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Opinions

Key points for imaging diagnosis and response assessment for hepatocellular carcinoma in Latin America

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1. Introduction

Hepatocellular carcinoma (HCC) represents a unique oncological diagnostic paradigm. During the late years of the last century, HCC diagnosis was made through biopsy, usually at advanced stages. In 2001, at an expert meeting from the European Association for the Study of the Liver, the foundations of the concept of non-invasive diagnosis of HCC were laid, given by the radiological presence of at least one nodule larger than or equal to 2 centimeters and an alpha-fetoprotein value greater than 400 ng/mL. Between 2005 and 2010, the concept of nodules and their size by imaging was unified to define HCC diagnosis, concluding that nodules larger than 1 cm visible in a single image qualified for the diagnosis of HCC with high specificity in the population at risk.

Usually, every tumor is biopsied; however, HCC, being specific to the liver and especially in the context of cirrhosis, breaks the oncological paradigm of biopsy rule and generates the premise that every hepatic nodule in the context of a cirrhotic patient might be an HCC until evidence proves otherwise. The pathogenesis of HCC in its development from a low-grade dysplastic nodule to an early HCC and an advanced HCC can be evaluated with high specificity (>95%) through a contrast-enhanced triphasic imaging study. This is explained by the fact that histologically, the greater the dysplasia of the nodule, the greater the eradication of the portal spaces with consequent angiogenesis and absolute arterial dependence of the nodule, which is evident in the arterial phase by imaging (Fig. 1).

However, some nodules might not show arterial hyper-enhancement or other specific signs at imaging evaluation (either wash-out on delay or portal phase or enhancement capsule), and thus, tumor biopsy may be mandatory in these cases. These atypical nodules, showing hypovascular signs, represent a diagnostic challenge in daily practice, particularly in small HCC (<2 cm in diameter).

On the other hand, expertise is mandatory to correctly interpret radiological signs to perform specific HCC diagnoses. In Latin America, there is a need for educational networking regarding HCC radiological diagnosis among oncologists and radiologists. Over the last decades, this educational effort has been made through hepatology or liver transplant associations, underlying the need for key opinion leaders in the region. However, educational efforts should be made in the medical community to expand healthcare access, improve surveillance, promote HCC diagnosis at early BCLC stages, and avoid unnecessary and risky tumor biopsies.

During November 30th and December 1st, 2023, this panel discussed the most frequent barriers in health care for the correct diagnosis of HCC in Latin America in the 5th annual Liver Cancer meeting in Buenos Aires, Argentina. This expert meeting was held at the Austral University Hospital, Argentina, with 80 participants from most Latin American countries, and with the sponsorship of the Latin American Association for the Study of Liver Diseases (ALEH) and the Latin American Liver Research Educational and Awareness Network (LALREAN). In this written proposal, we describe the most important point discussed in that meeting.

2. LI-RADS system: definition and diagnostic categorization

In 2008, the first Liver Imaging Reporting and Data System (LIRADS) committee was created by the American College of Radiology, and in 2011, v1 criteria and lexicon for the radiological diagnosis of HCC with computed tomography (CT) and magnetic resonance imaging (MRI) with extracellular contrasts were launched [1]. Over the years, LI-RADS has evolved to its latest version in 2018 [2,3]. LI-RADS is a standardized system for the acquisition, compression, interpretation, reporting, and collection of information from liver images. It was designed to improve medical communication between radiologists and other specialists, medical education, and clinical research. Additionally, it is endorsed and developed by the international medical community, being a living document in continuous review and updating.

LI-RADS promotes a system of standardization of radiological reporting and image acquisition to be used in high-risk HCC patients. In these patients, there must be a radiological finding in a dynamic study (CT/MRI). The timing of the images is given by a baseline phase without contrast, a late arterial phase, a portal phase, and an

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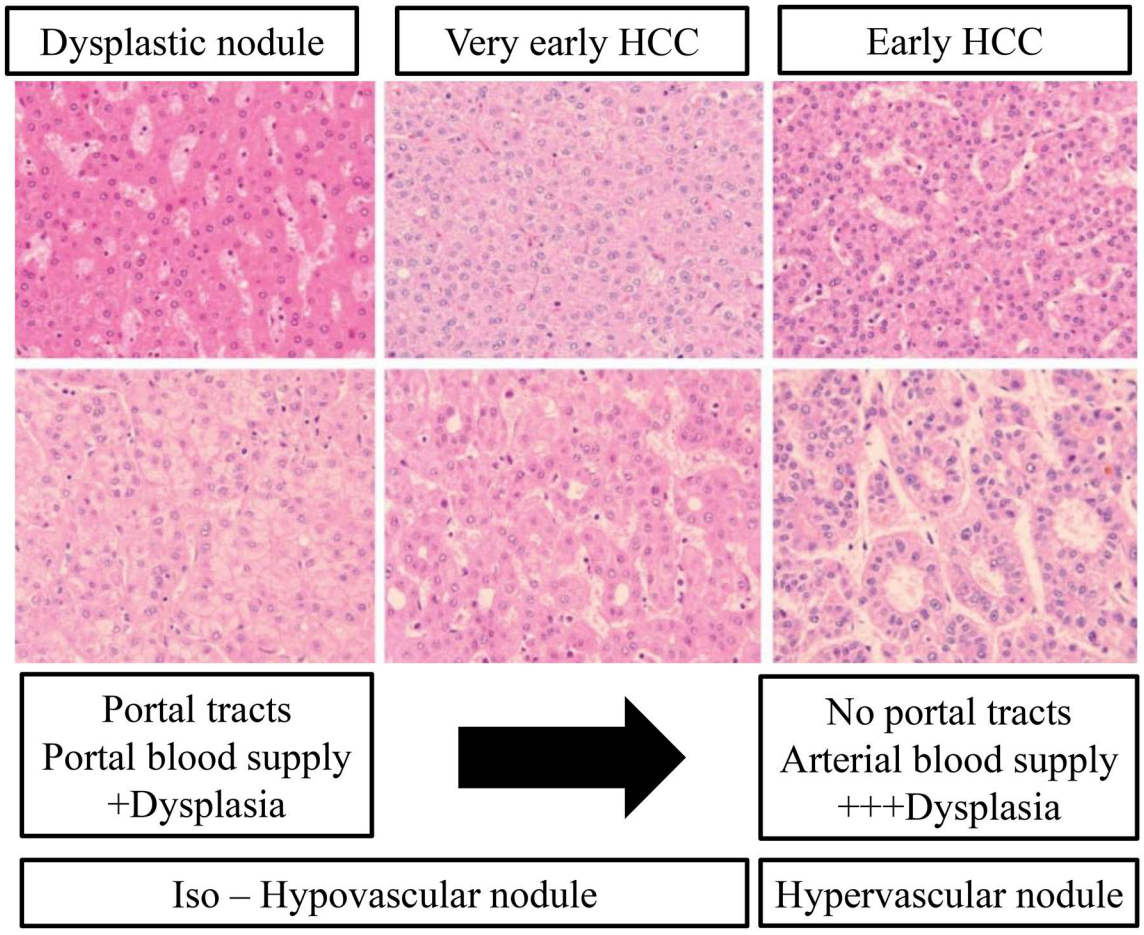

Fig. 1.

excretion phase obligatorily in the high-risk population for HCC. The high-risk population is represented by patients with cirrhosis, chronic hepatitis B, hepatitis C with advanced fibrosis, and current or previous HCC. Patients under 18 years of age, cirrhosis of vascular etiology, cirrhosis due to congenital fibrosis, or any entity not previously included are excluded from the LI-RADS application. For the correct use of LI-RADS, there are four steps. The first step is to use the five initial observational category options or alternatively use the diagnostic table for LIRADS 3, 4, and 5 for CT or MRI.

3. HCC diagnostic probabilities: pre and post-test applications

Initially, five possible options are evaluated to categorize radiological findings, considering I) LR-NC if the finding cannot be categorized due to omission or poor image quality, II) LR-TIV if there is definitely a tumor in the vein, III) LR-1 if the finding is definitely benign, IV) LR-2 if probably benign, and V) LR-M if it is probably or definitely malignant but not specific for HCC. That is if it has target enhancement, peripheral enhancement, or auxiliary characteristics representing malignancy (infiltrative appearance, marked diffusion restriction, severe ischemia or necrosis, or any characteristic that the radiologist considers non-specific aggressiveness for HCC). Once we evaluate all these possible observations and discard them, we can use the diagnostic table of CT/MRI of LIRADS 3, 4, and 5 to characterize lesions [1–3].

It is important to have clear *main lesion characteristics* to properly classify them. Initially, we categorize the lesion according to size and whether it has non-rim arterial phase enhancement (APHE). Arterial phase hyperenhancement must be unequivocally greater than the adjacent liver parenchyma and not in a rim or peripheral. This criterion is mandatory for the lesion to be categorized as LR 5 (rule in) (Fig. 2).

After evaluating APHE and the size of the finding, the three additional major criteria are studied. I) That it has non-peripheral washout of the lesion previously observed in the arterial phase; that is, it is more hypoattenuating or hypointense in the portal or late phase. II) That it has a capsule, which is a smooth and uniform border unequivocally thicker than the adjacent parenchyma, and finally, III) that the lesion shows eventual growth greater than 50% in less than six months. This is how the different categories of observation are joined in the diagnostic table, which reflects a different probability of hepatocellular carcinoma (Fig. 3).

The second step is to evaluate the radiological *auxiliary characteristics* of each lesion so that the radiologist can use them to improve detection and increase confidence. These auxiliary radiological characteristics can favor benignity or malignancy (exclusive or not for HCC) with the consequent re-categorization of the lesions. There is a rule that no lesion can upgrade from LR 4 to 5 due to auxiliary characteristics, but they can be downgraded from LR 5 to 4.

The third step, after re-categorization by auxiliary criteria, is to apply the *tiebreaker rules*. These are used only if the radiologist is undecided about a finding, always trying to classify dubious images as LR-3 or LR M due to their intermediate probability or with a high grade of diagnostic uncertainty (biopsy suggestion). Finally, the fourth step proposed by LI-RADS is to re-check everything exposed so that the final radiological report makes sense and supports a definite, probable, or indeterminate diagnosis according to the categorization of each lesion.

From an Epidemiological point of view, we need to define the clinical utility of sensitivity or specificity regarding diagnostic tests.

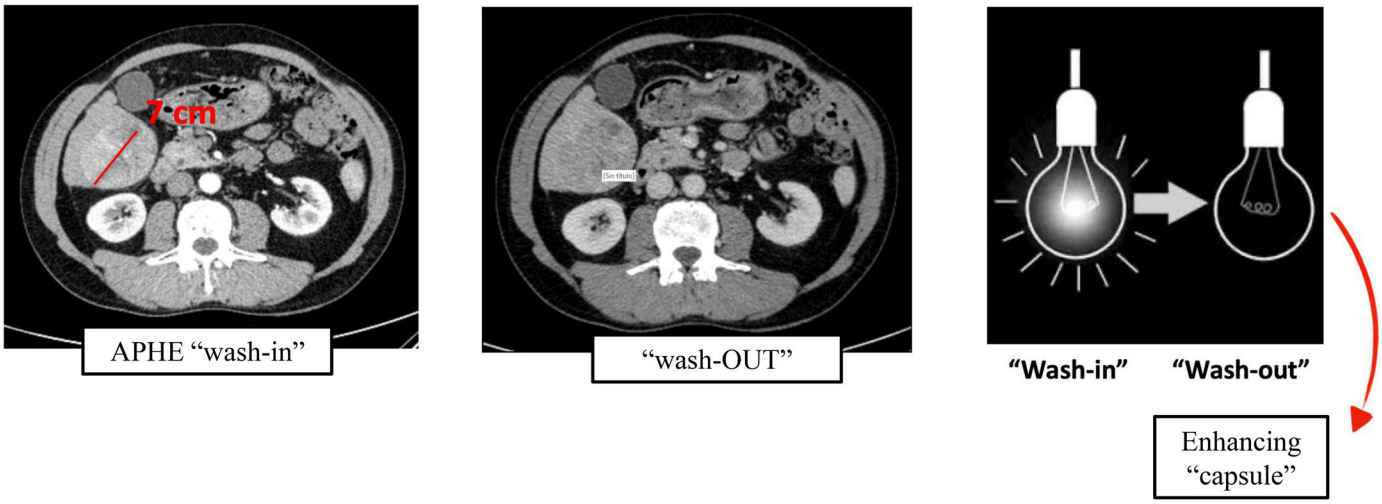

Fig. 2.

Second, probability is not the same as chance or odds; both are different forms of expressing the occurrence of the event of interest. The Bayes' Theorem deals with pre and post-test probabilities, depending on the accuracy of a test and the prevalence of the disease. Sensitivity and specificity are characteristics of a diagnostic test. A sensitive test should be used to rule out the disease, whereas a specific test confirms it (rule-in). In other words, the accuracy of tests is the sum of sensitivity and specificity divided by two and ranges between 0-1, with a value of 1 being the most perfect or accurate test. A nomogram including pre and post-test probabilities is helpful in the clinical setting. This clinical decision-making process is also applied to HCC diagnosis [2,3].

A systematic review showed the performance of each radiological sign for HCC diagnosis [4,5]. First, APHE showed a sensitivity above 80% in the population at risk for HCC. So, the absence of this finding may rule out HCC diagnosis in most patients, except in hypovascular HCC cases (less frequent). Second, small liver nodules (<10 mm) or pre-malignant HCC lesions depend at the initial histological stages on venous rather than arterial blood supply. This translated into the typical pattern of HCC diagnosis with APHE at very early or early HCC nodules, now developing blood supply from arteries rather than portal venous blood flow. As a consequence, non-rim APHE in nodules >10mm accounts for the first radiological sensitive sign and allows the radiologist and clinician to rule-out HCC diagnosis. Additional criteria, including enhancing capsule or non-peripheral washout, add specificity to HCC diagnosis and allow for rule-in HCC diagnosis. Threshold growth is rather non-specific for HCC diagnosis but has been included in the last consensus LIRADS report, showing increased sensitivity and overall odds for HCC diagnosis [6].

4. Is LI-RADS useful in decision-making?

Although LI-RADS recommends how to proceed in the nine possible observation categories (negative, LR-NC, LR-1, LR-2, LR-3, LR-4, LR-5, LR-M, LR-TIV), these guidelines are not validated for the decision-making process in the clinical setting, whether diagnostic or therapeutic [7]. Additionally, there is some degree of uncertainty when differentiating between LR-3 and LR-4 categories since at least 36% and 64% of LR-3 and four lesions are malignant, respectively [3–5,8,9]. Another observation is that LI-RADS is rather subjective, with a high dependence on the radiologist's experience for its correct use and a tendency to downgrade the diagnosis to lesser malignancy probabilities, following the tiebreaker rules proposed by the algorithm [10]. In this scenario, expertise and multidisciplinary team working is mandatory.

Two systematic reviews reported the probability estimated within each LR category [4,5]. The most recent one published last year reported probability estimates of HCC of 38% (95% Confidence Interval 27-49%) for LR-3 nodules, 73% (CI 65-82%) LR-4, and 96 % (CI 95-97%) for LR-5. Both systematic reviews included 17 to 49 publications, most of them being retrospective observational studies. One prospective validation study of the contrast-enhanced ultrasound (CEUS) LIRADS system was conducted in North American and European cohorts, showing sensitivity of 62.9% and specificity of 95.1% with a positive and negative likelihood ratios for HCC diagnosis of 12.6 and 0.4, respectively. Unfortunately, CEUS is not universally available in Latin America. Consequently, efforts should be made to identify the population at risk to adequately implement LIRADS and to correctly interpret its findings to promote precise LIRADS interpretation and categorization.

Arterial Phase Hyperenhancement (APHE)		No APHE		Nonrim APHE		
Observation size (mm)		<20	≥ 20	<10	10-19	≥ 20
Additional major features: • Enhancing capsule • Nonperipheral washout • Threshold growth	None	LR-3	LR-3	LR-3	LR-3	LR-4
	One	LR-3	LR-4	LR-4	LR-4/LR-5*	LR-5
	≥ Two	LR-4	LR-4	LR-4	LR-5	LR-5

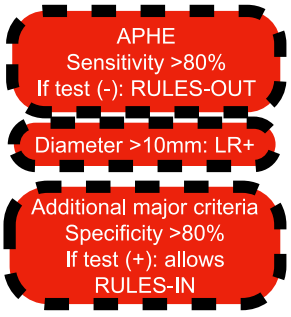

Fig. 3. Note: *Based on additional major feature: LR-4 is enhancing capsule and LR-5 if nonperipheral washout or threshold growth
Abbreviations: APHE: arterial phase hyperenhancement; LR: likelihood ratio

Several studies and publications provide support for the probability estimates of HCC based on LI-RADS, endorsing both the rule-in (specificity) and the rule-out (sensitivity) rules. For instance, Rimola *et al*. published a prospective study in 2012 evaluating the diagnostic accuracy of MRI combined with APHE for diagnosing solitary nodules measuring between 5 and 20 mm in diameter in cirrhotic patients [11]. They included 159 patients and concluded that 85% of HCC nodules exhibited APHE, enhancing specificity when assessing additional radiological features. Tang A conducted a systematic review in 2018, analyzing over 800 patients with hepatic nodules. This review assessed the evidence supporting LI-RADS major features for CT and MRI in HCC diagnosis. Tang *et al*. defined that APHE associated with wash-out in the portal or delayed phase improves specificity between 81−100% and achieves a sensitivity between 43-98% [3]. Moreover, they verified that wash-out in the portal phase and capsule appearance in the delayed phase demonstrated a specificity exceeding 90% and established that dysplastic nodules are rarely larger than 15 mm, thereby increasing the specificity cutoff to 10 mm for HCC. Regarding temporal growth, Tang demonstrated limited evidence validating growth as specific to HCC since it is a common characteristic of hepatic malignancies [3]. Therefore, to enhance specificity, a growth exceeding 50% within six months is considered a threshold, but consensus supporting robust evidence for this sign is still lacking [6].

Nevertheless, some flaws can be underlined in regard to LIRADS and its application in the clinical decision-making process in Latin America [12]. First, although it was proposed for all radiologist irrespective of their expertise, adherence to its application in the target population at risk has been only 32% [13]. This clearly shows that there is still a need for educational awareness in the medical community. Second, clinical recommendations following LIRADS may be arguable, particularly in managing LR-3 nodules, if the clinical decision-making process changes a particular treatment. In other words, the rule "wait and see or repeat" may not be applicable if curative therapies are indicated for a treatment/diagnostic procedure. Third, two studies have underlined the mixing of CI probabilities between LR-4 and LR-5 nodules [11,12], asking what the clinical aim and clinical difference of 80% versus 90% probability of cancer are. Does this difference mean any clinically significant value in following different treatment decisions? Finally, what is the kappa agreement between experts and non-expert radiologists for assessing and applying LIRADS? [14] Whether machine learning would solve these issues is rather a future not answer the question yet [15].

5. Response assessment

There are different end-points in cancer clinical research, and some of these are translated to clinical practice. First, overall survival is the most robust, non-biased end-point, and it is considered the key target for most of the Barcelona Clinic Liver Cancer (BCLC) stages [16]. Other end-points such as progression-free survival (PFS, either radiological progression or death), time-to-progression (TTP), or time-to-recurrence (TTR) are threatened by potential miss-classification bias. Consequently, these end-points are rather less robust than overall survival, and none of them has a significant and clinically relevant correlation [17].

Target and non-target lesions should be evaluated after locoregional, radical or systemic therapies for HCC, either using the new v2024 LIRADS CT/MRI Treatment Response Assessment (TRA) system that now has two separate Cores: 1) Nonradiation TRA Core for assessing TRA after nonradiation-based LRT or surgical resection 2) Radiation TRA Core for assessing TRA after radiation-based LRT; or Response Evaluation Criteria for Solid Tumors (RECIST) or modified RECIST criteria [18,19]. However, not all types of progressions demand a change in therapeutic approach or clinical decision-making process [20]. This depends on what is the objective and type of treatment. It has been shown that tumor progression within Milan criteria for liver transplantation is not associated with an increased risk of tumor recurrence after transplantation, and intrahepatic progression in BCLC-B or C stages is not associated with a worse prognosis [20]. Finally, disease control rate or even stable disease under immunotherapies (anti-PD-L1 or PD-1, or anti CTLA-4) have shown a benefit in overall survival even without tumor shrinkage. This demands further enhancement of multidisciplinary teamwork, underlying that not all progressions under conventional response criteria may be associated with a worse prognosis and demand a changing therapeutic option.

6. Conclusions

A high-risk patient studied with contrast-enhanced triphasic CT or MRI, presenting a nodule larger than 10 mm with APHE, exhibits a sensitivity exceeding 80% for HCC diagnosis. A negative result allows for excluding hepatic lesions (rule-out) at that time and recommends surveillance. If the patient presents a nodule with APHE and additional major criteria (enhancing capsule, non-peripheral wash-out, >50% growth), the study's specificity increases, and the test is positive (rule-in). The diagnosis of HCC has evolved from invasive methods to non-invasive imaging-based approaches with the introduction and application of LI-RADS to enhance diagnostic accuracy. Although its utility in clinical decision-making requires further research and consensus, LI-RADS remains a valuable and unique tool for the radiological evaluation of HCC in high-risk patients. Additionally, the benefits of disease control rate and stable disease under locoregional, radical, or systemic therapies with immunotherapy for HCC highlight the complexity of treatment response assessment. These findings emphasize the imperative for enhanced multidisciplinary teamwork, recognizing that conventional response criteria may not universally dictate prognosis or therapeutic changes.

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Conflicts of Interest

None.

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Author contributions

All authors contributed equally to this work. Each participated in the conceptualization, drafting, and revision of the opinion essay. All authors approved the final version and take responsibility for its content.

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