

Contrast-enhanced ultrasound algorithm (ACR CEUS LI-RADSv 2017) – a valuable tool for the noninvasive diagnosis of hepatocellular carcinoma in patients with chronic liver disease

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Abstract

Aims: to evaluate the accuracy of LR-5 category from the latest Contrast-Enhanced Ultrasound algorithm (ACR CEUS LI-RADSv 2017) for the noninvasive diagnosis of hepatocellular carcinoma (HCC), in a real-life cohort of high-risk patients. **Material and methods:** We retrospectively re-analysed the CEUS studies of 464 focal liver lesions (FLL) in 382 patients at high-risk for HCC (liver cirrhosis of any aetiology, chronic B or C hepatitis with severe fibrosis) using the ACR CEUS LI-RADSv 2017 algorithm. CEUS LI-RADS categories used for the diagnosis of HCC were: CEUS LR-5 (definitely HCC) and CEUS LR-TIV (HCC with macrovascular invasion). Contrast-enhanced CT, contrast-enhanced MRI, or histology were used as diagnostic reference methods to evaluate the CEUS LI-RADS classification of the 464 lesions. **Results:** According to the reference method, the 464 lesions were classified as follows: 359 HCCs, 68 non-HCC-non-malignant lesions and 37 non-HCC malignant lesions. The diagnostic accuracy of LR-5 category for the diagnosis of hepatocellular carcinoma was 76.9%. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were 71.9%, 94.3 %, 97.7% and 49.5%, respectively. **Conclusions:** LR-5 category from ACR CEUS LI-RADSv 2017 algorithm, has good sensitivity, excellent specificity, and PPV for the diagnosis of HCC. The HCC rate increases from LR-3 to LR-5.

Keywords: contrast-enhanced ultrasound; LI-RADS; hepatocellular carcinoma; diagnostic accuracy

Introduction

Hepatocellular carcinoma (HCC) represents more than 90% of primary liver cancers, with increasing incidence in Europe and worldwide [1]. Ultrasound (US) is the first choice imaging technique recommended for HCC screening and surveillance in patients with advanced fibrosis by all worldwide major liver societies [1,2]. Contrast enhanced ultrasound (CEUS) is frequently used for

the focal liver lesions (FLL) diagnosis, showing good diagnostic performance proved by several meta-analyses [3,4]. In daily practice, when an FLL is found in conventional ultrasound, in the same session a CEUS examination can additionally be performed, providing the final diagnostic and enabling early case management.

According to international guidelines, HCC can be diagnosed non-invasively based on a characteristic contrast enhancement pattern – hyperenhancement in the arterial phase followed by gradual and mild washout during the portal venous and late phases [5]. Accurate characterization of FLLs in cirrhotic liver is a main challenge in HCC diagnosis, due to the fact that a typical enhancement pattern is not present in all cases, well-differentiated HCCs often lacking the arterial hyper-enhancement, being iso- or even hypo-enhanced in the arterial phase and some well-differentiated HCC not showing washout [5-7].

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The European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) recommends CEUS to characterize FLLs that remain indeterminate or suspicious for carcinoma after conventional US, for every lesion identified or suspected during US surveillance in high-risk patients for HCC or in patients with a known history of malignancy [5,8]. Previous HCC guidelines of the European (EASL) [9] and American (AASLD) [2] Hepatology Societies do not accept a diagnosis of HCC obtained by CEUS, due to the possibility of misdiagnosis with intrahepatic cholangiocellular carcinoma (ICC) [10,11]. The latest EASL guideline recommends CEUS to be utilised when CT or MRI are contraindicated or inconclusive for HCC diagnosis [1].

The CEUS Liver Imaging Reporting and Data System (LI-RADS) algorithm can be used to issue a structured report for the diagnosis of HCC. The American College of Radiology (ACR) released in September 2017 the second version of a diagnostic algorithm for the characterization of focal liver lesions, in patients at risk of HCC, named the CEUS LI-RADSv 2017 that include eight distinct diagnostic categories: LR-1 (definitely benign), LR-2 (probably benign), LR-3 (intermediate malignancy probability), LR-4 (probably HCC), LR-5 (definitely HCC), LR-NC (cannot be categorized due to image degradation), LR-TIV (tumour in vein) and LR-M (probably or definitely malignant, but not HCC specific) [12].

This study aimed to assess the diagnostic accuracy of LR-5 category for diagnosing HCC in a real-life cohort of high-risk patients, evaluated in a tertiary Gastroenterology and Hepatology Department.

Material and methods

Study design and population selection

This study includes a retrospective re-evaluation of CEUS studies performed in a tertiary Gastroenterology and Hepatology Department in patients at high-risk for HCC (liver cirrhosis of any aetiology, chronic B or C hepatitis with severe fibrosis) diagnosed with at least one focal liver lesion on conventional ultrasound.

A total of 382 patients with 464 focal liver lesions evaluated between January 2010 to December 2018, were included in the final study cohort. The inclusion criteria were: patients at high-risk for HCC (the diagnosis of cirrhosis was established using clinical, biological, US and endoscopic criteria; the stage of fibrosis was assessed noninvasively using elastographic methods: Fibroscan or a point shear-wave elastography); FLL visible on conventional US and evaluated by CEUS; availability of a diagnostic reference standard method (CE-MRI, CE-CT or histology); availability of CEUS information report-

ing the vascular phases (arterial phase pattern; timing of onset and the degree of washout) either from the original report or from the assessment of recorded video clips and images. Patients who received systemic treatment for HCC (sorafenib) and those who had received loco-regional treatment (RFA, Radiofrequency ablation/TACE, Transarterial chemoembolization) were excluded. The study protocol was approved by the local Ethical Committee and was in accordance with the Helsinki Declaration of 1975.

CEUS evaluation

All selected patients underwent conventional B-mode of the liver before CEUS evaluation. CEUS examinations were performed according to the EFSUMB guidelines for the characterization of FLLs [5]. Four physicians with high expertise in hepatobiliary ultrasound and CEUS (level III Experts according to the EFSUMB classification) performed the CEUS examinations. During the study period, two ultrasound machines were used – Siemens Acuson S2000 ultrasound system (Siemens AG, Erlangen, Germany) and LOGIQ E9 system (General Electric Healthcare, Chalfont St Giles, United Kingdom); all contrast studies were performed using SonoVue® (Bracco Spa, Milan, Italy) as contrast agent. The amount of contrast used was different according to the US machines (2.4 ml or 1.6 ml, respectively). A 10 ml saline flush followed every intravenous bolus injection of contrast agent via the cubital vein. The lesion enhancement pattern was assessed and documented (video clips and images of the arterial, portal venous and late phase and a written report of CEUS pattern were recorded for each patient). Vascular phases were defined according to EFSUMB guidelines [5]. FLL enhancement was analysed, and the diagnosis was established according to the EFSUMB Guidelines [5].

CEUS LI-RADS v 2017 algorithm

An independent physician, not involved in the CEUS examination, re-evaluated all CEUS studies (written reports, video clips and images) and classified all FLLs according to the CEUS LI-RADSv 2017 scheme.

Diagnostic reference method

The CEUS LI-RADS diagnosis was compared with the final diagnosis based on the reference diagnostic method (CE-CT, CE-MRI or histology). All cases had CE-CT (n=231) or CT-MRI (n=233); some had both imaging methods (n=36).

The CT scanning protocol of the HCC involves performing a native phase and evaluating with contrast in dynamics. Contrast exploration included three phases with intravenous contrast: 1. Arterial phase (late arterial: 30-35 sec. from the beginning of the injection); 2. Portal phase (60-70 sec); 3. Parenchymal phase (3-5 minutes).

The contrast injection (1-1.5 ml/kg of iodinated contrast) was performed with an automatic syringe at a flow rate of over 3 ml/s.

The MRI scanning protocol involved performing several native sequences [T2 HASTE in the coronal and axial plane, T1 and T2 with extracellular fat suppression (T1FS, T2FS) in the axial plane, T1 with intracellular fat suppression (T1 in-phase and out-of-phase) in the axial plane as well as the diffusion sequence performed in axial plane] and then evaluation with contrast substance in dynamics. In the MRI examination for HCC, two types of contrast substances were used: extracellular contrast (ex: Gadovist) or hepatobiliary contrast with dual extracellular and intracellular behavior (Gd-EOB-DTPA-Primovist; Gd-BOPTA-Multihance). Contrast exploration for HCC characterization included three phases with intravenous contrast: 1. Arterial phase (late arterial <30 sec from the start of the injection); 2. Porto-venous phase (60-70 sec); 3. Extracellular phase (equilibrium)> 120 sec. If a hepatobiliary contrast agent was used, another phase was added - hepatospecific phase (2 hours for Multihance and 20 minutes for Primovist). The injection of the contrast agent is performed with the automatic syringe at a flow rate of 1-2 ml/s in different doses depending on the type of contrast agent administered.

The diagnosis of HCC from CE-CT or CE-MRI was made by the radiologist. The radiological diagnosis was based on the clinical-biological context and the typical enhancement patterns in the vascular phases for HCC.

Statistical Analysis

The statistical analysis was performed using IBM SPSS® statistics for Windows, V 20.0 (Armonk, NY: IBM Corp) and Microsoft Office Excel 2007. We calculated the sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), likelihood ratio and accuracy (Ac) of LR-5 category for HCC diagnosis. The results were expressed as percentages. Quantitative variables are expressed as a mean ± standard deviation, absolute numbers, and percentages.

Results

Patients and nodules characteristics included in the study are presented in Table I. According to patient history, clinical, imaging and endoscopic findings, most patients had liver cirrhosis (85.3%).

In all cases, CE-CT or CE-MRI was available and in 14 (3%) cases, histological findings were also available (4 cases- ICC; 1 case mixed HCC-CC; 6 cases of metastasis of extrahepatic malignancies, 1 case of high-grade dysplastic nodule, 2 cases of neuroendocrine tumours). The percentage of overall malignancy was 85.4% (396/464).

According to the reference methods, the 464 lesions were classified as follows: 359 HCCs, 68 non-HCC-non-malignant lesions (regenerative nodules, haemangiomas, fatty infiltration or simple cysts,) and 37 non-HCC malignant lesions (ICC, liver metastases, other malignancies).

Diagnostic performance

The diagnostic accuracy of LR-5 category for the diagnosis of HCC was 76.9%. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were 71.9%, 94.3 %, 97.7% and 49.5%, respectively. Positive likelihood ratio was 12.5 and negative likelihood ratio was 0.3 for HCC.

Combining LR-4 and LR-5 categories improves diagnostic performance accuracy (90.7%), sensitivity, and NPV in ACR CEUS LI-RADS, but with a lower specificity. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for the fusion of LR-4 and LR-5 were 95.5%, 74.3 %, 92.7%, and 82.9%, respectively.

The LR-5 pattern was described in 264 (56.9%) of all 464 nodules and corresponded to HCC in 258 (97.7%) of cases; the 6 remaining cases were metastasis of extrahepatic malignancies (4 nodules) and high-grade dysplastic

Table I. Baseline characteristics of study patients and nodules.

Patients (n=382)	
Age (years)	63±9.6(24-89)
Male	261(68.3)
Underlying disease	
– cirrhosis	326(85.3)
– chronic B or C hepatitis with severe fibrosis	56(14.7)
Aetiologies of cirrhosis	
HCV	140(42.9)
Alcohol	70(21.5)
HBV	55(16.9)
Multiple aetiologies	45(13.8)
Cryptogenic	16(4.9)
Nodules (n=464)	
Size (mm) on CEUS	4.6±3.2(0.8-17)
Malign	396(85.4)
Final diagnosis according to CE-CT/CE-MRI	
– Regenerative nodule	34(7.3)
– Haemangioma	9(1.9)
– Hepatic adenoma	5(1.1)
– Other specified benign lesions	20(4.3)
– HCC	359(77.4)
– ICC	9(1.9)
– Metastasis	23(5)
– Other specified malignancies	5(1.1)

The results are expressed as mean±SD (range) or number(%). HCV; hepatitis C virus, HBV; hepatitis B virus, CEUS; Contrast enhanced ultrasound, HCC; hepatocellular carcinoma, CE-CT; contrast enhanced computer tomography, CE-MRI; contrast enhanced magnetic resonance imaging.

nodules (2 nodules). There was no case of misdiagnosis with ICC.

The mean nodules' size for all HCCs (n=359) in our studied group was 4.6±3 cm (range, 0.8-6 cm), 28/359 nodules <2 cm and 331/359 ≥2 cm. There were 13/264 HCC nodules <2 cm in size included in the LR-5 category, of which just 1 nodule was incorrectly categorized as HCC.

According to the reference methods, the percentage of HCC in each CEUS LI-RADS category is shown in Table II.

There were 9/464 (1.9%) ICCs in the study cohort, from which 8 lesions were included in the LR-M category. Rim-like and heterogeneous enhancement in the arterial phase and washout in the portal venous and late vascular phases was the CEUS pattern for the ICC lesions. There were no malignant lesions reported in the LR-1 and LR-2 categories.

Examples of CEUS patterns in the three vascular phases corresponding to LR-3, LR-4, LR-5, LR-TIV and LR-M categories are shown in Figure 1-5.

Discussions

Several studies [4,13-15] have shown that CEUS is comparable to CE-CT and CE-MRI in HCC diagnosis. Thus, it can be used as the first step to characterize nodules detected on the US during HCC surveillance in high-risk patients, allowing an early evaluation and further management of the lesion and avoiding unnecessary imaging methods in the case of benign tumours (LR-1 lesions).

Hyperenhancement in the arterial phases is a key feature for HCC diagnosis. According to EFSUMB guidelines [5], a nodule with arterial hyperenhancement without washout in a cirrhotic liver is highly suspicious for HCC and further imaging is needed for the final diagnosis. In our study, hyperenhancement in the arterial phase was observed in 327/359 cases of HCC. Washout in HCC is usually mild and late, after 60 sec, but in some cases, it may be absent [16,17], a fact also observed in our study.

CEUS has a good performance for the diagnosis of HCC, although the size of the nodule can modify the sensitivity [18]. SRUMB (Romanian Society for Ultrasound in Medicine and Biology) study [13] showed lower sensitivity in small HCCs (≤2cm) (56.3%) as compared to HCCs >2cm (78.9%). In our study, CEUS had an overall sensitivity of 73.2% for all HCC; however, only 28 HCCs in our cohort were smaller than <2 cm.

Our results demonstrated that the LR-5 category had excellent specificity and good sensitivity for the diagnosis of HCC, similar to the results shown by Terzi et al in

Table II. Classification of the 464 nodules according to CEUS LI-RADSv 2017 and HCC rate (percentage) according to reference methods.

CEUS LI-RADS categories	Nodules (n=464)	HCC rate
LR-1	22	0(0)
LR-2	8	0(0)
LR-3	26	11(42.3)
LR-4	106	85(80.2)
LR-5	264	258(97.7)
LR-TIV	11*	11(100)
LR-M	38	5(13.2)

The results are expressed as number(%). *All LR-TIV (n=11) were contiguous with CEUS LR-5 and definitely due to HCC. HCC; hepatocellular carcinoma.

a large multicentre retrospective study [16]. The proportion of HCCs increased from LR-3 to LR-5. The HCC rate in LR-4 was 80.2%. We observed that the combination of LR-4 and LR-5 can improve diagnostic performance regarding accuracy, sensitivity and NPV in ACR CEUS LI-RADS, but with a lower specificity.

Differential diagnosis between ICC and HCC can be difficult in patients with liver cirrhosis; the risk of misdiagnosis was the main reason for the exclusion of CEUS as a first-line imaging method, equivalent to CE-CT and CE-MRI, from the previous AASLD and EASL guidelines [9]. However, there is strong evidence from the German DEGUM-Study with over 1000 patients and from the French multicentre study that showed the excellent value of CEUS for the characterization of HCCs [14,15]. We must highlight that in our study, there were no cases of ICC within the LR-5 category. There were 9/464 (1.9%) ICC diagnosed in our study; 8 lesions were included in the LR-M category and 1 lesion in the LR-4 category. The CEUS pattern of the 9 ICCs was: rim-like and heterogeneous enhancement in the arterial phase and washout in the portal venous and late vascular phases.

The CEUS LI-RADS algorithm was developed with the purpose to create standardized reports for HCC diagnosis in order to reduce variation between examiners and diagnostic errors in high-risk patients. Applying this step-by-step algorithm improves interobserver agreement, especially for less experienced examiners. Most studies showed that the LI-RADS system for all imaging methods has a good accuracy for HCC diagnosis [8,16,19,20].

In our study, the diagnostic accuracy of ACR CEUS LI-RADSv 2017 for the diagnosis of hepatocellular carcinoma was 76.9%, comparable to the results shown by An et al [21] in a recent study that compared the diagnostic accuracy of CE-CT and CE-MRI for the characterization of hepatic lesions using the LI-RADS algorithm. The results of this multicenter retrospective study showed that

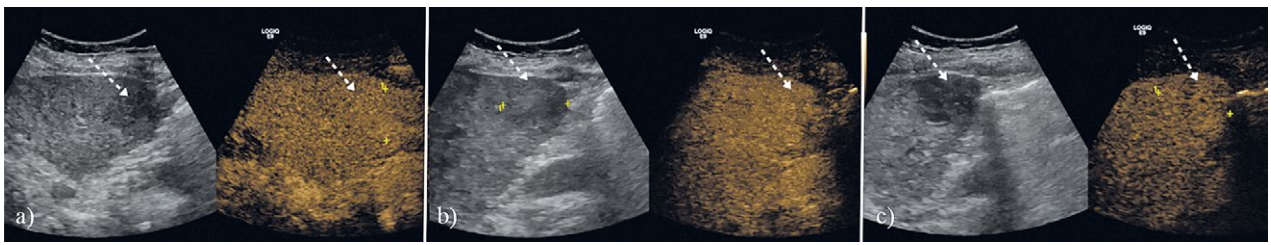


Fig 1. Contrast enhanced ultrasound, arterial phase (a): nodule 3.5 cm in size showing isoenhancement; portal venous phase (b) – showing isoenhancement; late vascular phase (c) – no washout. LR-3 lesion.

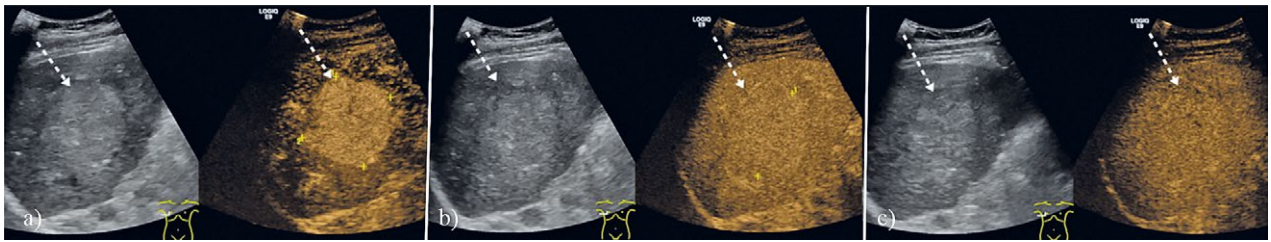


Fig 2. Contrast enhanced ultrasound - arterial phase (a): nodule 6.3 cm in size showing hyperenhancement; portal venous phase (b) – showing isoenhancement; late vascular phase (c) – showing isoenhancement, no washout. LR-4 lesion.

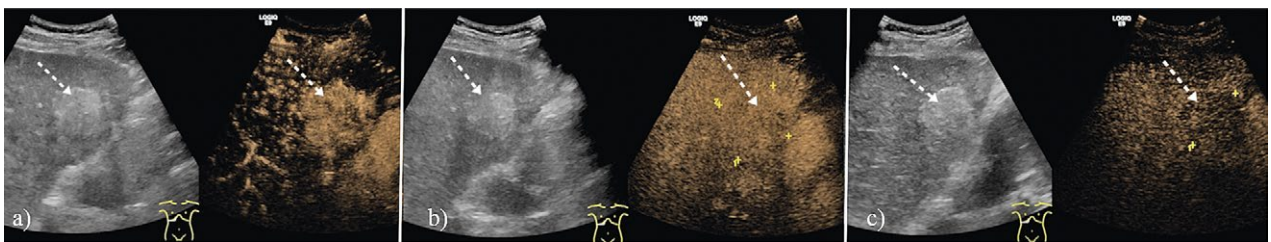


Fig 3. Contrast enhanced ultrasound, arterial phase (a): nodule 5.4 cm in size showing hyperenhancement; portal venous phase (b) – showing isoenhancement; late vascular phase (c) – showing mild and late washout. LR-5 lesion.

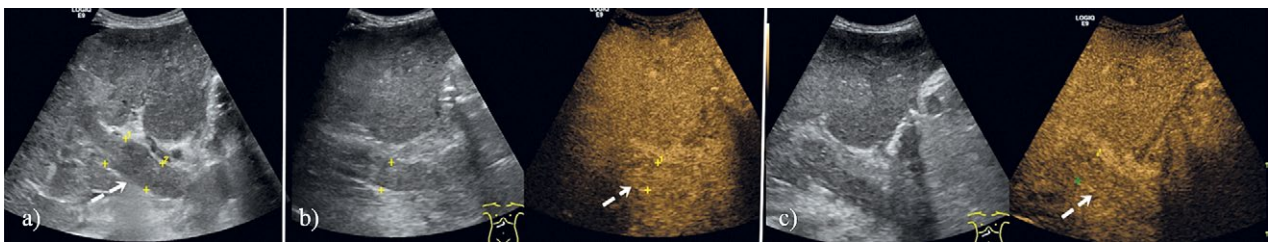


Fig 4. Standard ultrasound (a) and contrast enhanced ultrasound showing complete thrombosis of the portal vein, hyperenhancement of the thrombus in the arterial phase (b) and mild washout (c). LR-TIV.

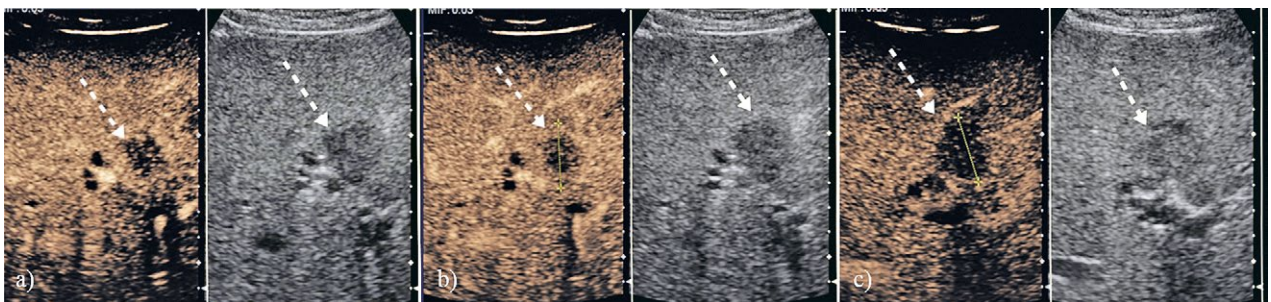


Fig 5. Contrast enhanced ultrasound, arterial (a) and portal venous (b) phase: nodule 2.7 cm in size showing rim hyperenhancement and nonenhancing central area; Late vascular (c) – showing marked washout. LR-M lesion.

MRI has a higher sensitivity and accuracy than CT for diagnosing hepatic malignancies – pooled sensitivities, specificities, and accuracies for categorizing LR-5/5V/M were 59.0% vs. 72.4% (CT vs. MRI; $p < 0.001$), 83.5% vs. 83.9% ($p = 0.906$), and 65.3% vs. 75.3% ($p < 0.001$), respectively.

Recent studies have compared CEUS and CE-CT/CE-MRI's performance to evaluate liver nodules using the LI-RADS reporting system. Zehao Tan et al [22] concluded that CEUS is a useful tool for reassessment of LR-3 or LR-4 lesions on CE-CT/CE-MRI and tends to be HCC if upgraded by CEUS. Ding et al [23] reported that the inter-modality agreement for LI-RADS category between CEUS and CE-CT/CE-MRI was fair (kappa value of 0.319; $p < 0.001$).

The data from our study showed further evidence in favour of the CEUS LI-RADS algorithm – good sensitivity, excellent specificity and PPV for the diagnosis of HCC. The calculated rates of HCC in each LI-RADS category were: LR-3: 42.3% (11/26); LR-4: 80.2% (85/106); LR-M: 13.2% (5/38). These results are comparable with the ones obtained by Terzi et al [16] (LR-3: 47%; LR-4: 86%; LR-M: 44%). The authors recommend biopsy for all LR-M lesions as well as for LR3 and LR4 lesions when CT or MRI are not diagnostic.

The final diagnosis of the remaining lesions from LR-3, LR-4 and LR-M are similar to the results reported by other published studies [16,23]. We observed a high rate of metastasis and a lower rate of HCC in the LR-M category of our study.

The study's strength is given by the large number of lesions analysed by ultrasound experts with a high expertise in hepatobiliary ultrasound and CEUS, all gastroenterologists with the advantage of clinical experience. A recent study performed by Schellhaas et al [24] that compared the sensitivity of CEUS LI-RADS, CEUS ESCULAP and CEUS on-site for HCC diagnosis showed the excellent performance of CEUS on-site. The reason for the high diagnostic accuracy of CEUS on-site was explained by the examiners' clinical experience and ultrasound expertise.

The limitations of the present study are: the retrospective nature, the single-centre study design and the lack of histology in all patients (only 14 biopsies were available). In addition, CT and MRI examinations were performed in radiological centres with different competence levels; therefore, in some cases, a second imaging method was needed for the final diagnosis.

Despite the limitations, our study provides useful information regarding the use of the CEUS LI-RADSv 2017 scheme for HCC diagnosis, supporting its use in daily clinical practice to optimize patient care.

Conclusions

In our study, more than 70% of all HCCs were correctly diagnosed using the LR-5 category from ACR CEUS LI-RADSv 2017 algorithm, demonstrating good sensitivity, excellent specificity, and PPV for the diagnosis of HCC. HCC rate increases from LR-3 to LR-5, and no malignancies were described in the LR-1 and LR-2 categories.

Conflict of interest: none

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