Diagnosis of Hepatic Nodules in Patients at Risk for Hepatocellular Carcinoma: LI-RADS Probability Versus Certainty

See "Accuracy of the Liver Imaging Reporting and Data System in computed tomography and magnetic resonance image analysis of hepatocellular carcinoma or overall malignancy—a systematic review," by van der Pol CB, Lim CS, Sirlin CB, et al, on page 976.

Unequivocal diagnosis with avoidance of false-positive results is very relevant in patients with liver disease in whom an imaging technique detects a nodule that raises the potential emergence of hepatocellular carcinoma (HCC). Although biopsy confirmation is standard in most cancers, several studies have shown that reliable HCC diagnosis may be established by imaging techniques in patients with chronic liver disease (namely, cirrhosis).[1,2] This capacity is due to 2 factors: first, a high pretest probability of HCC in patients with cirrhosis detected to have a nodule >10 mm, and second, a characteristic and specific dynamic pattern of contrast enhancement on computed tomography scanning, magnetic resonance imaging, and potentially, on contrast-enhanced ultrasound examination.[1–3] Thereby, a nodule >10 mm in a cirrhotic liver that presents with contrast enhancement in the arterial phase and washout in the portal or delayed venous phases may be confidently diagnosed with HCC. The 10 mm cut-off was defined years ago[4] because smaller nodules lack a high pretest probability of HCC. In addition, the increased arterial blood supply that characterizes HCC takes place when the nodules exceed 10–15 mm[1] and, thus, the dynamic imaging pattern would not exist. Hence, HCC diagnosis in small nodules would rely on a diagnostic biopsy that is highly unlikely to reach a conclusive result: such tiny HCC are well-differentiated, making it challenging for an expert pathologist to differentiate HCC from a benign condition despite using specific immunohistochemistry staining.[5–7] Indeed, a negative result may be from inadequate sampling. Furthermore, there are no data suggesting that the survival of patients with an HCC measuring 8 mm is significantly different from those with a 12-mm HCC. Finally, even if malignant, such tiny nodules may remain stable for a long period of time[8] and competing mortality risks related to underlying liver disease or severe comorbidities may downgrade the risk of cancer-related

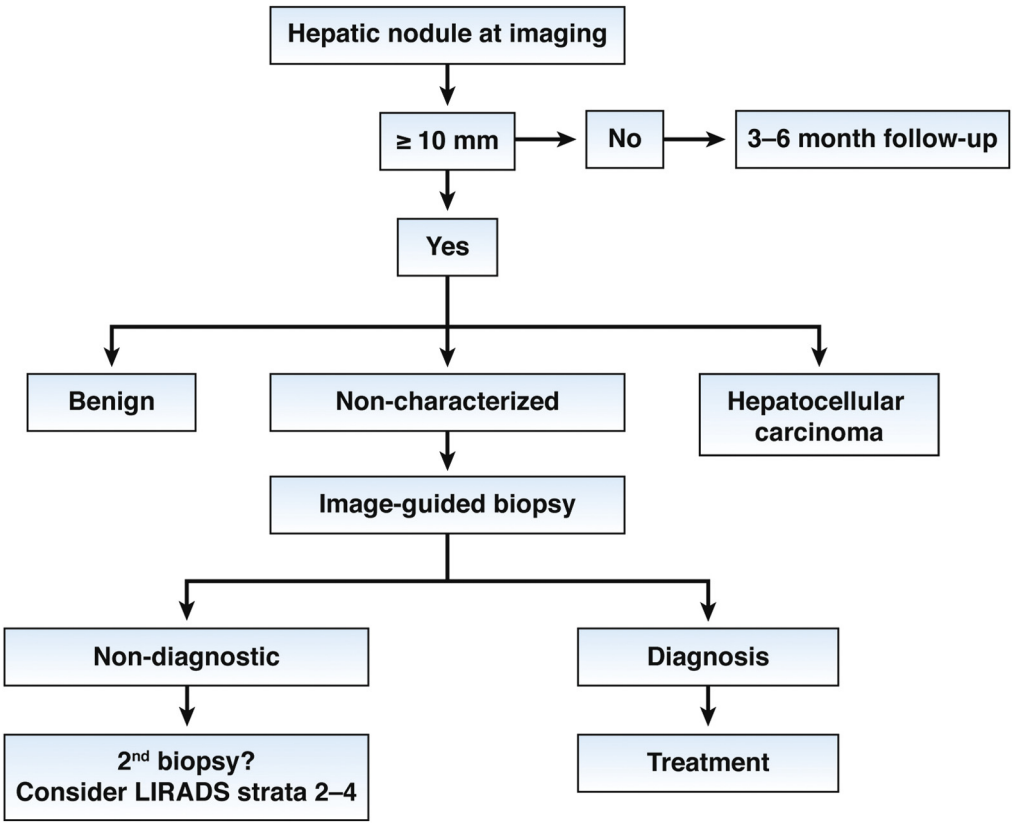

Figure 1. In the clinical setting the LI-RADS categories may be reduced to three and use the HCC likelihood to consider a second biopsy after a first non-diagnostic result.

mortality. Thus, engaging in a diagnostic work-up in nodules ≤10 mm creates challenges in diagnostic confidence, ambiguity regarding the risks versus benefits of treatment, and potentially a failure to decrease cancer-related mortality. This potential for overdiagnosis and overtreatment is a common controversy in oncology.[9] It has been evaluated within screening for breast,[10] prostate,[11] and colorectal cancer,[12] but limited information is available for liver cancer.[13] Following the 10-mm cut-off recommendations of European Association for the Study of the Liver (EASL)/American Association for the Study of Liver Diseases (AASLD) guidelines[14,15] may decrease overdiagnosis, but there is room for improvement.

The Liver Imaging Reporting and Data System (LI-RADS) proposal by the American College of Radiology was developed and repeatedly updated to allow a homogeneous reporting of imaging techniques for the diagnosis of hepatic nodules in patients at risk of HCC.[16,17] Its ultimate aim was to define the likelihood of such cancer according to the observed profile of the nodule, and link this categorization with clinical management. LI-RADS stratifies nodules in patients at risk for HCC into 5 categories. LR1 corresponds with benign entities such as angioma or cysts where there is little diagnostic or management uncertainty. From LR2 to LR5, the probability of HCC increases; this is what is reported by the systematic review and metanalysis by Van der Pol et al.[18] The authors performed a systematic review and meta-analysis of available retrospective studies and showed that LI-RADS categories stratify patients according to risk. However, retrospective studies have inherent limitations, so that there is a need for prospective investigations with an informative target population, well-defined gold standard diagnostic criteria, and homogeneous diagnostic work-up of the nodules. While awaiting such robust information, what is the value of the data by Van der Pol et al[18] and how should they impact patient management? In a clinically oriented analysis, it seems that the LI-RADS system defines 3 major groups of nodules: (1) benign, (2) noncharacterized that include LR2 to LR4, and (3) confirmed HCC (Figure 1). Benign lesions have always been classified as such and HCC criteria in LI-RADS are aligned with the well-established and validated EASL or AASLD criteria.[1,12,13] Thus, no major novelty appears. The core information is the risk stratification between LR2 and LR4 and the question is to what extent the different risk should dictate a different clinical management. We guess not. The lowest risk group, LR2 (nodules <20 mm), have a cancer risk of ≥10%: this is sufficiently high to pursue diagnosis by biopsy rather than to wait for 3–6 months to register evolutionary changes as suggested in the last AASLD guidelines if applying LI-RADS.[15] As expected, LR3 to LR4 (nodules of any size with a more suspicious imaging pattern) have even higher risks of HCC, and diagnostic biopsy to precede therapy would be the recommended option by physicians and likely, requested by patients. Thus, if a patient with a LR2 to LR4 nodule would be considered for HCC treatment if diagnosed, a diagnostic work-up of such nodules, including biopsy, should be initiated. Tumor markers alone may increase the likelihood, but not secure the desired >99% specificity offered by biopsy or specific imaging pattern.[14,15] If a patient would not be a candidate for treatment, stratification would also not modify the clinical management and, thus, the LR2 to LR4 stratification may have no clinical implications. It is important to recall that prior studies have shown a suboptimal concordance between computed tomography scans and magnetic resonance imaging for LR2 to LR4 categories[19] and that the interobserver variability is affected by years of experience.[20]

In summary, LI-RADS reporting may be useful to share information and ensure recognition of relevant imaging points by radiologists, but the data available suggest that, for clinical decision making, we may be better served by reducing the 5 LI-RADS strata to 3 clinically important strata: benign, needs further diagnostic evaluation, and HCC. The stratification may also inform whether to perform a second biopsy in nodules with a first nondiagnostic biopsy (this occurs in 30% of patients with HCC ≤20 mm), but no data are available to firmly sustain this proposal for evidence based practice.[21] Prospective studies to define the role of LI-RADS in the clinical realm are eagerly awaited.

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Conflicts of interest
The authors have made the following disclosures: Jordi Bruix reports consultancy for Arqule, Bayer-Shering Pharma, Novartis, BMS, BTG-Biocompatibles, Eisai, Kowa, Terumo, Gilead, Bio-Alliance, Roche, AbbVie, Merck, Sirtex, Ipsen, Astra-Medimmune, Incyte, Quirem, Adaptimmune, and Lilly; research grants from Bayer and BTG; educational grants from Bayer and BTG; paid conferences from Bayer, BTG, and Ipsen; paid talks from BayerShering Pharma, BTG-Biocompatibles, Eisai, Terumo, Sirtex, and Ipsen. Carmen Ayuso reports speaker fees, travel and research grants from Bayer, BTG, and Terumo.

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Hepatitis C Virus Infection, a New Modifiable Cardiovascular Risk Factor

See "Direct-acting antiviral therapy for HCV infection is associated with a reduced risk of cardiovascular disease events," by Butt AA, Yan P, Shuaib A, et al, on page 987.

Chronic hepatitis C virus (HCV) infection is a leading cause of liver-related morbidity and mortality worldwide.[1] In addition, chronic HCV infection is considered a systemic infection with many extrahepatic manifestations that can lead to poor quality of life and major economic burden.[2,3] Evidence of associations with stroke, coronary artery disease (CAD), peripheral arterial disease, and heart failure suggested that HCV infection might be a new cardiovascular (CV) risk factor.[4] Patients with HCV infection frequently have CV-associated risk factors such as diabetes, chronic kidney disease, or hypertension. However, it should be underlined that—as for all diseases or events—risk factors are rigorously defined by 4 types of evidence: (1) observational studies showing the presence of the factor before the event appearance; (2) prospective translational or clinical studies demonstrating an increased prevalence rate of the factor in patients who will develop the event, (3) mechanism of action studies, and (4) most important, outcome studies showing risk reduction when the putative factor is corrected. The study by Butt et al[5] adds major information in this field. From a