What should be done for patients with liver lesions in the LI-RADS 2 and 3 categories?

Matheus Alvarez, Fernando Gomes Romeiro

Department of Internal Medicine, Botucatu Medical School, UNESP - Universidade Estadual Paulista, São Paulo, Brazil
Correspondence to: Fernando Gomes Romeiro. Professor of Medicine, Botucatu Medical School, UNESP - Universidade Estadual Paulista, São Paulo, Brazil. Email: fgromeiro@gmail.com.

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Liver cancer is a health problem worldwide and approximately 90% of the tumors are hepatocellular carcinoma (HCC). The incidence of this tumor has been increasing and is expected to keep growing for the next 11 years in some countries such as the United States (1). As the main risk factor for developing HCC is liver cirrhosis and most cirrhotic patients can be diagnosed without biopsies, a big effort has been made in order to curb the disease impact. Probably the most important actions in this field are those focusing on avoiding the development of liver cirrhosis, such as the mass vaccination against hepatitis B and the early diagnosis of hepatitis C, which are the leading causes of cirrhosis and HCC in the Eastern and Western countries, respectively.

Likewise, the early diagnosis and the best treatment options can also reduce the HCC mortality. The diagnosis in non-cirrhotic patients still requires a liver biopsy, which is an invasive procedure that can cause pain and other complications, even when carried out by skilled doctors. On the other hand, most HCC patients are also stricken by liver cirrhosis and can be diagnosed through non-invasive exams such as computed tomography (CT) and magnetic resonance imaging (MRI). The first recommendations to establish and undoubtful HCC diagnosis in a cirrhotic liver were that the nodule should have a solid content with arterial contrast enhancement (wash-in) and a rapid elimination of the contrast medium in the venous phase (wash-out). This strategy has allowed to reach the right diagnosis in many patients, but the way that each radiologist uses to describe the tumors is largely variable.

Searching for similar rates of correct diagnosis achieved by the Breast Imaging-Reporting and Data System (BIRADS), the Liver Imaging-Reporting and Data System (LI-RADS) was developed at the University of California and later combined with another system created at the Thomas Jefferson University Hospital. The LI-RADS categories were established to classify observations as either a definite HCC (LR-5) or a definitely benign (LR-1) nodule, standardizing the liver tumor description, reducing the variability in liver images interpretation and improving the quality of the exams (2). Even though, the LI-RADS system still has some barriers to overcome, such as the differences between the data obtained from CT, MRI and other exams that can be performed using a contrast medium. Additional problems are the differences found in each device and the lack of a standardized technique that could be applied in any equipment.

Ultrasonography, CT and MRI contrast enhanced techniques can be used for diagnosis in cirrhotic and other high-risk patients, including liver transplant candidates with HCC. Nevertheless, there are some technical recommendations that must be followed as the use of multidetector CT with no less than 8 detector rows, examinations in the arterial, portal and delayed phase or the use of 1.5T–3.0T MRI with unenhanced T1-weighted sequences (in-phase and opposed-phase), T2-weighted and multiphase T1-weighted imaging. Even following these technical recommendations, Corwin *et al.* showed that an

important proportion of liver observations are categorized differently by CT and MRI using LI-RADS, proving that the imaging modality may affect the management of patients (3).

The LI-RADS categories were submitted to additional changes and new ones were created, until the 2018 version including 8 of them, as follows: non-categorized (LR-NC), definite benign (LR-1), probably benign (LR-2), intermediate probability of malignancy (LR-3), probably HCC (LR-4), definitely HCC (LR-5), definitely tumor-in-vein (LR-TIV) and probably or definitely malignant but not specific HCC (LR-M). The confidence to diagnose a typical HCC nodule (LR-5) has already been achieved and the need of further investigation for LR-3 and LR-4 tumors was also a clear message; however, the findings still had to be submitted to an evidence-based study to verify the accuracy of the system categories.

For instance, it was still necessary to check whether tumors described as LR-1 or LR-2 could really be managed as benign nodules or if they require some degree of awareness, but to answer this question the percentage of HCC in each LI-RADS category should be properly determined. With this aim in mind, van der Pol *et al.* carried out a systematic review about the amount of cancer nodules in each LI-RADS category (4). The authors searched databases looking for studies conveying the percentage of observations in each of the LI-RADS categories that were confirmed as malignancies according to follow-up images, histological evaluations or response to treatment. The 2014 and the 2017 LI-RADS versions were used (both are very similar to the current one).

After analysing more than 400 papers, only seventeen retrospective studies were included, comprising 2,482 HCCs and 217 non-HCC malignancies diagnosed in 2,760 patients, so the first message from the review is the lack of prospective studies on this issue. Of note, ten studies were considered at risk of bias. The review criteria required that the nodules had had radiological stability during 12 months to be considered as benign, but one study assessed a six-month stability. One of the first findings that deserve to be commented is the fact that studies using hepatobiliary specific gadolinium had the higher rates of HCC in LI-RADS 4 and 5 categories, suggesting that this contrast can bring additional information to the MRI exams regarding HCC diagnosis. This association was not observed in the LI-RADS categories 2, 3 and M, probably because the reduced amount of HCC in these categories. Even though, this finding deserve further investigation in prospective studies.

The rates of HCC and other malignancies were high in LI-RADS 4 and 5 categories and also significant in the LI-RADS 3 category, but the advantage of this review is that the percentages of these tumors in each category were properly estimated. None of the lesions in the LI-RADS 1 category were malignancies, confirming the practical applicability of the LI-RADS system. However, 13% and 14% of the LI-RADS 2 images were in fact HCCs or another neoplastic disease, respectively. The authors inferred that these rates can have been biased because of the low amount of LI-RADS 2 observations in the review. Only ten studies had reported such observations and half of them depended exclusively on histological analysis, whereas the others applied both a composite clinical reference and a pathology assessment. Even though, these percentages are a matter of concern. Another intriguing finding is that 36% of the tumors in the LI-RADS M category were in fact HCCs (4).

Some of the issues raised in this review can be addressed by its own results. For instance, the articles that had excluded patients with prior non-HCC malignancy had a higher rate of HCC for LI-RADS 5 and LI-RADS M compared to those that had not, thus explaining the high incidence of HCCs in the LI-RADS M category. On the other hand, the authors stated that the data were not enough to calculate the effect of different risk factors on the rates of HCC and non-HCC tumors in each category. Taken together, these findings show that clinical and radiological data should never be set apart, and none of them can be overlooked.

The results obtained by the authors can really change the clinical practice, because 38% of the nodules in the LI-RADS 3 category were HCCs and it is enough to perform a biopsy in these cases (4). Nevertheless, the management of lesions in the LI-RADS 2 category is still a challenge. The first thing is to keep the patient under a strict surveillance program, because in these programs the mortality rate is reduced by 37% (1). The reason seems to be that it avoids the loss of follow-up of such patients, leading to a higher rate of suspicion about the HCC development.

It would be also reasonable that patients in the LI-RADS 2 category with raising values of alpha-fetoprotein should be submitted to biopsies, but this test has a limited role on HCC diagnosis. Adding alpha-fetoprotein tests to ultrasonography exams increases the early detection rates by only 6% and can lead to false-positive results (1). According to van der Pol *et al.*, the management in these cases is not

straightforward because it would depend on the lesion size, location, technical conditions to perform a biopsy and many patients' factors. The authors stated that in their experience only a few LI-RADS 2 lesions are solid nodules that could be submitted to biopsy, because most of them are perfusion alterations caused by arterioportal shunts (4). So what should be done in these cases?

Despite the authors postulated that the 13% probability of HCC among LI-RADS 2 nodules should be considered provisional and at high risk of bias, their data suggest that the current management recommendations for this category may need to be revised to reflect this risk, including consideration for biopsy, especially for solid nodules ≥1 cm (4). Now this category is under a higher degree of suspicion than it was supposed before this review. In other words, all the radiological and clinical data should be taken into account before considering a LI-RADS 2 nodule as benign. In these cases, a reasonable new step to improve the radiological data could be an MRI exam with hepatobiliary specific gadolinium before deciding to perform a biopsy. This new step is only our personal opinion, but it is underpinned by the findings of van der Pol *et al.*, as commented above. We hope that this additional radiological study will avoid unnecessary biopsies and change the description to another category in some cases, facilitating the identification of both benign and malignant lesions.

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Footnote

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