

Usefulness of Contrast Enhanced Ultrasound Guidance in Percutaneous Biopsies of Liver Tumors

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Abstract

The performance of percutaneous echoguided biopsy in hepatic tumor diagnosis is limited by several factors, among which tumor characteristics such as tumor type, size and location play an important role. With all the advantages offered by ultrasound guidance, the overall sensitivity of this method in the tumor diagnosis has remained around 90%. Contrast enhanced ultrasound (CEUS) guided percutaneous biopsy is a new developed technique aimed at increasing the accuracy of percutaneous biopsies. With new ultrasound devices comprising the split-screen mode, which displays both the CEUS and background B-mode US image simultaneously on a single monitor, the procedure is now technically feasible. CEUS guided percutaneous liver biopsy should be applied in large tumors with consistent necrosis, in hypovascular tumors or in those invisible or poorly visible to conventional ultrasound. An increased accuracy was demonstrated in poorly visible or invisible hepatic lesions and when CEUS was used before biopsy.

Key words

Hepatic tumors – percutaneous echoguided biopsy – contrast enhanced ultrasound.

Current state of knowledge

In patients suffering from neoplasia (particularly those with advanced forms) detailed information on the tumor histology is necessary to offer evidence supporting the decision of a proper treatment such as chemotherapy. This becomes even more important when initiating certain new molecular or gene oncological therapies. In such cases, the tumor diagnosis is based on the histological data offered

by the tumor fragment, sampled usually by means of a percutaneous needle biopsy.

In spite of dramatic improvements in imaging and tumor markers in oncology over the last years, percutaneous liver biopsy continues to be used for tumor diagnosis. With all the advantages offered by ultrasound guidance, the overall sensitivity of this method in the diagnosis of liver tumors has remained around 90% [1]. Consistent progress has been made in the last years in terms of needle design [2] or ultrasound methods with a complementary role in guidance (Color or Power Doppler, 3D/4D ultrasound, navigation systems) [3-5].

The performance of percutaneous guided puncture biopsy in liver tumors is limited by several factors, among which tumor characteristics such as tumor type, size and location play an important role. Such performances are lower for large tumors due to the existence of tumor necrosis or fatty changes. Necrotic tissue cannot be identified on B-mode sonography, especially before liquefaction has occurred, possibly leading to an unsuccessful biopsy or a false-negative diagnosis [6]. In larger lesions, biopsy is performed therefore in the peripheral zone or a hypervascular area of the tumors.

Due to the difficulties in visualization and targeting, small lesions represent another cause of false negative result of percutaneous biopsy. Lesions which are deeply located (in posterior segments of the liver) or those in locations with risk for biopsy (i.e. near vascular structures, gallbladder, and colon) and those with low visibility on B mode ultrasound are also responsible for failures or an increased complication rate [6, 7].

Peculiarities of some liver tumors, where lesions are often invisible or poorly visible in B mode ultrasound (small liver metastasis or isoechoic hepatocellular carcinomas) require the use of several passages to target the lesions or contrast enhanced methods like CT or MRI to image the lesion. This approach inevitably increases costs, risk of complications and a degree of acceptance by the patient.

Contrast harmonic ultrasound and reasons for performing CEUS guided biopsy

Ultrasound harmonic imaging with 2nd generation

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contrast agents (SonoVue) (CEUS) has the capacity of emphasizing the macro and above all the microvascularization of various parenchyma and tumors. Beside the well accepted use in detection and characterization of various tumors, especially those located in the liver, the use of this technique has enabled the delimitation of the avascular, necrotic areas from the viable, active, vascularized regions of the tumors. The differentiation of viable from necrotic tumor areas is possible by depicting ring like enhancement or bolus enhancement in the arterial phase and contrast material washout in the portal or parenchymal phase. The necrotic areas usually present no enhancement in all vascular phases of CEUS and may appear echo free or slightly hypoechoic on the background of enhanced liver parenchyma.

First data published in the literature have reported that by using CEUS it may be possible to increase the accuracy of percutaneous needle biopsy in tumor diagnosis by targeting hyperperfused tumoral areas or increasing the conspicuity of liver metastasis. In these first reports the procedures were performed after injection of Levovist (Schering AG, Germany), a first generation contrast agent using pulse inversion harmonic imaging and stimulated acoustic emission [8-10].

Technique of CEUS guided liver biopsy

CEUS guided liver biopsy is performed using an ultrasound system capable of scanning at low MI (0.06-0.1) and a convex 2-5 MHz transducer for abdominal applications. An attached needle guide is not mandatory but should be used especially for biopsies performed in the arterial phase.

When using hexafluoride microbubbles (SonoVue, Bracco, Milan, Italy) a two-step algorithm may be used. Prior to the biopsy procedure the ultrasound contrast agent is prepared according to the manufacturer's recommendations (4.8 mL total) and a vial is divided into two doses of 2.4 mL each. Typically, the first dose is injected intravenously for the preprocedural planning CEUS and the second dose is used for the CEUS-guided biopsy. Each dose is immediately followed by a 10 mL normal saline flush [11, 12].

Using the 2-5 MHz transducer, imaging is performed in a split-screen mode, which displays the CEUS image on the right side and the background B-mode US image on the left side, simultaneously, on a single monitor. The mechanical index is usually set to 0.06-0.1. Focus is positioned at the bottom of the screen to minimize microbubble destruction. Field of view and gain were optimized to provide the clearest depiction of the lesion.

Preprocedural planning CEUS

The first dose is aimed at characterizing the target lesion in the arterial phase (10-30 seconds after injection) regarding the presence of hypervascular, hypovascular or avascular areas and to select a zone for biopsy. For liver tumors, scanning in portal (30-120 seconds after injection) and parenchymal phase (120-600 seconds after injection) is important to detect invisible or poorly visible lesions, to

characterize them and to select a proper one for a subsequent CEUS biopsy. Moreover, it is important to locate the target lesion with reference to surrounding intrahepatic anatomical landmarks, to measure the diameter and depth of the lesion, plan a safe needle trajectory, and rehearse the biopsy procedure, including the instruction to the patient to suspend respiration [11, 12].

CEUS guided biopsy procedure

After the skin is sterilized the predicted needle path is anesthetized with 2% lidocaine. Prior to the intravenous injection of the second dose of SonoVue, the needle is inserted into the biopsy guide and the skin entry. When the lesion begins to clearly appear following the contrast agent injection, the needle is advanced, via either an intercostal or subcostal approach.

In cases where large unenhanced areas are found on the planning CEUS, the needle is directed in the arterial phase into the enhanced, perfused areas. For poorly visible tumoral lesions in B mode ultrasound, the biopsy is performed in the parenchymal phase when the lesions wash out and the tissue to lesion contrast ratio is maximal.

The biopsy needles are clearly visible under CEUS conditions due to the fact that the needle causes tissue motion in the vicinity of the needle which generates harmonic signals, detected by the transducer. For automatic TruCut needle (i.e. Bard type) the presence of air in the side notch is easily visible after the automatic tissue retrieval [11]. Sometimes, the bright contrast enhancement in the surrounding parenchyma masks the echogenic biopsy needle in the CEUS image [12].

One technical difficulty is related to the short period of arterial enhancement available for puncture. If the tip of the needle is lost it may take some time to find it and to perform the biopsy without losing the arterial enhancement. This limitation may be overcome by the use of needle guides and an appropriate selection of the needle path in the planning of the CEUS.

Indications and results of CEUS guided liver biopsy for tumor diagnosis

The potential added value of CEUS in the diagnosis of liver tumors by means of percutaneous biopsy may be related to several factors:

a) targeting of the needle in the vascular, viable areas of tumors [8];

b) avoiding avascular areas (necrosis) in larger hepatic tumors, especially those with frequent necrosis such as metastases arising from colon or renal cancer (Fig.1) [8, 13, 14]. In the course of tumor development or after chemotherapy, the center of the tumor is often necrotised. The necrotic regions appear echofree or slightly hypoechoic in the background of enhanced liver parenchyma and can not be differentiated from the viable tumor.

After percutaneous ablative treatments for HCC or metastases, recurrences are possible. These new tumors are located around the treated area, are often large and can

not be differentiated from the treated, necrotic area using B mode sonography. (Fig.2). In certain conditions, in order to start a systemic therapy (e.g. with Sorafenib) a biopsy may be required.

CEUS has the advantage of depicting the viable portion that presents either a bolus or ring like enhancement in the arterial phase and washout in the portal or parenchymal phase and can guide a needle inside to sample a tissue specimen. The necrotic regions usually present with no enhancement in all vascular phases of CEUS [15];

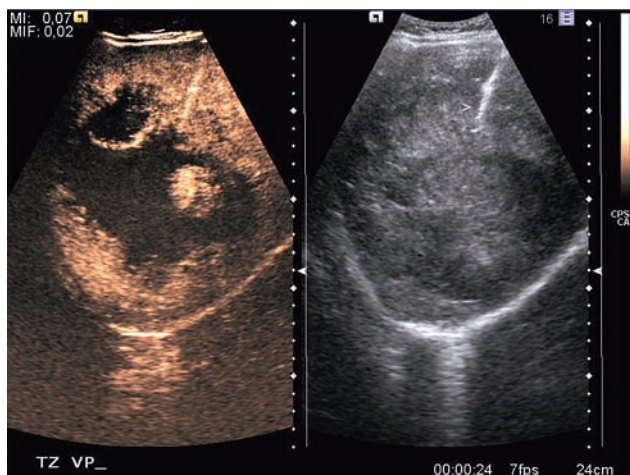


Fig 1. Large hepatic tumor with extensive necrosis – CEUS guided liver biopsy. The specimen was sampled from an enhanced marginal area. The entire length of the needle is seen (arrowhead).

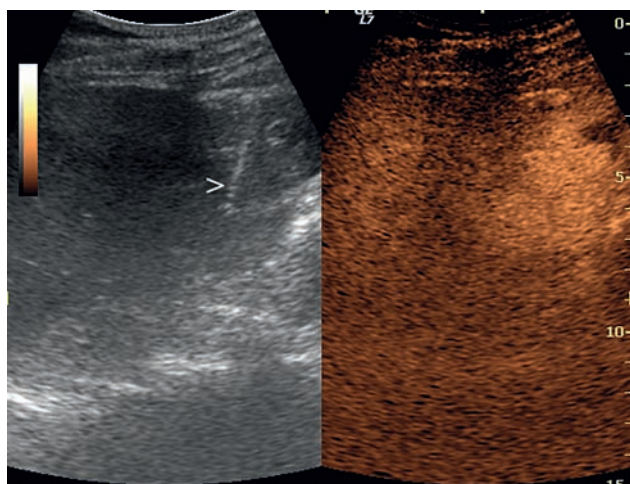


Fig 2. Large recurrence after percutaneous ethanol injection for HCC. Note the needle (arrowhead) inside an enhanced area near the treated unenhanced area (arrow). In the CEUS image the needle is not well visible.

c) avoiding hypovascular areas in certain tumors. The hypovascularity may be explained by the presence of marked fibrosis in cholangiocarcinoma or liver metastasis from pancreatic adenocarcinoma, fat areas in hepatocellular carcinomas (HCCs) and desmoplastic tissue in metastasis of sarcomas or pancreatic tumors;

d) targeting of otherwise invisible lesions (Fig.3) or those

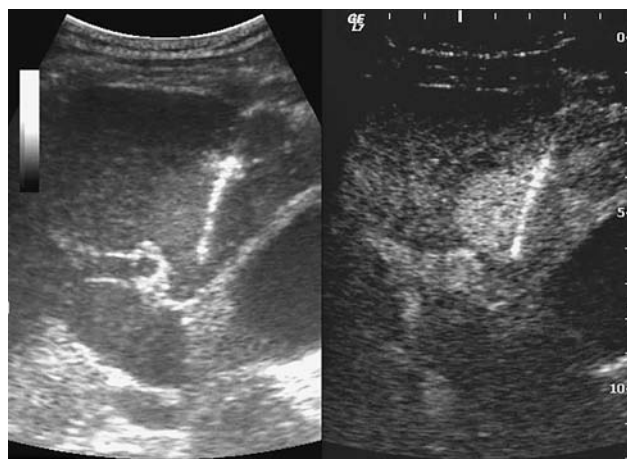


Fig 3 . A 2 cm enhanced lesions without wash-out in segment 5 in a patient with HCV related liver cirrhosis not seen at conventional US. CEUS was used as a guidance method.

hardly visible (small nodules of HCC on cirrhosis or small isoechoic liver metastases) (Fig.4) [9-11]. Ultrasound (US) is the most commonly used imaging modality to guide a biopsy in liver tumors but has a low sensitivity in detecting some hepatic lesions (55% per patient sensitivity in detection of liver metastasis from cancers of the gastrointestinal tract and 33-84% sensitivity in detection of HCC) [16, 17]. CEUS improves lesion conspicuity and allows a better visualization of focal hepatic lesions especially in patients with poorly visible tumors (small lesions or deeply located) on conventional ultrasound. CEUS can be used to visualize small metastasis (as small as 3 mm) that cannot be detected with conventional ultrasound and then to puncture them [13];

e) targeting potentially active areas (neoplastic or inflammatory) in complex cystic solid lesions. CEUS may depict the solid component of a cystic metastasis and can guide the needle in that area (Fig.5). Some benign lesions such as hepatic abscesses (bacterial including brucella, fungic i.e. candidosis, and parasitic i.e. fasciolosis), inflammatory pseudotumor, etc may have a cystic solid appearance and sometimes may display the wash-out phenomenon in or around the lesion [18-21]. The current recommendations in such lesions imply the use of clinical data and other imaging techniques for a better characterization but in many cases a biopsy is required to rule out malignancy [22]. CEUS may be used as guidance to avoid necrotic areas and to target the needle in the areas with washout (Fig.6);

f) percutaneous portal thrombus biopsy. Due to a superimposed “true thrombosis” some malignant thrombi have an inhomogeneous pattern of enhancement called “the mosaic pattern”. Targeting those active areas with CEUS guidance allows the sampling of tumoral tissue, thus increasing the accuracy on the biopsy (Fig.7) [23].

Discussion

Wu et al have demonstrated that by using CEUS before biopsy the accuracy of percutaneous biopsy in the diagnosis

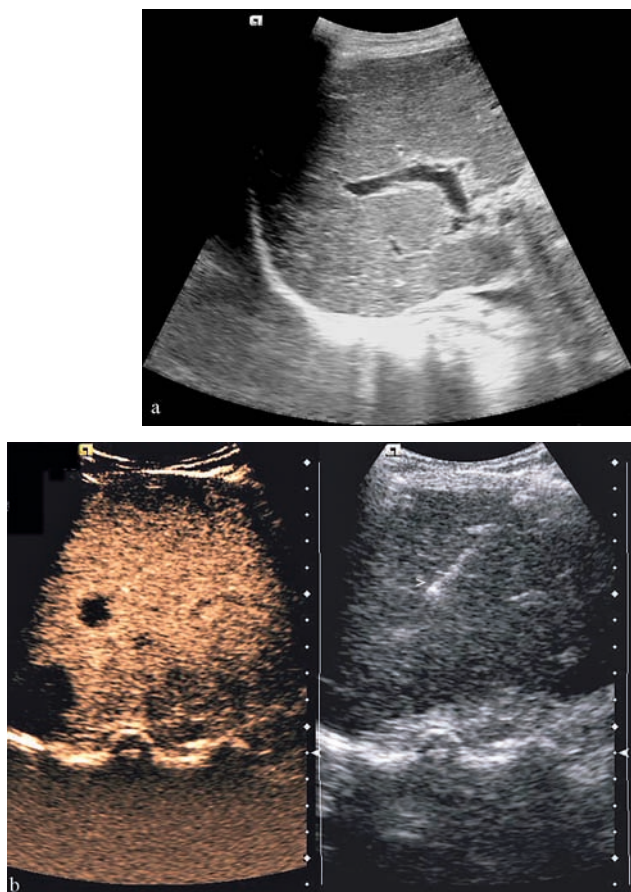


Fig 4. a) Inhomogeneous parenchyma without clear lesions in a patient with pancreatic adenocarcinoma. b) In the parenchymal phase, several metastases were depicted and punctured (arrowhead) with CEUS guidance.

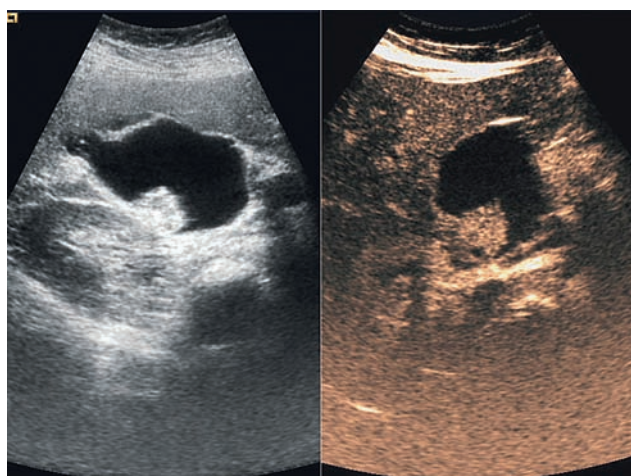


Fig 5. Cystic hepatic tumor in a patient operated for ovarian carcinoma. In the arterial phase the nodule inside the lesion was enhancing. That nodule was punctured with CEUS guidance (needle not seen).

of liver tumors (both benign and malignant) increases from 87% (obtained by classical guided technique) to 95.3%. The accuracy is even greater in lesions < 2 cm, 97.1% versus

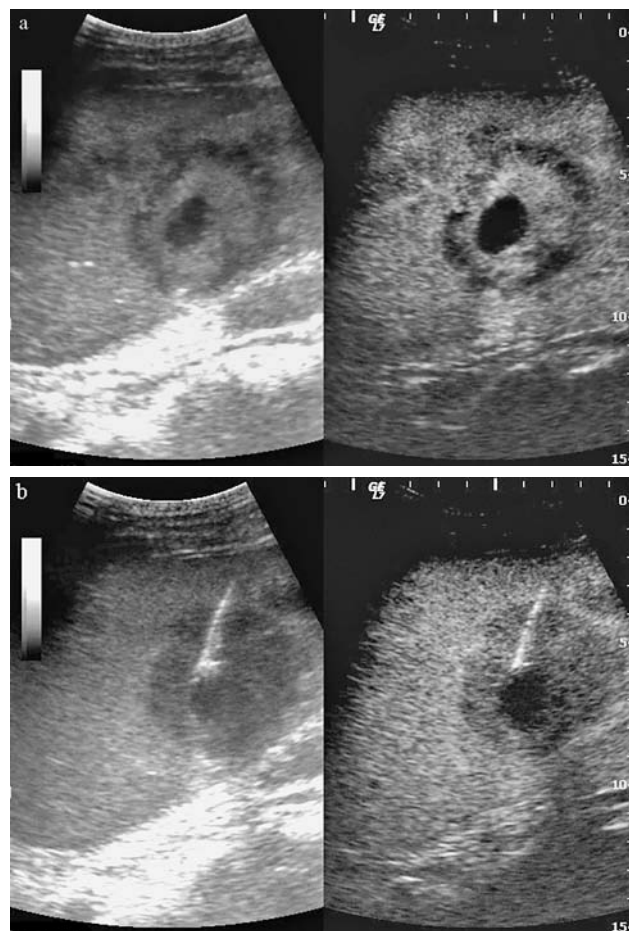


Fig 6. Complex liquidian lesion in a patient with pancreatic cystadenocarcinoma, biliary stenting and no signs of infection. The lesion enhanced in the arterial phase (a) and washed out in the parenchymal phase (b). A CEUS guided puncture was performed in the area with wash-out. Histology: inflammatory tissue.

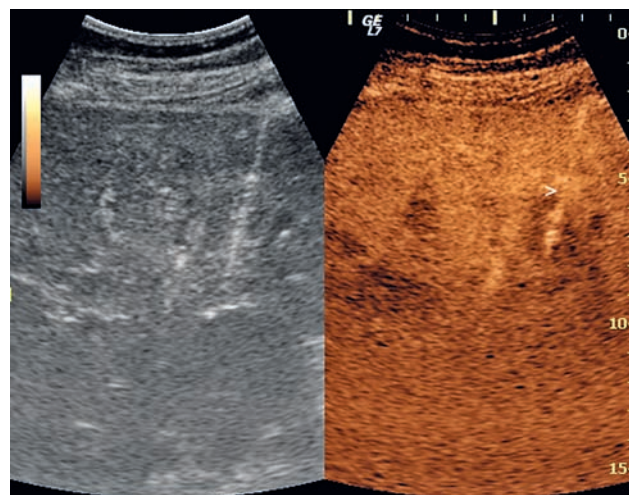


Fig 7. CEUS guided biopsy of a malignant PVT. Note the presence of the needle inside an enhancing area of the thrombus (arrowhead).

78.8% [13]. Another consequence of using CEUS in that study was a decreased number of passages needed. This study was however conducted on different patient groups.

Schlottmann et al [11] used CEUS with phase inversion at a low mechanical index to detect and target hepatic lesions. They evaluated 12 patients with hepatic tumors or abscesses that could not be analyzed and punctured under fundamental B-mode guidance. In 11 of the 12 interventions performed under contrast harmonic imaging, the procedure was successful.

In another prospective study that evaluated the technical feasibility of percutaneous real-time CEUS guided biopsy of focal hepatic lesions not confidently localized on B-mode, Yoon et al reported a technical success rate of 86% (38/44) and an overall sensitivity in the diagnosis of malignancy of 88% [12].

In 2006, Wu et al [24] demonstrated the clinical utility of CEUS in percutaneous biopsy of focal liver lesions. The biopsy success rate in the CEUS group was 98.7%, significantly higher than that reached in the US group (91.5%, $P = 0.0096$). The accurate diagnosis rate of malignant lesions ≤ 2 cm or less in size in the CEUS group was 97.4%, significantly higher than that in the US group (80.6%, $P = 0.0473$).

An important problem for patients with cirrhosis is the differential diagnostic between malignant and benign portal vein thrombosis (PVT). In some cases, HCC cannot be clearly identified at US, the only sign being a portal vein thrombosis. The use of CEUS permits the study in real time of the micro-vascular architecture of each thrombus, searching for global arterial enhancement typical of HCC neovascularity. Benign PVT does not show enhancement after ultrasound contrast agent administration. Malignant PVT has a characteristic behavior: during the arterial phase an intense and diffuse homogeneous contrast enhancement is seen, followed or not by a washout of contrast material from the thrombus.

Rossi et al [25] revealed the superiority of CEUS to sonography and color Doppler sonography for the detection and characterization of portal and hepatic vein thrombosis complicating hepatic malignancies.

Sorrentino et al [23] showed that CEUS is a useful tool in assessing the benign or malignant nature of the thrombus. Furthermore, they suggested that when cytology confirmation of malignant thrombosis is required, PVT biopsy could be guided by CEUS in the true malignant areas of the thrombus.

Our preliminary results have demonstrated the superiority of CEUS guided liver biopsy over the classical B mode guidance. The sensitivity of liver biopsy was significantly higher if performed with CEUS guidance in comparison with B-mode US guidance for all lesions (100% vs. 86.6%, $p < 0.05$), and for lesions larger than 4 cm it was 100% vs. 71.4 % ($p < 0.05$) [26].

These few studies published in the last years and the experience gained by several other authors have enabled this summary of the indications for CEUS guided liver biopsy (Table I).

Conclusions

CEUS guided percutaneous liver biopsy is a new, feasible

Table I. Possible indications for CEUS guided biopsy in liver tumors

1. Large hepatic tumors with necrotic or hypovascular areas (large metastasis, cholangiocarcinomas or HCCs).
2. Residual or renaescent tumoral areas after percutaneous ablative treatments.
3. Tumors invisible or poorly visible on B mode ultrasound.
4. Cystic tumors with solid component.
5. Complex lesions (with cystic-solid appearance) with wash out in parenchymal phase.
6. Portal vein thrombus with "mosaic picture" at CEUS.

technique that should be applied in large hepatic tumors with consistent necrosis, in hypovascular tumors or in those invisible or poorly visible to conventional ultrasound. The increased accuracy was demonstrated for poorly visible or invisible lesions.

CEUS guided PVT biopsy is a new, promising method with excellent results in establishing the nature of a portal thrombus.

Conflicts of interest

None to declare.

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