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Sonography

# Contrast-enhanced ultrasound identifies early extrahepatic collateral contributing to residual hepatocellular tumor viability after transarterial chemoembolization

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ABSTRACT

The mainstay of treatment for unresectable hepatocellular carcinoma is locoregional therapy including percutaneous ablation and transarterial chemo- and radioembolization. While monitoring for tumor response after transarterial chemoembolization is crucial, current imaging strategies are suboptimal. The standard of care is contrast-enhanced magnetic resonance imaging or computed tomography imaging performed at least 4 to 6 weeks after therapy. We present a case in which contrast-enhanced ultrasound identified a specific extrahepatic collateral from the gastroduodenal artery supplying residual viable tumor and assisting with directed transarterial management.



## Introduction

Initially reported in 1968, microbubble and ultrasound contrast research gained considerable momentum in the late 20th and early 21st century [1]. By 2000, clinical guidelines on the use of contrast-enhanced ultrasound (CEUS) had been established in echocardiography. In 2004, the European Federation of Societies for Ultrasound in Medicine and Biology established similar guidelines for CEUS in hepatology [2]. More recently, CEUS has been applied to pancreatic pathology, alimentary disease, and even extravascular (urinary, lymphatic, biliary, and subcutaneous) examinations [3].

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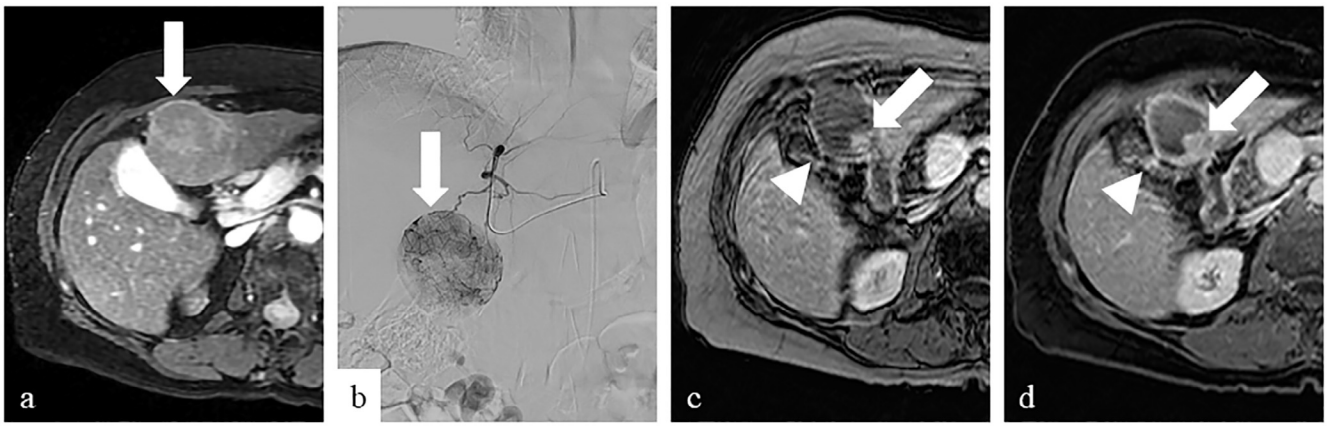


**Fig. 1 – (a) Fat saturated T2 post-contrast sequence magnetic resonance imaging (MRI) depicts a 5.5 cm segment 3/4b hepatocellular carcinoma (arrow). Transarterial chemoembolization of the lesion was subsequently performed (treatment #1). (b) Digital subtraction angiography via the distal left hepatic artery shows an avidly enhancing mass arising from segment 3/4b (arrow). To monitor treatment effect, (c) T1-weighted post-contrast sequence MRI was performed 5 weeks after transarterial chemoembolization and shows a 1.6 cm (arrow) and 1.1 cm (arrowhead) mildly enhancing nodular lesion with (d) persistent enhancement on delayed phase fat saturated T1 sequence. This was initially believed to reflect post-treatment inflammation and the patient was referred for interval MRI.**

In patients with hepatocellular carcinoma, locoregional therapy can be offered for whom surgical resection is not an immediate option [4]. Therapies include percutaneous ablation (chemical or thermal) and transarterial embolization (bland, radiomicrospheres, or chemotherapy) [4]. These therapies may serve as a bridge to transplant [4]. However, assessing treatment effect after locoregional therapy is essential to determining the success of downstaging or need for retreatment. The modified Response Evaluation Criteria in Solid Tumors (mRECIST) guidelines adapted from the American Association for the Study of Liver Diseases provide a standardized language to assess tumor response to locoregional therapy on imaging [5].

CEUS is increasingly being studied as a useful and early adjunct to cross-sectional imaging (computed tomography [CT] or magnetic resonance imaging [MRI]) for monitoring treatment effect [2,3]. Current literature concedes that cross-sectional imaging to evaluate response should be performed at least 4 to 6 weeks after treatment to distinguish viable tumor from postembolization inflammation [6–8]. In addition, the identification and management of residual disease requires an accurate characterization of the tumor vascular pedicle and a failure to appreciate parallel visceral or systemic vasculature can lead to treatment failure and organ damage from nontargeted delivery of embolization agents [9]. However, extra-anatomic (extrahepatic) collateralization to the hepatocellular tumor bed is not uncommon [9]. We report a case in which CEUS characterized a specific extrahepatic collateral to a hepatocellular carcinoma recurrence just 2 weeks after transarterial chemoembolization (TACE) —allowing for targeted management.

## Case report

A 68-year-old male with a known history of hepatitis C related cirrhosis, was diagnosed by CT abdomen with a 5.5 cm segment 3/4b hepatocellular carcinoma. The patient underwent a transjugular liver biopsy that confirmed cirrhosis. A hepatic venous pressure gradient of 13 mm Hg was reported. The patient's Model for End-Stage Liver Disease score was 9 (Child Pugh A).

The patient was referred to interventional radiology for evaluation for locoregional therapy. A preprocedural MRI was performed (Fig. 1a). The patient was prepared for TACE (ultimately TACE treatment #1). The patient underwent digital subtraction angiography (DSA) followed by conventional chemoembolization using a doxorubicin and mitomycin lipiodol suspension via the hepatic arterial segment 3 branch (Fig. 1b). Completion DSA showed sluggish to cessation of flow through the target artery. The patient then underwent an interval liver protocol MRI 5 weeks after TACE (treatment #1) to monitor for treatment effect with initial interpretation felt to be at least partial response by mRECIST criteria (Fig. 1c). Two smaller mildly enhancing lesions (1.6 cm and 1.1 cm) within the treated lesion both persisted on delayed phase (Fig. 1d) and were favored to reflect post-treatment granulation tissue rather than residual tumor disease. A follow-up MRI was recommended.

Follow-up MRI 12 weeks after this last MRI (and a total of 17 weeks after TACE treatment #1) revealed that both lesions now showed unambiguous evidence of arterial enhancement with washout (Figs. 2a and 2b) consistent with viable tumor. No extrahepatic arterial supply was appreciated on MRI. The patient underwent repeat arteriography that demonstrated a supply to the tumor from the segment 4 hepatic artery branch (Fig. 2c). Conventional chemoembolization was performed from this vessel (TACE treatment #2). Completion DSA showed sluggish to cessation of flow through the target artery.

To monitor treatment effect as part of a multicenter clinical trial (NCT02764801) with Institutional Review Board approval, CEUS was performed 2 weeks after this second TACE treatment (Figs. 3a and 3b). CEUS showed tumor viability and

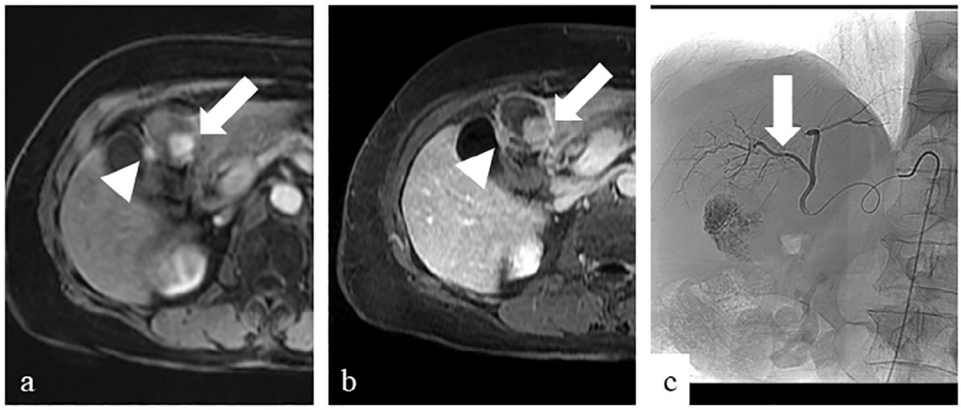


**Fig. 2 – Interval magnetic resonance imaging (MRI) was performed of the lesion 12 weeks after the last MRI (a total of 17 weeks after transarterial chemoembolization treatment #1) to monitor for residual tumor viability. (a) Fat saturated T1 post-contrast sequence MRI shows 2.3 cm (arrow) and 1.1 cm (arrowhead) arterially enhancing lesions (previously 1.6 cm and 1.1 cm) with unambiguous evidence of washout on (b) delayed phase fat saturated T1 sequence. Highly suggestive of residual tumor viability, the patient was taken back for transarterial chemoembolization (treatment #2). (c) Digital subtraction angiography depicts the left hepatic artery and selection of the medial segment (arrow) for intra-arterial treatment.**

perfusion via an extrahepatic collateral that was traced to the gastroduodenal artery (Fig. 3b). An MRI was performed 2 weeks after CEUS (a total of 4 weeks from the second TACE treatment) confirming arterial enhancement with continued washout of both lesions (Figs. 4a and 4b) consistent with stable disease by mRECIST criteria. Consequently, the patient was brought back for repeat treatment angiography and underwent coil embolization of the gastroduodenal artery (Figs. 4c and 4d) along with percutaneous ethanol injection of the tumor bed. Subsequent MRI (Figs. 5a and 5b) 1 week postcoil embolization showed complete regression of the larger lesion (partial response by mRECIST criteria owing to persistence of the smaller nodule). The tumor was successfully down-staged in preparation for potential liver transplantation.

## Discussion

In this patient, CEUS provided key information regarding both residual tumor viability and a specific collateral that was maintaining tumor perfusion. As noted, parasitized collateral arterial supplies can be a source failure of locoregional control [10]. Risk factors for the development of extrahepatic collateralization

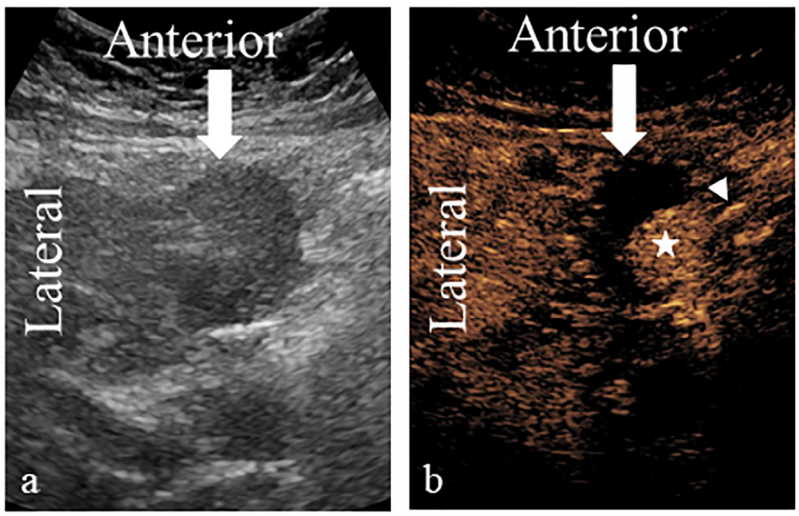


**Fig. 3 – Two weeks after transarterial chemoembolization treatment #2, contrast-enhanced ultrasound was performed to monitor for residual tumor viability as part of an experimental protocol. (a) Grayscale hepatic ultrasound demonstrates a heterogeneous hypoechoic tumor (arrow). (b) Contrast-enhanced hepatic ultrasound demonstrates post-treatment cavity (arrow) and presence of vascular residual tumor (star). Traceable extrahepatic collateral is identified (arrowhead). This was traced back to the gastroduodenal artery.**

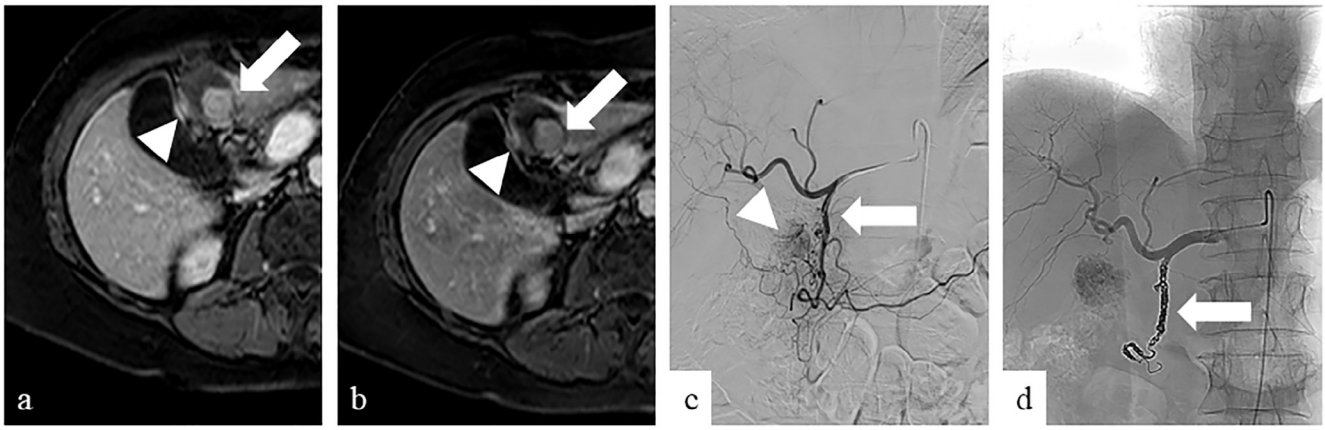


**Fig. 4 – Four weeks after transarterial chemoembolization treatment #2, magnetic resonance imaging was performed as part of our institutional standard-of-care to monitor for residual tumor viability. (a) Fat saturated T1 post-contrast sequence magnetic resonance imaging shows continued evidence of 2.2 cm (arrow) and 1.0 cm (arrowhead) arterially enhancing lesions (previously 2.3 cm and 1.1 cm) with washout on (b) delayed phase fat saturated T1 sequence. The patient was brought back to the interventional suite for additional treatment. (c) Digital subtraction angiography via the gastroduodenal artery demonstrates collateralization from the gastroduodenal artery (arrow) to the inferomedial portion of the tumor bed (arrowhead). (d) Angiography via the common hepatic artery shows successful coil embolization of the gastroduodenal artery (arrow) and no tumor enhancement.**

include tumor size (greater than 5 cm), tumor location (peripheral or nonperitonealized or exophytic extension), and hepatic artery attenuation (from intervention or tumor biology) [10,11]. Other commonly identified sources of aberrant hepatic tumor vascularization include the right inferior phrenic, omental branches, right internal mammary, right intercostal arteries, right renal or adrenal arteries, and the superior mesenteric artery [11]. In fact, the most commonly identified extrahepatic feeding vessels identified are the inferior phrenic artery (owing to the bare area of the liver) and omental branches (for exophytic masses) [11].

Post-treatment surveillance by MRI or CT is frequently delayed by at least 4-6 weeks after each treatment cycle to allow for maturation of granulation tissue, limit lipiodol-associated artifacts, and help separate viable tumor from postembolization inflammation [6,12]. In fact, treatment artifact may last for as long as 3 months [6,12]. Utilizing CEUS, tumor viability via a specific extrahepatic collateralization was appreciated in this patient within just 2 weeks after treatment, confirming the need for retreatment and assisting with planning.

CEUS is particularly suited for the vascular assessment of the viability of lesions. Contrast agents used in CEUS are

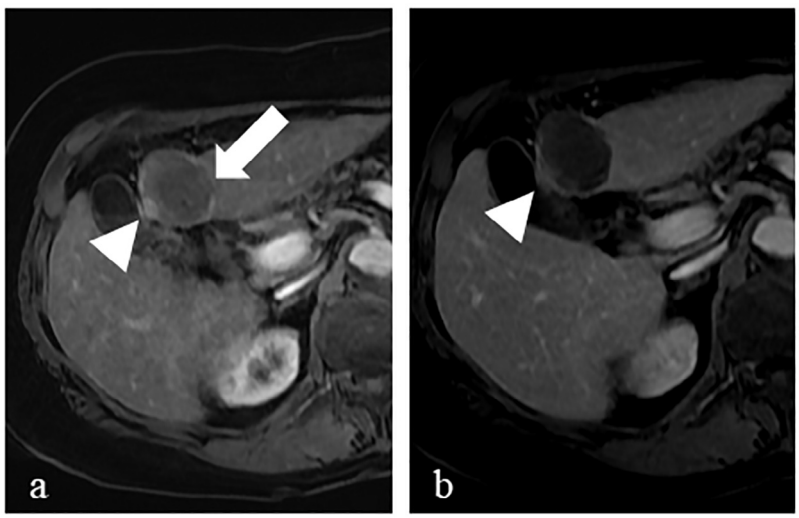


**Fig. 5 – One week after bland coil embolization of the gastroduodenal artery and ethanol ablation of the tumor, magnetic resonance imaging was again performed to monitor for residual tumor viability. (a) Fat saturated T1-weighted post-contrast sequence magnetic resonance imaging shows regression of the larger nodular lesion within the inferomedial treatment cavity (arrow) with persistence of the smaller 1.1 cm lesion (arrowhead) with washout (of the smaller lesion) on (b) delayed fat saturated T1 sequence.**

microbubbles of gas stabilized by a protein, lipid or phospholipid shell and approximate the size of circulating red blood cells [13,14]. They remain in the intravascular space until cleared by the lungs via exhalation—unlike CT and MRI contrast agents which can distribute into the interstitial space [15]. Furthermore, by establishing a difference in acoustic impedance between the surrounding tissues, ultrasound contrast agents improve signal enhancement within active vessels by up to 25 dB [14].

Additionally, CEUS has several advantages over cross-sectional imaging. Ultrasound contrast agents are not hepatotoxic or nephrotoxic [2]. There is no ionizing radiation exposure. There is no contraindication to imaging in patients with metallic implants. Compared with MRI, imaging is much more rapid and less anxiety-provoking to the patient. Finally, hepatic evaluation via CEUS may have a lower cost than MRI and CT [16].

However, notable limitations exist with CEUS examination. Ultrasound is operator-dependent with noted inter- and intrareader variability [12]. This may be emphasized in cases of limited examination (such as with obese body habitus) or multiple nontarget tumors [17]. New lesions may be missed [17]. It is not yet easily feasible to interrogate the entire liver (instead only known areas of interest) through all vascular phases with CEUS, unlike cross-sectional imaging [2]. Lesions that are exceedingly deep, anatomically obscured by the diaphragm or lung, or hypovascular may also be challenging to characterize by CEUS [2,18]. Additionally, interpretation of hepatic CEUS can be complicated in patients with cirrhosis because of heterogeneous parenchymal enhancement [2,17].

In this clinical case, CEUS not only showed early evidence of residual disease after TACE but also identified a specific collateral of concern. While certainly creating a comprehensive vascular roadmap with CEUS in the absence of cross-sectional imaging would be inordinately challenging, the benign safety profile of ultrasound contrast agents in combination with the potential for real-time imaging with sonography has spurred significant research interest [17,19–21]. Increasingly powered prospective randomized controlled trials are currently being performed and will add value to the limited body of literature on the role of CEUS in TACE treatment monitoring in hepatocellular carcinoma.

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