSA is used to guide the delivery of the drug-eluting beads. Yet, DSA only enables two-dimensional imaging. As a result, incomplete tumor enhancement may not be detected during hepatic DSA. This is especially true if the non-enhancing tumor parts are located anterior or posterior as hepatic DSA images are usually obtained in posterior-anterior or moderately oblique projections.

There are two important causes for incomplete tumor enhancement during hepatic DSA. The most important cause is the presence of extra-hepatic feeding arteries. Unfortunately, up to 37% of patients with HCC may have a collateral tumor supply through extra-hepatic arteries (5). Second, incomplete tumor enhancement may be due to a highly selective catheter position. Treatment at a (sub)segmental level carries the risk that the catheter is placed distally to additional hepatic feeders. Failure to detect absent enhancement of tumor parts during hepatic DSA may thus result in incomplete tumor treatment.

Different studies have shown that catheter-directed cross-sectional imaging such as CTHA and CBCT allow accurate multi-planar visualization of tumor enhancement and may improve tumor targeting (4-8). In the present study we compared CCEUS and CTHA as an adjunct to DSA to guide TACE. CCEUS proved to be safe and feasible. In 44.4% of patients, CCEUS provided information that was not evident on DSA and altered the treatment ap-

proach. The additional information provided by CCEUS was similar to that provided by CTHA. Although the number of patients in our study is limited, the findings suggest that CCEUS may improve trans-arterial liver tumor targeting, as does CTHA. In a viable tumor incomplete enhancement upon contrast injection from the hepatic arteries may indicate extra-hepatic tumor supply. Complete tumor enhancement upon contrast injection from a super-selective hepatic artery position allows the operator to feel confident that the entire tumor is targeted, whereas incomplete enhancement may prompt the search for additional feeding hepatic arteries. CCEUS offers an important advantage over CTHA. It can be repeated multiple times without increasing iodinated contrast volume or radiation, whereas computed tomographic imaging during TACE results in significant increase of the radiation dose to both the patient and operating staff (14,15).

Few centers have access to a hybrid CT/angiography system that allows CTHA images to be obtained without moving a patient between rooms. CBCT is available to many more interventional radiologists and is much more frequently used as an adjunct to DSA during TACE. CCEUS and CBCT were not compared in the present study. Yet, CCEUS may offer several additional advantages over CBCT. CBCT has a relatively long acquisition time (8-20sec) making this technique more susceptible to breathing artifacts, whereas breathing is not an issue in CCEUS. Another drawback of CBCT is the limited field of view (FOV). CCEUS is less hindered by limitations in the FOV as it can be repeated multiple times to cover larger areas without radiation or risk of contrast-induced nephropathy.

The standard volume of SF6 microbubbles of hepatic IVCEUS in our institution at the time of the study was 2.4ml. Modern high-end ultrasound machines enable good quality IVCEUS imaging with lower dosages and may therefore also allow the use of lower volumes of microbubbles for CCEUS then those used in this study.

The main limitation of our study is the limited number of patients. Second, the usefulness of CCEUS was not compared with CBCT, which is more widely used than CTHA. Yet, CTHA was used as the gold standard in the present study as this technique has better image quality and a larger field of view compared to CBCT. Furthermore, CCEUS was inferior to CTHA in providing information on extra-hepatic enhancement. Yet, the information provided by CCTA did not alter the treatment strategy and no extra-hepatic organ injury was seen.

In conclusion, CCEUS is a potentially useful imaging tool in adjunction to DSA when performing TACE. It may provide similar multi-planar information on tumor enhancement as CTHA without increasing iodinated contrast volume or radiation, yet further studies are warranted to determine the role of CCEUS.

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