Contrast-enhanced ultrasound liver imaging reporting and data system: Lights and shadows in hepatocellular carcinoma and cholangiocellular carcinoma diagnosis.

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Retrospective Study

Contrast-enhanced ultrasound liver imaging reporting and data system: Lights and shadows in hepatocellular carcinoma and cholangiocellular carcinoma diagnosis.

Vidili G *et al.* CEUS LI-RADS

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Abstract

BACKGROUND

Contrast-enhanced ultrasound (CEUS) is considered a second-line exam compared to computed tomography (CT) and magnetic resonance imaging (MRI) in the diagnosis of hepatocellular carcinoma (HCC), due to the risk of misdiagnosing intrahepatic cholangiocarcinoma (ICC). The advent of CEUS Liver Imaging Reporting And Data System (CEUS LI -RADS) might lead to overcome this limitation. Although data from literature seem promising, its reliability in real-life context has not yet been well established.

AIM

To test the accuracy of CEUS LI-RADS in correctly diagnosing HCC and ICC in cirrhosis.

METHODS

CEUS LI-RADS class was retrospectively assigned to 511 nodules identified in 269 patients affected by liver cirrhosis. The diagnostic standard for all nodules was either biopsy (102 nodules) or CT/MRI (409 nodules). Common diagnostic accuracy indexes such as sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were assessed for the following associations: CEUS LR-5 and HCC; CEUS LR-4 and 5 merged class and HCC; CEUS LR-M and ICC; CEUS LR-3 and malignancy. The frequency of malignant lesions in CEUS LR-3 subgroups with different CEUS patterns was also determined. Inter-rater agreement for CEUS LI-RADS class assignment and for major CEUS pattern identification was evaluated.

RESULTS

CEUS LR-5 predicted HCC with 67.6% sensitivity, 97.7% specificity and 99.3% PPV ($P < 0.001$). The merging of LR-4 and 5 offered an improved 93.9% sensitivity in HCC diagnosis with 94.3% specificity and 98.8% PPV ($P < 0.001$). CEUS LR-M predicted ICC

with 91.3% sensitivity, 96.7% specificity and 99.6% NPV ($P < 0.001$). CEUS LR-3 predominantly included benign lesions (only 28.8% of malignancies). In this class, the hypo-hypo pattern showed a much higher rate of malignant lesions (73.3%) than the iso-iso pattern (2.6%). Inter-rater agreement between internal raters for CEUS-LR class assignment was almost perfect agreement ($n = 511, k = 0.94, P < 0.001$), while the agreement among raters from separate centers was substantial ($n = 50, k = 0.67, P < 0.001$). Agreement was stronger for arterial phase hyperenhancement (internal $k = 0.86$, $P < 2.7 \times 10^{-214}$, external $k = 0.8$, $P < 0.001$) than for washout (internal $k = 0.79$, $P < 1.6 \times 10^{-202}$, external $k = 0.71$, $P < 0.001$).

CONCLUSION

CEUS LI-RADS is effective but can be improved by merging LR-4 and 5 to diagnose HCC and by splitting LR-3 into two subgroups to differentiate iso-iso nodules from other patterns.

Key Words: CEUS LI-RADS; Hepatocellular carcinoma; Intrahepatic cholangiocarcinoma; Cirrhosis; Contrast-enhanced ultrasound; Liver

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Core Tip: This is a retrospective study to evaluate the accuracy of Contrast-Enhanced Liver Imaging-Reporting And Data System (CEUS LI-RADS) in correctly diagnosing hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) in patients with cirrhosis. CEUS LR-5 showed 97.7% specificity for HCC with low sensitivity (67.6%), while the CEUS LR-4 and 5 merged class showed 93.9% sensitivity and 94.3%

specificity for HCC. CEUS LR-M predicted ICC with 91.3% sensitivity and 96.7% specificity. CEUS LR-3 predominantly included benign lesions (28.8% of malignancies) but was heterogeneous as the hypo-hypo pattern showed a higher rate of malignant lesions (73.3%) than the iso-iso pattern (2.6%).

INTRODUCTION

Liver cirrhosis plays an important role as a strong risk factor for primitive liver cancer, the seventh most commonly diagnosed malignancy worldwide and the third most common cause of cancer-related death[1]. In this scenario, the most prevalent malignant lesion is hepatocellular carcinoma (HCC), followed by intrahepatic cholangiocarcinoma (ICC), while other types of cancer are rare. The development of a malignant lesion represents a critical point in the clinical history of chronic liver diseases since it significantly reduces life expectancy, especially in the case of late diagnosis. Therefore, regular follow-up of these patients with six-monthly ultrasonography is mandatory for detecting solid focal liver lesions[2-5]. Contrast-enhanced ultrasound (CEUS) is a valid and safe imaging technique to characterize new onset nodules in liver cirrhosis, and its role is well recognized by national and international guidelines[2,6,7]. One of the limitations attributed to CEUS is the possibility of missing ICC cases, since about half of ICC nodules developed in a cirrhotic liver show the same enhancement pattern of HCC, as it was first reported in 2010[8]. Since then, subsequent studies have demonstrated that the timing and the intensity of the washout are different in HCC and ICC. In particular, for the vast majority of ICC nodules (50%-85%) the washout starts earlier than 60 *s*, while this is rarely observed in HCC. Furthermore, washout intensity during late phase is more marked in ICC than in HCC[9-18]. These findings led the American College of Radiology (ACR) to release the CEUS Liver Imaging Reporting And Data System (CEUS LI-RADS), as already done for computed tomography (CT) and magnetic resonance imaging (MRI). The algorithm was officially approved in June 2016, and the latest update was published in 2017[19].

CEUS LI-RADS is a standardized system for technique, interpretation, reporting, and data collection on focal liver lesions in patients at high risk for HCC. It encompasses features such as size, conventional ultrasound morphology, contrast enhancement behaviors, and dimensional variations in order to stratify the risk of HCC and to avoid ICC misdiagnosis[20-26]. In particular, CEUS LR-5 is a class specifically designed to include HCC. It encompasses nodules > 1 cm that show arterial phase hyperenhancement (APHE) that is not rim nor globular, followed by a late (> 60 *s*) washout of mild degree. Other CEUS LI-RADS categories such as CEUS LR-4 and 3 express a very probable and intermediate risk of HCC respectively, while CEUS LR-M has an intermediate/high risk of malignancy but without a typical HCC pattern. CEUS LR-M includes lesions of any size that show arterial phase rim enhancement pattern and/or early (before 60 *s*) washout and/or marked washout.

So far, only a few studies have shown real-life data resulting from the application of CEUS LI-RADS diagnostic algorithm in cirrhotic patients with suspicious nodules[27-35]. The aim of this study is to test the ability of CEUS LI-RADS to correctly diagnose focal liver lesions in patients affected by cirrhosis. In particular, we tested the accuracy of CEUS LR-5 and LR-M in correctly diagnosing HCC and ICC, respectively. In addition, we merged classes LR-4 and LR-5 and tested their accuracy in correctly diagnosing HCC as a joint class. Finally, we assessed the rate of malignancy for specific LR-3 class patterns.

MATERIALS AND METHODS

Study design and data collection

The present retrospective study involved patients with nodules developed in the presence of cirrhosis and visible at conventional ultrasound, for which it was possible to review the basal appearance and dynamic pattern of the ultrasound contrast agent. Cirrhosis was diagnosed on the basis of clinical data, biochemical parameters, imaging criteria and elastosonography.

We reviewed all the liver CEUS performed at our center (Medical Ultrasound Unit, University Hospital, Sassari, Italy) between December 2008 and January 2020. All exams aimed to characterize a new nodule developed in the context of surveillance programs for liver cirrhosis. Nodules located in different liver segments were analyzed separately with individual boluses of contrast. Within the same segment, only one target nodule was included for analysis based on best visualization criteria.

CT and/or MRI, when typical for HCC or definitely benign (hemangioma, hepatic fat deposition/sparing and hypertrophic pseudomass), were used as the gold standard imaging modalities. For all other cases, histology obtained by a percutaneous biopsy or surgical resection was considered the reference standard (see Figures S1 and S2).

Specifically, nodules showing a CT/MRI dynamic pattern with hyperenhancement during the arterial phase followed by washout in the portal or late phase (Figure S3), were diagnosed as HCC in accordance with both AASLD and AISF guidelines[2,36,37]. Benign lesions received a further two years follow-up; in case of any increase in size and/or CEUS enhancement variations, a biopsy was performed.

All cases in which it was not possible to review the timing and the degree of washout at CEUS (twenty-three cases) were excluded as well as when a validated diagnostic reference standard, either CT/MRI scan or histology, was not available (thirty-five cases). The algorithm of the study is shown in Figure 1.

Contrast-enhanced ultrasound examination and CEUS LI-RADS classification

All CEUS were performed by a physician with fifteen years of experience (G.V.) by using a second-generation ultrasound contrast agent (SonoVue®, Bracco, Milan, Italy).

The signal coming from the bubbles was detected through the following ultrasound scanners:

Acuson Sequoia 512 with 4C1 convex probe and cadence contrast pulse sequencing (CPS, Acuson Siemens, Mountain View, CA, USA) until 2014;

Aixplorer (SuperSonic Imaging, S.A., Aix en Provence, France) with a convex broadband probe (SC6-1) and dedicated software also known as Power Modulated Pulse Inversion (PMPI) from January 2015 until the end of the study.

The CEUS examination was performed continuously for 120 s starting from the injection of contrast. Subsequently, short clips lasting 15-30 *s* were recorded until 5 minutes after injection.

The CEUS LI-RADS patterns were established after evaluation of all clips and images, with particular attention to the behavior of intranodular contrast enhancement in dynamic phases.

The review process was independently performed by two operators (G.V. and M.A.) with fifteen years and two years of experience respectively. In case of disagreement, the class indicated by the more experienced operator was assigned.

The reviewers were blinded to patient identity and to final diagnosis. The specific targets of the review process were:

nodule size;

the presence of APHE and the type of filling (global, rim or peripheral discontinuous globular enhancement);

the presence of washout during portal and parenchymal phases, focusing on its timing (before or after 60 *s*) and intensity (mild or marked); washout before 60 *s* was considered early, while washout happening after 60 *s* was considered late.

Inter-rater reliability of CEUS LI-RADS class assignment and of CEUS major features between the two raters (internal agreement) was evaluated for all the nodules (n = 511). Inter-rater reliability among our center and two other operators from external centers (M.A.Z and G.I., both with more than twenty years of experience in CEUS) was also evaluated for a subgroup of 50 nodules (external agreement). To avoid an excess of typical HCCs, a total of twenty-six HCCs, eleven ICCs, eleven benign lesions, and two other malignancies were randomly selected for the external agreement analysis.

The entire process, including folder preparation, CEUS LI-RADS class assignment and dataset preparation for analysis, had a five-month duration. A systematic review of all CT and MRI scans was not performed.

Statistical Analysis

Descriptive statistics (median, IQR, range, percentage) were calculated for patients demographic and clinical characteristics (age, sex, etiology of cirrhosis, number, and size of nodules). The normal distribution of continuous variables was evaluated through Shapiro-Wilk test. Discrete and qualitative variables were expressed as frequency and percentage.

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), diagnostic accuracy, Youden's index, relative risk, odds ratio (OR), positive likelihood ratio (PLR) and negative likelihood ratio (NLR) were calculated to assess the accuracy of different CEUS-LR classes and subclasses in diagnosing HCC (LR-5, LR-4 and LR-4 and 5 merging class), ICC (LR-M) and malignancies (LR-3). The associations between different CEUS LI-RADS classes and definite diagnosis were evaluated with Pearson's chi-square test or Fisher's exact test. To determine the uncertainty of the estimates on sensitivity, specificity, PPV, NPV, and diagnostic accuracy, 95% confidence intervals (CIs) were calculated.

Cohen's k and Fleiss' k statistics were used to evaluate the interobserver agreement among different examiners in the assignment of the CEUS LI-RADS classes and identification of APHE (absent, homogeneous or rim-like) and washout (absent, late and mild or early and/or marked). In addition, to provide a visual impression of the agreement, a graphical representation was obtained through the agreement chart proposed by Bangdiwala[38].

All statistical tests were considered significant for a P value < 0.05.

Data were analyzed using Stata/MP version 17.0 (Statacorp LP, Texas, USA) and R version 4.1.1 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

A total of 511 nodules identified in 269 patients were considered in this study. Complete data relative to patients and nodules characteristics are shown in Table 1.

Four-hundred-fifty-two out of 511 nodules (88.5%) turned out to be malignant, consisting of 423 HCCs (82.8%), twenty-three ICCs (4.5%), three metastases (0.6%), and

three other malignancies (0.6%). Non-invasive diagnosis was obtained for 409 nodules (80%), while histology was pursued for 102 nodules (20%). Complete data concerning each definite diagnosis rate for every CEUS LI-RADS class are reported in Table 2. Table 3 shows the rate of HCC and ICC in different CEUS LI-RADS classes. The pathological findings for hepatic nodules are shown in Table S1.

The most prevalent pattern in arterial phase was homogeneous APHE (79.1% of all nodules), followed by isoenhancement (12.7%). In portal and late phases the majority of nodules showed a late and mild washout (60.7%) while the second most frequent pattern was isoenhancement (30.7%). See Table 4 and Table 5 for complete data on CEUS pattern in arterial and venous phase respectively.

LR-M nodules

Thirty-seven lesions (7.2%) were assigned to the CEUS LR-M class (Figure 2A). Twenty-one of these nodules turned out to be ICCs, eleven were HCCs, three were metastases, one was a lymphoepithelioma, and one was benign. CEUS LR-M predicted ICC with 91.3% sensitivity, 96.7% specificity, 56.8% PPV, 99.6% NPV, 96.5% diagnostic accuracy, $P < 0.001$ (see Table 6). If we focus on the CEUS behavior of ICC, sixteen out of twenty-one nodules (76%) showed a rim APHE, while eleven out of twenty-one nodules (52%) showed an early washout (see Table S2). HCC nodules reported as LR-M showed a rim APHE in six out of eleven cases (54.5%) and an early washout in seven out of eleven cases (63.6%; see Table S3).

LR 5 nodules

A total of 288 nodules (56.4%) were categorized as CEUS LR-5 (Figure 2B), of which 286 turned out to be HCC, and two were benign lesions. The median diameter of these nodules was 25 mm. The conclusive diagnosis was achieved by CT/MRI for 248 nodules and by histology for 40 nodules. CEUS LR-5 class predicted HCC with 67.6% sensitivity, 97.7% specificity, 99.3% PPV, 38.6% NPV, 72.8% diagnostic accuracy, $P < 0.001$ (see Table 6).

LR 4 nodules

One-hundred-fourteen nodules (22.3%) were reported as CEUS LR-4 (Figure 2C), of which 111 were HCC and three were regenerative nodules as confirmed by histology. The median diameter of these nodules was 21.5 mm. In 95 cases, the diagnosis was given by CT/MRI and in 19 cases by biopsy. CEUS LR-4 predicted HCC with 26.2% sensitivity, 96.6% specificity, 97.4% PPV, 21.4% NPV, 38.4% diagnostic accuracy, $P < 0.001$ (see Table 6). See Table 7 for data relative to different LR-4 patterns.

LR 4-5 merged class

The merging of CEUS LR-4 and CEUS LR-5 classes predicted HCC with 93.9% sensitivity, 94.3% specificity, 98.8% PPV, 76.1% NPV, 93.9% diagnostic accuracy, $P < 0.001$ (see Table 6).

LR 3 nodules

Sixty-six lesions (12.9%) were assigned to the CEUS LR-3 class (Figure 2D-E). Specifically, fifteen of these nodules were HCCs, two were ICCs, two were other malignancies, and forty-seven were benign lesions. The median diameter of these nodules was 16 mm. Fifty-three lesions were diagnosed non-invasively by CT/MRI, while thirteen by biopsy. CEUS LR-3 predicted benign lesions with 79.7% sensitivity, 95.8% specificity, 71.2% PPV, 97.3% NPV, 93.9% diagnostic accuracy, $P < 0.001$ (see Table 6). Nevertheless, lesions belonging to the CEUS LR-3 class showed great heterogeneity. In fact, iso-iso nodules (Figure 1D) were most likely benign (only one malignancy out of thirty-nine nodules), while other patterns showed a higher risk of cancer (eighteen malignancies out of twenty-seven). The second most frequent CEUS LR-3 pattern was the hypo-hypo pattern assigned to fifteen nodules (Figure 1E), of which eleven were malignant (seven HCCs, two ICCs, one lymphoma, and one carcinosarcoma). Rates of malignancy for the CEUS LR-3 class and its subclasses are shown in Figure 3. We calculated the correlation between specific CEUS LR-3

subgroups and malignancy, with analysis limited to CEUS LR-3 nodules (n = 66). We found that CEUS LR-3 iso-iso pattern predicted malignancy with 5.3% sensitivity, 19.1% specificity, 2.6% PPV, 33.3% NPV, 15.2% diagnostic accuracy, $P < 0.001$. Conversely, CEUS LR-3 hypo-hypo pattern predicted malignancy with 57.9% sensitivity, 91.5% specificity, 73.3% PPV, 84.3% NPV, 81.8% diagnostic accuracy, $P < 0.001$ (see Table 6). Table 7 reports data relative to different LR-3 patterns.

LR 1 -2 nodules

Only one nodule (0.2%) was categorized as CEUS LR-1, and five nodules (1%) as CEUS LR-2. All these nodules were found to be benign.

Interobserver agreement

The observed agreement between the two internal raters (X and Y) for the assignment of CEUS LI-RADS class was 95.7%, with Cohen's k = 0.94 (CI: 0.92-0.97, $P < 0.0001$), which accounts for an almost perfect agreement according to Landis and Koch classification[39]. The agreement is clearly visualized in Figure 4. Table S4 shows the assignments of the two raters.

The observed agreement among the three raters from different centers (A, B and C) for the assignment of CEUS LI-RADS class was 68% and Fleiss's k coefficient showed a value of 0.67 ($P < 0.0001$), which accounts for a substantial agreement. In particular, the agreement was almost perfect between raters A and B (k = 0.88, $P < 1.7 \times 10^{-68}$), substantial between raters A and C (k = 0.66, $P < 1.5 \times 10^{-14}$) and substantial between raters B and C (k = 0.61, $P < 8.5 \times 10^{-10}$). The agreement is visualized in Figure 5.

With regards to specific CEUS patterns, we found higher degree of agreement for APHE (internal k = 0.86, $P < 2.7 \times 10^{-214}$, external k = 0.8, $P < 0.001$) than for washout (internal k = 0.79, $P < 1.6 \times 10^{-202}$, external k = 0.71, $P < 0.001$).

DISCUSSION

CEUS LI-RADS is a valuable diagnostic tool for non-invasive differential diagnosis of focal liver lesions in patients with cirrhosis. Based on our experience, employment of this approach improves the performance of CEUS in the characterization of nodules, especially to discriminate between HCC and ICC.

In the current study, CEUS LR-5 was extremely specific for HCC with a very high positive predictive value (99.3%). Only two false-positive results were observed, which were not ICC. We can therefore maintain that CEUS LR-5 is an appropriate tool for non-invasive diagnosis of HCC with virtually no risk of ICC misdiagnosis. Our data agree with recent publications on the subject[28]. However, CEUS LR-5 Lacked sensitivity (67.6%) due to the large number of CEUS LR-4 nodules with a final diagnosis of HCC (97.4%). The high specificity of CEUS LR-5 for HCC combined with low sensitivity is confirmed by a recent prospective multicentric study that compared the accuracy of different CEUS algorithms for the non-invasive diagnosis of HCC[40] and by a recent meta-analysis[41].

Considering the high risk of HCC for the LR-4 class (97.4% PPV), the possibility of merging LR-4 and 5 classes was tested. By doing so, sensitivity in identifying HCC raised from 67.6% to 93.9%. The loss in specificity was low (from 97.7% to 94.3%), and was entirely attributed to two nodules > 10 mm classified as CEUS LR-4, which turned out to be benign. Data from the literature support such approach, showing that around 50% of HCCs do not display any washout in the portal and late venous phases at CEUS. In particular, Giorgio *et al.* demonstrated in their series that 55.4% of the biopsied HCC nodules < 20 mm show this pattern after APHE[42]. To confirm this, another paper written by Leoni *et al.* concluded that the hyper-iso pattern shows a high PPV (94%) for HCC and identifies nodules that are HCC or with a strong tendency to malignant progression. This pattern was detected in 36.2% (46 out 127) of HCCs[43].

In this regard, it should be considered that the introduction of the washout criteria in CEUS is based on findings from studies exploring the role of contrast-enhanced CT in the non-invasive diagnosis of HCC[44-46]. These findings were then extended to CEUS and MRI with little consideration for the differences in the pharmacokinetics of contrast

agents among these techniques and the importance of the nodule visibility at baseline. Indeed, the requirement for washout as a diagnostic criterion is less stringent for CEUS and MRI, since these techniques are better able to evaluate and determine whether APHE reflects the presence of a distinct nodule or merely abnormalities of intrahepatic vessels. CEUS, in particular, is performed to better characterize a nodule that has already been detected through conventional ultrasound.

Unfortunately, the introduction of washout in CEUS has significantly lowered the sensitivity of non-invasive diagnostic criteria for HCC. The inclusion of the hyper-iso pattern among criteria for non-invasive HCC diagnosis might be a solution to increase CEUS sensitivity. Using this strategy, it can be concluded that there is no significant risk of overestimating the diagnosis of HCC, as in our series 98% of the nodules with the hyper-iso pattern were HCCs and only 2% were benign nodules. These considerations and results agree with another paper on the combination of CEUS LR-4 and LR-5 criteria[47]. Furthermore, different studies demonstrated that the identification of washout has higher inter-rater variability than APHE identification[48,49]. These findings are also confirmed by the present study.

Regarding ICC, we observed that the majority of nodules (21/23, 91.3%) were correctly diagnosed using the LR-M class of risk. Only two ICC cases were not assigned to this class due to a hypovascular aspect in all phases. The high sensitivity and specificity of the CEUS LR-M class for ICC (91.3% and 96.7%, respectively) in our series of patients demonstrate that this class is a valuable diagnostic tool for this type of cancer. Still, this class is not entirely specific for ICC as other types of malignancy can be found, such as HCC, metastatic lesions and rarer malignancies[50]. We found that eleven out of thirty-seven nodules (30%) classified as LR–M turned out to be HCC. This was due to the presence of an early washout (63.6% of nodules) and/or a rim enhancement pattern (54.5% of nodules). These observations are in agreement with other papers previously published. In particular, a multicenter retrospective study published by Terzi *et al.* reported that about 40% of LR-M lesions were HCCs[28]. Another study by Wilson *et al.* identified that 35% of HCCs were reported to be LR-M[20]. Other authors

have attempted to decrease the risk of HCC misdiagnosis by proposing a modified LR-M class of risk with the introduction of new criteria, such as the shortening of washout timing to < 45 *s* or the possibility to detect a significant washout to < 3 minutes[51-53]. At the same time, Chen *et al.*were able to reduce the ICC misdiagnosis rate with CEUS LR-M from thirty-eight to twelve cases by considering other criteria such as the presence of an intratumoral vein or an unclear boundary of the intratumoral non-enhanced area[54]. We did not test these new criteria that require validation in multicentric and prospective studies. Another recent paper suggests that the integration of CEUS with the dosage of serum tumor markers (AFP and CA 19.9) improves the differentiation of LR-M nodules[55]. In this scenario, even though there are some limits related to LR-M, the adoption of this class of risk allows improvement of diagnostic performance of CEUS for ICC, overcoming the weak points that caused CEUS to be erased from the diagnostic flow charts of the most important hepatological international guidelines[3,8].

At present, CEUS LR-3 Lesions are considered to hold an intermediate risk of malignancy, which is around 50% according to a recent study published by Terzi *et al.*[28]. This rate was much lower in our case series (28.8%), which might be attributable to the lower figures of our study. Still, looking at data from single centers in the multicentric study by Terzi *et al.*, the rate of HCC in the CEUS LR-3 class ranged between 28.3% and 74.3%. One possible explanation for these results could be the high intrinsic heterogeneity of this class. Indeed, the algorithm only considers either the presence or absence of APHE, without any distinction between isoenhancement and hypoenhancement in all phases. However, in our clinical experience, hypo-hypo lesions are more likely to be malignant than iso-iso lesions. The present study confirms this observation: within the CEUS LR-3 class, the PPV for malignancy moves from 28.8% for CEUS LR-3 overall class to 2.6% for CEUS LR-3 iso-iso nodules and 73.3% for CEUS LR-3 hypo-hypo nodules (Table 5). These considerations agree with papers published before the advent of CEUS LI-RADS, when the problem of hypovascular nodules, which represent around 10% of HCC, was highlighted[56-58]. Likewise, we should be aware of the possibility of detecting ICC nodules in this class when a nodule shows

hypoenhancement in all the phases. This was indeed the case for two out of fifteen (13%) hypo-hypo nodules in our study. In light of these observations, we believe it might be advantageous to split the CEUS LR-3 class into two subgroups (*e.g.*, CEUS LR-3a and CEUS LR-3b) in order to separate iso-iso lesions from other patterns. To the best of our knowledge, this is the first study suggesting a CEUS LR-3 refinement based on real-life results. We believe that more attention should be put on the behavior of the nodule enhancement rather than to the size of the lesion alone.

Finally, the excellent inter-rater reliability of this classification system has been demonstrated. Thus, the use of CEUS LI-RADS in clinical practice could improve the reproducibility of CEUS and partially reduce the gap due to the difference in experience, as suggested by a recent paper[59].

Obviously, our study has some critical shortcomings, namely its retrospective nature and the limited number of nodules analyzed. These drawbacks are explained by the fact that data were collected from a single center. Another debatable aspect of our investigation is the limited number of biopsies. In relation to this, we wish to point out that current guidelines do not routinely recommend biopsy for nodules with typical HCC pattern on CT or MRI[4,37]. HCC is, in fact, the only tumor for which non-invasive imaging diagnostic criteria are recognized, as established since 2005[36].

Further prospective multicentric studies are warranted to confirm our findings and to investigate whether our considerations could be applied to the general population of patients with cirrhosis.

CONCLUSION

The present study supports the use of CEUS LI-RADS in the characterization of focal liver lesions in liver cirrhosis and the usefulness of LR-5 and LR-M classes to diagnose HCC and ICC, respectively. In addition to that, our findings suggest that the merging of LR-4 and LR-5 classes provides innovative benefit in terms of HCC diagnostic accuracy. Furthermore, it seems reasonable to split the CEUS LR-3 class into two subgroups to differentiate the risk of malignancy between iso-iso nodules, which

are more likely to be benign, and other patterns, namely hypo-hypo nodules, which are more likely to be malignant and not specific for HCC.

ARTICLE HIGHLIGHTS

Research background

Patients affected by liver cirrhosis are at high risk of developing hepatocellular carcinoma (HCC) and other malignancies such us intrahepatic cholangiocellular carcinoma (ICC). Diagnostic tools to characterize new-onset nodules in cirrhosis include contrast-enhanced ultrasound (CEUS), but this technique has been challenged for the possibility of misdiagnosing HCC and ICC.

Research motivation

The contrast-enhanced ultrasound liver imaging reporting and data system (CEUS LI-RADS) aims to refine CEUS interpretation in order to better differentiate HCC from other malignancies. Nevertheless, its effectiveness in real-life context has not yet been well established.

Research objectives

To test the accuracy of CEUS LI-RADS in correctly diagnosing HCC and ICC in cirrhosis with LR-5 and LR-M class respectively. To evaluate the performance of LR-4 and 5 merging class in the diagnosis of HCC. To investigate the rate of malignancies in different LR-3 patterns.

Research methods

This study consecutively collected 511 nodules in 269 cirrhotic patients from December 2008 to January 2020. A CEUS LI-RADS class was retrospectively attributed to each nodule based on review of CEUS examination. Common diagnostic accuracy indexes were assessed for the following associations: CEUS LR-5 and HCC; CEUS LR-4 and 5 merged class and HCC; CEUS LR-M and ICC; CEUS LR-3 and malignancy. The

diagnostic standard was either biopsy or CT/MRI. The frequency of malignant lesions in CEUS LR-3 subgroups with different CEUS patterns was also determined.

Research results

CEUS LR-5 showed 97.7% specificity for HCC with low sensitivity (67.6%), while the CEUS LR-4 and 5 merged class showed 93.9% sensitivity and 94.3% specificity for HCC. CEUS LR-M predicted ICC with 91.3% sensitivity and 96.7% specificity. CEUS LR-3 predominantly included benign lesions (28.8% of malignancies) but was heterogeneous as the hypo-hypo pattern showed a higher rate of malignant lesions (73.3%) than the iso-iso pattern (2.6%).

Research conclusions

HCC diagnosis could benefit from the merging of CEUS LI-RADS classes 4 and 5. In addition, the splitting LR-3 class could be advantageous to differentiate iso-iso nodules from other patterns with a higher risk of malignancy.

Research perspectives

Further prospective multicentric studies are necessary to confirm and extend our findings to the general population.

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