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Integration of clinical and biological data into the non-invasive diagnostic management of HCC (LIRADS) algorithm: Contribution for LIRADS-4 nodules

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Abstract

Background: The Liver Imaging Reporting and Data System (LI-RADS) standardizes the interpretation and reporting of imaging examinations in patients at risk for Hepatocellular Carcinoma (HCC). For focal liver nodules LI-RADS assigns categories (LR-1 to 5, LR-M, LR-TIV), which reflect the relative probability of benign or malignant lesion. In this retrospective study, we sought to optimize the diagnosis of Hepatocellular Carcinoma (HCC) in patients with LI-RADS category 4 (LR-4) nodules according to a combination of clinical and biological parameters and LI-RADS 2018 classification.

Materials and methods: Between December 2015 and July 2018, 60 pathologically confirmed nodules were classified LR-4 or LR-5 according to imaging data. Imaging data were correlated with pathological and Clinico-biological data to provide the relative prevalence of HCC using either LI-RADS 2018 criteria alone or together with clinical and biological data.

Results: 60 nodules were analyzed in patients with (sex ratio male/female, 7:2; median age, 66.1 years) liver disease due to hepatitis C virus (n=17), hepatitis B virus (n=6), alcoholic (n=16) or nonalcoholic (n=19) Steatohepatitis, and rare diseases (n=2). Cirrhosis was present in 95% of cases. According to LIRADS 2018 classification 33 nodules were classified LR-4 and 27 were classified LR-5. The global prevalence of HCC was 91% in LR-4 nodules. The prevalence of HCC reached 100% in LR-4 nodules present in patients with chronic viral hepatitis C (present or eradicated), with nonalcoholic steato-hepatitis and / or those with AFP > normal range (Composite LI-RADS Criteria), providing respective sensitivity of 90% (95% CI: 73-98), specificity of 100% (95% CI: 29-100), positive predictive value (PPV) of 100% (95% CI: 87-100) and negative predictive value (NPV) of 50% (95% CI: 12-88).

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Conclusion: These preliminary results suggest that LR-4 nodules in patients with chronic viral hepatitis C, nonalcoholic Steatohepatitis and / or abnormal AFP have a high probability of HCC, and that the integration of these data in a composite clinical and biological LI-RADS criteria could increase the sensitivity of HCC classification without reducing its specificity.

Introduction

Hepatocellular Carcinoma (HCC) is the sixth most prevalent cancer and a leading cause of death from cancer worldwide [1]. Early detection is vital for the successful treatment and prognosis of patients with HCC. Unique among solid organ tumors, HCC may be diagnosed by imaging alone in cirrhotic and other high-risk patients, without the need for biopsy. Diagnosis of HCC is based primarily on contrast-enhanced imaging data, typically Computed Tomography (CT) and Magnetic Resonance (MR) imaging [2,3]. Therefore, there is an ongoing need to improve the predictive value of these non-invasive imaging techniques for the diagnosis of HCC.

The Liver Imaging-Reporting and Data System (LI-RADS) is a comprehensive system for standardizing the acquisition, interpretation, reporting, and data collection of CT and MR liver imaging that is currently applied to patients with HCC risk factors (cirrhosis or hepatitis B infection) [4]. The LI-RADS endorsed by the American College of Radiology, has been updated two years in a row, in 2017 and 2018, in order to become congruent with AASLD guidance recommendations. The LI-RADS is now integrated in the AASLD clinical practice guidance for HCC [3,5]. In LI-RADS 2018, the definition of threshold growth was revised and simplified to ≥50% diameter increase in <6 months to achieve concordance with definitions advocated by AASLD and the Organ Procurement and Transplantation Network (OPTN). Another major revision was applied to 10-19 mm nodules showing nongrim Arterial Phase Hyperenhancement (APHE) with nonperipheral "washout" which are now classified as LR-5, matching the diagnostic rules advocated by AASLD. While there is agreement that LR-5 nodules should be treated as HCC, the appropriate response to LR-4 nodules has not yet been standardized. Some researchers have reported that combining both categories (LR-4 and LR-5) to diagnose HCC yields a marked increase in sensitivity without a concurrent loss in specificity [6-8]. However, others feel that identifying LR-4 nodules as HCC, while increasing sensitivity, results in an unacceptably decrease in specificity, and that the LR-4 and LR-5 categories should not be combined for the diagnosis of HCC [9,10]. Therefore, there is a need to identify additional criteria that can increase the diagnostic accuracy for HCC of the LI-RADS categories, in particular LR-4 nodules.

The purpose of the retrospective study presented here was to optimize the characterization of LR-4 nodules using a combination of clinical and biological criteria in patients with nodules classified as LR-4 in whom, if present, HCC was pathologically confirmed. To this aim, we analyzed a series of resected or biopsied hepatic lesions classified as LR-4 and LR-5 with pathological analysis.

Materials and methods

Patients

This was a retrospective, single-center study approved by the Institutional Review Board (IRB). Between December 2015 and July 2018, all consecutive patients with either liver cirrhosis, or chronic HBV infection, with a liver nodule explored by MR or CT imaging and then by histological analysis were eligible. The following clinical and biological features were recorded: Gender, age, fibrosis stage (assessed with the METAVIR scoring system), risk factors of liver disease, and Alpha-Foetoprotein (AFP) serum levels. We defined abnormal AFP if the value was more than 6 ng/ml [11].

Imaging techniques

CT imaging

All CT examinations were performed at our institution with a multidetector CT (Revolution CT®, GEMS, Milwaukee, USA). All scans were obtained during breath-hold and comprised 4 phases including an unenhanced phase followed by a late arterial phase covering the entire liver using bolus tracking, a portal venous phase (70 to 90s delay after injection) extending from the diaphragm to the iliac crest, and a delayed phase (5 min) centered on the liver. A total of 1.5 ml/kg of iodine contrast media, with an iodine concentration of 350-400 g/L (Iomeprol, Iomeron®, Bracco, Milan, Italy) was injected with a power injector at a rate of 3-4 ml/s.

MR imaging

MRI was performed using a 1.5 T (Magnetom Avanto, Siemens Healthcare, Erlangen, Germany) or 3.0 T (Magnetom Skyra, Siemens Healthcare, Erlangen, Germany). MRI examination included a Gradient Recall Echo (GRE) in-phase and opposed-phase T1-weighted sequences, a breath-hold-fat-suppressed Turbo-Spin-Echo (TSE) T2 weighted sequences, breath-hold Half-Fourier Acquisition Single-Shot Turbo Spin-Echo (HASTE) T2 weighted sequences, diffusion weighted imaging acquired with 10 b values ranging from 0 to 800 s/mm² and pre-contrast and post-contrast 3D volumetric interpolated breath-hold examination (CAIPIRINHA VIBE Controlled Aliasing in Parallel Imaging Results in Higher Acceleration Volumetric Interpolated Breath-Hold Examination) T1-weighted sequences. For dynamic- contrast enhanced sequences, 0.1 ml/kg of Gd-BOPTA (Multihance, Bracco, Milan Italy) was intravenously injected at 2 ml/s, followed by a 20 ml saline chaser at 2 ml/s.

Image analysis

Two senior abdominal radiologists (with 8 and 25 years of experience) independently reviewed the images. The observ-

ers were blinded to imaging reports, clinical history and final diagnosis.

The following tumor characteristics were collected: Number, size and location using Couinaud's segmentation. Major features of LI-RADS 2018 were analyzed including nonrim APHE, nonperipheral "washout", "enhancing" capsule and diameter increase over time when a previous examination was available. The size was measured on the sequence in which margins were clearest. In addition, the following LI-RADS 2018 ancillary features were analyzed: Nonenhancing "capsule", restricted diffusion, mild-moderate T2 hyperintensity, fat in mass, more than adjacent liver, nodule in nodule architecture and subthreshold growth.

A LI-RADS category was assigned to each nodule according to the LI-RADS 2018 [5]: LR-1 (definitely benign), LR-2 (probably benign), LR-3 (intermediate probability of HCC), LR-4 (probably HCC), LR-5 (definitely HCC), LR-TIV (definitely tumor in vein) and LR-M (probably malignant, not specific for HCC). LR-1, LR-2 and LR-3 were excluded of the study.

In case of disagreement on the LI-RADS categories between the two readers, images were reviewed together, and a consensus categorization was achieved.

Imaging data were correlated with pathological, clinical and biological data.

Pathological data

A final diagnosis was performed according to established morphological and immuno- phenotypical criteria of hepatic lesions. Tumor grades were scored using the modified nuclear grading scheme outlined by Edmondson and Steiner.

Statistical analysis

Results are presented as median [interquartile range] for continuous variables and numbers (%) for categorical ones. Comparison of characteristics between the two groups (HCC and non-HCC) was performed by Mann-Whitney test and Fisher's exact test for continuous and categorical data respectively. A p value <0.05 was considered significant. A composite criterion was identified by including clinical and biological variables statistically associated with the diagnosis of HCC.

A decision tree is proposed for the diagnostic strategy of LR-4 nodules according to this composite criterion. Analysis was performed by means of SPSS and Stata statistical packages.

Results

Patient characteristics

In our cohort, the sex ratio male/female was 7:2 and the median age was 66.1 [59.9 - 69.7] years. Liver disease was due to hepatitis C virus (n=17), hepatitis B virus (n=6), alcoholic (n=16) or nonalcoholic (n=19) Steatohepatitis, and rare diseases (n=2). Cirrhosis was present in 95% of cases. HCC or non-HCC pathological diagnosis was made. Forty-one patients had AFP levels higher than normal range, with median level of 13.2 [IQR 4.6-25.3] in patients with HCC nodules and 3.8 [IQR 2.9-4.5] in patients without HCC nodules. The median tumor burden was 28mm [IQR 15-42.8] in HCC nodules and 17mm [IQR 11.3-25] in non HCC nodules; 60% of nodules was bigger than 2 cm (n. 36/60) (Table 1).

Imaging analysis and nodule categorization according LI-RADS classification

Among the 60 nodules, 33 were classified as LR-4 and 27 as LR-5. HCC diagnosis was confirmed in 30/33 LR-4 nodules (90.9%) and 26/27 LR-5 nodules (96.3%). According to LI- RADS 2018 classification, the positive predictive value (PPV) of LR-4 and LR-5 for HCC was 90.9% (95%CI: 75.7-98.1) and 96.3% (95%CI: 81.0-99.9) respectively.

Imaging features of Li-RADS 4 nodules

The imaging features of the 33 nodules classified as LR-4 are presented in Table 2. Twenty- nine nodules were diagnosed on MRI and 4 on CT. The median size of LR-4 nodules was 24 mm [16-42 mm]. No nodule was smaller than 10 mm; 21/33 (63.6%) nodules measured 20 mm or larger. Nonrim APHE was present in 5 cases (15.2%), nonperipheral "washout" in 22 cases (66.7%), "enhancing" capsule in 10 cases (30.3%), mild-moderate T2 hyperintensity in 17/29 cases (58.6%) and restricted diffusion in 13/29 cases (44.8%).

Imaging features of HCC tumors in LR-4

Final pathological examination yielded 30 HCC in LR-4 group (Table 3). Nonrim APHE was observed in 4 HCCs (13.3%). The presence of nonperipheral "washout" was observed in 22 HCCs (73.3%), and "enhancing" capsule in 10 HCCs (33.3%). The two most frequent ancillary features on MR imaging associated with HCC were a mild to moderate T2 hyperintensity (n=15/26, 57.7%) and restricted diffusion (n=13/26, 50%), Figure 1.

Imaging features of Non-HCC tumors in LR-4

In 3 cases the pathological analysis ruled out the diagnosis of HCC in the LR-4 group (Table 3): One regenerative nodule (22 mm, nonrim APHE, no "washout", Figure 2), one well differentiated adenocarcinoma (12 mm, nonrim APHE, no "washout", T2 hyperintensity) and one fatty nodule (26 mm, no nonrim APHE, no washout, fat in mass).

Imaging features of Li-RADS 5 nodules

The imaging features of the 27 nodules classified as LR-5 are presented in table 2. Sixteen nodules were diagnosed on MRI and 11 on CT. The median size of LR-5 nodules was 33 mm [33-42.5]; 12/27 (44.4%) nodules measured between 10 mm and 19 mm. 15 nodules (55.6%) were larger than 20 mm. Nonrim APHE was present in all cases, nonperipheral "washout" in 25/27 (92.5%), and "enhancing" capsule in 10/27 (37%).

Twenty-six of the twenty-seven LR-5 nodules were confirmed as HCC by pathology, and a single LR-5 nodule corresponded to a regenerative nodule. The latter was a 11 mm nodule with rim APHE, nonperipheral washout, with neither restricted diffusion nor mild-moderate T2 hyperintensity.

Diagnostic accuracy of LR-4 classification and of composite LR-4 criteria

Pathological diagnosis confirmed HCC for 30 nodules (HCC group), and ruled out HCC in 3 cases (non-HCC group) of LR-4 (Table 3). Among the 33 nodules classified LR-4, the prevalence of HCC was 100% in patients with chronic viral hepatitis C (present or eradicated) (n=10/10) and with nonalcoholic steatohepatitis (NASH) (n=10/10; p 0.04). All patients with LR-4 nodules and high AFP (21/33, 70%, p 0.01) were in the HCC

Table 1: Demographic and clinico-pathological features of 60 patients with LR-5 and LR-4 observations.

	HCC n.56 (%)	Non-HCC n.4 (%)	p value
Age m (ds)	66.2 (60.1-70.4)	58.7 (43.3-64.9)	0.090
Male sex	50 (89%)	3 (75%)	0.566
Cirrhosis	53 (94.6%)	4 (100%)	1
Risk factor of HCC			
HCV	17 (30.4%)	0 (0%)	-
HBV	5 (8.9%)	1 (25%)	-
Alcohol	14 (25%)	2 (50%)	0.017
NASH	19 (33.9%)	0 (0%)	-
Other	1 (1.8%)	1 (25%)	-
AFP med ng/ml [IQR]	13.2 (4.6-25.3)	3.8 (2.9-4.5)	0.021
High AFP	41 (73.2%)	0 (0%)	0.008
Tumor Size (mm) med [IQR]	28 (15-42.8)	17 (11,3-25)	0.156

Table 2: Imaging analysis of LR-4 and LR-5 nodules.

	LR-4 n.33 (%)	LR-5 n.27 (%)	p value
Tumor Size (mm) med (IQR)	24 (15-42)	28 (13-42)	1
10-19 mm	12 (36.4%)	12 (44.5%)	0.601
≥20 mm	21 (63.6%)	15 (55.5%)	
Imaging features			
Nonrim APHE	5 (15.1%)	27 (100%)	<0.001
Nonperipheral Washout	22 (66.6 %)	25 (92.5%)	0.025
Mild-moderate T2 hyper-intensity	17/29 (58.6%)	0	0.001
Restricted diffusion	13/29 (44.8%)	0	0.001
Enhancing capsule	10 (33.3%)	10 (37%)	0.596
Threshold growth	6 (18.2%)	0	0.028

Table 3: Demographic, clinico-pathological features and imaging analysis of LR-4 nodules in HCC et non HCC groups.

	HCC n.30 (%)	Non-HCC n.3 (%)	p value
Age m (ds)	66.2 (59.4-70.2)	60.8 (53.6-)	0.281
Male sex	28 (93%)	2 (66.7%)	0.288
Cirrhosis	29 (96.7%)	3 (100%)	1
Risk factor of HCC			
HCV	10 (33.3%)	0	-
HBV	2 (6.7%)	0	-
Alcohol	8 (26.7%)	2 (66.7%)	0.041
NASH	10 (33.3%)	0	-
Other	0 (0%)	1 (33.3%)	-
AFP med ng/ml [IQR]	9.8 (4.4-14.3)	3.6 (2.9-)	0.011
High AFP serum	21 (70%)	0	0.04
Tumor Size (mm) med [IQR]	26 (15-42.3)	22 (12-22)	0.491
Imaging features			
Nonrim APHE	4 (13.3%)	1 (33.3%)	0,400
Nonperipheral Washout	22 (73.3%)	0	0.03
Mild-moderate T2 hyperintensity	15/26 (57.7%)	2 (67.6%)	1
Restricted diffusion	13/26 (50%)	0	0.232
Enhancing capsule	10 (33.3%)	0 (0%)	0.536
Threshold growth	6 (20%)	1 (33.3%)	0.523

Table 4: Diagnostic performance of the proposed composite LR-4 criterion for HCC diagnosis among LR-4 nodules.

	HCC LR-4 nodules n=30	Non HCC LR-4 nodules n=3	Composite LR-4 criteria
Composite LR-4 criterion +	27	0	Se: 0.90 (0.73-0.98) Sp: 1 (0.29-1) PPV: 1 (0.87-1) NPV: 0.50 (0.12-0.88)
Composite LR-4 criterion -	3	3	

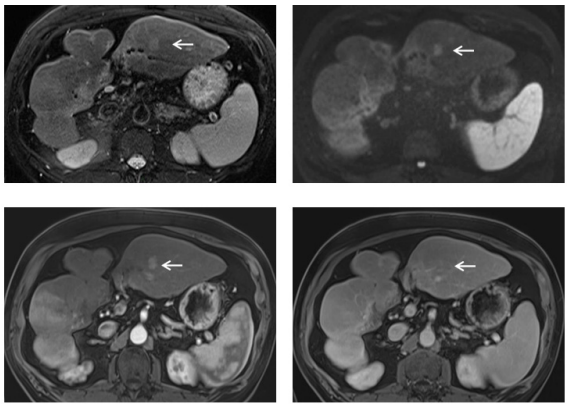

Figure 1: A 62-year-old male with HVC-related cirrhosis. Contrast-enhanced MR imaging was performed showing a 14 mm nodule (arrow) with signal hyper-intensity on T2-weighted images (A), signal hyper-intensity on diffusion (B), non-rim APHE (C), and no wash-out on portal venous or delayed phase images (D and E). The nodule was classified LR-4 on MR-imaging. Percutaneous biopsy was performed and showed a moderately- differentiated HCC nodule. The AFP level was abnormal (270 ng/ml).

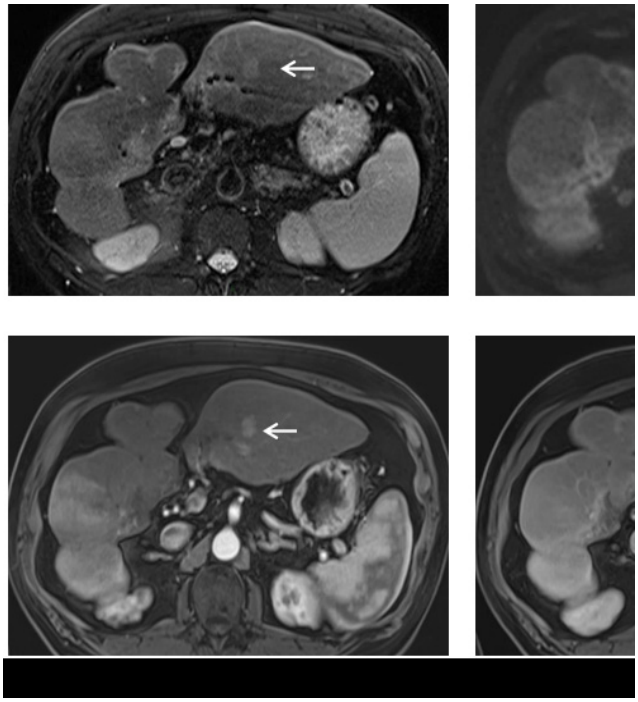

Figure 2: A 53-year-old male with alcohol-related cirrhosis. Contrast-enhanced MR imaging was performed showing a 22 mm nodule (arrow) with signal hyper-intensity on T2-weighted images (A), signal hyper-intensity on diffusion (B), non-rim APHE (C), and no wash-out on portal venous or delayed phase images (D and E). The nodule was classified LR-4 on MR-imaging. Percutaneous biopsy was performed and showed a regenerative nodule. The AFP level was normal.

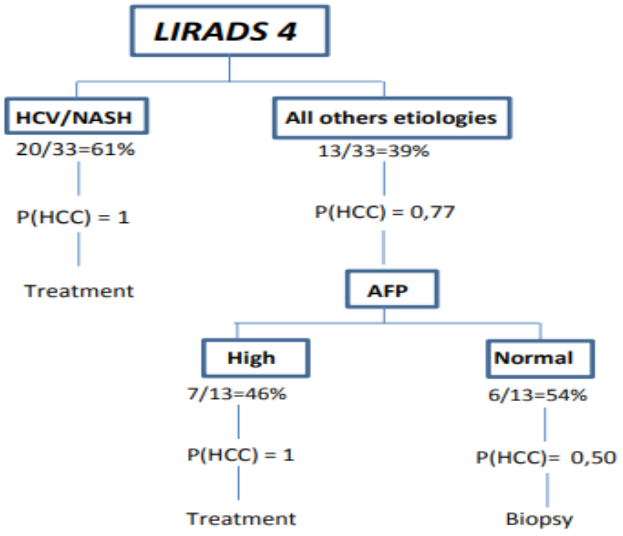

Figure 3: Decisional algorithm of diagnosis for LR-4 nodules.

group. Combining chronic HCV and/or NASH and/or high AFP to a LR-4 finding allowed a diagnosis of HCC in 27 of 30 nodules HCC histologically confirmed with sensitivity=0.9 [0.73-0.98]; specificity=1 [0.29-1]; PPV=100% [0.87-1] and NPV=50% [0.12-0.88]. A decisional diagnostic algorithm is proposed in Figure 3 illustrating the potential of composite LR-4 criterion.

Discussion

The study suggests than incorporating clinical and biological data could further improve the sensitivity of LR-4 nodules for the diagnosis of HCC without impacting specificity, as LR-4 nodules in patients with chronic viral hepatitis C, nonalcoholic steatohepatitis and / or abnormal AFP have a high probability of HCC.

In this retrospective study, 60 nodules with histological analysis were classified LR-4 and LR-5 according to LI-RADS 2018 classification. These imaging data were correlated with pathological, clinical and biological data. The preliminary results from the study confirm previous findings regarding the high specificity and positive predictive value of LR-5 for the diagnosis of HCC [12].

Previously, hepatic lesions were categorized as positive, negative or indeterminate for HCC. However, this resulted in a broad range of indeterminate lesions. The LI-RADS expands the indeterminate category to include probably benign (LR-2), intermediate probability of HCC (LR-3), and probably HCC (LR-4) [4]. While this has led to more nuanced clinical decision- making, there is still considerable debate about how to treat cases of indeterminate HCC. LR-4 observations have a high probability of being HCC but management choice is individualized and based on transplant/surgical candidacy, comorbidities, and liver function. Multidisciplinary discussion is recommended to determine individualized management, and may include repeat or alternative imaging modality, biopsy, or presumptive treatment [2].

In particular, using LR-4 to categorize HCC is a disputed subject. Darnell, et al. reported that if both the LR-4 and LR-5 categories are combined as definitely indicating HCC, specificity is maintained (96%) but the sensitivity is substantially increased to 65% compared with 42% specificity if just LR-5 is considered indicative of HCC [6]. Considering only those lesions classified as LR-5, the LI-RADS proposal yielded sensitivity, specificity, and positive and negative predictive values of 42.3%, 98.2%, 97.8%, and 47.4%, respectively, for confident HCC diagnosis in nodules detected during US surveillance in cirrhosis. Considering LI-RADS categories 4 and 5 together as definitive for HCC, the sensitivity, specificity, and positive and negative predictive values were 65.4%, 96.4%, 97.1%, and 59.6%, respectively. Consistent with these findings, Basha, et al. reported that using a threshold of more than LR-3 for HCC diagnosis produced a specificity of 90% and a sensitivity of 73% [8]. They concluded that combining LR-4 and LR-5 categories would improve accuracy and sensitivity with no significant impairment of specificity or PPV.

However, Choi, et al. reported a significantly lower sensitivity for LR-4 versus LR-5 in predicting HCC (42.7% [95% CIs: 36.3, 49.4] and 57.3% [95% CIs: 50.6, 63.7], respectively) [9]. Similarly, Ronot et al. found that combining LR-4 and LR-5 categories led to a decrease in specificity and therefore, they strongly believe that these categories should not be combined for the diagnosis of HCC [10]. Additionally, reports indicate that the majority of LR-4 nodules remain stable or are downgraded without progressing to LR-5 [13,14]. In a recent systematic review, the pooled percentage of observations confirmed as HCC were 94% for LR-5 and 74% for LR-4 and the percentage of HCCs confirmed differed significantly among LR groups 2-5. Finally van der Pol et al., [12] concluded that increasing LI-RADS categories contained increasing percentages of HCCs and this could allow physicians to better quantify the risk of HCC associated with each liver observation and to made a more active management strategy of hepatic nodules.

Taken together, these findings suggest that for observations without a definite diagnosis by imaging like LR-4, clinicians should not rely solely on the LI-RADS category but look to other factors such as tumor markers when making decisions about patient management.

AFP is the most commonly utilized biomarker to predict HCC in clinical practice. However, it is not recommended for routine screening because of its low sensitivity and specificity [2,15]. Specifically, AFP levels are high in only 40-60% of HCC cases and only 10-20% of early HCC [16]. Furthermore, while viral hepatitis C is considered one of the most important risk factors for developing HCC [17], and non specific elevations of AFP are frequent in patients with ongoing chronic hepatitis C [18,19]. Nevertheless, multivariate analyses do suggest that elevated AFP levels in patients with sustained virological response to viral hepatitis C are predictive of HCC development [20,21]. Furthermore, hepatitis C virus infection is a significant independent risk factor predictive of LR-4 observations being upgraded to LR-5 [14]. Therefore, we sought to determine the correlation between HCC, elevated AFP levels and chronic viral hepatitis C in patients with LR-4 category nodules.

Conclusions

In the present study, among the 33 nodules classified LR-4, the prevalence of HCC was almost 100% in patients with abnormal AFP and / or those with chronic viral hepatitis C (present or eradicated) or non-alcoholic steatohepatitis (n = 10/30), with sensitivity of 72.4% (95% CI: 52.8-87.3) and specificity of 100% (95% CI: 54.1-100). These data strongly suggest that elevated AFP levels, HCV infection and NASH are good predictors of HCC in patients with LR-4 nodules.

Limitations

This study had limitations including its retrospective nature. It was performed at a single center and had only a modest number of LR-4 and LR-5 observations and no LR<4 included in the analysis for the estimation of sensibility and specificity. In addition, only LR-4 nodules confirmed on pathology were included in this study, which could have biased the probability of malignancy in these selected patients. Furthermore, the small number of non-HCC nodules and the absence of cases with some relevant characteristics in the non-HCC group have made multivariate analysis impossible. However, at our institution, and in accordance with Li-RADS 2018 recommendations, all LR-4 nodules are referred to targeted biopsy. Larger multicenter studies are needed to confirm and expand our results. In conclusion, combining the LI-RADS with pathological and clinico-biological factors could provide a powerful tool for the diagnosis of HCC. In particular, our results suggest that LR-4 nodules in patients with chronic viral hepatitis C, either present or previously eradicated, and / or elevated levels of AFP, should be treated as HCC.

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