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

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

MATERIALS AND METHODS: From December 2010 to December 2011, a pilot study was conducted including nine 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 CCTA were performed in addition to DSA. Alterations of treatment plan based on CCEUS were recorded and compared with CCTA.

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

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

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 arteriography (CCTA) and cone-beam computed tomography (CBCT) when performing transarterial liver therapies.[4–8] These techniques allow accurate multiplanar visualization of tumour enhancement and improve identification of tumour-feeding arteries. The image quality of CCTA is

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superior to CBCT as a result of higher soft-tissue contrast resolution and CCTA 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 CCTA or CBCT. CCEUS enables real-time visualization of tumour 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 in patients with intermediate stage HCC and to compare CCEUS with CCTA.

Materials and methods

Patients

The study was improved 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 Eastern Cooperative Oncology Group (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 five 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 contraindication to doxorubicin, known hypersensitivity to sulphur hexafluoride (SF6) micro-bubbles, known right-to-left intra-cardiac shunts, severe pulmonary hypertension, and pregnancy.

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 2.4 ml SF6 microbubbles (SonoVue, Bracco International, Amsterdam, The Netherlands) through a cannula in the median cubital vein (IVCEUS). Additional boluses of 2.4 ml of microbubbles were given, if the distance between different tumours was such that the enhancement of each tumour could not be analysed optimally during a single injection. Sufficient time was allowed 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 6 F vascular sheath. Using a 5 F C2 catheter (Terumo, Tokyo, Japan) selective DSA from the coeliac axis (CA), common hepatic artery (CHA), and proper hepatic artery (PHA) was performed with pump injection of a contrast agent (iohexol, 300 mg iodine/ml; Omnipaque 300, GE Healthcare, Shanghai, China). Angiography from the superior mesenteric artery (SMA) was performed in individual cases when hepatic tumour 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 CCTA. A 2.2 or 2.7 F Progreat catheter (Terumo, Tokyo, Japan) was then used to catheterize the lobar artery of the tumour-bearing lobe(s) and selective DSA was performed. Again, this was followed by CCEUS and then CCTA with the micro-catheter in the same position. Finally, the (sub) segmental arteries were catheterized using the micro-catheter and sequential DSA, CCEUS, and CCTA were performed. In patients with bi-lobar disease, imaging at a lobar and (sub)segmental level was first performed on one side followed by TACE of the tumours in that lobe. After that, images were obtained at a lobar and (sub)segmental level on the other side and the tumours in the other lobe were treated.

DSA images were obtained with breath-hold, 3 frames/s and 50 mAs/120 kV for anteroposterior projections. Using a Mark V ProVis injector (Medrad, Warrendale, PA, USA), contrast medium was injected at 6 ml/s for 25 ml for the CA, 5 ml/s for 15 ml for the PHA, 3 ml/s for 12 ml for lobar injections, and 1–2 ml/s for 6–10 ml for (sub)segmental injections. CCEUS was performed using contrast harmonic imaging on a high-performance 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 1 ml were used for the PHA, 0.5 ml for the lobar artery and 0.3–0.5 ml for (sub) segmental arteries. During the injection, the entire tumour volume was scanned to assess the presence of unenhancing areas. CCTA was performed using a hybrid 16-section 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 medium volume for CCTA was calculated using the equation

$$\text{volume} = (\text{scan delay} + \text{scan time}) \times \text{flow rate}$$

with the scan delay being the time between the start of injection and enhancement of the region of interest at DSA. CCTA images were acquired using the following parameters: 16 × 1 collimation, pitch factor = 15, helical pitch = 0.938, 120 kV tube voltage and 160 effective mAs tube current. The radiation dose used to perform CCTA 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-Beads (Biocompatibles, Surrey, UK).

First, one vial of 100–300 μm beads was injected, followed by one vial of 300–500 μm beads. The beads were loaded with a total of 150 mg doxorubicin (75 mg 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 analysed by the interventional radiologist performing the procedure and a treatment plan was formulated. CCEUS images were then analysed to see whether CCEUS provided additional information to DSA. CCEUS images were compared to pre-procedural IVCEUS images. If incomplete tumour enhancement was seen at CCEUS from the hepatic arteries, this prompted a search for extra-hepatic feeding arteries. If tumour 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-Beads. The information obtained with CCEUS was classified into three categories[1]: no change in treatment plan[2]; identification of additional tumour feeding arteries[3]; alteration in location of injection of the drug-eluting beads. After this, CCTA images were analysed to see whether CCTA provided information not evident on DSA and CCEUS.

IVCEUS images obtained before and after TACE were retrospectively compared to see whether complete devascularization of the tumours was achieved.

Results

Patient and tumour 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) tumours per patient. The mean maximal tumour size was 45.3 mm (range 10–145 mm).

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 tumour-feeding arteries. Both patients had a right liver lobe tumour with a dominant vascular supply from the right hepatic artery. At DSA from the right hepatic artery, incomplete tumour enhancement was not evident. Yet, at CCEUS, there was incomplete enhancement of the tumour and this eventually helped in identifying additional tumour supply from the middle hepatic artery (Fig 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-Beads. In these cases CCEUS enabled more selective chemo-embolization while ensuring that the entire tumour was accurately targeted (Fig 2).

Table 1
Baseline patient and tumour characteristics.

Patient and tumour characteristics	Value
Age, years	
Mean	67
Range	58–79
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)
Tumour burden ($n = 9$)	
Unilobar	6 (66.7)
Bilobar	3 (33.3)
No. nodules ($n = 9$)	
1–3	8 (88.9)
>3	1 (11.1)
Tumour diameter ($n = 19$), cm	
1–3	10 (52.6)
3–5	2 (10.5)
5–10	3 (15.8)
>10	4 (21.1)

Data are *n*(%) unless otherwise stated.

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

The use of CCTA did result in additional information on extra-hepatic enhancement that was not provided by DSA and CCEUS. In four patients (44.4%), CCTA 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 medium was injected from the intended location of release of the drug-eluting beads. This information did not alter the treatment plan. None of these four 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 tumours in five patients (55.6%). The four patients with residual enhancement at IVCEUS all had large liver tumours (>10 cm). 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 tumour 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 tumour-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 tumour while preserving the non-tumorous liver

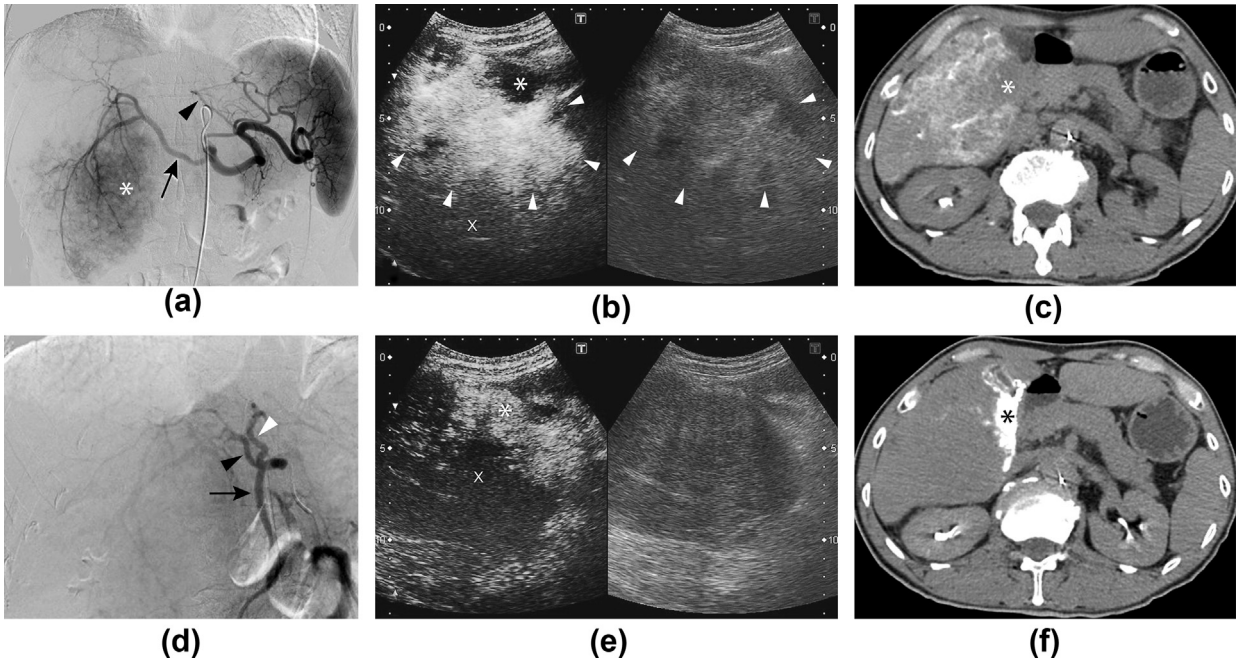

Figure 1 A 58-year-old man with right liver lobe HCC with a maximal diameter of 12 cm. (a) DSA image from the CA shows tumour enhancement (asterisk) through the right hepatic artery (RHA; arrow). There is a left hepatic artery (LHA) that originates from the left gastric artery (arrowhead). No middle hepatic artery (MHA) is seen. (b) CCEUS (left) and B-mode (right) images during injection of SF6 microbubbles into the RHA. Marked arterial enhancement of the tumour (arrowheads) is seen compared to the non-tumorous liver parenchyma (cross-mark). (c) CCTA image from the RHA also shows absent enhancement in part of the tumour (asterisk). (d) DSA image 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). The 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 tumour supply (asterisk) through the MHA with absent enhancement in the rest of the tumour (cross-mark). (f) CCTA image from the MHA also shows enhancement of part of the tumour through the MHA.

parenchyma and extra-hepatic organs. To achieve this, it is generally recommended to deliver the beads as selectively 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 chemoembolization.[13]

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

There are two important causes for incomplete tumour 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 tumour supply through extra-hepatic arteries.[5] Second, incomplete tumour 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 tumour parts during hepatic DSA may thus result in incomplete tumour treatment.

Different studies have shown that catheter-directed cross-sectional imaging, such as CCTA and CBCT, allow accurate multiplanar visualization of tumour enhancement and may improve tumour targeting.[4–8] In the present study, CCEUS was compared to CCTA 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 at DSA and altered the treatment approach. The additional information provided by CCEUS was similar to that provided by CCTA. Although the number of patients in te present study is limited, the findings suggest that CCEUS may improve trans-arterial liver tumour targeting, as does CCTA. In a viable tumour, incomplete enhancement upon contrast medium injection from the hepatic arteries may indicate extra-hepatic tumour supply. Complete tumour enhancement upon contrast medium injection from a super-selective hepatic artery position allows the operator to feel confident that the entire tumour is targeted, whereas incomplete enhancement may prompt the search for additional feeding hepatic arteries. CCEUS offers an important advantage over CCTA. It can be repeated multiple times without increasing iodinated contrast medium volume or radiation, whereas CT imaging during TACE results in a significant increase of the radiation dose to both the patient and operating staff.[14,15]

Few centres have access to a hybrid CT/angiography system that allows CCTA 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

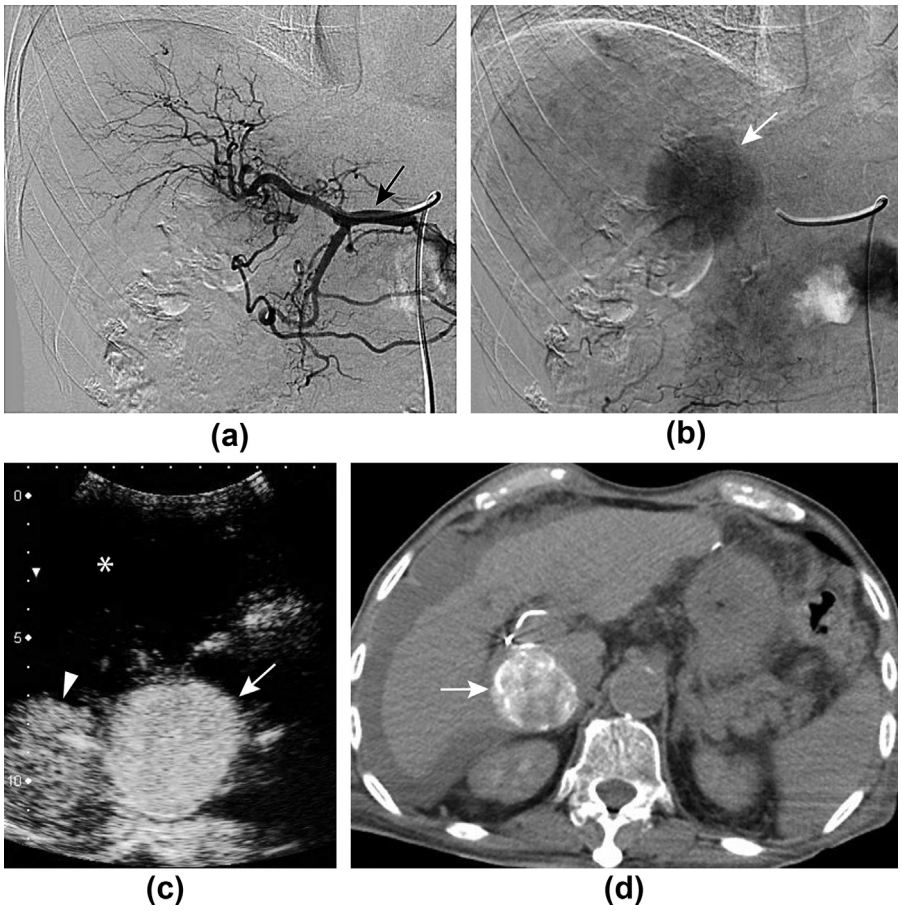

Figure 2 A 79-year-old man with a 4.5 cm HCC at the border of segment 6 and the caudate lobe. (a–b) DSA image from the common hepatic artery (black arrow) in the arterial (a) and parenchymal (b) phase with opacification of the tumour (white arrow). (c) CCEUS image from the subsegmental artery showed complete tumour 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) CCTA confirmed enhancement of the entire tumour upon injection of contrast medium into the subsegmental artery. CCEUS and CCTA thus ensured complete tumour 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 tumour (not shown).

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 (8–20 s) making this technique more susceptible to breathing artefacts, 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 medium-induced nephropathy.

The standard volume of SF6 microbubbles of hepatic IVCEUS at the time of the study was 2.4 ml. 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 the present study.

The main limitation of the present study is the limited number of patients. Second, the usefulness of CCEUS was not compared with CBCT, which is more widely used than CCTA. Yet, CCTA was used as the gold standard in the present study as this technique has better image quality and a larger FOV compared to CBCT. Furthermore, CCEUS was inferior to CCTA 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 multiplanar information on tumour enhancement to CCTA without increasing iodinated contrast medium volume or radiation, yet further studies are warranted to determine the role of CCEUS.

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