Published in final edited form as:

Ultrasound Q. 2020 September ; 36(3): 218–223. doi:10.1097/RUQ.0000000000000513.

Contrast-enhanced Ultrasound Identifies Patent Feeding Vessels in Transarterial Chemoembolization Patients With Residual Tumor Vascularity

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Abstract

Transarterial chemoembolization (TACE) of hepatocellular carcinoma (HCC) often requires retreatment and identification of feeding vessels supplying the residual/recurrent tumor is an important step in treatment planning. The objective of this study was to determine if contrast-enhanced ultrasound (CEUS) could correctly identify the vessel supplying the residual tumor. To date, 69 patients have undergone CEUS follow-up of HCC TACE therapy at our institution as part of an ongoing institutional review board approved trial ([NCT02764801](#)). The CEUS examinations were performed before HCC TACE as well as 1 to 2 weeks and 1 month after treatment using a Logiq E9 scanner with a C1–6 curved array transducer (GE Healthcare, Waukesha, WI). The CEUS images obtained 2 weeks after initial TACE treatment were reviewed, and any feeding vessels supplying the residual HCC were identified. Digital subtraction angiograms during the retreatment TACE were used as reference standard for feeding vessel identification. Thirteen patients with viable HCC post-TACE were included in this study. In these cases, the sonographer correctly identified 85% (11 of 13) of the feeding vessels later confirmed by angiography. Importantly, one of the false-negative cases involved a segment 8 tumor with parasitic blood supply from the medial left hepatic artery. In this case, CEUS identified a largely treated tumor with some residual internal flow, but was unable to visualize any major hepatic vascularity supplying the tumor. In conclusion, CEUS appears to be a valuable tool for planning retreatment of residual HCC post-TACE.

Keywords

contrast-enhanced ultrasound; hepatocellular carcinoma; transarterial chemoembolization

Hepatocellular carcinoma (HCC) is the fifth leading cause of death in men and seventh in women, with approximately 42,000 estimated new cases in the United States.¹ There is a high mortality rate associated with HCC, because the diagnosis is usually made at an

advanced stage.² The prevalence of HCC has increased worldwide over the past 20 years.³ The increase is associated with common risk factors, such as hepatitis B and C infection, alcohol abuse, fatty liver disease, and autoimmune hepatitis.^{2,4}

Surgical resection and liver transplantation represent definitive treatment of HCC.⁵ Liver-directed therapies, including transarterial chemoembolization (TACE), are considered a preferred option for those with tumor confined to the liver with stable parenchymal liver disease but for whom surgical resection is not an option.⁶ In transplant-eligible patients, TACE is used as a bridging therapy, in those whose tumor burden is outside the criteria for transplant, TACE may be used to downstage the disease.^{7,8} For patients ineligible for transplantation, locoregional therapies are used to palliate the disease.⁹ Transarterial chemoembolization is the current standard of care for patients with intermediate stage HCC according to the Barcelona Clinic Liver Cancer guidelines.¹⁰ Transarterial chemoembolization is a minimally invasive image-guided procedure that involves the injection of a chemotherapeutic drug and an embolic agent into the feeding arteries via a catheter. The goal is to create an ischemic environment and trap the chemotherapy within the tumor. In conventional TACE (C-TACE), an emulsion of chemotherapy mixed with iodized oil (lipiodol) followed by gelatin sponge particles are administered via transarterial approach. In drug-eluting beads TACE (DEB-TACE), the microsphere (a hydrophilic nonionic polymer) binds doxorubicin via ion exchange. Preparation time depends on bead size and varies from 30 minutes to 2 hours. The bead functions as both a drug carrier and an embolic agent.^{5,10}

Contrast-enhanced magnetic resonance imaging (MRI) or computed tomography (CT) is the gold standard for monitoring treatment response to TACE. The Society of Interventional Radiology Quality Improvement Guidelines recommends contrast-enhanced MRI or CT 4 to 6 weeks post-TACE to evaluate treatment response.¹¹ This time interval is needed to differentiate viable tumor from postembolization inflammation.^{11,12} Viable tumor can be challenging to distinguish from inflammation when peripheral ring-like enhancement is observed on contrast-enhanced CT or MRI.¹² This finding can persist for up to 3 months post-TACE. Alternatively, contrast-enhanced ultrasound (CEUS) can be used to evaluate residual tumor vascularity in real time without the risks of ionizing radiation or nephrotoxicity.^{12,13}

The United States Food and Drug Administration has approved CEUS for echocardiography, characterization of focal liver lesions and vesicoureteral reflux. One commercially available ultrasound contrast agent, DEFINITY® (Lantheus Medical Imaging, Inc., North Billerica, MA), is comprised of perfluoro-carbon gas microbubbles 1.1 to 3.3 µm in diameter with a lipid shell, similar in size to red blood cells.^{14,15} Contrast-enhanced ultrasound is particularly useful for evaluating the vascular components of a tumor.^{16–18} Several studies have evaluated the therapeutic response of TACE using CEUS as an early predictor of treatment response to monitor tumor viability with real-time enhancement patterns.^{19–23}

As TACE is often an iterative process, sonographers performing CEUS examinations have the potential to assist the interventional radiologist through identification of residual tumor feeding vessels. The purpose of this study was to determine if a sonographer performing

CEUS can identify the intrahepatic or extrahepatic vasculature supplying the residual HCC before retreatment.

MATERIALS AND METHODS

Patient Population

This study was approved by the institutional review board of Thomas Jefferson University and all participants provided written informed consent. Hepatocellular carcinoma was confirmed via cross-sectional imaging and Liver Imaging Reporting and Data System class 5. As part of an ongoing clinical trial (NCT# 02764801), patients underwent CEUS before HCC TACE as well as 1 to 2 weeks and 1 month after TACE. The treatments were performed by multiple interventional radiologists. At our institution, the standard of care for imaging HCC Liver Imaging Reporting and Data System 5 tumors is a baseline contrast-enhanced cross-sectional scan (pre-treatment) followed by a 4- to 6-week scan (posttreatment). The 1-month CEUS scan posttreatment was compared with the 4- to 6-week cross-sectional imaging study. Patients with residual HCC on posttreatment MRI or CT who required TACE retreatment were included in this analysis (Fig. 1).

CEUS Preparation and Technique

Patients were examined using a Logiq E9 ultrasound scanner (GE Healthcare, Waukesha, WI) with a C1–6 curved array transducer operating in a coded harmonic imaging mode with a low mechanical index ($MI < 0.2$). Before the contrast administration, the sonographer acquired grayscale still images with and without measurements and video clips of the tumor in two imaging planes. Before the contrast injection, the sonographer used color and pulsed wave Doppler to help visualize any major vascularity surrounding the tumor. Patients then received 1 bolus injection of 0.2 to 0.3 mL of Definity (Lantheus Medical Imaging, North Billerica, MA) followed by a 10-mL saline flush for baseline CEUS imaging. Before the CEUS examination, the sonographer reviewed the baseline CT/MRI for anatomical guidance. For the 1 to 2 weeks and 1 month post-TACE CEUS scans, the sonographer monitored residual enhancement within the treatment cavity. For patients with viable tumor post-TACE, the sonographer attempted to identify the feeding vasculature on CEUS during the early arterial phase (Fig. 2).

Data Analysis

The CEUS examinations were performed by two ARDMS certified, sonographers with 8 and 2 years of CEUS experience, respectively. Data analysis was performed by the second sonographer, who was blinded to the follow up cross-sectional imaging. Viable tumor was reported as residual enhancement within the treated mass or nodular peripheral enhancement.^{12,17} All the follow-up CEUS examinations were reviewed frame by frame during the arterial phase to confirm the presence of early arterial blood flow. These findings were compared with the reference standard. The latter was determined by an interventional radiologist with over 10 years of experience who identified the feeding vessel from the TACE arteriograms. The interventional radiologist and sonographer aimed for consistent anatomical terminology by using the Couinaud set of terminology for the blind reads

throughout this study. The interventional radiologist was blinded to the CEUS examinations results.

RESULTS

Of 69 patients enrolled to date, 13 patients had residual tumors that required retreatment by TACE. Of these, 12 were men and 1 was a woman. The mean age was 65.5 ± 6.6 years (range, 47–71 years). The average body mass index was 28.3 ± 3.7 kg/m² (range, 22.1–33.3 kg/m²). Seven patients were white, 3 patients African American, 2 patients Asian, and 1 patient Hispanic. Ten patients received C-TACE for the initial and retreatment procedures, whereas 2 received DEB-TACE for the initial and retreatment procedures. The final patient received the C-TACE for the initial embolization and DEB-TACE for the retreatment.

Patients included in this study had 1 tumor evaluated with CEUS. The average tumor size was 4.7 ± 2.6 cm (range, 1.9–8.5 cm). Tumor locations included Couinaud segments 2 (n = 2), 4a (n = 2), 4b (n = 1), 5 (n = 1), 6 (n = 1), 7 (n = 3), and 8 (n = 3). In these patients with residual tumor, the sonographer correctly identified 85% (11/13) of the feeding vessels on the post-TACE CEUS examinations. These results are summarized in Table 1. An example of this process is provided in Figure 3.

The correctly identified tumor feeding vessels included the extrahepatic gastroduodenal artery and intrahepatic segment 2, segment 4, segment 7/8 trunk, anterior right, posterior right, segment 5, segment 7 arteries. In 1 patient, the inferior-medial portion of the tumor enhanced during the post-TACE CEUS examination (patient 4). The sonographer was able to trace the blood supply back to the gastroduodenal artery on CEUS (Fig. 4). An MRI performed 2 weeks after the CEUS examination confirmed viable segment 4b tumor. In another case, the residual blood supply was derived from both intrahepatic and extrahepatic vessels (patient 13).

There were two discordant cases in this study. One case consisted of a segment 4a tumor with unconventional vascular supply. Traditionally, a segment 4a tumor is fed by the left hepatic artery. In this particular case, the tumor parasitized a blood supply from the segment 8 branch of the right hepatic artery. The tumor was located in the dome of the liver. Tumor visualization was obscured by overlying lung limiting the sonographer's ability to evaluate tumor viability using CEUS (Fig. 5). The second discordant case consisted of a segment 6 tumor measuring 7.9 cm. For the initial TACE, the interventional radiologist treated an accessory right hepatic artery branch that supplied the majority of the tumor. When the patient was retreated, the interventional radiologist accessed the residual HCC via the anterior right hepatic artery. On CEUS imaging, there was heterogeneous enhancement in the tumor with extensive necrosis, making visualization of the adjacent feeding vessels difficult.

DISCUSSION

In this study, we reported an accuracy of 85% (11/13) using CEUS to identify the feeding vessel in patients with persistent viable tumor after their initial TACE. In all patients, the residual enhancement was clearly visualized by CEUS (100% detection of residual disease).

The decision to retreat was based on the patient's clinically indicated cross-sectional imaging performed 4 to 6 weeks post-TACE and residual tumor enhancement as demonstrated on repeat angiography.

In patients with residual disease, interventional radiologists will routinely perform a second TACE before considering other options.²⁴ Contrast-enhanced ultrasound is an established imaging technique that has many advantages over cross-sectional CT and MRI. It is cost effective, provides real-time imaging, there is no exposure to ionizing radiation, and can yield diagnostic information similar to cross sectional imaging.²⁵ Shaw et al.¹⁷ found accuracy rates of 93% to 100% with CEUS at both 1 to 2 weeks and 1 month after TACE compared with CT and MRI. Contrast-enhanced ultrasound has the potential to identify those in need of retreatment at an early time point than the conventional 4- to 6-week imaging follow-up. Color Doppler imaging was occasionally performed to aid in initial identification of the feeding vascularity. However, research has shown color Doppler to have limited sensitivity to detect blood flow on the perfusion level.²⁵

Although the results are promising, this study has several limitations. A relatively small number of patients were retreated with TACE, thus limiting the sample size. Contrast-enhanced ultrasound of liver tumors was limited in some patients by high BMI, tumor locations high in the dome of the liver, or simply obscured by overlying lung or bowel.

This pilot study demonstrated that CEUS can assist in the evaluation of tumors postembolization, and potentially do so at an earlier time point than conventional imaging modalities. It has also shown a high level of accuracy in identifying the intrahepatic or extrahepatic feeding vessel to the residual tumor. Future work includes validating this technique in a larger patient population and with other locoregional therapies for HCC.

Acknowledgments

This study was sponsored by NIH R01 CA194307. Ultrasound contrast agent was provided by Lantheus Medical Imaging and equipment provided by GE Healthcare. J.R.E. and F.F. report research support and speaker fees from Lantheus Medical Imaging and research support from GE Healthcare. A.L. reports speaker fees and research support from GE Healthcare.

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FIGURE 1.
Study design.

FIGURE 2.

Incomplete HCC embolization with feeding vessel off the right hepatic artery 2 weeks post-TACE treatment. A, Grayscale ultrasound showing a segment 6 HCC tumor (calipers) measuring 7.9 cm (B) Color Doppler image of the right hepatic artery branch (arrow) supplying the residual tumor (C) CEUS image in the early arterial phase 22 seconds postcontrast injection demonstrating branch of right hepatic artery (arrow) feeding the viable portion of the tumor (D) Digital subtraction angiography confirming presence of residual HCC with prominent feeding arterial branch (arrow).

FIGURE 3.

Incomplete HCC embolization with feeding vessel off the left hepatic artery (A) Large segment 2 tumor (calipers) with Color Doppler imaging of the left hepatic artery feeding the caudal portion of the tumor (B) The circle highlighting the tumor and on CEUS an arrow showing early active arterial supply originating from the left hepatic artery (C) Late arterial phase CEUS image at 24 seconds postinjection with visible viable tumor post-TACE treatment fed by the left hepatic artery (D) Cone-beam CT image during retreatment with prominent feeding vessel (arrow) originating from the left hepatic artery supplying the residual tumor deposit.

FIGURE 4.

Incomplete HCC embolization with feeding vessel off the gastroduodenal artery. A, Baseline CEUS examination of a segment 4b tumor measuring 3.7 cm (circle) demonstrating uniform arterial phase hyperenhancement (arrow) 25 seconds postcontrast injection (B) Late arterial CEUS images demonstrating residual viable tumor with a feeding artery (arrow) arising from the gastroduodenal artery. C, Angiography images confirming residual viable tumor with a feeding artery (arrow) arising from the gastroduodenal artery and (D) Angiography images after successful coil embolization of the gastroduodenal artery (arrow) with no active enhancement within the tumor.

FIGURE 5.

False negative CEUS examination. A, CEUS examination before treatment demonstrated a segment 4a tumor measuring 2.1 cm (arrow) with homogeneous arterial phase hyperenhancement. B, CEUS imaging 2 weeks posttreatment demonstrates nodular peripheral enhancement and hyper-enhancement within the medial and distal portions of the tumor, but the specific feeding vessel is unclear. The tumor was adjacent to the right hepatic artery which demonstrated enhancement. However, the patient's lung base obscured portions of the tumor fed by the left hepatic artery. C, Cone-beam CT image obtained during retreatment shows residual blood flow to the tumor (arrow) via the left hepatic artery.

TABLE 1.

Interpretation of Residual Feeding Vascularity

Patient Number	Sonographer Interpretation on CEUS	Interventional Radiologist Interpretation on Angiography	Tumor Size, cm	Tumor Location
1	Segment 5 hepatic artery	Segment 5 hepatic artery	2.1	Segment 7
2	Segments 5, 7, and 8 hepatic arteries	Segments 5, 7, and 8 hepatic arteries	7.1	Segment 7
3	RT hepatic artery	LT hepatic artery	2.1	Segment 4a
4	Gastroduodenal artery	Gastroduodenal artery	3.7	Segment 4b
5	Segments 2 and 4 hepatic arteries	Segments 2 and 4 hepatic arteries	6.1	Segment 2
6	Segment 5 hepatic artery	Segment 5 hepatic artery	2.5	Segment 5
7	RT posterior hepatic artery	RT posterior hepatic artery	1.9	Segment 7
8	Segments 4 and 7/8 hepatic arteries	Segments 4 and 7/8 hepatic arteries	2.4	Segment 8
9	LT medial hepatic artery	LT medial hepatic artery	8.5	Segment 4a
10	Segments 4 and 5 hepatic arteries	Segments 4 and 5 hepatic arteries	5.1	Segment 8
11	RT anterior hepatic artery	RT anterior hepatic artery	2.8	Segment 8
12	Segment 2 hepatic artery	Segment 2 hepatic artery	8.1	Segment 2
13	RT posterior hepatic artery	RT anterior hepatic artery	7.9	Segment 6