Contrast-enhanced Ultrasound for the Characterization of Focal Liver Lesions – Diagnostic Accuracy in Clinical Practice[1] (DEGUM multicenter trial)

Kontrastmittelsonografie bei B-Bild-morphologisch unklaren Leberraumforderungen – Diagnostische Treffsicherheit im klinischen Alltag (DEGUM-Multicenter – Studie)

Authors D. Strobel[1], K. Seitz[2], W. Blank[3], A. Schuler[4], C. Dietrich[5], A. von Herbay[6], M. Friedrich-Rust[7], G. Kunze[8], D. Becker[9], U. Will[10], W. Kratzer[11], F. W. Albert[12], C. Pachmann[13], K. Dirks[14], H. Strunk[15], C. Greis[16], T. Bernatik[1]

Affiliations Die Institutsangaben sind am Ende des Beitrags gelistet.

Key words
- abdomen
- tumor liver
- contrast-enhanced ultrasound

Zusammenfassung

Ziel: Ziel der Studie war, den diagnostischen Stellenwert der Kontrastmittelsonografie in der Differenzialdiagnose von Leberläsionen im klinischen Alltag in einem multizentrischen Ansatz zu evaluieren.

Material und Methoden: 1349 Patienten (Männer n = 677, Frauen n = 672) mit einem im B-Bild und Farb-Doppler unklaren Lebertumor wurden von Mai 2004 – Dezember 2006 in 24 Krankenhäusern mit Kontrastmittelsonografie nach einem standardisierten Protokoll (Pulsinversionstechnik, mechanischer Index < 0,4) untersucht. Tumortypische Vaskularisationsmuster und das Kontrastmittelenhancement der Lebertumoren wurden während der arteriellen Phase, portalvenösen Phase und Spätphase (> 2 Minuten nach intravenöser Bolusinjektion) nach einem standardisierten Protokoll dokumentiert und analysiert. Basierend auf tumortypischen Vaskularisationsmustern erfolgte eine Differenzierung in maligne und benigne Leberläsionen. Wenn möglich, wurde eine spezifische Tumordiagnose gestellt. Die Ergebnisse der Kontrastmittelsonografie wurden mit der korrekten Enddiagnose (basierend zu 75% auf histologisch gesicherten Befunden bzw. in den übrigen Fällen mit CT oder MRI) verglichen.

Ergebnisse: Basierend auf dem Goldstandard wurden 573 benigne Leberraumforderungen (Hämangiome n = 242, fokal noduläre Hyperplasien n = 170, Leberzelladenome n = 19, andere benigne Läsionen n = 142) und 755 maligne Leberraumforderungen (Metastasen n = 383, hepatozelluläre Karzinome n = 279, andere maligne Läsionen n = 93) eingeschlossen. Die diagnostische Treffsicherheit der Kontrastmittelsonografie lag im Vergleich zur korrekten Enddiagnose bei 90,3%. Die Kontrastmittelsonografie erkannte korrekt 723/755 maligne Läsionen (Sensitivität 95,8%) und 476/573 benigne Läsionen (Spezifität 83,1%). Die

Abstract

Purpose: To evaluate the diagnostic benefit of contrast-enhanced ultrasound for the differential diagnosis of liver tumors in clinical practice.

Materials and Methods: From May 2004 to December 2006 1349 patients (male 677, female 672) with a hepatic tumor lacking a definite diagnosis based on B-mode ultrasound and power Doppler ultrasound were examined at 14 hospitals by contrast-enhanced ultrasound using a standardized protocol (pulse/phase inversion imaging, mechanical index < 0.4). The Tumor status was assessed based on the vascularity pattern and contrast enhancement seen in focal lesions during the arterial, portal, and late phase. The diagnosis established after contrast-enhanced ultrasound was compared to histology (> 75% cases) or in some cases to CT or MRI.

Results: The final diagnosis of hepatic tumors included 573 benign hepatic tumors (hemangiomas n = 242, focal nodular hyperplasia n = 170, hepatocellular adenoma n = 19, other benign lesions n = 142) and 755 malignant hepatic tumors (metastases n = 383, hepatocellular carcinoma n = 279, other malignant lesions n = 93). The overall diagnostic accuracy of contrast-enhanced ultrasound in comparison to the correct final diagnosis based on the combined gold standard was 90.3%. Contrast-enhanced ultrasound was able to correctly assess 723/755 malignant lesions (sensitivity 95.8%) and 476/573 benign lesions (specificity 83.1%). The positive predictive value of contrast-enhanced ultrasound for the diagnosis of a malignant tumor was 95.4% and the negative predictive value of contrast-enhanced ultrasound was 95.7%.

Conclusion: Contrast-enhanced ultrasound clearly improves the differential diagnosis of he-

received 1.7.2008
accepted 28.8.2008

Bibliography
DOI 10.1055/s-2008-1027806
Published online 2008
Ultraschall in Med 2008; 29: 499 – 505 © Georg Thieme Verlag KG Stuttgart · New York ·
ISSN 0172-4614

Correspondence
Deike Strobel
Internal medicine I, University of Erlangen
Ulmenweg 18
91058 Erlangen
Tel.: ++ 49/91 31/8 53 50 00
Fax: ++ 49/91 31/8 53 52 52
deike.strobel@uk-erlangen.de

[1] Parts of this manuscript were presented at the ultrasound Dreiländertreffen 2007, Leipzig.

positive Voraussagekraft für das Vorliegen eines malignen Tumors lag bei 95,4%, die negative Voraussagekraft für das Vorliegen eines malignen Tumors lag bei 95,7%.

Schlussfolgerung: Die Kontrastmittelsonografie zeigt auch in einem multizentrischen Ansatz an einer großen Anzahl von Lebertumoren eine sehr hohe diagnostische Treffsicherheit in der Differenzierung von Leberraumforderungen, die im B-Bild und im Farb-Doppler unklar sind. Diese im B-Bild und Farb-Doppler unklaren Leberläsionen können in > 90% korrekt in der Kontrastmittelsonografie differenziert werden. Somit können durch den Einsatz von Ultraschallkontrastmitteln im klinischen Alltag strahlenbelastende Computertomografien, teure MRI-Untersuchungen und invasive Biopsien deutlich reduziert werden.

patic tumors and is very helpful in clinical practice when B-scan or power Doppler morphological criteria are missing (page 16).

Introduction

B-mode ultrasound is the most frequently used imaging technique for a number of abdominal disorders because of its relatively low cost, noninvasiveness, and broad availability. The incidental finding of a liver lesion that needs to be characterized is one of the most common clinical issues, and the prevalence of benign liver lesions in the general population is high [1, 2]. Unenhanced ultrasound (US) of the liver provides good spatial resolution and inherent soft-tissue contrast and is sufficient for characterizing many liver lesions. Typical morphological B-scan features allow focal lesions such as cysts, hyperreflexive hemangiomas in a nonsteatotic liver, or typically localized focal fat accumulations or fatty sparing to be specifically diagnosed by conventional ultrasound without further diagnostic procedures [3–5]. Unfortunately in daily practice many lesions do not fulfill these diagnostic B-scan criteria. In these lesions it is impossible to differentiate benign from malignant lesions. In hypervascular hepatic tumors such as focal nodular hyperplasia or hepatocellular carcinoma, power or color Doppler imaging of liver lesions has revealed characteristic vascular patterns suggesting a tentative tumor diagnosis. However, these techniques are limited with respect to the visualization of small and fine tumor vessels and their high susceptibility to motion artifacts [6–8]. Therefore, the detection of a solid focal liver lesion with basic ultrasound frequently necessitates further investigation (e.g. computed tomography (CT) and magnetic resonance imaging (MRI) with intravascular administered contrast agents or biopsy.

Microbubble contrast agents and contrast-specific ultrasound techniques now offer the potential to show enhancement of liver lesions in sonography just as in contrast-enhanced CT and MR imaging [9–11]. Contrast agents in ultrasound are gas-filled microbubbles which are administered in very small volumes (bolus 0.1–4.8 ml) intravenously. The microbubbles remain intravascular for several minutes and do not diffuse into the interstitium [12]. Contrast-specific ultrasound techniques use the nonlinear acoustic effects of microbubbles and provide high resolution images of tissue vascularization. Liver tumors show characteristic and specific vascular patterns during different phases of liver perfusion, from the early arterial phase to the portal-venous phase. Contrast-enhanced ultrasound (CEUS) is the only imaging modality that allows visualization of those vascular patterns in real time [13–16]. There is increasing consensus that contrast agents improve the ability of ultrasound to characterize focal liver lesions in comparison to unenhanced ultrasound. Several studies have shown a diagnostic benefit of using CEUS. Most were single center studies with a limited number of patients [17–20] or focused on certain tumor entities [21–24]. Multicenter studies focusing on the diagnostic accuracy of CEUS are very limited and did not include large numbers of patients [25–26]. In this paper we report the results of a prospective multicenter study initiated by the German Society for Ultrasound in Medicine (DEGUM). The aim was to evaluate the diagnostic value of CEUS for the differentiation of focal liver lesions in clinical practice.

Material and Methods

Study population

This prospective study received approval from the institutional ethical review board. All patients gave written informed consent. Consecutive patients with a solid liver tumor visible during routine ultrasound were recruited for CEUS at the time of their ultrasound examination. Patients with liver lesions diagnosed from characteristic B-mode echomorphology, such as patients with cysts or typical hemangiomas (in a nonsteatotic liver), were not included in the study. Malignant liver tumors with tumor infiltration in hepatic vessels were also not included. Patients who were critically ill or had severe pulmonary hypertension or unstable angina were excluded, as were pregnant and nursing women. Between 2004 and December 2006 1349 patients (677 men and 672 women; mean age 59.8 years; range 12–91 years) were recruited at fourteen ultrasound centers at four university hospitals and ten non-university hospitals. In the majority of patients (n = 841; 62.3%) the focal liver lesion was an incidental finding. In 234 patients (17.3%) an underlying liver cirrhosis and in 364 patients (27.0%) an extrahepatic malignancy was known.

Ultrasound technique

The following Ultrasound systems were used: Elegra and Sequoia (CPS and CCI) (Siemens Medical Solutions), HDI 5000 (Philips Medical Systems); EUB 8500, 6500 and 6000+ (Hitachi); Aplio (Toshiba); LOGIQ 9 (GE Healthcare); SSD-6500 (Aloka). Ultrasound was performed by physicians with more than five years' experience with liver ultrasound and at least two years' experience with contrast-enhanced liver ultrasound. The ultrasound examination was performed according to the following standardized protocol, assessed at a consensus meeting.

Baseline ultrasound

Each patient underwent a complete examination of the liver in fundamental B-mode. The echo pattern of the liver was graded

as follows: normal echo pattern, increased liver echogenicity suggestive of fatty liver, or irregular echo pattern and irregular liver surface (liver cirrhosis image). To provide a baseline reference of the liver tumor, the location according to the Couinaud classification [27], size and echogenicity of the tumor were assessed. The Description of the tumor was based on the echogenicity of the lesion in comparison to the surrounding liver tissue (hypoechoic, isoechoic, hyperechoic), echo texture (homogeneous, inhomogeneous), margins (well-defined, regularly defined), and a hypoechoic tumor boundary ("halo sign"). In addition, color and power Doppler images were used to assess tumor vascularity. The pulse repetition frequency, gain and wall filter of color and power Doppler ultrasound were adjusted appropriately. Tumor vascularity was defined as hypervascular, isovascular or hypovascular compared to the surrounding liver parenchyma.

Contrast-enhanced ultrasound

Ultrasound contrast agents are not nephrotoxic or cardiotoxic and the incidence of hypersensitivity or allergic events appears lower than in the case of current X-ray or MR contrast agents [28]. A second-generation blood pool agent, BR1 (SonoVue), consisting of phospholipid-stabilized shell microbubbles filled with sulfur hexafluoride gas was used in this study. This agent is isotonic to human plasma and devoid of antigenic potential [29]. An intravenous bolus of 1.2 to 4.8 ml Sonovue (BR1; Bracco, Milan, Italy) was injected in a cubital vein using an at least 20G needle followed by a 10 ml saline flush. The dose of contrast agent depended on the specific contrast software in the ultrasound units used in each center. In addition the volume of contrast agent was able to be adjusted by the clinician performing the ultrasound. In deeply situated small liver lesions or in the presence of a fatty or cirrhotic liver, a double dose or second bolus of contrast agent could be injected for sufficient contrast enhancement in the lesion and liver parenchyma. The bolus injection was followed by immediate scanning of the focal lesion for up to five minutes using specific contrast software (phase or pulse inversion imaging) with a mechanical index < 0.4.

Liver tumor characterization

Liver tumor characterization was based on: a) real-time assessment of contrast enhancement of the focal lesion (hypoenhanced, isoenhanced, hyperenhanced) in comparison to the surrounding liver parenchyma during the arterial phase (5 – 25 sec), portal-venous phase (25 – 60 sec), and late phase (> 120 sec after contrast injection), b) location of the initial contrast enhancement in the lesion (center, periphery), and

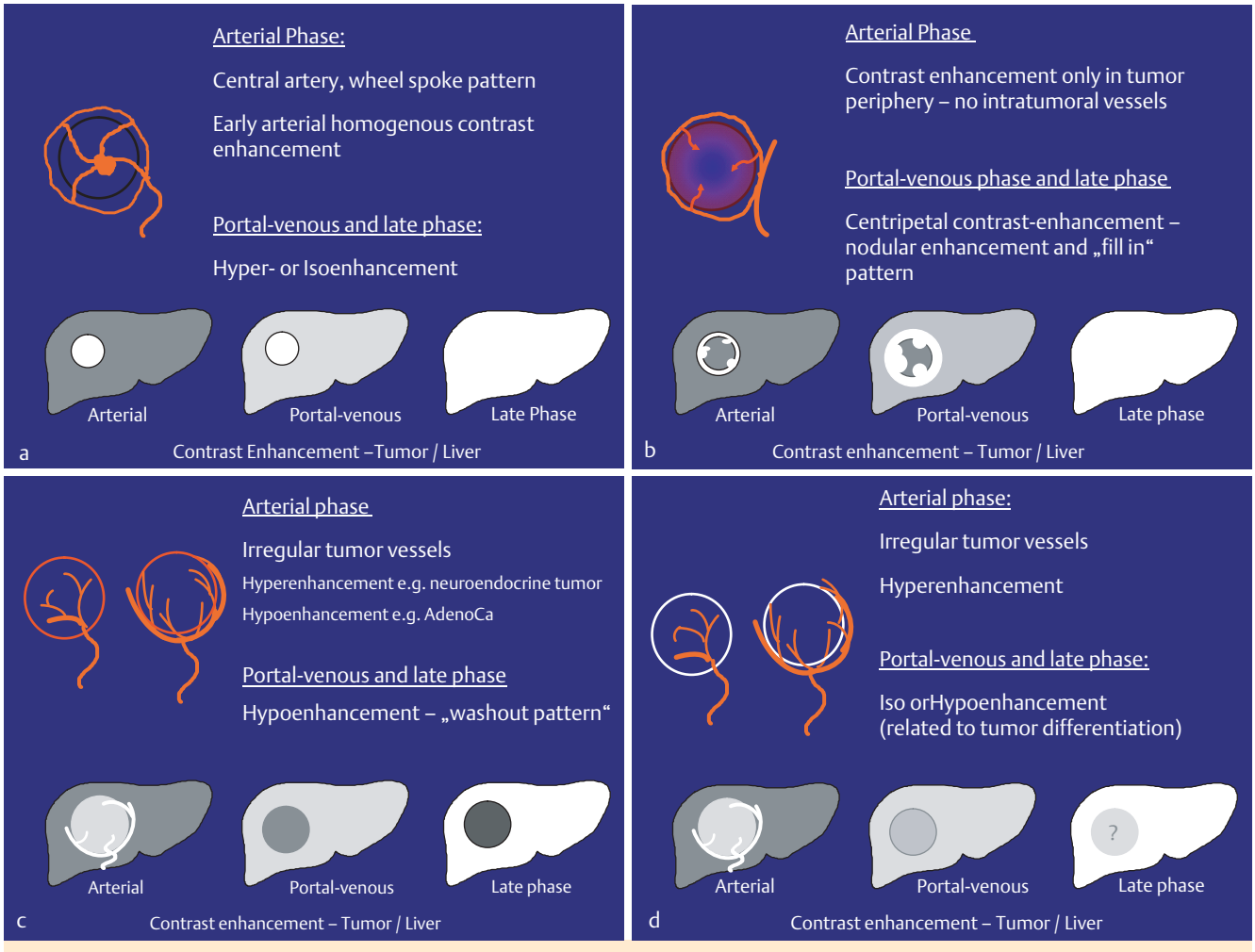

Fig. 1 Typical vessel architecture and contrast enhancement pattern. **a** Focal nodular hyperplasia, **b** hemangioma, **c** metastatic liver lesion, **d** hepatocellular carcinoma.

Abb. 1 Typische Gefäßarchitektur und Kontrastmittelspeicherung. **a** Fokal noduläre Hyperplasie, **b** Hämangiom, **c** Metastase, **d** Hepatozelluläres Karzinom.

c) specific vascularization pattern (wheel spoke pattern, irregular arteries, nodular enhancement, rim sign) in the arterial and portal-venous phases (fill-in pattern, wash-out pattern) [8, 14, 28]. The following criteria were used for the differential diagnosis of liver tumors (**Fig. 1**). Focal nodular hyperplasia: An initial radial centrifugal vascularity in the early arterial phases (wheel spoke pattern) followed by sudden complete contrast enhancement of the lesion in the arterial phase and iso- or hyperenhancement of the lesion in the portal-venous and late phase was defined as characteristic of focal nodular hyperplasia. Hemangioma: An initial solitary circular vascularity pattern (without any central intratumoral vascularity) in the arterial phase followed by a nodular fill-in pattern during the portal-venous phase was defined as typical of hemangioma. Metastasis: An irregular chaotic intratumoral vascularity with or without a circular vascularity pattern in the arterial phase followed by a wash-out (hypoenhancement of the tumor) in the late phase was considered suspicious for malignancy (e.g. metastasis in a noncirrhotic liver). Hepatocellular carcinoma: An irregular chaotic intratumoral vascularity and hyperenhancement in the arterial phase followed by iso- or hypoenhancement in the late phase was considered suspicious for hepatocellular carcinoma in a cirrhotic liver. If no tumor-specific vascularity pattern in the arterial or portal-venous phase could be noted, contrast enhancement in the late phase was used to classify the lesion: an isoenhanced lesion in the late phase was classified as benign, a hypoenhanced lesion in the late phase with enhancement in the arterial and/or portal-venous phase was classified as malignant. In patients with multiple liver lesions, each lesion was analyzed separately with one bolus injection of contrast medium per lesion. Tumors were diagnosed at the time of the ultrasound exam. All ultrasound examinations were digitally stored as images or clips in the patient documentation system of each ultrasound unit.

Tumor diagnosis reference (gold standard)

The majority of tumors were histologically confirmed (histology n = 1006; cytology n = 19). Final diagnosis was based on all available imaging and clinical data, including histology and follow-up information. Final diagnosis without histological/cytological confirmation was made in patients with clear diagnosis of hemangioma or FNH at CEUS, in whom a biopsy was not ethically justified. In these cases imaging modalities (CT and/or MRI) and follow-up were judged as the reference standard. All CT examinations employed a commercially available multidetector CT scanner (Siemens Somatom Sensation, Somatom Emotion; Toshiba, Asteion/VR). MRI examinations employed a 1.5 T imaging system (Siemens Magnetom Avanto, Magnetum Symphony, Sonata; Philips Intera).

Statistics

Data relating to the patient characteristics, ultrasound system and ultrasound examinations were analyzed using online data forms, which were part of the study protocol and were completed by each examiner. The accuracy of CEUS for the characterization of focal liver lesions was assessed in terms of lesion status and specific lesion type. The Tumor status was assessed as benign, indeterminate or malignant. The Sensitivity was calculated as the percentage of true positive malignancies divided by the number of malignant lesions based on the final diagnosis. The Specificity was calculated as the number of true negative malignancies (i.e. classification as benign) divided by the number of benign lesions based on the final reference diagnosis. Indeterminate classifications were rated as false classifications in both calculations. The Accuracy was calculated as the sum of true negatives and true positives divided by the total number of patients. The positive predictive value was calculated as the number of true positive malignancies divided by all positive classifications from CEUS. The negative predictive value was defined as the number of true negatives (i.e. classification as benign) divided by all negative classifications from CEUS.

Preparation of the online data forms, quality control of the enormous amount of data, calculation and statistical analysis were performed by an independent statistics institute, the Medidata Group, Konstanz, Germany. The work of Medidata Group was financially supported by Bracco Research Pharma, Konstanz, Germany. The authors had exclusive control of the data and information presented in the manuscript. There was no other financial support.

Results

A total of 1349 liver lesions from the fourteen ultrasound departments (4 university hospitals, 10 non-university hospitals) were included in the study. Baseline characteristics of the patients are given in **Table 1**.

Baseline ultrasound

Fundamental B-mode showed a normal echo pattern of the liver parenchyma in 702 patients (52.0%); a hyperechogenic texture (fatty liver image) was found in 329 patients (24.4%); an inhomogeneous echo pattern was seen in 410 patients (30.4%); 261 patients showed echomorphological signs of liver cirrhosis (19.3%). Focal liver lesions were located throughout all segments of the liver. The mean size of the 1349 liver lesions was 41.6 ± 28.6 mm with a range of 1 – 210 mm. Of the 1349 liver lesions, 811 were hypoechoic (60.1%) in comparison to the surrounding liver parenchyma, 339 were hyperechoic (25.1%) and 199 were isoechoic (14.8%). In comparison to the surrounding liver parenchyma 648 lesions were hypovascular, 288 isovascular and 279 hypervascular. Assessment of tumor vascularization

Table 1 Baseline characteristics of the patients.

Characteristic	Value[1]
Age – years	59.8 ± 14.6 (range 12 – 91)
Sex	
– male – number (%)	677 (50.2)
– female – number (%)	672 (49.8)
Weight – kg	72.3 ± 12.45 (range 39 – 148)
Body mass index – kg/m²	25.0 ± 3.56 (15.1 – 46.7)
Underlying liver disease – number (%)	
Liver cirrhosis	234 (17.3%)
Extrahepatic malignancy	364 (27.0%)
Liver tumor as incidental finding	841 (62.3%)

[1] Plus-minus values are means ± SD.

via power Doppler ultrasound was prevented by motion artifacts in 134 liver lesions (9.9%).

Contrast-enhanced ultrasound

CEUS was able to be assessed with sufficient diagnostic quality in 1280/1349 patients (94.9%). In 69 patients (5.1%) the quality of CEUS was reduced due to technical or patient-related factors: In 38 patients limited penetration of the contrast signal and attenuation due to adiposity, steatosis of the liver, calcifications in the lesions or air interference were observed. In 18 patients lesions showed inhomogeneous or incomplete contrast enhancement. In 8 patients the location of the lesions was limiting.

Real-time assessment of the successive vascular phases of liver perfusion revealed the following tumor contrast enhancement in comparison to the surrounding liver parenchyma: arterial phase: 885/1349 liver lesions were hyperenhanced (65.6%), 364/1349 were isoenhanced (26.9%), 94/1349 were hypoenhanced (6.9%); portal-venous phase: 356/1349 were hyperenhanced (26.39%), 571/1349 were isoenhanced (42.3%), 414/1349 were hypoenhanced (30.7%); late phase: no lesion was hyperenhanced, 493/1349 liver lesions were isoenhanced (36.5%), 829/1349 were hypoenhanced (61.4%).

Diagnostic accuracy

21 of the total 1349 lesions studied (0.2%) were unclear even in the combined gold standard (histology and/or CT and/or MRI). Of the remaining 1328, 573 were benign and 755 malignant in the final diagnosis. Histological confirmation was available in 1006/1349 liver lesions (74.6%), CT in 269/1349 liver lesions (19.9%), and MRI in 269/1349 liver lesions (19.9%). The overall diagnostic accuracy of CEUS in comparison to the correct final diagnosis based on the combined gold standard was 90.3%. Only 92 out of 1349 lesions (all lesions unclear in B-mode and power Doppler) remained unclear after contrast-enhanced ultrasound (6.8%).

Differentiation of malignant and benign liver lesions

In the differentiation of malignant and benign liver lesions, CEUS correctly identified 723/755 malignant and 476/573 benign liver lesions, resulting in a sensitivity of 95.8% and a specificity of 83.1%. Counting the 69 patients, in whom the quality of CEUS was insufficient, as false negative, the sensitivity of CEUS was 87.7%. The positive predictive value of CEUS for the classification of malignant lesions was 95.4% (n = 723/820) and the negative predictive value was 95.9% (n = 476/508) (**Table 2**).

In terms of the clinical background, 841 liver lesions were found as incidental findings (benign lesions n = 414, malignant lesions n = 410). In 364 patients the liver lesions were found on the basis of a known extrahepatic malignancy (benign liver lesions n = 106, malignant liver lesions n = 255). In patients with an underlying liver cirrhosis 233 liver lesions were studied (benign lesions n = 32, malignant lesions n = 198).

Discussion

Several studies have recently demonstrated that the diagnostic performance and reliability of liver lesion characterization can be improved by real-time CEUS. On the basis of tumor contrast enhancement in the arterial, portal-venous, and late phases, typical vascularization patterns have been described which can be assessed in a dynamic real-time exam beginning with contrast injection and lasting up to 5 minutes. In the arterial phase, typical vascularization patterns such as wheel-spoke pattern in FNH, a nodular peripheral enhancement pattern in hemangiomas or an irregular hypervascularity in hepatocellular carcinoma and in hypervascular metastases (e.g. neuroendocrine tumors) have been described. In tumor entities such as hypovascular metastases (e.g. metastases of gastrointestinal adenocarcinoma) or in some cholangiocellular carcinomas, the contrast enhancement in the arterial phase may be weak, but still visible. However, the differentiation of a liver lesion is not based on the arterial phase alone [15]. If contrast enhancement of a liver lesion in the arterial phase is followed by wash-out of contrast and marked hypoenhancement in the portal or late phase, this pattern is considered typical of a malignant liver lesion. If contrast enhancement in the arterial phase is followed by iso- or hyperenhancement of liver lesions in the portal and late (late) phase, this pattern is considered typical of a benign liver lesion, except in cirrhotic patients. In liver cirrhosis HCC are characterized by hyperenhancement in the arterial phase followed by iso- or hypoenhancement in the late phase [23].

Based on these well described enhancement patterns, several studies showed improved differential diagnosis using CEUS in comparison to conventional ultrasound (B-scan and color/power Doppler). Most of these studies are single center studies or focus on the characterization of contrast enhancement patterns in certain tumor entities using CT or MRI techniques and in some cases histology as a reference. To date, Multicenter studies focusing on the diagnostic accuracy of CEUS have included only small numbers of patients [25, 26].Therefore, the clinical benefit of CEUS in everyday routine differentiation of liver lesions is not yet well defined.

This study was designed to evaluate the diagnostic value of CEUS in a multicenter trial including university and non-university hospitals, using a reasonably high diagnostic reference standard, which should be histology in most cases. Indeed, more than 75% of the liver lesions in our study had a confirmed histological diagnosis. In contrast to other studies, we included only liver lesions that were unclear based on sonomorphological criteria in B-scan and color or power Doppler ultrasound performed by sonographically experienced clinicians. In the current clinical algorithm, patients lacking a definite tumor diagnosis with sonography are referred for contrast-enhanced imaging techniques such as CT or MRI or have to undergo an invasive procedure such as tumor biopsy. With

Table 2 Diagnostic value of contrast-enhanced ultrasound (CEUS) for tumor differentiation.

CEUS	Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy
All lesions (n = 1 328)	95.8% (n = 723/755)	83.1% (n = 476/573)	95.4%(n = 723/820)	95.9% (n = 476/508)	90.3% (n = 1 199/1 328)
Lesions > 2 cm (n = 999)	96.5% (n = 571/592)	86% (n = 350/407)	96.5% (n = 571/592)	96.4% (n = 350/363)	92.2% (n = 921/999)
Lesions ≤ 2 cm (n = 329)	93.3% (n = 152/163)	75.9% (n = 126/166)	91.5% (n = 152/166)	94.7% (n = 126/133)	84.5% (n = 278/329)

the development of ultrasound contrast agents, we are now able to differentiate liver lesions not only by echomorphology in B-mode and macrovascularization in Doppler mode, but also by assessing lesion microvascularization using ultrasound. The clinical background of the 1349 patients included in this study reflects the reality in most hospitals, where liver tumors are frequently detected as incidental findings (62.3%). However, patients with a known extrahepatic malignancy (27% of patients in our study) and patients with underlying liver cirrhosis (17%) were also included. As usual in clinical practice in Germany, the ultrasound exam was performed with knowledge of the clinical background of the patient and the tumor diagnosis was assessed at the time of CEUS by the clinician performing the exam. Regardless of the patient's clinical background and the provisional tumor diagnosis made by the clinicians, the most important question for CEUS was to clarify whether the lesion was malignant or benign. In our study more than 90% of the 1349 lesions lacking a definite diagnosis in B-mode and Doppler techniques were able to be correctly diagnosed by CEUS with a high predictive value for malignant lesions (PPV > 95%), indicating the high diagnostic value of this new imaging technique. Furthermore, in comparison to the surrounding liver parenchyma the enhancement pattern of liver lesions during the 3 phases of liver perfusion provides a specific criterion for differentiation of malignant and benign liver lesions with a sensitivity of 95.8% and a specificity of 83.1%.

Despite the very high diagnostic accuracy of CEUS in this study (90.3%) there are limitations. CEUS has the same limitations as all ultrasound techniques in patients with extreme meteorism or obesity, and therefore is not suitable for all patients. However, other imaging techniques such as CT or MRI have their own limitations associated with radiation or patient-related factors such as allergies, renal insufficiency, claustrophobia, extreme obesity or interference with metal foreign material [30–33]. Ultrasound contrast agents are safe, well-tolerated and have very few contraindications [34, 35]. Ultrasound is an imaging method that depends on the experience of the examiner (as is true for all diagnostic and especially imaging procedures). Our multicenter trial included ultrasound physicians who had a high level of experience with ultrasound imaging. According to the qualification certificates of the German Society for Ultrasound in Medicine (DEGUM), all participants in the study had a level II or III qualification (more than 6000 or 10000 ultrasound exams) and had worked with ultrasound contrast agents in the liver for more than two years. It is therefore not possible to transfer these results to the broad range of ultrasound diagnostics throughout the country. Training is clearly needed to learn this excellent technique. Furthermore, the use of CEUS is currently limited to a modern high-end ultrasound machines, which are still unavailable at some hospitals due to price. Another limitation of the study may be that there was no blinded review of the images. However, the study was designed to reflect the diagnostic algorithm in clinical reality, where the ultrasound diagnosis of a tumor is made at the time of examination by the physician in knowledge of the clinical context of the patient.

In view of the high accuracy of CEUS, we would like to suggest the immediate use of CEUS in the diagnostic algorithm for focal liver lesions lacking a definite diagnosis in B-mode and Doppler ultrasound. The immediate use of contrast-enhanced ultrasound shortens the waiting time for patients who are terrified by the diagnosis of an undefined liver tumor. In the case of a confident diagnosis of a benign liver lesion in CEUS, further imaging procedures or biopsy can be avoided. Due to the high number of incidental benign findings in the liver, the use of computed tomography, which exposes the patient to radiation [36], and of costly procedures such as MRI can be reduced by the availability of CEUS in clinical practice. In the case of a malignant tumor diagnosis in CEUS, further imaging will be needed for tumor staging and treatment decisions in many patients. Tumor biopsy remains the method of choice whenever tumor status based on imaging modalities is unclear.

Abbreviations

US = ultrasound, CEUS = contrast-enhanced ultrasound, CT = computed tomography, MRI = magnetic resonance imaging, FNH = focal nodular hyperplasia, HCC = hepatocellular carcinoma.

Conflict of interest: No conflicts of interest exist.

Affiliations

[1] Internal medicine I, University of Erlangen
[2] Internal medicine, KKH Sigmaringen
[3] Internal medicine, KH Reutlingen
[4] Internal medicine, KH Geislingen
[5] Internal medicine, KH Caritas Bad Mergentheim
[6] Internal medicine, University of Tübingen
[7] Internal medicine, University Homburg/Saar
[8] Internal medicine, KH Villingen-Schwenningen
[9] Internal medicine, KH Rendsburg-Eckernförde
[10] internal medicine, Klinikum Gera
[11] Internal medicine, University of Ulm
[12] Internal medicine, KH Kaiserslautern
[13] Internal medicine, Israelitisches Krankenhaus Hamburg
[14] Internal medicine, KH Bayreuth
[15] Radiology, University of Bonn
[16] Research Center, Bracco

References

1 *Edmondson H, Craig J.* Neoplasms of the liver. In: Schiff L (ed). Diseases of the liver. Philadelphia: Lippincott, 1997, 1987; 8th ed: 1109
2 *Karhunen PJ.* Benign hepatic tumors and tumour like conditions in men. J Clin Pathol 1986; 39: 183–188
3 *Rumack CM, Wilson SR, Charboneau JW et al.* Diagnostic ultrasound. 2005; 3 rd ed
4 *Seitz K, Schuler A, Rettenmaier G.* Klinische Sonographie und sonographische Differenzialdiagnose. 2007; 2nd ed
5 *Cosgrove D, Dewbury K, Wilde P.* Clinical Ultrasound: a comprehensive text. 1992
6 *Reinhold C, Hammers L, Taylor CR et al.* Characterization of local hepatic lesions with duplex ultrasound: findings in 198 patients. Am J Roentgenol 1995; 164: 1131–1135
7 *Lee MG, Auh YH, Cho KS et al.* Color Doppler flow imaging of hepatocellular carcinomas: comparison with metastatic tumors and hemangiomas by three step grading color hues. Clin Imaging 1996; 20: 199–203
8 *Strobel D, Raeker S, Martus P et al.* Phase inversion harmonic imaging versus contrast-enhanced power Doppler ultrasound for the characterization of focal liver lesions. Int J Colorectal Dis 2003; 18: 63–72
9 *Burns P, Wilson S.* Focal liver masses: Enhancement patterns on contrast-enhanced images – concordance of US scans with CT scans and MR images. Radiology 2007; 242: 162–174
10 *Catala V, Nicolau C, Vilana R et al.* Characterization of focal liver lesions: comparative study of contrast-enhanced ultrasound versus spiral computed tomography. Eur Radiol 2007; 17: 1066–1073
11 *Liu GJ, Xu HX, Lu MD et al.* Enhancement pattern of hepatocellular carcinoma: comparison of real-time contrast-enhanced ultrasound and contrast-enhanced computed tomography. Clin Imaging 2006; 30: 315–321
12 *Greis C.* Technology overview: SonoVue (Bracco, Milan). Eur Radiol 2004; 14: P11–P15

13 *Celli N, Gaiani S, Piscaglia F et al.* Characterization of liver lesions by real-time contrast-enhanced ultrasonography. Eur J Gastroenterol Hepatol 2007; 19: 3–14
14 *von Herbay A, Vogt C, Willers R et al.* Real-time imaging with the sonographic contrast agent SonoVue: differentiation between benign and malignant hepatic lesions. J Ultrasound Med 2004; 23: 1557–1568
15 *Nicolau C, Vilana R, Catalá V et al.* Importance of evaluating all vascular phases on contrast-enhanced sonography in the differentiation of benign from malignant focal liver lesions. Am J Roentgenol 2006; 186: 158–167
16 *Ricci P, Laghi A, Cantisani V et al.* Contrast-enhanced sonography with SonoVue: enhancement patterns of benign focal liver lesions and correlation with dynamic gadobenate dimeglumine-enhanced MRI. Am J Roentgenol 2005; 184: 821–827
17 *Bleuzen A, Huang C, Olar M et al.* Diagnostic accuracy of contrast-enhanced ultrasound in focal lesions of the liver using cadence contrast pulse sequencing. Ultraschall in Med 2006; 27: 40–48
18 *Xu HX, Liu GJ, Lu MD et al.* Characterization of small focal liver lesions using real-time contrast-enhanced sonography: diagnostic performance analysis in 200 patients. J Ultrasound Med 2006; 25: 349–361
19 *Migaleddu V, Virgilio G, Turilli D et al.* Characterization of focal liver lesions in real time using harmonic imaging with high mechanical index and contrast agent levovist. Am J Roentgenol 2004; 182: 1505–1512
20 *Wen YL, Kudo M, Zheng RQ et al.* Characterization of hepatic tumors: value of contrast-enhanced coded phase-inversion harmonic angio. Am J Roentgenol 2004; 182: 1019–1026
21 *Dietrich CF, Mertens JC, Braden B et al.* Contrast-enhanced ultrasound of histologically proven liver hemangiomas. Hepatology 2007; 45: 1139–1145
22 *Dietrich CF, Schuessler G, Trojan J et al.* Differentiation of focal nodular hyperplasia and hepatocellular adenoma by contrast-enhanced ultrasound. Br J Radiol 2005; 78: 704–707
23 *Strobel D, Kleinecke C, Hänsler J et al.* Contrast-enhanced sonography for the characterisation of hepatocellular carcinomas – correlation with histological differentiation. Ultraschall in Med 2005; 26: 270–276
24 *Mörk H, Ignee A, Schuessler G et al.* Analysis of neuroendocrine tumour metastases in the liver using contrast enhanced ultrasonography. Scand J Gastroenterol 2007; 42: 652–662
25 *Leen E, Ceccotti P, Kalogeropoulou C et al.* Prospective multicenter trial evaluating a novel method of characterizing focal liver lesions using contrast-enhanced sonography. Am J Roentgenol 2006; 186: 1551–1559
26 *Quaia E, Stacul F, Gaiani S et al.* Comparison of diagnostic performance of unenhanced vs. SonoVue – enhanced ultrasonography in focal liver lesions characterization. The experience of three Italian centers. Radiol Med 2004; 108: 71–81
27 *Couinaud C.* Segmental and lobar left hepatectomies, studies on anatomical conditions. J Chir 1952; 68: 697–715
28 *EFSUMB Study Group.* Guidelines for the use of contrast agents in ultrasound. Ultraschall in Med 2004; 25: 249–256
29 *Schneider M, Arditi M, Barrau MB et al.* BR1: a new ultrasonographic contrast agent based on sulfur hexafluoride-filled microbubbles. Invest radiol 1995; 30: 451–457
30 *Thomsen HS, Morcos SK.* Radiographic contrast media. BJU Int 2000; 86: 1–10
31 *US Food and Drug Administration.* Gadolinium-containing contrast agents for magnetic resonance imaging (MRI): Omniscan, OptiMARK, Magnevist, ProHance, and MultiHance. FDA Alert, 2006
32 *Dillman JR, Ellis JH, Cohan RH et al.* Frequency and severity of acute allergic-like reactions to gadolinium-containing i. v. contrast media in children and adults. Am J Roentgenol 2007; 189: 1533–1538
33 *Li A, Wong CS, Wong MK et al.* Acute adverse reactions to magnetic resonance contrast media – gadolinium chelates. Br J Radiol 2006; 79: 368–371
34 *Piscaglia F, Bolondi L Italian Society for Ultrasound in Medicine and Biology (SIUMB) Study Group on Ultrasound Contrast Agents.* The safety of Sonovue in abdominal applications: retrospective analysis of 23188 investigations. Ultrasound Med Biol 2006; 32: 1369–1375
35 *Jakobsen JA, Oyen R, Thomsen HS et al.* Safety of ultrasound contrast agents. Eur Radiol 2005; 15: 941–945
36 *Brenner DJ, Hall EJ.* Computed tomography – an increasing source of radiation exposure. N Engl J Med 2007; 357: 2277–2284