Contrast-Enhanced Ultrasound (CEUS) for the Characterization of Focal Liver Lesions in Clinical Practice (DEGUM Multicenter Trial): CEUS vs. MRI – a Prospective Comparison in 269 Patients

Kontrastverstärkte Sonografie (CEUS) zur Charakterisierung fokaler Leberläsionen in der klinischen Routine (DEGUM-Multicenterstudie): CEUS vs. MRI – ein prospektiver Vergleich bei 269 Patienten

Authors K. Seitz[1], T. Bernatik[2], D. Strobel[2], W. Blank[3], M. Friedrich-Rust[4], H. Strunk[5], C. Greis[6], W. Kratzer[7], A. Schuler[8]

Affiliations Affiliation addresses are listed at the end of the article.

Key words
- liver tumor
- focal liver lesion
- contrast-enhanced ultrasound (CEUS)
- MRI
- tumor characterization

Parts of this manuscript were presented at the Ultraschall Dreiländertreffen 2008 (Davos)

received 3.3.2010
accepted 27.6.2010

Bibliography
DOI http://dx.doi.org/10.1055/s-0029-1245591
Published online July 22, 2010
Ultraschall in Med 2010; 31: 492–499 © Georg Thieme Verlag KG Stuttgart · New York · ISSN 0172-4614

Correspondence
Dr. Karlheinz Seitz
Department of Internal Medicine, District Hospital Sigmaringen
Hohenzollernstr. 40
72488 Sigmaringen
Germany
Tel.: ++ 49/75 71/1 00 22 91
Fax: ++ 49/75 71/1 00 22 83
k.seitz@klksig.de

Zusammenfassung

Ziel: In der prospektiven Studie wurde der diagnostische Stellenwert der CEUS bei neu festgestellten fokalen Leberläsionen im klinischen Routinebetrieb evaluiert. Ein wichtiger Aspekt ist der Vergleich mit der Kernspintomografie (MRI).

Material und Methoden: 1349 Patienten mit im fundamentalen Ultraschall neu entdeckten fokalen Leberläsionen wurden von 05/2004 bis 12/2006 prospektiv mit einer standardisierten CEUS untersucht. Ziel war die Bestimmung der Tumordignität und -entität. 269 Patienten wurden nach der CEUS standardisiert mit MRI untersucht. Die definitive Diagnose stützte sich bei typischem Leberhämangiom und Fokal Nodulärer Hyperplasie (FNH) auf die MRI als „diagnostischen Goldstandard", auf beweisende klinische Befunde, zusätzliches Follow-up (Subgruppe A) oder die Histologie (Subgruppe B). 262 Patienten erfüllten den festgelegten diagnostischen Standard.

Ergebnisse: Im Subkollektiv (n = 262) wurde die Tumordignität mit CEUS und MRI 225-mal (85,9%) und die -entität 204-mal (77,9%) konkordant beurteilt. In Subgruppe A (n = 180) war die Tumordignität in 169 (93,2%) und die -entität in 160 Fällen (88,9%) konkordant, hier dominierten Leberhämangiome (n = 122) und FNH (n = 43). Die Subgruppe B (n = 82) beinhaltete überwiegend maligne Läsionen (n = 55), nur wenige Hämangiome (n = 8) und FNH (n = 5). Die Tumordignität war konkordant in 56 (68,3%), die -entität in 44 Fällen (53,7%). CEUS und MRI ließen keine statistisch gesicherten Unterschiede erkennen.

Schlussfolgerung: CEUS und MRI sind in der klinischen Routine zur Charakterisierung und Differenzierung neu entdeckter Lebertumoren gleichwertig. Sie unterscheiden sehr zuverlässig benigne und maligne Läsionen und erkennen Leberhämangiome und FNH sicher. Auch Metastasen und HCC werden mit hoher Sicherheit erkannt.

Abstract

Purpose: The aim of this prospective multicenter study was to assess the diagnostic role of CEUS in the diagnosis of newly discovered focal liver lesions in clinical practice. One important aspect is the comparison of CEUS with magnetic resonance imaging (MRI).

Materials and Methods: From 05/2004 to 12/2006, standardized CEUS was performed prospectively on 1349 patients with focal liver lesions that had been newly detected by fundamental ultrasound in order to determine tumor differentiation and tumor entity. 269 patients had a standardized MRI after CEUS. In typical liver hemangioma and focal nodular hyperplasia (FNH), the definitive diagnosis was based on the MRI as the "diagnostic gold standard" and on clinical evidence and additional follow-up (subgroup A) or on histology (subgroup B). 262 patients met the diagnostic standard that had been set.

Results: In the subcollective (n = 262), the tumor differentiation (malignant or benign) of CEUS and MRI was concordant in 225 cases (85.9%), and the assessment of tumor entity in 204 cases (77.9%). In subgroup A (n = 180), concordant results for tumor differentiation were obtained in 169 (93.2%) and for tumor entity in 160 (88.9%) cases. Liver hemangiomas (n = 122) and FNH (n = 43) were most frequent. Subgroup B (n = 82) comprised mainly malignant liver lesions (n = 55), with only a few of hemangiomas (n = 8) or FNH (n = 5). Tumor differentiation was concordant in 56 (68.3%) and tumor entity in 44 cases (53.7%). There were no statistically proven differences between CEUS and MRI.

Conclusion: CEUS and MRI are of equal value for the differentiation and specification of newly discovered liver tumors in clinical practice. CEUS and MRI are extremely reliable for the differentiation of benign and malignant lesions, the diagnosis of liver hemangiomas and FNH. The characterization of metastases and HCC is also very reliable.

Introduction

The detection and characterization of focal liver lesions in routine examinations under different clinical conditions is a diagnostic challenge, because there is a wide range of possible diagnoses that can often be either harmless or life-threatening. Focal liver lesions are often first discovered by fundamental ultrasonography, which can only establish a definitive diagnosis of simple cysts, hyperechoic hemangiomas in non-steatotic livers and focal fatty sparing lesions [1]. Following several studies regarding the detection, characterization and differentiation of liver tumors, two guidelines for CEUS have been published [2, 3]. This has also long been described in textbooks [1, 4] but has not yet become part of routine clinical practice [5–8]. The introduction of ultrasound contrast agents has led to some competition between imaging techniques used to diagnose liver disease. The purpose of the DEGUM multicenter study is to investigate the performance of CEUS in a large patient cohort with focal liver lesions recently discovered by fundamental ultrasound but not yet diagnosed definitively. Several articles from this study covering topics such as diagnostic accuracy, tumor vascularity and "CEUS vs. spiral CT" have already been published in this journal [9–11]. The study presented here fits perfectly into this series, and compares CEUS with MRI, a much more complex technique in terms of the equipment required.

Materials and Methods

Basic information about the DEGUM multicenter trial relating to the accuracy of a total of 1349 cases has been described in detail by Strobel et al. [9]. Therefore, the following description refers only to the subcollective of 269 patients who were examined with both CEUS and MRI.

Study Population

This study was approved by the ethical review board of the University of Erlangen. All patients gave written informed consent. Consecutive patients with a newly detected focal liver lesion visible during routine ultrasound were recruited for CEUS at the time of the initial US examination. Patients with typical findings of simple cysts, hyperechoic hemangioma in a non-steatotic liver or fatty sparing lesions without clinical signs and symptoms were excluded, as were patients with malignant tumors infiltrating hepatic vessels. No patients had to be excluded because they were suffering from critical diseases, pulmonary hypertension, or unstable angina, and there were no pregnant or nursing women. The design of the study specified that final tumor diagnosis should be achieved primarily by histology (gold standard). If clinically necessary, an SCT or MRI scan could be ordered by the clinician in the work-up. A total of 1349 patients were included between May 2004 and December 2006. This cohort has already been described in detail [9], as well as a subcollective of 267 patients, who underwent SCT [10]. Another subset of 269 patients, presented here, underwent MRI (**Fig. 1**, **Table 1**). No patient had previously undergone SCT or MRI.

Ultrasound Technique

Ultrasonography was performed by physicians with more than 5 years experience in ultrasound diagnosis of the liver and at least two years experience with CEUS in liver tumors. The US examinations were performed with different "high-end US devices" and different "contrast software" available at the local study centers according to a standardized protocol assessed by a consensus meeting.

Contrast-Enhanced Ultrasound (CEUS)

The second-generation blood pool agent SonoVue® (Bracco, Milan, Italy) was used as the contrast agent for CEUS. The microbubbles consist of a phospholipid shell filled with sulfur hexafluoride [12]. A bolus of 1.2–4.8 ml was administered intravenously in a cubital vein using a 20 G needle followed by a 10 ml saline flush. The amount of SonoVue® was determined by the physician performing CEUS according to the US system, CEUS software and the individual situation. The dose could be doubled or a second bolus could be given to obtain optimal CEUS imaging. Imaging started immediately after the injection for up to 5 minutes (if possible) with a mechanical index < 0.4. Liver tumor characterization and differentiation was based on EFSUMB Guidelines 2004 [2]. The following criteria were used: after IV injection of the microbubbles, the contrast enhancement in the lesion was described in relation to the surround-

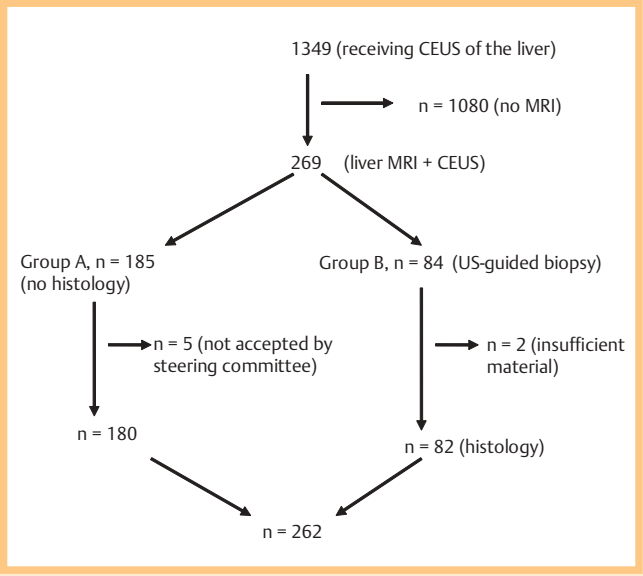

Fig. 1 Study Population.

Abb. 1 Patientenkollektiv.

Table 1 Demographic data and diagnostic standard of the subset with MRI.

total number of patients	269
sex	male 111 female 158
age (y)	mean 52.9 (16–82)
subgroup A (without histology)	185[1]
sex	male 58 female 127
age (y)	mean 49.9 (16–82)
subgroup B (with histology)	84[2]
sex	male 53 female 31
age (y)	mean 59.6 (28–82)

[1] 5 patients were excluded because their definitive clinical diagnosis was not accepted by the steering committee of the study.

[2] In 2 patients histological specification of the tumor was not possible.

ing parenchyma of the liver (hypo-, iso-, hyperenhanced) during the arterial phase (5 – 25 sec), portal phase (25 – 60 sec) and late phase (> 120 sec after bolus injection). The location and distribution of the contrast agent in the lesion (center, periphery) and the specific vascular pattern in the arterial phase (wheel spoke sign, chaotic or irregular arteries, nodular enhancement, rim sign) as well as the portal venous phase (fill-in, wash-out pattern) were documented and described. Contrast enhancement in the late phase was decisive for distinguishing between malignant (hypoenhanced) and benign (iso- or hyperenhanced) lesions. In patients with multiple liver lesions, the dominant lesion (that means lesions suspicious for malignancy or, if probably benign, the biggest lesion) was analyzed first. Lesions with identical fundamental US echogenicity and identical enhancement in the late phase were accepted as lesions with an identical diagnosis. In cases of lesions with different sonomorphology or a different appearance in the late phase, each lesion was analyzed separately with additional contrast agent injection per lesion. All US data were stored as digital images and video clips. The definitive CEUS diagnosis was made at the time of the US examination by the physician performing CEUS.

Magnetic Resonance Imaging (MRI)

The MRI diagnosis was carried out according to the following minimum standards laid down by H. Strunk (Department of Radiology, University Hospital Bonn):

MRI scanner: Minimum 1.5 Tesla

Procedure

1. T1 weighted localizer
2. T2 TSE axial (5 mm slice thickness)
3. T2 TSE SPIR axial (5 mm slice thickness)
4. T1 spoiled TE gradient sequence (FFE, Grasp, Flash), optional in phase and out of phase technique
   Breath-hold axial + if necessary T1 water sel. (5 – 8 mm slice thickness)
5. 3D-TFE dynamics (breath-hold) native, arterial, portal venous using Gd-DTPA (Prohance® 15 ml, Gadoteridol 78.61 mg/ml), 5 – 8 mm slice thickness), in the differential diagnosis of existing lesions that may be hemangiomas or cysts, plus, prior to contrast agent: T2 TSE with long echo time (150 msec)
6. T1 spoiled TE gradient sequence (FFE, Grasp, Flash)
   Breath-hold axial + if necessary T1 water selective. After contrast agent (see above)
7. Optional, after consultation: to rule out HCC in a case of cirrhosis or for pre-operative diagnosis before liver surgery or metastasectomy: Infusion of Endorem® (0.075 ml/kg body weight) or Resovist® (start directly after infusion). The procedure must start within 45 to 60 seconds of the start of infusion.
   T1 TSE axial (TE: 60 msec)
   T2 TSE axial (TE: 90 msec)

The specific details of the MRI under these settings were defined by the local radiologist performing the MRI. All reporting radiologists had access to the patient's clinical information. All MRI studies were reported by senior radiologists on PACS workstations. The MRI criteria for tumor differentiation (malignant or benign) and specification (tumor entity) are well known and widely used [13, 14]. Resovist® was used in 88 of 269 (32.7%) MRI studies. CEUS was performed up to 4 weeks prior to MRI examination.

Tumor Diagnosis Reference (Gold Standard)

This subcollective of patients with liver tumors consists of 269 persons. In 185 patients with 185 analyzed liver lesions (subgroup A), the final diagnosis was always made by MRI or based on proven clinical data including the follow-up. The diagnosis was based on characteristic findings in cases of typical liver hemangioma or FNH [13, 14]. In 121 cases of hemangioma and 41 cases of FNH, MRI diagnosis was generally accepted as the diagnostic gold standard and therefore fine needle biopsy was not in principle ethically justified. 18 cases were diagnosed on the basis of definitive clinical data (biochemical markers, microbiology or additional SCT) and follow-up (minimum: > 6 months). The steering committee of the study ruled out 5 patients since the conditions for achieving a clinically definitive diagnosis were not accepted. Histological diagnosis in 84 patients (subgroup B) was based on ultrasound-guided needle biopsy in 82 cases, while in two cases the histological specimen was not conclusive. The (immuno)histological work was carried out by local pathologists, all of whom had experience with the histology of needle biopsies. Altogether the subcollective consists of 262 patients (subgroup A: n = 180; subgroup B with histology: n = 82). The diagnostic drop-out rate was 7 patients out of 269 (2.6%).

Statistics

All baseline data relating to the patients, US systems, ultrasound examination and MRI examination were analyzed by the local investigators using an anonymized online data form. CEUS and MRI with all relevant diagnostic criteria as well as the histological findings and other essential clinical data were recorded accurately in an online database. The focal liver lesion was assessed as benign, malignant or indeterminate and a specific tumor diagnosis (e.g. FNH, hemangioma, metastasis, HCC) was made, if possible, on the basis of the criteria mentioned above. The database allows us to extract, for instance, different groups of patients, even single CEUS criteria, histological diagnosis and so on for all desired statistical evaluations. For all patients of the presented subcollective, concordance and discordance of tumor differentiation (malignant, benign) as well as tumor-specific diagnoses were calculated. For patients with histological verification (subgroup B), the sensitivity, specificity, accuracy, negative predictive value and positive predictive value were calculated. Indeterminate classifications were rated as false classifications in all calculations. A statistical analysis of subgroup A was not performed because MRI was used as the diagnostic gold standard in most of the cases. The online data forms, quality control of the data, calculations and statistical analysis were performed by Medidata (Konstanz, Germany), an independent professional statistics institute. The service of Medidata was financially supported by Bracco Research (Konstanz, Germany). The authors have exclusive control of the data and information regarding the DEGUM multicenter trial on CEUS for the characterization of focal liver disease.

Results

269 of the 1349 patients taking part in the DEGUM multicenter study assessing CEUS underwent both CEUS and MRI under standardized conditions. The diagnostic gold standard set for the study was achieved in 262 cases, and the drop-out rate was 2.6%. Demographic data are given in **Table 1**. The average age was 52.9 years. There were more women than

men (f:m = 1.4:1). The mean age in subgroup A was around 10 years younger than in subgroup B, and subgroup A was predominantly female (f:m = 2.2:1) while subgroup B was predominantly male (m:f = 1.7:1).

In the whole subcollective concordant results for tumor differentiation (malignant or benign) were obtained in 225 cases (85.9%). Discordant results were found in only 13 patients (5.0%), while the remaining 24 (9.1%) cases were classified as "indeterminate". The results for tumor entity were concordant in 204 of 262 cases (77.9%), discordant in 27 cases (10.3%) and "indeterminate" in 31 cases (11.8%) (**Table 2**). Indeterminate means that no definitive diagnosis could be found by CEUS or MRI regarding tumor differentiation or regarding tumor entity.

In subgroup A, comprising 180 patients without histological verification, matching findings for tumor differentiation (benign or malignant) were obtained in 169 cases (93.2%), while opposing findings were obtained four times (2.2%) and seven cases (4.6%) were indeterminate. 167 of the 169 concordant findings were correct (corresponding with MRI). Subgroup A is made up almost exclusively of benign lesions (177 out of 180), and the number of matching correctly assessed typical findings of liver hemangioma (n = 120) and FNH (n = 41) was accordingly high. Of the three metastases (the only malignant lesions in this subgroup), three were correctly identified by CEUS and two by MRI. The other diagnoses are listed in **Table 3**.

Subgroup B includes 82 patients with histologically confirmed tumor lesions. 55 of these were malignant and 27 benign. Corresponding tumor entities are given in **Table 3**. Matching results in CEUS and MRI for tumor differentiation were obtained for 56 of the 82 lesions (68.3%). The findings were discordant in 9 cases (10.8%), while a significant proportion were classified as "indeterminate" by both CEUS and MRI (n = 17; 20.7%). 48 of the 56 concordant assessments (85.7%) were correct. **Table 4** shows the distribution of concordant, correct, unclear and incorrect tumor differentiation in CEUS and MRI. Tumor entities were concordant in 44 of 82 (53.7%), 17 (20.7%) were discordant and 21 (25.6%) were indeterminate (**Table 2**). 55 of the 82 tumors confirmed by histology (67.1%) were malignant: mainly HCC (n = 29) and metastases (n = 22). Five cases of HCC, metastases and CCC were correctly identified as malignant by both CEUS and MRI, but were incorrectly classified within these entities. The 27 benign tumors included eight hemangiomas and 5 cases of FNH. In subgroup B, CEUS correctly classified 57 of the 82 tumor entities (69.5%), compared with 51 (62.2%) for MRI (**Table 5**).

The most common tumor entities diagnosed with CEUS and MRI for subgroups A and B are summarized in **Table 6**. The statistical analysis of the tumor-specific diagnoses in subgroup B is presented in **Table 7**. Looking at the subgroup as a whole, the values for accuracy, sensitivity, specificity, PPV and

Table 2 Concordant and discordant findings in CEUS vs. MRI.

total (n = 262)	concordance	discordance	indeterminate
tumor differentiation	225 (85.9%)	13 (5.0%)	24 (9.1%)
tumor entity	204 (77.9%)	27 (10.3%)	31 (11.8%)
subgroup A (no histology: n = 180)			
tumor differentiation	169 (93.2%)	4 (2.2%)	7 (4.5%)
tumor entity	160 (88.9%)	10 (5.6%)	10 (5.6%)
subgroup B (with histology: n = 82)			
tumor differentiation of which correct	56 (68.3%) 48	9 (10.9%)	17 (20.7%)
tumor entity of which correct	44 (53.7%) 41	17 (20.7%)	21 (25.6%)

Table 3 Differentiation of diagnosed liver lesions.

diagnosis	subgroup A n = 185 (no histology)	subgroup B n = 84 (with histology)
hemangioma	122[1]	8
FNH	43[1]	5
HCC	–	29
CCC	–	2
liver adenoma	–	1
metastasis	3	22
fatty sparing lesion	2	3
abscess	1	2
necrosis/scar		3
cyst + hemorrhage echinincoccus	4 + 1 2	–2
hemangioendothelioma	–	1
angiosarcoma	–	1
angiomyolipoma	–	1
regenerative nodule	–	1
peliosis	–	1
other benign lesion	2	–
without defined entity	5[2]	2[2]
total	180	82

[1] 2 cases diagnosed by classical finding in concordant CEUS and SCT.
[2] Removed from analysis.

Table 4 CEUS vs. MRI: Results of tumor differentiation in subgroup B (histologically confirmed).

benign histologically confirmed n = 27			malignant histologically confirmed n = 55		
	CEUS	MRI		CEUS	MRI
correct benign	18	17	correct malignant	50	45
CEUS + MRI both correct	14	14	CEUS + MRI both correct	41	41
indeterminate	6	3	indeterminate	3	6
incorrect malignant	3	7	incorrect benign	2	4

NPV tend to be higher for CEUS than for MRI. The difference is just below the threshold for statistical significance. Analysis of the two methods showed that there was also no significant difference between them with respect to the most common tumor entities which are most easily distinguished (hemangioma, FNH, HCC and metastases).

Discussion

Many publications have noted that CEUS of the liver provides significantly more information with regard to the number of tumors, tumor differentiation and specification [15–28], especially when compared with fundamental ultrasound but also in contrast with spiral CT[29–33]. However, CEUS is still not used often enough for various reasons, even though it is well tolerated [5–7]. Large multicenter studies are the only way in which a breakthrough for the widespread and primary use of CEUS in the primary diagnosis of liver tumors can be achieved. The experience of Italian and French investigators [34, 35], together with the first publications from the DEGUM multicenter study [9–11], have more than confirmed experience already available from single-center or small-scale multicenter studies. The DEGUM study was designed to focus specifically on the value of CEUS in everyday clinical practice in cases of unclarified focal liver lesions in the fundamental B-image, as was already explained in our earlier publications. The interesting part of the findings of our study, focusing on the benefits of CEUS in routine clinical practice, is the observation that CEUS is just as good as SCT and MRI in this situation as well, and that the outcomes are not different from conventional radiological studies with blinded review. To date, relatively few large-scale studies have compared the role of CEUS with

Table 5 Subgroup B: Correct diagnoses with CEUS and MRI.

diagnosis	final diagnosis n	CEUS correct positive	MRI correct positive
HCC	29	23	24
Metastasis	22	17	14
Hemangioma	8	5	6
FNH	5	4	3
focal hypersteatosis or hyposteatosis	3	2	
CCC	2	1	1
abscess	2	1	2
echinococcus	2	1	1
necrosis/scar	2		
adenoma	1	1	
regenerative nodule	1		
hemangioendothelioma (malignant)	1	1	
angiosarcoma (malignant)	1	1	
angiomyolipoma	1		
peliosis	1		
“degenerative” lesion	1		
still unclear after biopsy[1]	(2)[1]		
total	84	57	51

[1] Excluded.

Table 6 Diagnoses with CEUS and MRI in common tumor entities in subgroup A and B.

diagnosis	n	CEUS	n	MRI	n
hemangioma subgroup A no histology	122	correct HCC	121 1	correct indeterminate metastasis	120 1 1
Hemangioma subgroup B with histology	8	correct metasasis indeterminate	5 2 1	correct metastasis	6 2
FNH subgroup A no histology	43	correct	43	correct indeterminate	41 2
FNH subgroup B with histology	5	correct adenoma	4 1	correct indeterminate adenoma	3 1 1
HCC subgroup B with histology	29	correct metastasis indeterminate adenoma	23 3 2 1	correct metastasis indeterminate CCC	24 1 3 1
metastasis subgroup B with histology	22	correct CCC malignant/ indeterminate indeterminate hemangioma	17 1 1 2 1	correct CCC indeterminate hemangioma benign/indeterminate benign/cyst benign/scar indeterminate	14 1 2 1 1 1 1 1

Table 7 Diagnostic value of CEUS vs. MRI in subgroup B with histology. All statistical values are given in percent, the values presented in line 1 (all) and 2 (subgroup B) refer to tumor differentiation, benign vs. malignant (Tu Diff).

diagnosis	method	accuracy	sensitivity	specificity	PPV	NPV
All (ref. 9) n = 1328 Tu Diff	CEUS	90.3	95.8	83.1	95.4	95.9
Subgroup B **n = 82** **Tu Diff**	CEUS MRI	82.9 75.6	90.9 81.8	66.7 63.0	94.3 86.5	90.0 81.0
hemangioma n = 8	CEUS MRI	80.5 81.7	62.5 75.0	82.4 82.4	71.4 75.0	96.8 96.8
FNH n = 5	CEUS MRI	84.1 84.1	80.0 60.0	84.4 85.7	100.0 75.0	98.5 98.5
HCC n = 29	CEUS MRI	79.3 78.0	79.3 82.8	79.2 75.5	95.8 82.8	91.3 95.2
metastasis n = 22	CEUS MRI	75.6 73.2	77.3 63.6	75.0 76.7	73.9 73.7	95.7 88.5

that of MRI [36–40]. MRI is an important and powerful, but expensive and time-consuming technique, which is also regarded as nearly noninvasive. The debate surrounding the considerable radiation exposure associated with CT and the possibility that it might trigger cancer [41] has also led to increasing attention being paid to CEUS and MRI as alternative imaging methods. It is therefore important to know which method is most appropriate for any given diagnostic query. The DEGUM study used histological confirmation as the diagnostic gold standard for solid tumors, while SCT or MRI with characteristic contrast agent kinetics was accepted for hemangioma and FNH. Some focal lesions were verified by means of laboratory evidence and a minimum of six months of follow-up. In the DEGUM study individual investigators were given the option of using MRI or spiral CT in their hospitals. The aim was to permit customary diagnostic methods in the everyday work-up and to use the latest technical imaging equipment as necessary.

269 of the 1349 patients with focal liver lesions underwent MRI as a second imaging procedure after CEUS. This is equivalent to 19.9% of the total cohort and is almost the same number of patients as underwent SCT investigation. The drop-out rate of seven patients (2.6%) is low, in line with international experience in multicenter studies, and does not detract from the findings. Concordant tumor differentiation was obtained by CEUS and MRI in the majority of patients (85.9%), and only 2 of 225 concordant findings were incorrect. Discordant tumor differentiation occurred only 13 times (5%). Concordance was slightly lower in the CEUS vs. SCT subcollective (80.5%) of our study [10]. The proportion of concordant findings for tumor entity was 77.9%, close to the figure of 75.2% in our CEUS vs. SCT subcollective. The slight superiority of CEUS findings compared to MRI and SCT is all the more remarkable in view of the fact that the MRI and SCT procedures were carried out in the knowledge of the clinical findings, and blinding versus the CEUS finding was not required either.

A possible objection against the study might be that there could be a selection bias in favor of CEUS due to the study design, because only primarily US-detected focal liver lesions were included. There are two main arguments against this. The results of our previous papers [9–11] are in accordance with the literature as discussed above. With respect to our cohort of 1349 patients, the composition of our cohort and our subcollectives cannot be statistically altered by a potential of an additional 5% of patients with overlooked focal liver lesions. Moreover, we have to keep in mind that we do not have another option for recruiting patients with focal liver lesions in daily practice.

Subgroup A (180 patients) was made up almost exclusively of benign lesions. No other liver malignancies were found, apart from three cases of liver metastasis. These entities are of course heavily over-represented, bearing in mind the fact that MRI was used as the gold standard for diagnosing hemangiomas and FNH (122 hemangiomas and 43 cases of FNH out of a total of 180 cases), and excellent concordance/discordance outcomes were observed (95.6% and 2.2%) for these tumors which are easy to differentiate using CEUS or MRI. For the same reason, very good figures for concordant and discordant diagnoses were also reported for tumor specification (94.4 and 5.6%). These excellent results are achieved when the characteristic contrast agent kinetics criteria of a pure blood pool agent are applied consistently to cases of FNH and hemangioma made up mainly of vascular components, as was shown in our publication on tumor-specific vascularization patterns [11]. The excellent procedure outcomes are plausible since the remaining focal lesions consisted of the three metastases and 12 diagnoses that could certainly be expected, such as a number of fatty sparing lesions that cannot always be clearly defined in a fundamental B-mode image, cysts, and one abscess. These findings confirm that CEUS and MRI produce a high proportion of identical results and are of equal value in cases of liver hemangioma and FNH that are easily and clearly determined. In 161 of the 165 correctly characterized cases of liver hemangioma and FNH that were identified by both techniques (**Table 6**), the conventional CEUS or MRI finding establishes the diagnosis with such a degree of certainty that the combined use of both methods cannot significantly improve the result. If dual investigation does not improve diagnostic accuracy, the corollary is also true: in cases of possible hemangioma or FNH with an uncertain diagnosis, introducing a second imaging technique is only likely to increase certainty in exceptional cases, such as when one technique produces a poor-quality image.

The absence of these easy-to-diagnose tumor entities in a patient subset usually means that the patient subset is “problematic”. This can easily be seen in subgroup B. The differential diagnosis of solid tumors is much broader here, where the number of cases is smaller (**Table 5**). The 82 focal liver lesions included only eight cases of hemangioma and five of FNH. CEUS, MRI and histology were used to diagnose them, but unfortunately our online input mask does not reveal the reason for “triple diagnosis”. 14 other benign lesions of varying etiology and 55 malignant lesions (HCC, CCC, metastases and two angiomatous tumors) completed subgroup B. This mix of malignant, benign and rare tumor entities highlights the limits of any imaging diagnostic technique. The well-known saying “ultrasound does not produce histology” applies to all procedures that employ contrast agents. The proportion of concordant findings with respect to tumor status was only 68.3% in this difficult group (56 out of 80). 10.9% of the findings (9 out of 80) were discordant, and in the remaining 15 indeterminate cases (18.8%) at least one of the techniques used was not even able to determine whether the tumor was benign or malignant (Tables **2** and **4**). This results in a much lower degree of concordance in tumor entity. Only 44 of the 80 cases (53.7%) produced concordant diagnoses, 41 of which were correct. Discordant results were reported in 20.7% of the cases (17 out of 80); this included five cases in which both CEUS and MRI drew incorrect distinctions between HCC, CCC and metastasis. In 27 of the remaining 29 cases, either CEUS or MRI was unable to produce a diagnosis, and in two cases neither of the methods was able to do so. In total, 57 of the cases in subgroup B were correctly diagnosed by CEUS and 51 were correctly diagnosed by MRI.

In statistical terms (**Table 7**), a comparison between CEUS and MRI in this diagnostically problematic subgroup B shows no significant differences with respect to accuracy, sensitivity, specificity, NPV and PPV for the diagnosis of HCC, hemangioma, FNH or metastasis. Understandably, some of the values are much lower than those for the cohort as a whole. When considering the entire subgroup, CEUS tended to perform better, but the difference was just below the threshold for significance. The statistical calculation performed for our CEUS/SCT comparison subgroup, which was almost twice as large (158 patients undergoing histology), found a trend toward better results for both CEUS and SCT [10]. Analysis of our data cannot

provide a clear explanation of this, as we did not inquire as to preference for MRI or SCT. It may be that clinicians used MRI more often than SCT to diagnose tumor entity. This suggestion is in any case backed up by the composition of the two subgroups, with a much higher proportion of simple diagnoses in subgroup A and very hard-to-diagnose cases in subgroup B. The literature [36–39] also shows other strong evidence for CEUS and MRI being equally good. Poorer sensitivity in small HCCs (< 10 to 20 mm) has occasionally been reported [40, 41]. This is hard to understand since we found that small tumors in particular are easier to diagnose with CEUS. Overall, the outcomes for concordance in tumor characterization and tumor specification by CEUS, MRI or SCT are equivalent and highly satisfactory. These outcomes are based on reliable differentiation between benign and malignant processes and tumor specification as hemangiomas, FNH, liver metastases and HCC, which in Western Europe is usually associated with cirrhosis. However, patients are most interested in the certainty of their individual diagnosis. Three studies with different designs [9, 34, 35] found CEUS to produce excellent results in a total of over 2500 patients. It is therefore not surprising that CEUS is regarded as a diagnostic revolution in the ultrasound diagnosis of liver disorders [42]. CEUS can be used for a wide range of applications and is safe [43, 44]. Duplicate investigations are expensive and, as described above, offer little additional information. The advantages of CEUS over SCT and MRI are its known better temporal and spatial resolution as well as its contrast agent dynamics, of which excellent records are available. It is therefore logical that practitioners who have the choice between these three imaging techniques should opt for CEUS, the least invasive procedure, in the first instance. SCT poses problems in terms of radiation and contrast agents, MRI is very time-consuming and the gadolinium-based contrast agent used can in rare cases cause nephrogenic systemic fibrosis, which is a dreadful condition [45, 46]. Practitioners should therefore consider performing USFNB and histology tests to confirm the diagnosis if there is any doubt.

If the quality achieved with CEUS, MRI and SCT is not comparable locally, the quality lack should be analyzed and resolved. The EFSUMB guidelines [3] are extremely helpful in this regard. "CEUS first" [5, 7] should have become accepted practice long ago, but there are various issues: training, equipment, charging to cover costs and in some countries the attitude of the medical profession and whether the use of microbubbles is permitted.

Conclusions

1. CEUS and MRI are equally useful in everyday clinical practice to differentiate between newly discovered solid liver tumors, primarily detected by US.
2. A typical finding of CEUS or MRI is sufficient to diagnose liver hemangiomas and FNH. This means that histological confirmation is usually unnecessary in these cases, and patients with a harmless condition do not have to be exposed to the risk of potentially dangerous post-puncture bleeding.
3. Atypical findings in CEUS or MRI do not lead to a definitive diagnosis. The percentage of non-decisive findings depends on the composition of the analyzed subgroups. Discordant and indeterminate findings are mainly related to rare liver lesions. Ultrasound-guided needle biopsy is therefore still vital both for oncological indications and to establish a definitive diagnosis of rare tumor entities that cannot be adequately assessed by imaging techniques.
4. CEUS should be performed immediately if a fundamental ultrasound discovered a previously unknown liver lesion that is morphologically indistinct in the B-image. This approach is rational, saves a considerable amount of time in reaching a definitive diagnosis, and avoids unnecessary mental distress (tumor anxiety) in many patients.
5. A radiological section imaging technique (MRI, MDCT) is usually necessary in tumor staging (extra-abdominal finding, osseous lesions) and before liver surgery.
6. When performed skillfully, CEUS can substantially reduce the costs of diagnosing liver tumors by avoiding duplicate examinations.
7. Finally, the logistical conditions (quality of equipment, investigator proficiency, adequate remuneration to cover costs) need to be created so that the procedure can become more widely used as a matter of routine.

Abbreviations

CCC: cholangiocellular carcinoma
CEUS: contrast-enhanced ultrasound
DEGUM Deutsche Gesellschaft für Ultraschall in der Medizin
DEGUM German Society for Ultrasound in Medicine
FNH: focal nodular hyperplasia
HCC: hepatocellular carcinoma
MRI: magnetic resonance imaging
PPV: positive predictive value
NPV: negative predictive value
SCT: spiral computed tomograpphy
US: ultrasound

Acknowledgement

The active support of the participating centers for patient recruitment is greatly acknowledged: Department of Internal Medicine, Klinikum Villingen-Schwenningen (G. Kunze), Department of Internal Medicine, KKH Eckernfoerde (D. Becker); Department of Gastroenterology, SRH Waldklinikum Gera (U. Will), Westpfalz Klinikum Kaiserslautern (F.W. Albert), Department of Internal Medicine University of Tuebingen (A. von Herbay).

Affiliations

[1] Department of Internal Medicine, District Hospital Sigmaringen
[2] Department of Medicine I, University of Erlangen
[3] Department of Internal Medicine, Klinikum am Steinenberg Reutlingen
[4] Department of Internal Medicine 1, J-W-Goethe-University Hospital Frankfurt
[5] Department of Radiology, University Hospital Bonn
[6] Braccon Research, Konstanz
[7] Department of Internal Medicine I, University of Ulm
[8] Department of Internal Medicine, Helfenstein Klinik, Geislingen

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