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Can contrast-enhanced ultrasonography characterize focal liver lesions and differentiate between benign and malignant, thus providing a one-stop imaging service for patients?☆

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KEYWORDS

Ultrasound;
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Cost benefit.

Abstract *Purpose:* Contrast-enhanced ultrasonography (CEUS) displays high sensitivity and specificity in characterizing focal liver lesions (FLLs). We attempted to determine how often CEUS provides an unequivocal diagnosis of FLLs that does not require additional imaging studies.

Materials and methods: Seventy-three patients with 146 FLLs were scanned with B-mode, Doppler, and contrast-enhanced US (2×2.4 ml SonoVue, low MI, 4–6 MHz curved array transducer, Toshiba Aplio/Siemens—Acuson Sequoia). Data were digitally stored and transferred to a work station with the GE PACS system. Images were reviewed by a consultant radiologist experienced in CEUS and interpreted in accordance with the criteria for characterizing FLLs published by the European Federation of Societies for Ultrasound in Medicine and Biology. Diagnoses were compared with those based on computed tomography (CT) and/or magnetic resonance (MR) findings if these were available. However, our aim was to assess the frequency with which CEUS provided diagnoses that were considered reliable enough to exclude the need for other imaging studies. Therefore, the CEUS diagnoses were not necessarily confirmed by other methods.

Results: Based on CEUS findings alone, 130/146 (89.0%) FLLs could be classified as benign or malignant, and in 118/146 (80.8%) cases, the lesion could be specifically identified. The other 28/146 (19.2%) FLLs could not be characterized based on CEUS data alone. In 58 (80.8%) of the 73 patients with multiple FLLs, CEUS findings were sufficient to establish the benign vs. malignant nature of all the patient's lesions; in 51/73 (69.9%) patients, all the lesions could also be characterized with CEUS. In the remaining cases, at least one lesion required additional imaging to determine whether it was malignant (14/73, 19.2%) or to establish its identity (22/73, 30.1%). In 4/73 (5.5%) patients, CEUS revealed additional lesions not detected on B-mode US.

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Conclusions: CEUS alone was sufficient to classify 89.0% of the FLLs as benign or malignant, and in 80.8% it was also regarded as sufficient to identify the lesion. It served as a one-stop diagnostic test for 80.8% of the patients, reducing the need for CT–MR scans and providing savings in terms of radiation exposure, time, and money.

Sommario *Obiettivo:* L'ecocontrastografia ha elevate sensibilità–specificità nel caratterizzare le lesioni focali epatiche. Tuttavia, a tutt'oggi non è stata valutata come metodica di imaging decisiva tale da non richiedere altre indagini di imaging. Nel presente studio è stata valutato in quanti casi l'ecocontrastografia ha fornito risultati tali da non richiedere altre indagini di imaging (in genere TC o RM).

Materiali e metodi: 73 pazienti con 146 lesioni focali epatiche sono stati esaminati con ecografia basale, Doppler e ecocontrastografia (2 × 2.4 ml SonoVue, a basso indice meccanico (IM), trasduttori da 4–6 MHz, Toshiba Aplio/Siemens–Acuson Sequoia). I dati sono stati registrati in formato digitale e trasferiti alla work station attraverso un sistema PACS (GE) e rivisti da un Consulente Radiologo con elevata esperienza in ecocontrastografia, facendo riferimento ai criteri per la caratterizzazione delle lesioni focali epatiche dell'EFSUMB. Il confronto con TC–RM è stato effettuato solo nei casi in cui queste modalità di Imaging fossero disponibili, poiché lo scopo era di valutare l'accuratezza diagnostica dell'ecocontrastografia, indipendentemente dalla conferma di altre modalità di imaging. Pertanto le diagnosi fornite dall'ecocontrastografia non sono state successivamente necessariamente comprovate da altre modalità di imaging.

Risultati: 118/146 (80.8%) lesioni focali epatiche sono state caratterizzate dall'ecocontrastografia. L'ecocontrastografia non ha caratterizzato 28/146 lesioni focali epatiche (19.2%). 130/146 lesioni (89.0%) sono state differenziate tra benigne e maligne. In 51/73 (69.9%) pazienti, tutte le lesioni sono state caratterizzate. Nei rimanenti 22/73 (30.1%), almeno una lesione non è stata caratterizzata. In 4/73 (5.5%) pazienti, l'ecocontrastografia ha rivelato altre lesioni rispetto all'ecografia basale. L'ecocontrastografia ha discriminato lesioni (benigne–maligne) in 59/73 (80.8%) casi. Non ha differenziato lesioni focali epatiche (benigne–maligne) in 14/73 (19.2%) pazienti, necessitando integrazione con altre metodiche di imaging.

Conclusioni: L'ecocontrastografia caratterizza l'80.8% e differenzia l'89% (benigne–maligne) delle lesioni focali epatiche. In 80.8% dei pazienti non sono state pertanto necessarie altre metodiche di imaging, risparmiando pertanto esposizione di radiazioni ai pazienti, tempo e denaro.

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Introduction

Ultrasonography (US) is the first modality used for liver imaging in neoplastic and chronic hepatic diseases [1]. The addition of contrast agents increases [2–4] the sensitivity and specificity of US in imaging focal liver lesions (FLLs) to levels comparable to that of three-phase contrast-enhanced computed tomography (CECT) [5]. Contrast-enhanced US (CEUS) and helical CT are similar in terms of diagnostic accuracy and correlation degree [6]. Different studies have revealed accuracy rates of 85–95% for diagnosis of all types of FLLs [7], 75–94.5% for hepatocellular carcinomas (HCCs) [2,7,8], 92–94% for metastases [9], and 99.4% for hemangiomas [2]. High sensitivity rates have also been published, i.e., 88% for hemangiomas [2], 92.8% for HCC [8], and 87–94% for metastases [9].

In everyday clinical practice, doctors face cases in which the FLL has not been fully characterized, although it has been determined to be benign or malignant, which is often what the referring physician and the patient really need to know. For this purpose, CEUS has a specificity of 92.7% [8] and a sensitivity of 98% for all FLLs [10].

In both situations (characterization and benign/malignant differentiation), the clinical question is answered, partially or completely, without requiring the patient to undergo other imaging studies. Therefore, CEUS can replace CT, magnetic

resonance (MR), or even biopsy in the investigation of FLLs, providing a definitive answer for the patient.

There are cases, however, in which CEUS fails to provide a diagnosis or provides a diagnosis that is equivocal. In these patients, additional imaging is needed. There are also patients with multiple FLLs, one or more of which cannot be characterized with CEUS. In these cases, CEUS fails to provide a diagnosis, and the patient must then be referred for additional imaging or for biopsy. Although the success rate of CEUS in finding and characterizing FLLs has been studied, no effort has been made to assess its effectiveness as the final imaging procedure for the patients themselves. Thus far, there have been no attempts to analyze the percentage of FLLs conclusively diagnosed with CEUS alone vs. those in which referral for additional imaging is required. We investigated to what degree CEUS scanning is successful and how often it is inconclusive or equivocal, requiring further imaging, usually CT or MR.

Materials and methods

We studied retrospectively 146 FLLs in 73 patients (28 males, 45 females, aged 27–90 years). In keeping with selection criteria, the population included patients with first-time findings and those with one or more lesions that had already been detected with B-mode US or other imaging modalities but had not been definitively

Fig. 1 Distribution of the 146 FLLs in the 73 patients.

diagnosed. The numbers of lesions per patient are summarized in Fig. 1.

All patients initially had B-mode, color, and power Doppler US examinations performed with a Toshiba Aplio (Tokyo, Japan) or Siemens—Acuson Sequoia (Berlin/Munich, Germany) scanner and a 4–6 MHz curved array transducer. After intravenous (IV) injection of 4.8 ml of SonoVue (Bracco, Milan, Italy) divided into two doses of 2.4 ml, scanning was performed at a low mechanical index ($MI < 0.2$) in a contrast-specific mode (contrast pulse sequence, CPS, on the Sequoia and vascular recognition imaging, VRI, on

the Aplio). The liver was examined continuously for up to 7 min. Scanning was performed by sonographers and registrar or consultant radiologists who were experienced in the CEUS technique. Still images and clips were digitally stored and transferred through a PACS system (Centricity 2.0, General Electric Medical Systems). Each examination was then evaluated by the examiner himself/herself together with a consultant radiologist with 11 years of CEUS experience, who made the diagnosis after reviewing the findings with the examiner. Therefore, this was not a blinded study.

FLLs were diagnosed according to the criteria published by the European Federation of Societies for Ultrasound in Medicine and Biology (guidelines for the use of contrast agents in ultrasound) [11]. Lesions were classified as malignant when they failed to present contrast enhancement during the late phase and thus appeared as defects (Fig. 2), while solid lesions retaining contrast enhancement throughout the scanning period were classified as benign.

Characterization of benign lesions mainly depended on their arterial-phase hemodynamics. Hemangiomas are known to show peripheral nodular enhancement with centripetal filling (Fig. 3). Focal nodular hyperplasia (FNH) is characterized by very early enhancement proceeding from the center to the periphery, sometimes with a non-enhancing central scar (Fig. 4). Adenomas display arterial-phase enhancement at the center of the nodule and in the peripheral capsule. Enhancement persists throughout the late phase. (No adenomas were diagnosed in our study.) Hepatic cysts appear as defects in all phases. If part of a cyst enhances, malignancy and infection need to be ruled out. Abscesses appear as round, hypo- or anechoic lesions with thick walls and echogenic debris, fluid levels, or gas. On color Doppler and CEUS, the walls

Fig. 2 Enhancement of a liver metastasis at different points in time after injection of SonoVue: (a) 6 s, (b) 21 s, (c) 36 s, and (d) 4 min 47 s. The lesion shows early enhancement and then appears as a defect during the late phase.

Fig. 3 Enhancement of a left lobe hemangioma (arrow) before (a) and at different times after injection of SonoVue: (b) 13 s, (c) 21 s, and (d) 49 s. Early peripheral nodular enhancement is followed by centripetal filling.

appear hypervascular. Focal fatty sparing is a common cause of diagnostic doubts. CEUS almost always eliminates this problem by producing homogeneous enhancement throughout the liver. Ischemic areas due to portal vein thrombosis or hematomas show decreased enhancement.

Malignant lesions show marked differences in comparison with normal liver tissue. In the arterial-phase, HCC is usually characterized by rapid, increased enhancement. In the late phase, its appearance is variable, but it usually appears as a defect. Metastases have variable appearances in the early phase depending on whether they are hypo- or hypervascular. In the late phase, they typically appear as defects.

In our study, CEUS findings were compared with those of CT and MR only when findings with these modalities were available because the aim of the study was to determine how often reliable diagnoses were reached with CEUS alone. Therefore, CEUS diagnoses were not necessarily confirmed by other methods. When the CEUS findings provided a diagnosis, no additional imaging studies were performed. In 42 cases, we had access to the results of CT examinations performed on a variety of scanners, in or outside our hospital. In most of these cases, the CT examination had been performed ≤ 2 months before or after the CEUS examination. In fewer than 10 cases, this time span was longer (4–7 months). To avoid exposing the patient to needless radiation, repeat CT scans were not performed in these cases. US and CEUS findings were compared with those of CT. Comparison with MR

findings was possible in eight cases (interval between US–CEUS and MR: 0 days–5 months) and with nuclear medicine tests in five (interval between US–CEUS and these tests: < 1 month).

Results were analyzed to assess the following aspects:

1. How many of the lesions detected on B-mode US, CT or MR were confirmed by CEUS?
2. How many of the lesions detected on CEUS could be specifically diagnosed?
3. How many of the lesions detected on CEUS were classified as benign or malignant without further characterization?
4. How many patients had all their lesions characterized by CEUS?
5. How many patients had all their lesions classified as benign or malignant?
6. How many patients required additional imaging studies to characterize at least one lesion or to determine whether it was benign or malignant?
7. How does the number of lesions affect the CEUS success rate? We studied the percentage of CEUS failures in lesion characterization as a function of lesion number (patients with one lesion vs. those with 2–6 lesions). Two-sided Fisher's exact test (GraphPad InStat Software, San Diego, CA, USA) was used, and a *P*-value of less than 0.05 was considered statistically significant.
8. How does the size and location of lesions affect CEUS success rates?

Fig. 4 Enhancement of focal nodular hyperplasia before (a) and at different times after injection of SonoVue: (b) 7 s, (c) 11 s, and (d) 29 s. The scar (arrow) showed no enhancement at any time.

Results

All FLLs imaged on B-mode, CT, or MR were visualized on the CEUS study. In 4/73 (5.5%) patients, CEUS revealed 1–3 additional lesions that had not been seen on the B-mode US study.

Most (118/146, 80.8%) of the FLLs were characterized based on CEUS findings, as described in Fig. 5. The remaining 28 lesions (19.2%) could not be characterized. In 4/28 (14.3%) uncharacterized lesions, B-mode US had not detected any abnormality. These were spotted on CT/MR or were incidental findings on CEUS. In the majority of cases (16/28, 57.1%), the benign/malignant nature of the lesion could not be established either. In other words, when a “difficult” lesion was scanned, it was usually not easy to characterize it or to determine whether it was malignant. The remaining 12/28 lesions (42.3%) were classified as benign ($n = 11$) vs. malignant ($n = 1$).

Of 146 lesions examined, the majority (130, 89.0%) were correctly classified as benign (98, 75.4%) or malignant (32, 24.6%).

Fig. 5 Classification of FLLs characterized by CEUS.

Table 1 FLL characterization failure rate as a function of lesion number

Number of lesions	Uncharacterized lesions	Percentage
Total (1–6 lesions)	28/146	19.2
1	8/34	23.5
2	8/38	21.1
3	3/30	10
4	6/28	21.4
5	1/10	10
6	2/6	33.3

With reference to the impact of the CEUS scan on patient management, all of the patient's lesions were characterized in 51/73 (69.9%) cases. In the remaining 22/73 (30.1%) cases, at least one of the patient's lesions could not be characterized.

In determining only whether a lesion was benign or malignant, CEUS was successful in 59/73 (80.8%) cases. In these patients, CEUS provided a "one-stop" imaging diagnosis with no further imaging needed.

CEUS was unable to provide a definitive diagnosis on the presence of malignancy in 14/73 (19.2%) patients, who thus had to be referred for additional imaging studies.

Effect of lesion number: characterization failure rates as a function of lesion number are summarized in Table 1. There was no statistically significant difference in the failure rate among patients with different numbers of lesions. Therefore, in our study group, lesion number did not affect the success or failure rate.

Effect of lesion size and location: 19 (67.9%) of the 28 uncharacterized lesions had diameters of <2 cm, and in 3/28 (10.7%) cases, the uncharacterized lesion was in an area of the liver that was difficult to scan on baseline US and CEUS. In 8/28 (28.6%) cases, the uncharacterized lesion was the only lesion. In the remaining 20/28 cases, additional lesions were seen.

Discussion

The imaging arsenal for diagnosis of FLLs usually includes US, CT, and MR. US without contrast enhancement has limited accuracy in characterizing these lesions [12], as benign and malignant lesions have similar echo patterns and Doppler vascular characteristics. When contrast agents are used, the sensitivity and specificity improve significantly and become comparable to those of CT [5]. Assessment of the hepatic vasculature throughout the early and late phases is critical for characterizing these lesions [10].

In the past, CEUS was performed with contrast agents like Levovist (SHU 508A; Schering, Berlin, Germany), which has to be insonated with high-acoustic power causing microbubble destruction in order to obtain useful non-linear signals. This technique requires intermittent scanning, and the arterial-phase is difficult to monitor [8]. By comparison, non-destructive, low-acoustic power US scanning is used with SonoVue (BR1; Bracco, Milan, Italy). As a result, target structures can be imaged continuously during all phases of enhancement.

Although the introduction of US contrast agents has improved sonographic imaging of FLLs, there are still cases

in which one or more FLL cannot be reliably characterized. Even more importantly, it is sometimes impossible to tell whether these lesions are benign or malignant. Very often, this is what the referring doctor and the patient really need to know. For example, once an FLL has been characterized as benign, it does not make a great deal of difference whether the lesion is a hemangioma, regenerating nodule, or focal nodular hyperplasia (FNH). When CEUS is not able to provide a definitive answer to either the first or second clinical question, additional imaging studies are needed.

In our study, we included all patients with one or more FLLs that had been detected as incidental findings on B-mode US or had been imaged with CT or MR with inconclusive results. We assessed the percentage of lesions whose presence was confirmed by CEUS and the percentage that were characterized or at least classified as benign vs. malignant. In patients with multiple FLLs, we also examined the number of cases in which all the lesions were characterized or classified as benign vs. malignant by CEUS. Although comparison with CT and MR was studied and used when available, concordance between CEUS findings and those of other imaging modalities was not the focus of this study. We wanted to determine how often CEUS provided a diagnosis that was considered sufficient by the physician who ordered the study, regardless of whether or not this diagnosis was confirmed by additional imaging studies. When interpreters reporting CEUS studies reached a definite diagnosis, no further imaging was performed.

CEUS was successful in characterizing 80.8% and differentiating (malignant/benign) 89.0% of FLLs. It was also successful in providing a "one-stop" method for characterizing and establishing the benign/malignant nature of all lesions present in the liver in 69.9% and 80.8% of all cases, respectively. This 10% shortfall between lesion- and patient-based success rates is due to the fact that some patients had multiple lesions. For example, if a patient had four lesions and only three of them could be characterized, the lesion-based success rate was 75%. At the patient level, however, this case was considered a CEUS failure because additional imaging studies had to be performed to characterize the fourth lesion. Altogether, success rates were high regardless of whether the analysis was based on FLLs or patients.

In two cases, CEUS also provided answers to diagnostic questions that could not be resolved by the other imaging modalities. In one case, an FLL that could not be characterized on B-mode US was identified by CEUS as FNH based on its early enhancement with the typical spoke-wheel appearance and persistent echogenicity in the late phase. In the other case, lesions were too small to be characterized on CT were diagnosed as cysts on CEUS.

In four cases, CEUS revealed additional lesions that had been missed on B-mode US. In one of these patients, a 70-year-old man who had undergone Whipple's operation for periampullar cancer, B-mode US showed two indeterminate FLLs (one echogenic and one with mixed echogenicity). After contrast administration, a third lesion was also observed. All three appeared as late defects and were diagnosed as metastases. Another patient, a 66-year-old woman with grade III endometrial adenocarcinoma, presented two subcentimeter hypoechoic FLLs on B-mode US. On CEUS, both of these lesions, as well as a third that was echopoor, were characterized as simple cysts. The third patient

Fig. 6 (a) A 2 cm segment VI lesion is seen as a late defect on CEUS, 4 min 45 s post SonoVue injection. (b) CECT: the lesion is again seen as a defect. Both modalities interpreted the lesion (arrows) as a malignancy.

was a 73-year-old man with a mass located in the head of the pancreas. B-mode US revealed an echo-poor FLL measuring 1 cm that was suspected to be metastatic. CEUS characterized this lesion and three others as cysts. Finally, the fourth patient, a 55-year-old woman with chronic pancreatitis, had an indeterminate lesion on CT. B-mode US revealed a 1.5-cm, echo-poor FLL in segment VI. CEUS characterized this lesion and two others (total: three) as metastases.

However, CEUS also had its limitations. In six patients, CEUS added no diagnostic information, as it did not provide a final diagnosis. CT or MR was also non-diagnostic in these cases. For example, in one patient, a late phase defect (2 cm) in segment VI was considered to represent a primary or secondary malignancy on CEUS. CT confirmed the malignancy of the lesion but was also unable to determine whether it was primary or secondary (Fig. 6).

Fig. 7 (a) Echogenic segment VII lesion on B-mode US. On CEUS; (b) the lesion disappears and is considered benign. CECT (c) shows the lesion as a late defect, suggestive of a metastasis.

Most of the uncharacterized lesions (19/28—67.9%) had diameters of <2 cm, and 3/28 (10.7%) were located in an area difficult to reach on the baseline US and CEUS scans (peripheral subcapsular, under a rib or close to the falciform ligament). Therefore, lesion size affected the success rate, but the location of the lesion had less of an effect.

In five cases, CEUS was unable to characterize lesions that were indeterminate on B-mode US. In four of these, however, the question of whether they were benign or malignant was successfully answered. (All four were considered benign on CEUS.)

In three cases, CEUS proved to be inferior to the other imaging modalities, providing indeterminate results when CT or MR was diagnostic. One of these cases involved a lesion that appeared cystic on CT and could not be characterized on B-mode US. CEUS was also inconclusive, identifying the lesion as focal fat, hemangioma, or a metastasis. On T2-weighted MR, the lesion showed high signal intensity suggestive of metastasis, and the same picture emerged from the nuclear medicine study. In the other two cases, CEUS findings were indeterminate for lesions characterized by CT as a cyst and a regenerating nodule.

Finally, there was one case in which the CEUS diagnosis was in contrast with CT findings. The patient was a 72-year-old man with a history of colon cancer, previous colectomy, and radiofrequency (RF) ablation for hepatic metastases. CEUS provided a definitive diagnosis that was possibly incorrect. In addition to RF areas, B-mode US revealed an echogenic lesion in liver segment VII. CEUS confirmed the presence of RF cavities but indicated that the segment VII lesion represented focal fatty changes (hypervascularity and complete late phase filling). This diagnosis was later contradicted by CT findings, which were indicative of a metastatic lesion (Fig. 7). However, since there was no histological diagnosis for this lesion, it is impossible to say whether the CT diagnosis was correct. The lesion was located very deep in the liver parenchyma, where CEUS performance is known to be poor.

Altogether, however, there were few cases in which CEUS proved to be of limited value: in the majority, it was very useful. One should also keep in mind the obvious and well-known advantages of US over CT and MR (lower cost, wider availability, lack of ionizing radiation and allergy to contrast agents in the case of CT).

However, it should not be concluded that CEUS is already a routine, daily practice in all radiology departments. Limitations still exist [13]. About 60% of US systems in the West lack the software for contrast imaging, and most cannot be upgraded. Thus, the technology to use and view contrast agents is often not available. In addition, even if an appropriate system is available, performing a CEUS scan requires skill and experience, and CEUS is not yet a part of routine radiology training programs in most countries. Finally, CEUS is more time-consuming than conventional US, mainly because of the time needed for IV catheter placement. This makes it difficult to perform in a very busy US department with only one or two machines.

In conclusion, although with abovementioned limitations, our study demonstrated CEUS to be very helpful in

imaging patients with focal liver lesions. With adequate modernization of equipment and specific training for physicians, CEUS may prove to be even more useful for diagnostic work-up of focal liver lesions.

Conclusions

CEUS characterized the majority (118/146, 80.8%) of focal liver lesions. CEUS diagnosed the majority (130/146, 89.0%) of focal liver lesions as malignant or benign. CEUS was successful in providing one-stop imaging diagnosis for all the lesions in 51/73 (69.9%) of patients. CEUS was successful in providing one-stop differentiation of benign and malignant lesions in 59/73 (80.8%) of patients. Rates of failure in identifying and characterizing focal liver lesions were related to lesion size but not to lesion number or lesion location.

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