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Contrast-enhanced ultrasound (CEUS) has excellent diagnostic accuracy in differentiating focal liver lesions: results from a Swiss tertiary gastroenterological centre

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Summary

INTRODUCTION: Focal liver lesions (FLLs) are common on conventional ultrasound. Contrast-enhanced ultrasound (CEUS) is highly accurate for differentiating between benign and malignant FLLs, with an accuracy comparable to that of contrast-enhanced CT and contrast-enhanced MRI. Notably, there is no evidence supporting the routine use of CEUS for evaluating benign and malignant FLLs in Switzerland. In this study, we assessed the use of CEUS in a clinical routine setting in a tertiary Swiss gastroenterology centre.

METHODS: We analysed all CEUS investigations performed on new or unclear FLLs in our department between November 2011 and March 2013. In all patients, the CEUS results (benign versus malignant FLLs) were compared with CT or MRI findings. To avoid interobserver variation, CEUS was performed by a single experienced gastroenterologist using one ultrasound device (Acuson Sequoia 512®, Siemens, Erlangen, Germany). All patients were examined using the intravenous application of 1.5–2 ml Sonovue®. An FLL with arterial enhancement with wash-out in any vascular phase was defined as a malignant FLL. Malignant FLLs were confirmed by histology.

RESULTS: The study included 112 patients. None of them experienced side effects after injection of Sonovue®. The final diagnoses included malignant FLLs (n = 37) and benign FLLs (n = 75) that ranged in size from 7 to 120 mm. The biopsy-proven malignant FLLs (n = 37) included hepatocellular carcinoma, metastatic cancers, peripheral cholangiocarcinoma and primary B-cell lymphoma. CEUS correctly identified 36 out of 37 malignant FLLs, showing a sensitivity of 96–97.2% and a negative predictive value (NPV) of 94.1–98.5%. In contrast, CT/MRI did not identify three metastatic cancers, one HCC, one peripheral cholangiocarcinoma and one primary B-cell lymphoma in the liver as malignant FLLs, resulting in a sensitivity of 80.6–80.9% and an NPV of 78.9–89.8%. All these malignant FLLs were correctly classified by CEUS.

CONCLUSIONS: In daily clinical practice, CEUS is a fast imaging tool which uses a renal-independent contrast agent and shows excellent accuracy for differentiating between malignant and benign FLLs in about five minutes. The use of CEUS helps to avoid false negative results from CT/MRI and improves sensitivity. CEUS should be the first diagnostic step for investigating new or unclear FLLs.

Keywords: focal liver lesion, contrast-enhanced ultrasound, tumour dignity, benign liver tumour, haemangioma, liver metastasis, differentiation, wash-out, blood pooled contrast agent, sulphur hexafluoride

Introduction

Focal liver lesions (FLLs) are common, with a prevalence of 5% in imaging series [1] and 20% in autopsy series [2]. Conventional ultrasound is most frequently used as the initial imaging modality in the liver. Prospective multicentre

ABBREVIATIONS:

CEUS	contrast-enhanced ultrasound
CI	confidence interval
CT	computed tomography
EASL	European Association for the study of the liver
EFSUMB	European Federation of Societies for Ultrasound in Medicine and Biology
ENT	ear nose throat
EKSG	ethics review committee St Gallen
FLLs	focal liver lesions
FNH	focal nodular hyperplasia
HBV	chronic hepatitis B HCV = chronic hepatitis C
HCC	hepatocellular carcinoma
MRI	magnetic resonance imaging
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NPV	negative predictive value
PPV	positive predictive value
SOR	standard of reference

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trials and meta-analyses report that the accuracy of contrast-enhanced ultrasound (CEUS) for differentiating between benign and malignant FLLs is not inferior to multi-phase, contrast-enhanced computer tomography (CT) or contrast-enhanced magnetic resonance imaging (MRI) [3–6]. CEUS can be performed immediately after conventional ultrasound and is both cost-effective and safe, since patients are not exposed to radiation and side effects are very uncommon [7, 8]. Notably, there is no evidence supporting the routine use of CEUS for evaluating FLLs in a clinical setting, especially in Switzerland. In this study, we assessed the use of CEUS in a clinical routine setting in a tertiary Swiss GI centre. Specifically, we investigated whether CEUS could differentiate between benign and malignant liver tumours.

Materials and methods

We retrospectively analysed all CEUSs of new or unclear FLLs performed at the Kantonsspital St. Gallen in Switzerland between November 2011 and March 2013. The anonymised data acquisition was approved by the ethics review committee of the canton of St Gallen (EKSG13/163). In all patients, the CEUS results (benign versus malignant FLLs) were compared with the corresponding CT or MRI findings. CEUS was performed by a single experienced gastroenterologist (level II or higher according to the EFSUMB [9]) using one ultrasound device (Acuson Sequoia 512®, Siemens, Erlangen, Germany) to avoid interobserver variation. A specific contrast agent (microbubbles, consisting of gas bubbles stabilised by a shell) was administered by an intravenous line. The vascular architecture of the lesion was evaluated in real time and with a higher temporal resolution than is possible with other imaging modalities, and was compared to the adjacent liver tissue. All patients were examined using the intravenous application of Sonovue® (Bracco SpA, Milan, Italy), which was introduced in 2001 and is licensed in Europe. It contains sulphur hexafluoride in a phospholipid shell. This can be performed in the same session using the same ultrasound device if it is equipped with specific software for CEUS. The 1.5 to 2.0 ml contrast agent dose was administered as a bolus injection into the antecubital vein using an intravenous line. The line was at least 20G to avoid microbubble destruction during injection. After injection of Sonovue®, the contrast enhancement of lesions was examined during the three vascular phases, i.e. during the arterial phase, the portal venous phase and the late venous phase (table 1) [8], using a timer. Intermittent scanning lasted up to five minutes. Arterial enhancement ("wash-in") of the contrast agent in an FLL followed by hypoechoic appearance ("wash-out" = black hole in the liver parenchyma) in the portal venous or late venous phase was considered to indicate malignant FLL (fig. 1). We used a high mechanical index / power to destroy the microbubbles during the arterial phase to represent typical vascularisation of the lesion. An FLL with arterial enhancement without wash-out in any vascular phase was defined as a benign FLL [8, 10]. When the results were unclear, the Sonovue® injection was repeated a second or third time. Representative still images and video clips were recorded.

Histology was used as the standard of reference (SOR) (n = 44). In cases that lacked a biopsy of the FLLs, the SOR was defined as either a concordant finding of CEUS with multiphasic CT or MRI (n = 53; intravenous CT contrast agent: Visipaque 320®, GE Healthcare; and intravenous MRI contrast agent: Primovist®, Bayer) or a concordant finding during follow-up CEUS (n = 15; mean follow-up: 41 months). Group A included only patients that had histology as the SOR. Group B included all 112 patients. Malignant FLLs were confirmed by histology. Liver biopsy was performed with a tru-cut needle (Biopince®, Argon Medical Devices, Plano, U.S.A.) over a coaxial needle to avoid tumour seeding. To occlude the needle track in order to avoid tumour seeding and bleeding complications, an absorbable haemostatic gelatine sponge (Spongostan®, Ferrosan Medical Devices A/S, Søborg, Denmark) was injected over the coaxial needle.

Statistics

Due to the retrospective nature of the analysis, it was not possible to statistically analyse the diagnostic accuracy of CEUS versus CT and MRI in all FLLs. We compared the data from patients with FLLs who were analysed with CT/MRI and with CEUS. These dichotomous values are reported as the percentage of assessable patients (%). We determined the sensitivity and specificity, the negative and positive predictive values (NPV and PPV) and the accuracy of each method (CT/MRI and CEUS). If both methods showed concordant results, the result was considered valid. If CT/MRI and CEUS did not agree about whether the lesion was benign or malignant, the FLLs biopsy or the result of follow-up was considered to be the SOR. Confidence intervals (95% CI) for sensitivity, specificity, PPV, NPV and accuracy were calculated by bootstrapping using the package pROC in the statistical software R, version 3.5.1 (URL https://www.R-project.org/).

Results

The study included 112 patients (range 16–86 years), 32 of whom had cirrhosis. Patient characteristics (distribution of gender, age, number of hepatic diseases, type of tumour and indication for initial imaging) are shown in table 2. There were no minor or major side effects after the injection of Sonovue®. In the 112 patients with new or unclear FLL, the final diagnoses included malignant FLLs (n = 37) and benign FLLs (n = 75) that ranged in size from 7–120 mm. The majority of FLLs (63%) were larger than 20 mm in diameter. Thirty-seven percent of FLLs were small (up to 20 mm), and 17% were subcentimetric (<11 mm) (table 3). A total of 44 FLLs were confirmed by histology. The malignant FLLs (n = 37) included hepatocellular carcinoma (HCC) (n = 18; only one patient had chronic hepatitis B but no cirrhosis); metastatic cancer (n = 17); peripheral cholangiocarcinoma in a cirrhotic liver (n = 1); and primary B-cell lymphoma (n = 1) (table 2 and fig. 2). In malignant FLLs, CEUS was the first diagnostic imaging in 62%

Table 1: Vascular phases in contrast-enhanced ultrasound (CEUS) of the liver: visualisation periods (in seconds) after the injection of the contrast agent Sonovue® [8].

Phase	Start (sec.)	End (sec.)
Arterial	10–20	30–45
Portal venous	30–45	120
Late venous	>120	240–360

of the patients (n = 23). The aetiology of all benign FLLs is described in figure 2.

CEUS correctly identified 36 out of 37 malignant FLLs, showing a sensitivity of 96% in group A and of 97.2% in group B. The NPV of CEUS for the classification of malignant FLLs was 94.1–98.5% (table 4). CEUS did not classify one HCC as a malignant FLL because the contrast agent did not show typical wash-in and wash-out patterns in this particular case. In contrast, MRI (n = 4) and CT (n = 2) did not identify three metastatic cancers, one HCC, one peripheral cholangiocarcinoma and one primary B-cell lymphoma in the liver as malignant FLLs. These six false negative results are reflected in the lower sensitivity of 80.6–80.9% and the lower NPV of 78.9–89.8% (table 4). All these malignant FLLs were correctly classified by CEUS. These divergent results are shown in table 5, which summarises all malignant lesions which were misclassified by imaging in comparison to histology.

Table 3: Diameter of focal liver lesions (FLLs).

FLL diameter	n	%
<11 mm	19	17
11–20 mm	23	20
>20 mm	70	63

The diagnosis of benign FLLs was slightly more accurate by CT/MRI than by CEUS: CT/MRI showed a specificity of 93.7–94.6% and a PPV of 89.2–94.4%. CEUS classified 68 out of 75 benign FLLs correctly (specificity 84.2–90.6%, PPV 83.7–88.8%). CEUS showed four false positive results in liver haemangiomas that showed wash-out, and there were three additional cases that were not clearly classified as benign FLLs by CEUS.

The overall diagnostic accuracy of CEUS was 90.9% for histologically-confirmed malignant FLLs, and its overall accuracy in all 112 patients was 92.8% (table 4). This was slightly higher than the accuracy of CT/MRI. The accuracy of CEUS versus CT/MRI was comparable between groups A and B.

Discussion

Focal liver lesions are commonly found with conventional ultrasound in clinical practice. Distinguishing between be-

Figure 1: Contrast-enhanced ultrasound (CEUS) of (A) a cholangiocarcinoma showing early arterial enhancement and (B) wash-out in the venous phase. CEUS of a primary B-cell lymphoma demonstrating (C) early arterial enhancement at 15 seconds and (D) wash-out in the portal venous phase. CEUS of a haemangioma showing centripetal enhancement (E) at 21 seconds and (F) at 43 seconds.

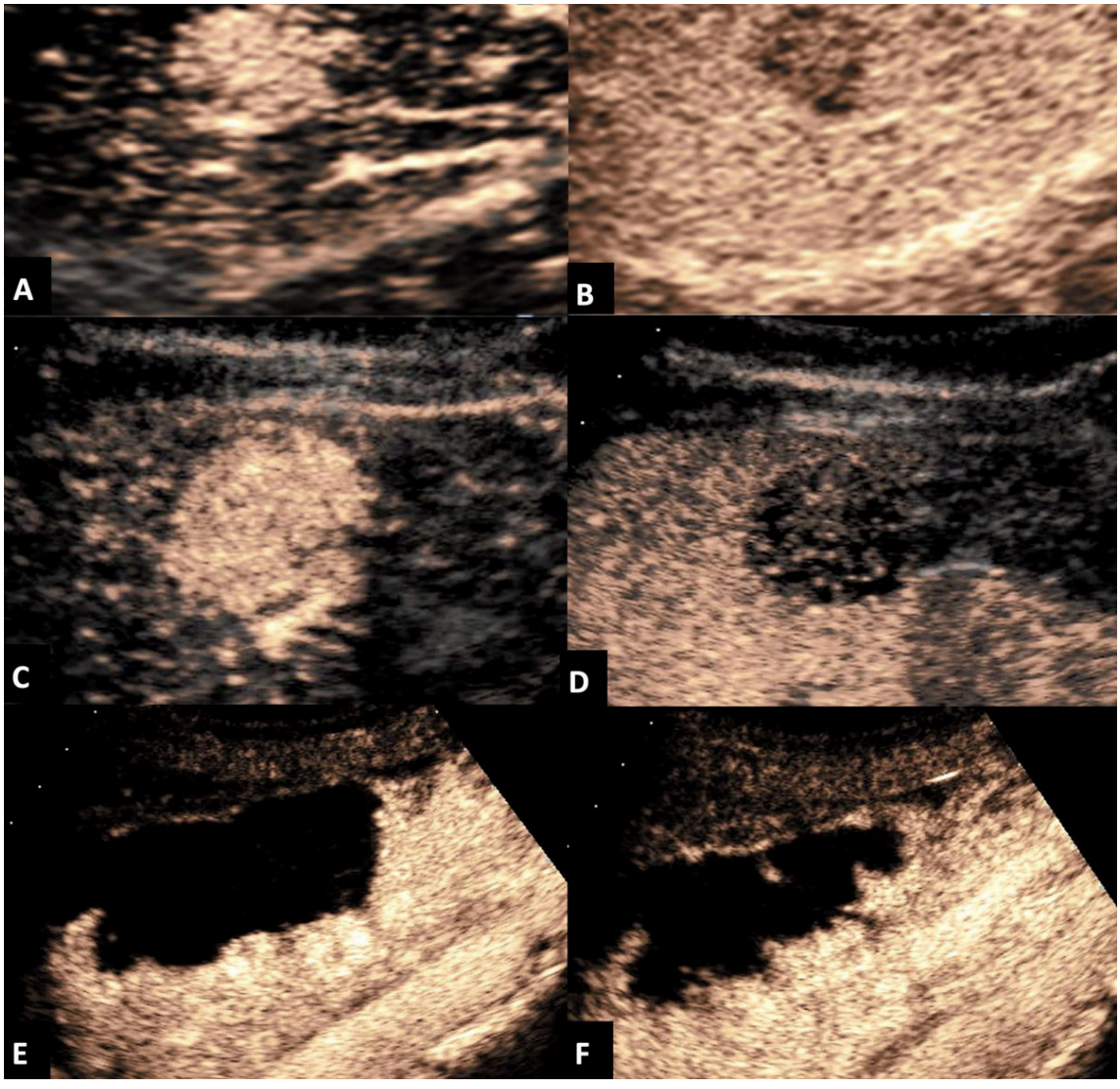


Table 2: Patients characteristics (n = 112).

Patient characteristics	Gender (m/f)		61 / 51
	Age in years (mean/range)		58 / 16–86
Malignant liver lesions (n = 37)			
Gender (m/f)			26 / 11
Age in years (mean/range)			67 / 43-88
Presence of liver disease (n = 19)	Aetiology	Alcoholic	13
		HBV	2
		HCV	2
		NAFLD / NASH	2
	Cirrhosis		15
Type of tumour	Hepatocellular carcinoma		18
	Colon		4
	Pancreas		4
	Cholangio / gallbladder		3
	Lung		2
	ENT, anal, breast, prostate, kidney, lymphoma		6
Indication for imaging	Screening in cirrhosis		16
	Clinical symptoms		7
	Tumour staging		6
	Jaundice / elevated liver enzymes		4
	Incidental finding		2
	Tumour follow-up		2
Benign focal liver lesions (n = 75)			
Gender (m/f)			35 / 40
Age in years (mean/range)			54 / 18-86
Presence of liver disease (n = 30)	Cirrhosis		17
Indication for imaging	Screening in hepatic disease		30
	Incidental finding		26
	Unclear		8
	Extrahepatic neoplasia		7
	Cystic fibrosis		2
	Trauma		2
ENT = ear nose throat; HBV = chronic hepatitis; HCV = chronic hepatitis C; NAFLD = non-alcoholic fatty liver disease; NASH = non-alcoholic steatohepatitis			

nign and malignant FLLs is crucial for determining the next diagnostic and therapeutic steps and for establishing the appropriate follow-up interval. This real-life analysis of CEUS was performed with the intravenous contrast agent Sonovue® (Bracco SpA, Milan, Italy). It analysed the accuracy of CEUS for evaluating both new and unclear

Table 4: Comparison of the diagnostic accuracy of contrast-enhanced ultrasound (CEUS) versus computed tomography / magnetic resonance imaging (CT/MRI). Analysis of the imaging accuracy in patients with histology as the standard of reference (group A, n = 44). Accuracy of imaging techniques in all study patients (group B, n = 112).

Group A	**Sensitivity**	**NPV**	**Specificity**	**PPV**	**Accuracy**
CEUS	97.2%	98.5%	90.6%	83.7%	92.8%
95% CI	91.0 to 100	95.7 to 100	82.7 to 97.3	74.0 to 94.4	87.5 to 97.3
CT/MRI	80.6%	89.8%	94.6%	89.2%	89.6%
95% CI	67.7 to 93.5	83.6 to 96.4	87.5 to 100	78.6 to 100	82.8 to 95.4
Group B	**Sensitivity**	**NPV**	**Specificity**	**PPV**	**Accuracy**
CEUS	96%	94.1%	84.2%	88.8%	90.9%
95% CI	88.0 to 100	82.4 to 100	68.4 to 100	82.4 to 100	81.8 to 97.7
CT/MRI	80.9%	78.9%	93.7%	94.4%	86.4%
95% CI	61.9 to 95.2	65.2 to 94.1	81.2 to 100	83.3 to 100	75.7 to 97.3
CI = confidence interval; NPV = negative predictive value; PPV = positive predictive value					

Table 5: Summary of all malignant lesions which were misclassified by imaging in comparison to histology.

Histology	**CT**	**MRI**	**CEUS**
Metastasis	-	*No metastasis*	Metastasis
Metastasis	*No metastasis*	-	Metastasis
Metastasis	*Not classified*	-	Metastasis
HCC	*Not classified*	*Not classified*	HCC
HCC	-	HCC	*Not classified*
B-cell lymphoma*	-	*Not classified*	Malignant
Cholangiocarcinoma*	-	*Haemangioma*	Malignant

CEUS = contrast-enhanced ultrasound; CT = computed tomography; HCC = hepatocellular carcinoma; MRI = magnetic resonance imaging *Italic type = false negative result* *see figure 1

FLLs compared with CT/MRI. The analysis confirmed the excellent accuracy of CEUS for routine assessment of FLLs in conditions that ensured no interobserver variability and no differences in device resolution due to the use of a single ultrasound device. In experienced hands, we found that CEUS was a simple and safe imaging modality that could differentiate benign FLLs from malignant FLLs in about five minutes with a sensitivity of 96–97.2% for malignant FLLs and a specificity of 84.2–90.6% for benign FLLs. The fact that there was just one false negative CEUS result reflects its excellent sensitivity and a very high NPV. These results were comparable to CT and MRI findings. Our results reproduced the excellent accuracy of CEUS found in prospective multicentre trials and meta-analyses [3–5].

CEUS is not inferior to CT and MRI for differentiating FLLs [4, 5], even for small (≤20 mm) and subcentimetre (<11 mm) FLLs [6]. A meta-analysis of 45 studies involving 8147 FLLs (including 2238 HCCs, 1775 metastatic cancers, 153 cholangiocarcinomas and 583 other malignant FLLs) found that CEUS has a significantly better sensitivity (93%) and a comparable specificity (90%) to CT/MRI, regardless of whether the SOR included histology or whether the studies were blinded or unblinded [3].

The advantage of CEUS is the real-time ultrasound with higher temporal and spatial resolution and the depiction of early arterial phase enhancement, which is sometimes missed in CT and MRI because of their lower frame rates. This could explain the excellent results using CEUS compared to CT and MRI in our study. The most important feature of CEUS for detecting a malignant FLL is the identification of a wash-out that occurs mostly during the portal venous and late venous phases (see table 1). Sonovue® is a pure blood pool agent and is not phagocytosed by reticuloendothelial cells, while the majority of contrast agents for CT and MRI are cleared from the blood pool into the extravascular space [8]. Contrast agents for CT and MRI diffuse into the tumour interstitium while the CEUS contrast agents remain strictly intravascular. Therefore, discordant results have been shown in some lesions during the portal venous and late venous phases [11]. This difference in the pharmacokinetics of the contrast agents could conceal wash-out in CT and MRI and may explain the better sensitivity for malignant FLLs of CEUS (only one false negative result for CEUS and six malignant FLLs missed by CT/MRI in our analysis). Considering our data, the CT/MRI false negative results could have been prevented by using CEUS as the first line imaging modality.

In our analysis, false positive results using CEUS were in most cases due to atypical haemangiomas with arterioportal or arteriovenous shunts that had wash-out patterns which mimicked those of malignant FLLs. We believe that using the newest high-end ultrasound devices and appropriately experienced examiners will likely improve the rate of false positive results for haemangiomas. This is particularly likely when specific centripetal enhancement in the arterial and portal venous phases is demonstrated (see fig. 1).

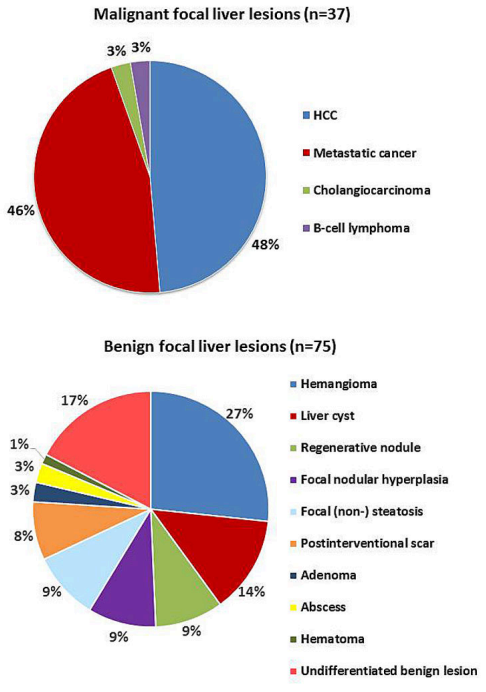
Limitations of our study include the retrospective design and the limited number of patients, particularly when compared to large multicentre studies. A further limitation is the use of different reference standards. Ideally, all lesions would be confirmed by histology, which would serve as the SOR. In our study, malignant lesions were biopsied or resected. We have used histology as the SOR when biopsies were available, and CT/MRI for the remaining lesions. In addition, we have reviewed the follow-up of all liver lesions that were initially classified as benign until March 2019 (mean follow-up: 78 months): none of these lesions were misdiagnosed, all patients remained free of malignancy. CEUS also has some limitations in terms of its use in obese patients, in patients with meteorism and in detecting subdiaphragmatic lesions, especially in segments VI and VII. Under these conditions, FLLs may not be detected by conventional ultrasound or CEUS. CEUS also has limited penetration, especially in steatosis, and deep-seated lesions may not be accessible.

However, CT and especially MRI are not always available and are relatively expensive, which restricts their use. Particularly in young patients, exposure to unnecessary radiation should be avoided. CEUS can be performed immediately after conventional ultrasound without a diagnostic delay, and takes about five minutes.

A major advantage of CEUS is its safety profile. Life-threatening anaphylactic reactions have been reported at a rate of 0.001% in abdominal CEUS, with no deaths in a series of >23,000 patients [7]. Cardio-, hepato- and nephrotoxic effects have not been reported when using CEUS contrast agents. Therefore, there is no need to perform laboratory tests to assess liver, kidney or thyroid function before performing CEUS [12]. In addition, there is some debate regarding MRI contrast agents due to the observation of gadolinium deposition in the liver, brain and bones [13–15].

Regarding the economic impact of CEUS, not only does it have excellent tolerance and safety profiles, but it is also more cost-effective than CT/MRI [16, 17].

Figure 2: Aetiology of malignant and benign focal liver lesions in 112 patients.



Considering its diagnostic value and its safety profile, CEUS is an ideal first line imaging modality for FLLs, especially in non-cirrhotic patients. It has recently been implemented in the guidelines of the European Association for the Study of the Liver (EASL) [18, 19]. The use of CEUS for diagnosing FLLs in patients with liver cirrhosis and for screening for malignant FLLs is not discussed in this paper.

Conclusions

In daily clinical practice, CEUS shows excellent accuracy for differentiating malignant from benign focal liver lesions using a 1.5 to 2 ml intravenous renal-independent contrast agent. CEUS is rapid, with results available in about five minutes, and it has no side effects (with the exception of very rare pseudoallergic reactions). Especially in times of "smarter medicine" and dramatically increasing costs for healthcare, CEUS has the potential to reduce the quantity of CT and MRI imaging and helps to avoid false negative results from CT/MRI, thereby improving sensitivity. We recommend CEUS as first line diagnostic imaging modality for investigating new or unclear FLLs.

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