Unclear Focal Liver Lesions in Contrast-Enhanced Ultrasonography – Lessons to be Learned from the DEGUM Multicenter Study for the Characterization of Liver Tumors

Kontrastmittelsonografie zur Charakterisierung fokaler Leberläsionen – DEGUM-Multicenterstudie

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Key words
- abdomen
- ultrasound
- neoplasms

Zusammenfassung

Ziel: Klärung der Problemsituationen der Kontrastmittelsonografie an einem großen multizentrischen Kollektiv.

Material und Methoden: Bei 1349 B-Bild morphologisch unklaren Leberraumforderungen wurde eine Kontrastmittelsonografie (CEUS) nach einem standardisierten Protokoll mit Dokumentation der hämodynamisch relevanten Perfusionsphasen (früharteriell, arteriell, portalvenös, Spätphase nach 2 min) durchgeführt. Die mittels CEUS gestellten Diagnosen wurden mit der Enddiagnose (Histologie: n = 1006; NMR: n = 269; CT: n = 269 – Mehrfachuntersuchung möglich) verglichen.

Ergebnisse: Von den insgesamt 1349 eingeschlossenen Leberläsionen konnten 20 auch nach Ausschöpfen aller zur Verfügung stehenden Ergebnisse inkl. Histologie nicht geklärt werden (im Übrigen 573 benigne und 756 maligne). Mittels CEUS konnten von den 1349 im B-Bild + Duplex unklaren Läsionen 1257 mit einer Richtigkeit von 90,3% bezüglich ihrer Dignität beurteilt werden. Die Sensitivität, Spezifität, die positive und negative Vorhersagekraft für maligne Leberläsionen betrugen 95,8%, 83,1%, 88,2% und 93,7%. Bei 92 Leberläsionen (6,8%) blieb die Diagnose bzw. Dignität auch nach CEUS unklar. Hierbei handelte es sich bei 67 um letztlich benigne Läsionen. Bei 39 Läsionen war die Dignitätsbeurteilung mittels CEUS falsch, wobei allerdings nur bei 8 Läsionen die nach CEUS gestellte Diagnose „sicher benigne" falsch war.

Schlussfolgerung: Die Kontrastmittelsonografie erwies sich auch in dieser multizentrischen Studie als hervorragende Methode zur Klärung von im B-Bild unklaren Leberläsionen. In Einzelfällen ist jedoch die Diagnose benigne Leberläsion falsch.

Abstract

Purpose: To discuss the difficulties of contrast-enhanced ultrasound (CEUS) in a large multi-center trial.

Materials and Methods: CEUS was performed on 1349 liver lesions with an unclear diagnosis after native ultrasound using a standardized protocol (phase inversion; low MI < 0.4; Sonovue Bolus 1.2 – 4.8 ml). The early arterial, arterial, portal venous and late phase > 2 min. were documented. The diagnosis based on CEUS results was compared to the final diagnosis (histology: n = 1006; MRI: n = 269; CT: n = 269 – multiple examinations possible).

Results: Of the 1349 enclosed liver lesions, 20 could not be definitively diagnosed even using all diagnostic steps including histology (the others were proven to be benign n = 573 or malignant n = 756). Of the 1349 unclear liver lesions, 1257 could be differentiated with an accuracy of 90.3% using CEUS. The sensitivity, specificity, and positive and negative predictive value for malignant liver lesions was 95.8%, 83.1%, 88.2% and 93.7% respectively. 92 liver lesions (6.8%) could not be definitively diagnosed using CEUS. Most of them were benign (n = 67) on final diagnosis. The CEUS diagnosis was wrong for 39 lesions. However, only 8 lesions classified as benign by CEUS turned out to be malignant. In 3 cases HCC proven by histology was incorrectly diagnosed by CEUS as adenoma and 2 lesions incorrectly diagnosed by CEUS as FNH turned out to be an HCC and a metastasis. Two lesions diagnosed by CEUS as hemangiomas turned out to be an HCC and a metastasis. One lesion classified as benign by CEUS was ultimately diagnosed as a lymphoma.

Conclusion: Even in this multi-center trial, CEUS proved to be an excellent method for clarifying liver lesions remaining unclear after native ultrasound. The CEUS diagnosis of benign was only incorrect in a few cases.

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Introduction

A large number of frequently found benign focal liver lesions, such as cysts, typical hemangiomas and focal fatty changes, can be characterized clearly and reliably with B-scan ultrasound (US) [1–3]. In addition some malignant liver lesions show clear signs of malignancy such as vascular infiltration and diffuse liver metastases. For the assessment of lesions which remain unclear in basic B-scan ultrasound, contrast-enhanced ultrasound (CEUS) is an excellent diagnostic tool [4–7]. The clinical benefit of CEUS for the assessment of tumor malignancy and tumor-specific diagnosis has been demonstrated in two large multicenter studies [8–11].

Benign lesions are usually characterized by isoenhancement in the late phase of CEUS. In addition the tumor entity of benign lesions can be clarified in the majority of cases of focal nodular hyperplasia (FNH) and hemangioma based on the specific vascularization pattern in the arterial and portal venous phase as described before [9]. Liver metastases are uniformly characterized by contrast hypoenhancement in the late phase. The contrast enhancement pattern of liver metastases in the arterial phase and portal venous phase is variable. Reflecting tumor morphology, hypervascular metastases (e.g. neuroendocrine tumors or melanoma lesions) show pronounced contrast enhancement in the arterial phase, whereas metastases from gastrointestinal adenocarcinoma show minor arterial contrast enhancement.

Primary malignant liver tumors like hepatocellular carcinomas (HCC) are characterized by arterial hyperenhancement in >90% of cases. In addition, an irregular vascular pattern can be identified in the early arterial phase in large (>3 cm) HCC. In the portal venous and late phase, the majority of HCCs show contrast hypoenhancement. However some HCCs remain isoenhanced [12–18]. Using these characteristic tumor vascularity patterns, CEUS can identify tumor malignancy in more than 90% of liver lesions which are unclear in basic B-scan ultrasound.

However, a small number of liver lesions remain unclear even after CEUS or are incorrectly classified by CEUS. In this paper we present the data of the DEGUM multicenter study for characterization of the 1349 liver lesions focusing on lesions, which remain unclear after CEUS or were misleadingly classified by CEUS in order to identify potential pitfalls.

Patients

The approval of this study was given by the local ethical review board. 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 nonsteatotic liver or fatty spearing lesions without clinical signs and symptoms were ruled out as well as patients with malignant tumors infiltrating hepatic vessels. Between 2004 and December 2006, 1349 patients were recruited. Detailed information regarding patient characteristics has been previously described [8].

Contrast-Enhanced Ultrasound (CEUS)

All ultrasound exams were performed by physicians with more than 5 years of experience with diagnostic ultrasound of the liver and at least two years of experience with CEUS in liver tumors. The US examination was performed with various high-end US devices according to a standardized protocol assessed by a consensus meeting. For CEUS the second-generation blood pool agent SonoVue® (Bracco Milano, Italy) was used as the contrast media. A bolus of 1.2–4.8 ml was administered intravenously in a cubital vein using a 20G needle followed by a 10 ml saline flush. The amount of SonoVue® was determined by the physician performing CEUS and was dependent on the US system, CEUS software and the individual situation. To obtain optimal CEUS imaging, the dose could be doubled or a second bolus could be given. Imaging started immediately after injection for up to 5 min (if possible) with a mechanical index <0.4.

Liver tumor characterization and differentiation were based on EFSUMB Guidelines 2004 [17]. The following criteria were used: after I.V. injection of the microbubbles the contrast enhancement in the lesion was described in relation to the surrounding parenchyma of the liver (hypo-, iso-, hyperenhanced) during the arterial phase (5–25 sec), portal phase (25–60 sec) and the late phase (>120sec after bolus injection). The location and distribution of the contrast media in the lesion (center, periphery) and 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) have been previously documented and described in detail [9]. For a full description of the methods, see the partial results already published [8].

Results

Of the total 1349 hepatic lesions, tumor malignancy could be assessed in 1257 using CEUS (**Fig. 1**). Of the 1257 lesions diagnosed using CEUS, 63% were investigated using US systems with Cadence Contrast Pulse Sequencing (CPS) technology, whereas only 37% of the 92 lesions that were non-diagnostic in CEUS were examined by CPS technology. However, various ultrasound systems were involved in this multicenter study. Therefore, the effect of the US system that was used cannot be clearly demonstrated.

Only 92 lesions (6.8%) of 1349 hepatic lesions remained unclear after CEUS (**Fig. 1**). The histological diagnosis was assessed in 86 of these 92 lesions (n=67 benign lesions, n=19

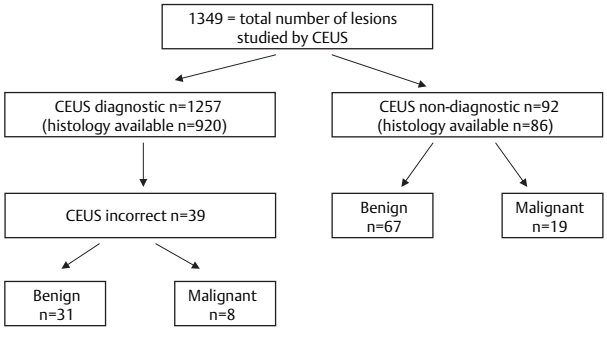

Fig. 1 lesions remaining non-diagnostic after CEUS and lesions with incorrect diagnoses by CEUS.

Abb. 1 Anzahl der nach CEUS unklar gebliebenen oder mit CEUS falsch eingestuften Läsionen

total n = 86	benign lesions n = 67		malignant lesions n = 19	
isoenhancement (n = 30)	hemangioma	8	HCC	9
	regenerative nodule	3	metastasis	1
	adenoma	2		
	focal fat	2		
	FNH	2		
	inflammatory lesion	1		
	peliosis hepatis	1		
	hamartoma	1		
hypoenhancement (n = 56)	FNH	8	metastasis	7
	hemangioma	12	HCC	1
	scarring	3	CCC	1
	abscess	3		
	necrosis	3		
	echinococcus	32		
	hamartoma	2		
	regenerative nodule	2		
	cyst	1		
	focal siderosis	1		
	hematoma	1		
	inflammatory lesion	1		
	angiomyolipoma	1		
	fibrosis	1		
	focal cirrhosis	1		
	adenoma	1		
	granuloma	1		
	lipoma	1		
	Foc. decrease in fat	1		
	Foc. increase in fat	1		

Table 1 Late phase contrast enhancement and histology of 86 liver lesions that were non-diagnostic in CEUS.

Table 2 Lesions incorrectly classified as malignant by CEUS (n = 31).

CEUS diagnosis		final diagnosis (histology)
metastasis	9	hemangioma
metastasis	4	FNH
metastasis	2	Foc. decrease in fat
metastasis	2	adenoma
HCC	6	regenerative nodule/adenoma
metastasis	8	scarring/inflammation

Table 3 Lesions incorrectly classified as benign by CEUS (n = 8).

CEUS diagnosis		final diagnosis (histology)
adenoma	3	HCC
hemangioma	1	HCC
FNH	1	HCC
hemangioma	1	metastasis
FNH	1	metastasis
benign	1	NHL

malignant), while 6 lesions remained unclassified even in histology. The histological tumor diagnoses of the 86 lesions not classified in CEUS are given in **Table 1**. 30 of the 86 lesions were isoenhanced, and 56 were hypoenhanced in the late phase of CEUS. In 10 of 30 lesions with late phase contrast isoenhancement, histology confirmed tumor malignancy including 9 HCCs. These 9 patients did not have a known clinical history or sonomorphological signs of liver cirrhosis. Contrast hypoenhancement in the late phase of CEUS was seen in 56 of 86 lesions which remained unclear in CEUS. 47 of these 56 hypoenhanced lesions were histologically benign, including 12 hemangiomas and 8 focal nodular hyperplasias (FNH).

In 39 of 1257 lesions classified in CEUS, the assessment of tumor malignancy in CEUS was false (**Fig. 1**), including 31 lesions misleadingly classified as malignant and 8 lesions misleadingly classified as benign. Histological diagnoses are given in **Tables 2, 3**.

The incorrect classification of benign lesions as malignant lesions in CEUS was due to contrast hypoenhancement in the late phase. Thus a number of hemangiomas and FNHs also showed hypoenhancement in the late phase (**Fig. 2**).

Malignant lesions incorrectly classified as benign in CEUS (n = 8) were histologically found to be 5 HCCs, 2 metastases and one lymphoma. One neuroendocrine metastasis was misleadingly classified as FNH in CEUS because of strong arterial hyperenhancement with signs of radial vessels and isoenhancement in the portal venous and late phase after 2.5 min (**Fig. 3**).

Discussion

Contrast-enhanced ultrasonography allows reliable accurate diagnosis of tumor malignancy in > 90% of liver lesions which cannot be characterized in conventional B-scan and Doppler ultrasound US [8, 9]. Tumor malignancy remains unclear even after CEUS only in a small number of liver lesions (6.8%). In our study these lesions were predominantly benign with contrast hypoenhancement in the late phase of CEUS. The finding of late phase contrast hypoenhancement in some benign liver lesions can be easily explained by pathomorphology in some lesions like scars and inflammatory pseudotumors. Also in the case of FNH rare variants with pronounced fibrosis as a potential sign of tumor regression have been described. Due to the suspicion of malignancy based on late phase hypoenhance-

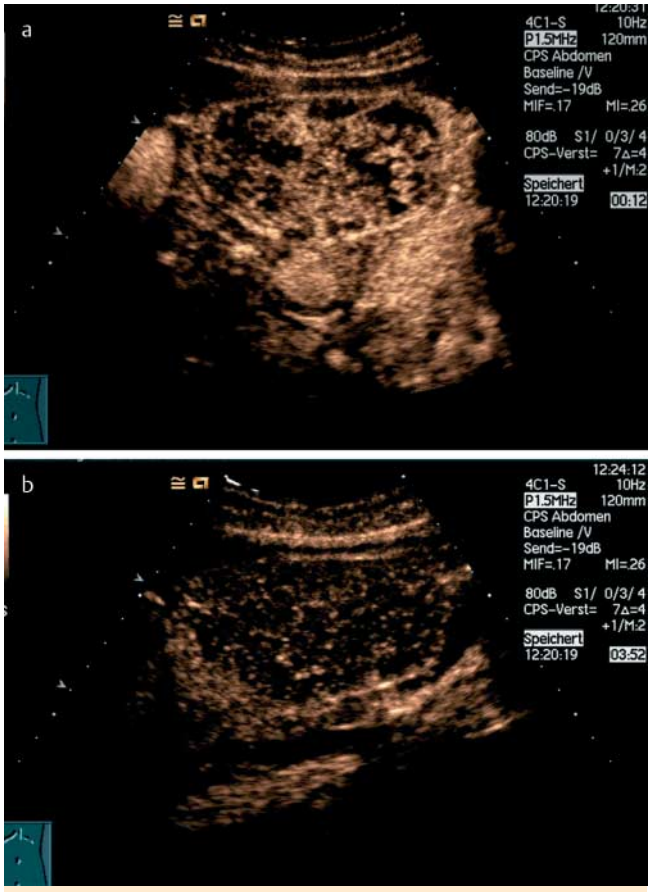

Fig. 2 Image of an FNH in the left hepatic lobe, hypocontrasted in the late phase. **a** Arterial phase with signs of radial vessels with a centripetal course. **b** Late-phase image of the same lesion.

Abb. 2 Darstellung einer in der Spätphase hypokontrastierten FNH im linken Leberlappen. **a** arterielle Phase mit angedeutet radiären Gefäßen mit zentripetalem Verlauf, **b** Spätphasendarstellung derselben Läsion.

ment, tumor diagnosis in these rare FNH variants (6.4% of all FNH in our study) requires tumor biopsy.

Some hemangiomas also showed hypoenhancement in the late phase (22% of all hemangiomas in our study). However, there might also be technical pitfalls which may lead to contrast hypoenhancement in the late phase of CEUS like continuous insonation of a liver lesion or the use of a high mechanical index which leads to bubble destruction especially in the near field or over a longer sonication time. In the case of hemangiomas with very slow fill in of the contrast agent, artificial late phase hypoenhancement may be caused by excessive sonication, particularly when using certain ultrasound systems. The lesson to be learned is not to scan a liver lesion continuously for up to 4 or 5 min. A short continuous sonication time frame from the start of contrast influx in the lesion up to the end of the arterial phase followed by a stop of sonication until the late phase in order to prevent destruction of the contrast agent should be recommended.

Fortunately only a very small number (8/1257) of liver lesions were misleadingly classified as benign, including five cases of HCC. In these HCCs underlying cirrhosis was not known (clinical background of the patient, no signs of cirrhosis in ultrasound). Although it is known that HCC can occur even in a non-cirrhotic liver in a few cases, the diagnosis of HCC in contrast-enhanced imaging techniques depends on the knowledge of cirrhosis. This is also implicated in the European guidelines for the noninvasive diagnosis of HCC which allow diagnosis of HCC in CEUS (and other contrast-enhanced imaging techniques like MRI and CT) only in tumor lesions in cirrhotic livers. This leads to the requirement that all clinical information and B–mode image criteria of liver cirrhosis (including high-frequency ultrasound of the liver surface) have to be assessed in order to minimize this problem.

Two metastases were also incorrectly interpreted as benign lesions due to isoenhancement in the late phase. One potential pitfall could be a late-phase examination stopped prior to wash-out of contrast enhancement. In our study design the start of the late phase was defined as early as 2 min. In hyper-

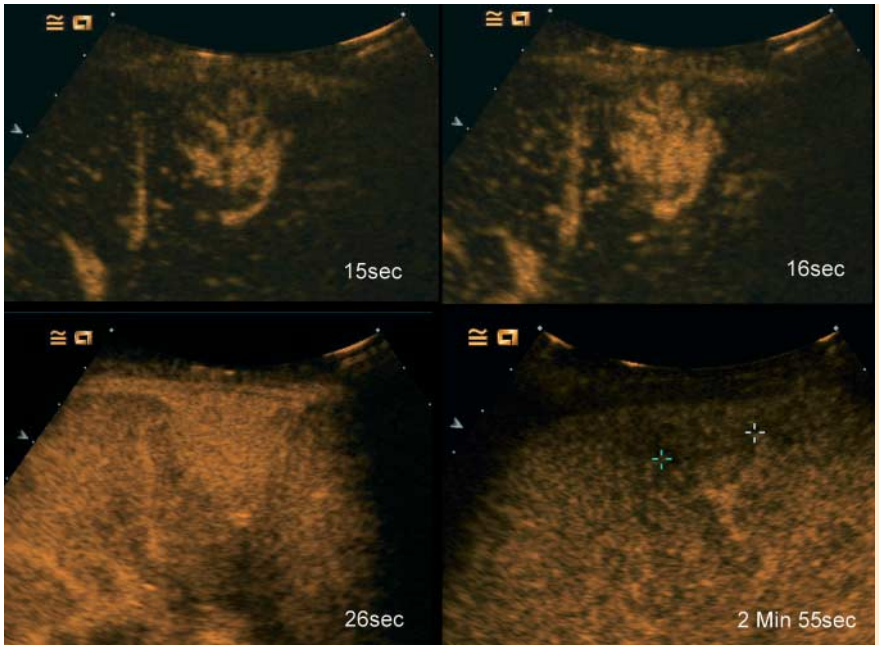

Fig. 3 Metastasis of a neuroendocrine tumor incorrectly interpreted as FNH.

Abb. 3 Metastase eines neuroendokrinen Tumors – nach CEUS als in der Spätphase isoenhanced damit fälschlicherweise als benigne eingestuft.

vascular liver metastases and in some HCC, contrast hypoenhancement in the late phase cannot be identified in the late phase at 2 min, but may be identified at 3 to 4 min. Some small metastases of neuroendocrine tumors might even be isoenhancing for up to 5 min [19]. Therefore, in lesions showing hyperenhancement (hypervascularization) in the arterial phase, the late phase should be examined after at least 4 min so that contrast hypoenhancement is not missed.

A limitation of this presentation is the small number of liver entities which remained unclear in CEUS and the broad histological range of benign liver lesions. Therefore, CEUS, like other imaging techniques, cannot be a substitute for histological evaluation. The high diagnostic reliability of CEUS for the assessment of tumor malignancy in the most frequent liver lesions like hemangioma, FNH, liver metastasis and HCC clearly reduces the need for further imaging techniques and tumor biopsy in benign liver lesions.

Conclusions

1. Only 6.8 % of liver lesions remain unclear in CEUS.
2. CEUS for the characterization of liver lesions should be started with a short continuous scanning interval in the arterial phase followed by a stop of scanning until the late phase.
3. The late phase may be defined at as early as 2 min, but in liver lesions showing arterial hyperenhancement, a second short sonication should be performed at a later time point (at least 4 min). A second bolus injection of contrast media might be needed in case of weak contrast enhancement.
4. Clinical information is essential for the differential diagnosis of all liver lesions but especially in the case of HCC.
5. In liver lesions which remain unclear in CEUS, tumor biopsy has to be considered.

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