

Contrast enhanced ultrasound guided biopsies of liver lesions not visualized on standard B-mode ultrasound – preliminary experience

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Background: To assess the technical success of contrast enhanced ultrasound (CEUS) guided biopsies of liver lesions poorly visualized on B-mode ultrasound.

Methods: Patients were selected during the procedure based on the real-time clinical scenario of unsatisfactory B-mode ultrasound lesion visualization and all patients would have otherwise undergone CT guided liver lesion biopsy. A total of 26 patients underwent CEUS guided biopsy and were included in this retrospective analysis. The review of the patients' files included demographic information, lesion characteristics on imaging, procedural details and pathology outcome. Technical success was defined as concordance between the radiological findings, pathology report and clinical follow-up—demonstrating lack of need for re-biopsy or re-biopsy with identical pathological results. Patients with less than 2 months follow-up were excluded from the study.

Results: CEUS guided liver biopsy was successful in 23 out of 26 patients (88.5%). The average procedure time was 30.7±12.3 minutes and the average lesion size was 2.2±1.7 cm. The majority of lesions (80.8%) were hypoechoic on the delayed phase of CEUS. The mean number of samples taken from each lesion per procedure was 3.2 (±1.7).

Conclusions: CEUS guidance biopsies of focal liver lesions (FLL) that were difficult to visualize on B-mode ultrasound demonstrated high success rate and may be an evolving image guidance modality in selected patients to avoid CT guided procedures.

Keywords: Contrast-enhanced ultrasonography (CEUS) guided interventions; liver lesions

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Introduction

Distinguishing benign from malignant focal liver lesions (FLL) is crucial in determining prognosis and patient management (1). Although FLL can be characterized to a certain extent based on ultrasound and cross-sectional

imaging (2), histological pathology from tissue biopsy remains the diagnostic gold standard to determine patient management (3-6). Furthermore, subsequent management with targeted cell therapy may require tissue acquisition for genetics analysis. Imaging modalities used for guidance

of liver biopsies are primarily B-mode ultrasound (US) and computed tomography (CT). B-mode US is the preferred modality for image guided liver lesion biopsy. Compared to US, CT is less frequently used for visualization during biopsy due to concerns about radiation exposure, lack of real time imaging which extends procedure time, and increased costs (7). However, guidance by B-mode US can be challenging due to lack of visualization of FLL that are slightly hyperechoic, hypoechoic or isoechoic to surrounding liver parenchyma. In such cases, B-mode US guided hepatic biopsy has been shown to produce low diagnostic yield (1,8-10) and per current standard these patients need to undergo a CT guided procedure.

Contrast enhanced ultrasound (CEUS) is an evolving technique and involves intravenous administration of microbubble contrast agents which has the potential to improve real-time US guided FLL characterization and biopsy. Studies have demonstrated that CEUS is capable of increasing sensitivity and specificity in detection of malignant hepatic masses compared to B-mode US, citing its advantages in capturing liver perfusion phase patterns to better delineate lesion borders from the surrounding parenchyma (11-17). This led to approval of one US contrast agent for characterization of FLL in adult as well as pediatric patients by the U.S. Food and Drug Administration in April 2016 (18). A very limited number of studies however have investigated the value of CEUS guided procedures. The major potential benefits of CEUS in comparison to B-mode US are higher detection rate of poorly visible lesions, decreased number of samples required and avoidance of sampling necrotic areas of larger liver lesions (1,19-21).

In this retrospective analysis we report our institutional experience with CEUS guided liver biopsy of FLL not well visualized on B-mode US. The patients were selected based on a real-time clinical scenario during the procedure when lesions were poorly visualized on standard B-mode ultrasound. These patients would have otherwise been rescheduled for a CT guided procedure. The purpose of the study was to assess the technical success of CEUS guided biopsies of liver lesions poorly visualized on B-mode ultrasound.

Methods

Subjects

This retrospective study was approved by the local institutional review board of our hospital and the study was HIPAA

compliant. The charts and images of 26 patients that underwent CEUS guided liver biopsy were systematically reviewed. All the patients were selected for the procedure based on prior FLL characterization on cross-sectional imaging demonstrating suspicious features (contrast CT or MRI). They had suboptimal lesion visualization on initial B-mode US and met clinical criteria to undergo CEUS guided liver lesion biopsy based on a real-time clinical scenario. These were all patients who were brought back to the ultrasonography procedure room and if CEUS guided biopsy would have not been available, these patients would have had to be rescheduled for CT guided biopsy on another day. Exclusion criteria included less than 2 months of follow-up due to inability to determine technical success rate and cases in which the entire procedure was performed under fusion of US with CT or MRI without substantial involvement of CEUS guidance.

CEUS guided biopsy

CEUS guided biopsy was performed under moderate conscious sedation using Fentanyl and Versed or under general anesthesia. In all patients, either Definity (Lantheus Medical Imaging; composed of perflutren lipid microspheres) or Lumason (Bracco Imaging; composed of sulfur hexafluoride lipid microspheres) were injected intravenously as a single bolus within approximately 20 seconds, followed by a 10 mL saline flush through a peripheral upper extremity vein. The dosage of contrast material ranged between 0.8 and 1.0 mL for Definity or between 2.4 and 4.8 mL for Lumason. After lesion localization, biopsy was performed using a 17 G co-axial system with an 18 G Temno Evolution biopsy device (Allegiance, McGaw Park, IL, USA).

Study parameters

Each case was analyzed individually in regards to the following parameters: demographic information, contrast material used, lesion size and location, FLL appearance on standard B-mode US and on CEUS, procedural technical details, the pathology outcome and technical success. The appearance on CEUS is related to the delayed phase since this phase is crucial when performing CEUS guided procedures. Success was defined as conclusive histopathological diagnosis concordant with imaging appearance and clinical follow-up—without need for re-biopsy, or re-biopsy with identical pathological results.

Results

Twenty-six patients were included in our study, 16 males and 10 females. The average age was 62.1 (± 17.3) years. Seven patients (26.9%) had cirrhosis due to different etiologies. All of the patients had clinical follow-up of at least 2 months and the mean follow-up period was 7.1 (± 4.6) months. The average procedural time recorded was 30.7 (± 12.3) minutes. All patients tolerated contrast agent administration well without side effects. Definity was used as contrast material in 19 patients (73%). The remaining seven patients (27%) received Lumason. The mean number of samples taken from each lesion was 3.2 (± 1.7).

Eleven lesions (42.3%) were invisible on B-mode US and the remaining lesions were poorly visualized. Twenty-one of the lesions (80.8%) were predominantly hypoechoic on the delayed phase of CEUS. The average lesion largest dimension was 2.2 (± 1.7) cm. In 18 patients (69.2%) the lesion diameter was smaller than 2 cm. Demographic data of the patients and lesion characteristics are listed in *Table 1*.

Pathology results revealed a malignant neoplasm (HCC or metastasis) in 15 cases (57.7%). The pathology outcome of the patients is listed in *Table 2*. Procedural success was achieved in 23 cases (88.5%), demonstrating concordance between the pathology results and the clinical and imaging follow-up. In the three unsuccessful cases, the pathology result showed no evidence of malignancy but the follow-up imaging or repeated biopsy procedure revealed different findings. Thus in these three cases a re-biopsy was needed and therefore CEUS guided biopsy failed to reveal the final pathology to determine further patient management. Biopsy pathology outcome, procedural details and technical success are listed in *Table 2*. Representative examples from four patients (patients #4, #5, #21, #24) are presented as *Figures 1-4*.

Discussion

CEUS for FLL involves intravenous injection of a microbubble contrast agent, in order to delineate the lesion from the surrounding liver parenchyma. In this study we administered Definity (Lantheus Medical Imaging, N. Billerica, MA, USA) and Lumason (Bracco Imaging, Monroe Township, NJ, USA). Definity is a second-generation US contrast agent consisting of lipid-stabilized perflutren microbubbles that act as a blood pool agent and true intravascular tracer, essentially not accumulating in the liver parenchyma. After activation of its component lipid microspheres by shaking the vial, Definity can be

administered over approximately 10 to 30 seconds followed by 10 mL of IV saline flush, usually over 10 seconds. Lumason is a blood pool contrast agent composed of sulfur hexafluoride microbubbles with a phospholipid shell. During US imaging, a single 2.4 mL bolus of Lumason with 5 to 10 mL saline is injected and followed with IV saline push; a second Lumason 2.4 mL bolus may be given as clinically deemed necessary (21-23).

Multicenter studies have shown that ultrasound contrast agents have an excellent safety profile with incidence of serious adverse events ranging from 0.0086% to 0.031% (24-27). Furthermore, these contrast agents do not pose nephrotoxicity risks as they are fully excreted via the respiratory tract (28-30). This is particularly useful when considering that some patients with malignant FLL may require nephrotoxic iodine-based contrast agents at some point for liver-directed angiography based treatment.

Despite the cost and safety advantages of US as a guidance modality for percutaneous FLL biopsy, one of its drawbacks is the lack of consistency in accurate lesion visualization. Studies have shown deficiencies in B-mode US guided liver biopsies, as sensitivities for metastatic liver lesions were as low as 41% (9). Another study showed that the procedural success rate for liver biopsy after a single puncture pass was 23.4% with B-mode US, compared to 43.0% with CEUS (1) and that up to 30% of lesions were unable to be visualized on pre-treatment US for HCC (10). Therefore CEUS may be helpful to increase biopsy yield by superior visualization as shown in this study.

Several studies have suggested that administration of a contrast agent in patients with poorly visible hepatic lesions on US may improve diagnostic accuracy and reduce the number of puncture passes required to obtain a specimen for pathological diagnosis (1,19-21). These researches presented similar success rates in comparison to our results. A series by Schlottmann *et al.* demonstrated a success rate of 92% of CEUS guided liver biopsies (20). Yoon *et al.* showed a sensitivity of 88% for CEUS guided biopsies in the detection of liver malignancy (21). Sparchez *et al.* compared CEUS and conventional ultrasound guidance in percutaneous biopsies of liver tumors and showed an increased sensitivity of procedures performed under CEUS guidance, especially in large and poorly visible lesions (19). The technical success rate in our study was 88.5% and it needs to be considered that these were all selected patients which were not candidates of B-mode ultrasound guided biopsy because of lack of lesion visualization.

In this paper, we report our preliminary experience with

Table 1 Demographic data and lesion characteristics on an individual basis

Patient number	Age	Gender	FLL segment	Largest FLL dimension (cm)	Appearance on B mode US	Appearance on CEUS
#1	25	F	4A	4	Hyperechoic	Hyperenhancing
#2	61	F	6	1.5	Invisible	Hypoehancing
#3	84	F	6	1.5	Invisible	Hypoehancing
#4	53	M	4A	1.8	Hypoechoic	Hypoehancing
#5	69	M	7	1.6	Invisible	Hypoehancing
#6	54	M	7	1.9	Subtle hypoechoic	Hypoehancing
#7	79	M	7	1.3	Subtle hypoechoic central hyperechoic area, calcification	Hypoehancing
#8	51	M	6	1.1	Invisible	Hypoehancing
#9	34	F	4B	0.9	Invisible	Subtle hypoehancing
#10	75	M	8	1.1	Invisible	Hypoehancing
#11	81	F	4A	1	Subtle hyperechoic	Mixed, predominately hypoehancing with central hyperechoic
#12	74	M	6	4.4	Mixed predominately hyperechoic with central hypoechoic	Hypoehancing-delayed
#13	42	F	8	1.4	Invisible	Subtle hypoehancing
#14	64	M	4A	1.6	Invisible	Hypoehancing
#15	54	F	4A	2.1	Subtle hypoechoic	Hypoehancing
#16	66	M	4A	2.4	Invisible	Hyperenhancing, with peripheral hypoechoic rim
#17	69	M	4A	1.5	Hypoechoic	Ring enhancement with a hypoehancing center
#18	82	M	6	4.2	Invisible	Mixed, predominately hypoehancing
#19	83	M	4A	1.8	Hypoechoic	Hypoehancing
#20	65	F	3	1.8	Invisible	Mixed, predominately hypoehancing
#21	66	M	5	1.5	Mildly Hypoechoic	Hypoehancing
#22	25	F	8, 5, 4B	7.6	Poorly defined isoechoic	Mixed, predominately hypoehancing
#23	62	M	7	6.5	Mildly hyperechoic	Hypoehancing
#24	74	M	4A	2	Hypoechoic	Hypoehancing
#25	43	F	4A	0.9	Invisible	Hypoehancing
#26	80	M	2	0.9	Hypoechoic	Hyperenhancing

FLL, focal liver lesion; CEUS, contrast enhanced ultrasound; M, male; F, female.

CEUS guided biopsies of FLL that are poorly visualized on standard B-mode US based on a retrospective analysis. The decision to perform CEUS was made in the procedure suite based on clinical criteria. The alternative to a CEUS guided intervention under these circumstances, would have

been a CT guided approach, therefore these cases can be considered challenging. Our method of patient selection mimicked a realistic clinical work flow, where only cases that failed under standard B-mode ultrasound were selected for CEUS guided procedures. This meant that only more

Table 2 Pathology outcomes of the patients

Pathological diagnosis	No. [%]	Rate of procedural success
Hepatocellular carcinoma	6 [23]	6/6
Metastatic adenocarcinoma	8 [31]	8/8
Lymphoma	1 [4]	1/1
Hepatitis/non-specific liver injury	6 [23]	5/6
Normal liver parenchyma	5 [19]	3/5

complex cases were included in this study.

CEUS guided biopsy was successful in 23 out of 26 cases (88.5%) in obtaining a diagnostic specimen concordant with imaging and clinical follow-up. Meanwhile the unsuccessful cases (3/26, 11.5%) demonstrated no signs for liver malignancy on pathology, which was discordant with prior (CT/MR) imaging findings and follow-up, and therefore future re-biopsy was decided to be clinically necessary to determine further patient management.

This study has several limitations. The relatively small

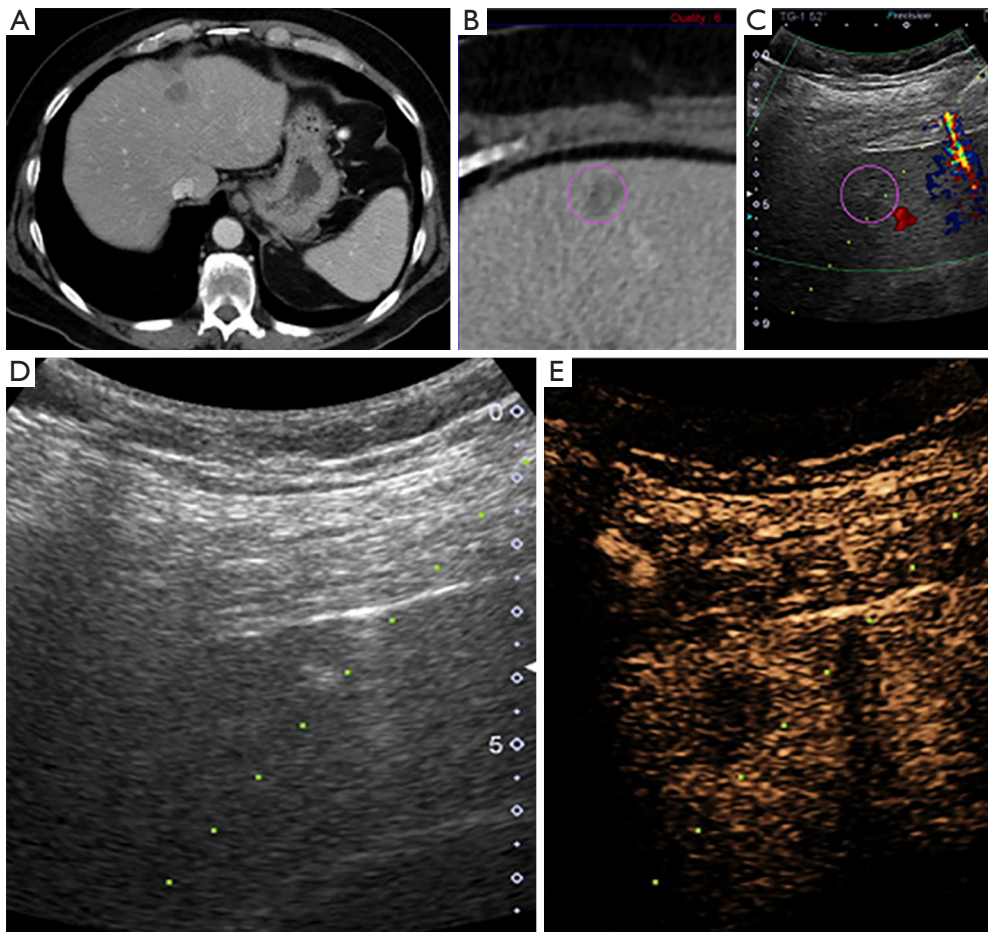


Figure 1 Patient #4. A 53-year-old male with metastatic colorectal carcinoma presented with a new hypodense liver lesion in segment 4A on CT, measuring 1.8×1.5 cm (A); CT/US fusion was attempted but did not significantly improve lesion visualization (B,C); the lesion revealed to be mildly hypoechoic on B-mode ultrasound (D); after intravenous Definity contrast administration, the lesion demonstrated lower enhancement on the delayed phase in comparison to the surrounding liver parenchyma, making it clearly visible and facilitated biopsy (E). Pathology demonstrated metastatic adenocarcinoma consistent with colonic primary.

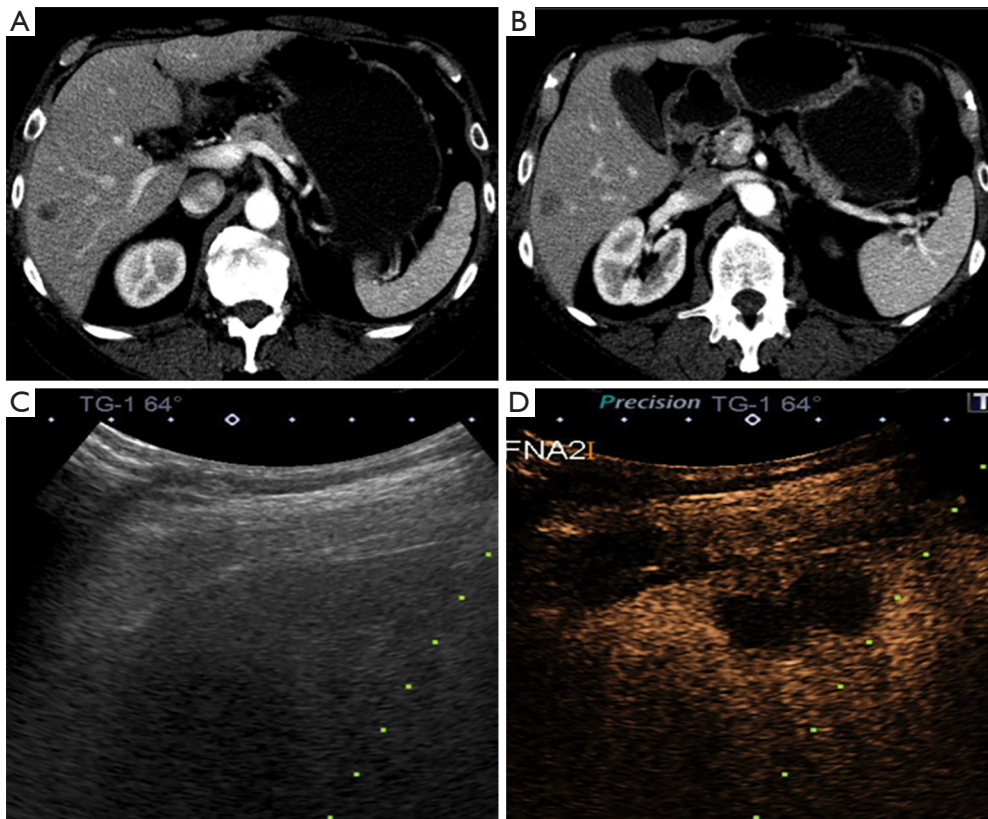


Figure 2 Patient #5. A 69-year-old male with a history of hepatitis C and HCC, presented with two heterogeneous predominantly hypodense new liver lesions in segments 5 and 7 on CT (A,B), which were not visualized on B-mode ultrasound (C); the lesion in segment 5 measured 1.8 cm and the lesion in segment 7 measured 1.6 cm. After contrast administration, the lesions were well demarcated from surrounding enhancing parenchyma and both lesions showed irregular margins without significant contrast enhancement (D). CEUS guided biopsy was performed for the 1.6 cm lesion located in segment 7. Pathology demonstrated malignant cells compatible with poorly differentiated adenocarcinoma. HCC, hepatocellular carcinoma; CEUS, contrast enhanced ultrasound.

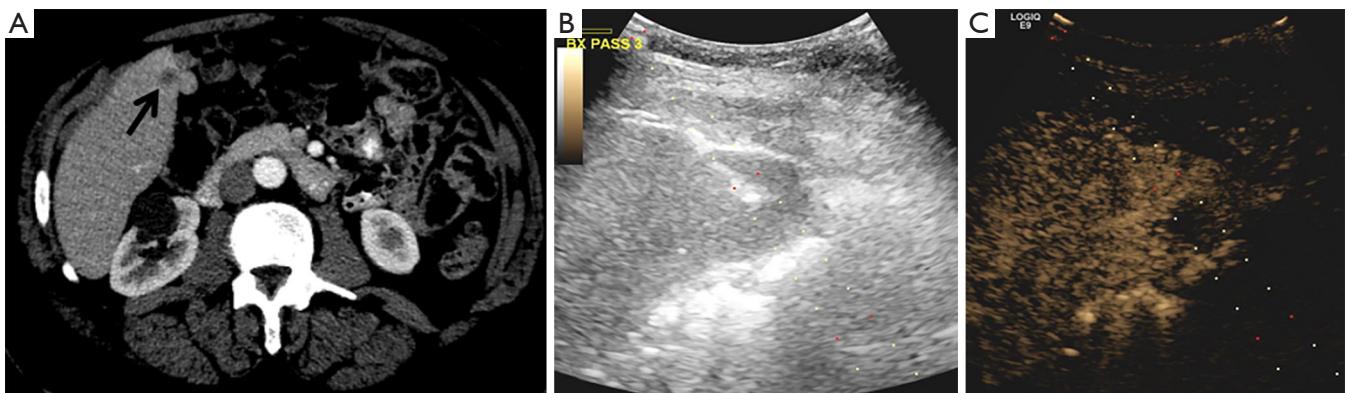


Figure 3 Patient #21. A 66-year-old male with history of gastric adenocarcinoma presented with a new hypodense lesion in segment 5 of the liver based on CT (A); on B-mode US the lesion is mildly hypoechoic and almost invisible (B); after contrast injection, the lesion is hypoenhancing with clear delineation of the lesion borders (C). Pathology confirmed metastatic disease from gastric adenocarcinoma.

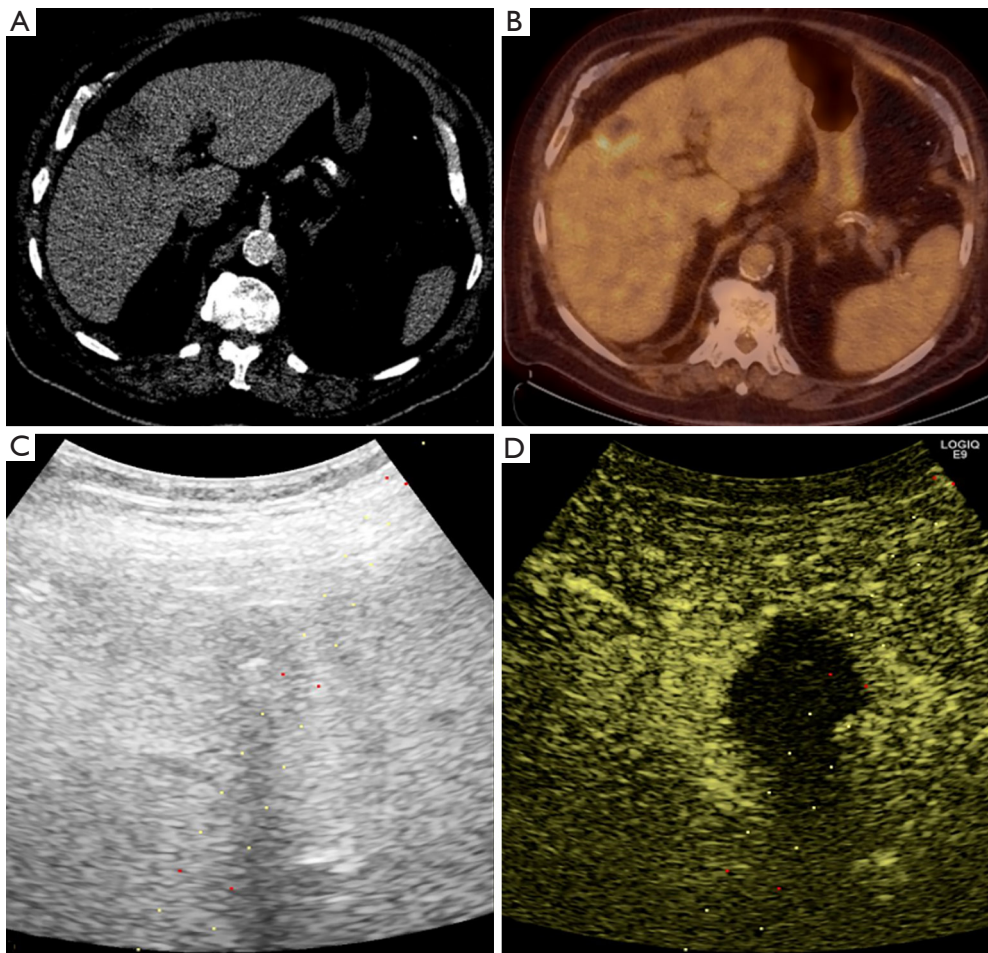


Figure 4 Patient #24—a 74-year-old male with history of hepatocellular carcinoma and colorectal carcinoma. Patient underwent radiofrequency ablation of a liver lesion in segment 4A previously, and now came back with suspected local recurrence. The ablation area is visible on CT (A) as a hypodense area; FDG-PET/CT (B) demonstrates mild peripheral metabolic activity; on B-mode US the lesion appears as subtle hypoechoic (C) and after contrast injection the area is hypoechoic with superior delineation of the lesion borders (D). Pathology excluded recurrent disease and this is concordant with the imaging findings of a hypodense FLL on CT with mild peripheral hypermetabolism on FDG-PET/CT. FLL, focal liver lesions.

number of subjects was related to our institutional approach to select only challenging cases for CEUS guided biopsy as opposed to have every consecutive patient undergo CEUS guidance including cases which we were able to perform with regular B-mode ultrasound. This reflects a representative sample of lesions that truly required CEUS for better imaging guidance in a real-life clinical scenario. Another limitation is that there is inevitable subjectivity in evaluating FLL visualization on B-mode US due to lack of quantitative parameters. Furthermore, our study design was retrospective and thus we did not have a control group with which to compare study parameters. Prospective studies

with a control group are warranted to confirm the results of this study and develop selection criteria for patients with FLL requiring tissue diagnosis.

In summary, this retrospective study demonstrated that in selected cases the addition of contrast enhancement to US can improve technical success rate and facilitate FLL guided biopsy in selected patients with poorly visualized FLL on standard B-mode US. In the past these selected patients would have undergone CT guided FLL biopsy. A larger prospective study is warranted to confirm these results and to develop criteria in which subjects CEUS guided FLL biopsy is advisable.

Acknowledgements

None.

Footnote

Conflicts of Interest: The results of the paper were partially presented as oral talk at the Society of Interventional Radiology 2017 Annual Meeting in Washington, DC in March 2017 and at the Digestive Disease Intervention Meeting 2016 in San Diego, CA in October 2016.

Ethical Statement: This study was approved by the institutional review board of University Hospitals Cleveland Medical Center (IRB No. 06-16-31). A waiver of informed consent was granted due to the retrospective fashion of the study.

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