# Radiological diagnosis of hepatocellular carcinoma does not preclude biopsy before treatment
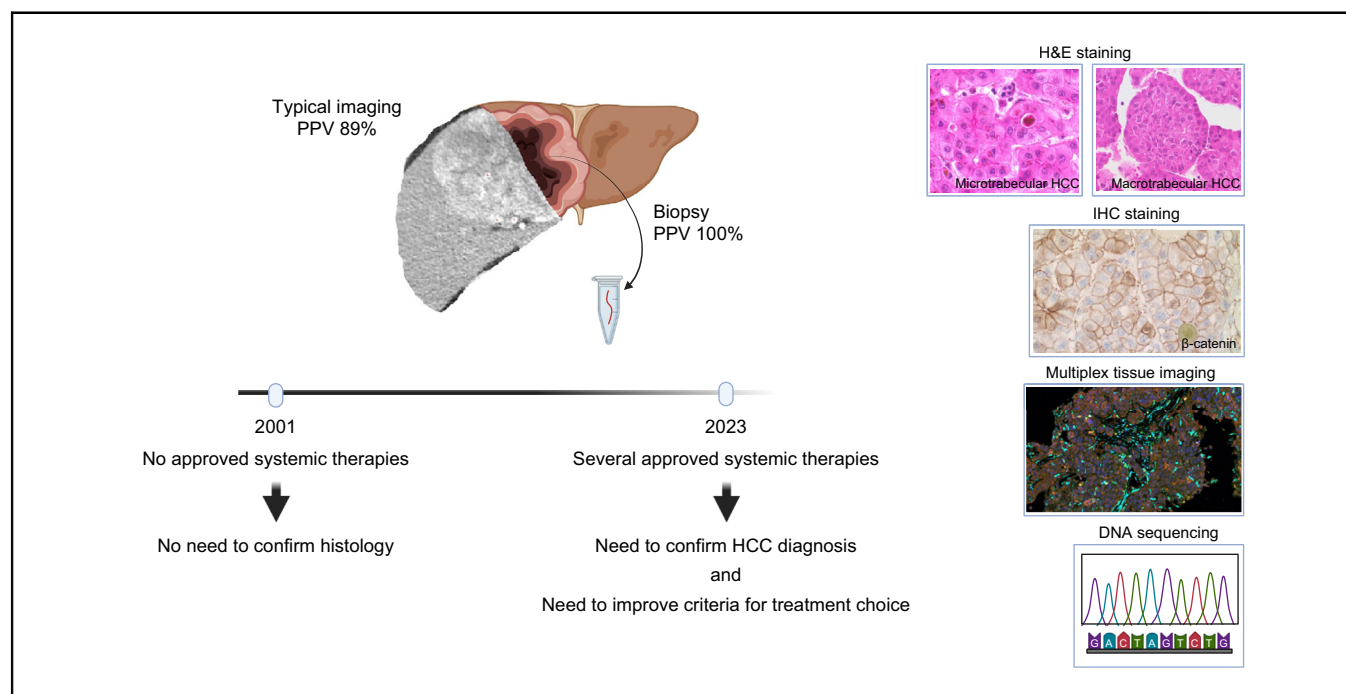
## Authors

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## Graphical abstract



Typical imaging
PPV 89%

Biopsy
PPV 100%

H&E staining

Microtrabecular HCC    Macrotrabecular HCC

IHC staining

β-catenin

Multiplex tissue imaging

DNA sequencing

2001 — No approved systemic therapies → No need to confirm histology

2023 — Several approved systemic therapies → Need to confirm HCC diagnosis and Need to improve criteria for treatment choice

## Highlights

- Radiological-only diagnosis of HCC is still widespread.

- Therapeutic advances require formal proof of tumor histology.

- The LI-RADS 2018 and AASLD criteria have a good positive predictive value.

- The study shows that among LR-5 nodules, 11% were misclassified.

- Half of patients with macrotrabecular HCC were not classified as LR-5.

## Impact and Implications

Although biopsy is not required for hepatocellular carcinoma diagnosis when the LI-RADS criteria are met according to current guidelines, our study underscores the limits of radiology and the need for biopsy when hepatocellular carcinoma is suspected. Histological findings could change therapeutics of liver tumors even if only for a small proportion of patients. Histological proof of the type of cancer is a standard in oncology.

# Radiological diagnosis of hepatocellular carcinoma does not preclude biopsy before treatment

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**Background & Aims:** The diagnosis of hepatocellular carcinoma (HCC) in patients with cirrhosis relies on non-invasive criteria based on international guidelines. The advent of systemic therapies warrants reconsideration of the role of biopsy specimens in the diagnosis of HCC. Accordingly, we investigated the diagnostic performance of the LI-RADS 2018 and the AASLD 2011 criteria.

**Methods:** Consecutive patients with cirrhosis who underwent a biopsy for suspected HCC between 2015 and 2020 were included. The available imaging studies (computed tomography and/or magnetic resonance imaging) were blindly reviewed by two independent radiologists. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were assessed for LI-RADS, AASLD, and biopsies.

**Results:** In total, 167 patients underwent both available biopsy and imaging. Of the 137 relevant biopsies, 114 patients had HCC (83.2%), 12 (9%) had non-HCC malignant lesions, and 11 (8%) had benign nodules. The PPV and NPV of the biopsies were 100% and 62%, respectively; 30 biopsies were non-contributive. The PPV and NPV of the LI-RADS categories were 89% and 32.8% for LR-5 and 85.5% and 54.5% for LR-4 + 5 + TIV, respectively. The PPV and NPV of the 2011 AASLD criteria were 93.2% and 35.6%, respectively. The interobserver kappa (k = 0.380) for the LR-5 categories was reasonable. Of 100 LR-5 nodules, 11 were misclassified, in particular one case was a colorectal metastasis, and two cases were cholangiocarcinomas, of which nine were identified through biopsy, whereas six were correctly classified according to LI-RADS (LR-M or LR-TIV). Fifty percent of macrotrabecular HCC and 48.4% of poorly differentiated HCC (Edmonson 3 and 4) were not classified as LR-5.

**Conclusions:** LI-RADS 2018 did not outperform the AASLD 2011 score as a non-invasive diagnosis of HCC. Tumor biopsy allowed restoration of an accurate diagnosis in 11% of LR-5 cases. A combined radiological and histological diagnosis should be considered mandatory for good treatment assessment.

**Impact and Implications:** Although biopsy is not required for hepatocellular carcinoma diagnosis when the LI-RADS criteria are met according to current guidelines, our study underscores the limits of radiology and the need for biopsy when hepatocellular carcinoma is suspected. Histological findings could change therapeutics of liver tumors even if only for a small proportion of patients. Histological proof of the type of cancer is a standard in oncology.

## Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer in the world with more than 900,000 cases per year[1] and has seen a dramatic increase in incidence over the past few decades. Most cases of HCC develop in the context of liver cirrhosis, with an annual incidence of 2% to 8% per year[2]; these represent

approximately 85% of primary liver cancers.[3] Ultrasound screening programs allow 70% of HCCs to be diagnosed at an early stage, which permits radical treatment.[4] Once the nodule is detected, additional cross-sectional imaging (computed tomography [CT] and/or magnetic resonance imaging [MRI]) is required for characterization.

Imaging plays a critical role in HCC diagnosis. Since imaging-based diagnosis of HCC in the context of a cirrhotic liver was first accepted in 2001[5] and updated in 2005,[6] dynamic imaging explorations have demonstrated a typical diagnostic pattern. Imaging features rely on the peculiar vascular derangement occurring during hepatic carcinogenesis.[7] Tumoral neo-angiogenesis is responsible for hypervascularization in the late arterial phase and the wash-out period during portal venous and/or delayed phases, which is the typical hallmark of HCC. Given the high pre-test

probability of HCC in cirrhosis and the associated vascular derangement not observed in all other solid cancers, a diagnosis of HCC can be established without biopsy-confirmation when a radiologically typical cirrhosis is confirmed. Furthermore, there has been no validated systemic treatment for patients with advanced HCC, and transarterial chemoembolization has not been fully recognized as a standard of care for intermediate HCC.

Since 2001, the European Association for the Study of Liver (EASL) and American Association for the Study of Liver Diseases (AASLD) diagnostic algorithms have published guidelines for how multiphasic contrast-enhanced CT and MRI should be performed. These guidelines have improved with the progress of imaging technologies; the alpha-fetoprotein (AFP) assay disappeared from the diagnostic algorithms after 2011. The 2011 AASLD criteria stated that a nodule >10 mm with 'wash-in' and 'wash-out' on one multiphased image can be confirmed to be an HCC.[8]

The Liver Imaging Reporting And Data System (LI-RADS)[9] was created in 2011; it was adopted in the most recent AASLD guidelines in 2018 (Fig. 1).[10] The LI-RADS criteria stratify the increasing probability of a lesion being an HCC (LR-1 to LR-5) based on the presence of major and auxiliary criteria. It also establishes other category codes (LR-M [malignant but not HCC] or LR-TIV [tumor in vein]) for patients at risk of HCC or other hepatic malignant neoplasms (*e.g.* cholangiocarcinoma [CCA] or hepatocholangiocarcinoma [HCC-CCA]). It is assumed that the average probability of HCC is 0% for an LR-1 observation, 11% for LR-2, 33% for LR-3, 80% for LR-4, and 96% for LR-5. Among cases categorized as LR-M, 42% were HCC and 57% were another tumor besides HCC.[11–13] Biopsy was dismissed to the third line after the failure of two different imaging techniques to classify the lesion (notably for observations classified as LR-4, LR-M, or LR-TIV) (Fig. 1).

Recent meta-analyses in 2019,[14] 2020,[15] and 2022[16] have evaluated the diagnostic performance of LI-RADS 2014, 2017, and 2018 criteria for the diagnosis of HCC. However, these meta-analyses group studies were marked by extremely diverse populations, an insufficient number of studies, as well as a low number of nodules with disparities in sizes and stages. With regard to LI-RADS 2018, few studies are available containing histological data; these studies have reported data on selected subpopulations (resected patients,[17] only HBV,[18] or with specific MRI agents[19,20]). Furthermore, recent practice studies comparing CT and MRI data with histology are lacking.

Therefore, our study investigated the performance of LI-RADS 2018 for the diagnosis of HCC in routine practice in a population of patients with cirrhosis and compared its performance with that of the AASLD 2011 criteria.

## Patients and methods

This study was a monocentric study, based on data collected at the Grenoble Alpes University Centre from January 2015 to March 2020. The study protocol was in accordance with the Declaration of Helsinki of 1975 and was approved by the local ethics committee.

### Study design

Patients were accrued prospectively after 2015 following the decision of our center to biopsy any patient with a suspicion of HCC when possible. Unbiopsied patients suspected of HCC were those for whom surgery was considered from the onset, or for

patients with ascites, low platelets, clotting disorder, or poor accessibility, although certain logistical difficulties may have contributed to the absence of biopsies when the delay was considered unethical. Between January 2015 and March 2020, a total of 220 consecutive patients with cirrhosis and suspected of HCC were included in this study, following approval from the multidisciplinary tumor (MDT) team. Multiphasic imaging studies based on CT and/or MRI as well as a liver biopsy were required inclusion criteria. In accordance with the LI-RADS 2018 criteria, patients with suspected benign or secondary liver tumors and those with no risk factors for chronic liver disease (healthy liver) were excluded from the main analysis. Following the exclusion of patients without imaging or proof of cirrhosis, 167 patients were analyzed (Fig. 2). In total, 63 patients (38%) had undergone biopsy during a thermal ablation procedure, whereas the other patients had a biopsy for histological proof before treatment.

### Histology

Histological data were collected from ultrasound-guided liver biopsies in tumoral and non-tumor livers to confirm tumor histology and the stage of surrounding liver fibrosis. A single pathologist with expertise in liver pathology specified the grade of differentiation (Edmondson-Steiner grading system): the rchitecture (trabecular, macrotrabecular, pseudoglandular), the tumor subtype (squirrelly, steatohepatic, massive macro-trabecular, fibrolamellar, clear cell), and the presence of micro-vascular and/or nervous invasion. All samples were reviewed according to the 2019 World Health Organization classification.

### Imaging techniques and analyses

Each imaging study was blindly reviewed in terms of histological data, by two radiologists specialized in abdominal imaging: Reviewer 1 (R1) had 5 years of experience and Reviewer 2 (R2) had 15 years of experience. Only abdominal CT scans with at least an arterial and a portal and/or late phase images and MRI scans with extracellular contrast agents were reviewed. For each biopsied nodule, the LI-RADS 2018 algorithm was applied. Evaluation of size parameters, hypervascularization in the arterial phase (HVPA), as well as the number of major and minor criteria allowed the nodule to be classified as having an increased probability of HCC risk (LR-1 = certainly benign to LR-5 = definite HCC). Venous vascular invasion was classified as LR-TIV. The LR-M category corresponded to nodules that were probably or certainly malignant but not specific to HCC.
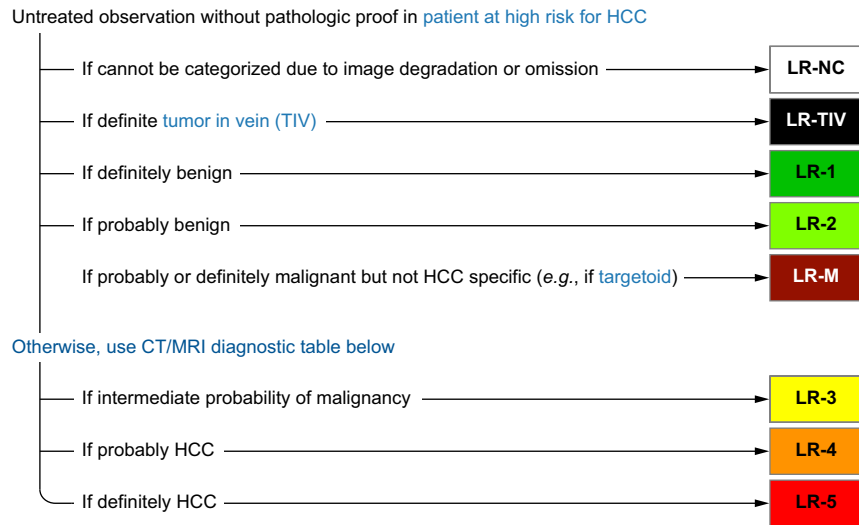
If more than one examination modality was available for the same nodule, all scans were analyzed. In patients for which both CT and MRI were performed, only the highest LI-RADS (LR-1 to LR-5) was used as the final LI-RADS.

Apart from size, wash-in (i.e. arterial phase hyperenhancement) and wash-out (i.e. contrast attenuation at the portal/late time relative to the liver parenchyma) were reported according to the 2011 AASLD algorithm. Therefore, the LI-RADS v.2018 algorithm and the AASLD 2011 criteria were applied for each nodule on all available images.

### Statistical analysis

Categorical variables were reported as the number of cases and percentages; quantitative variables were reported by their means and standard deviations, or by medians and IQRs, if their distribution was not normal. The normality of the quantitative variables was verified graphically. The percentage of patients

**A**

Untreated observation without pathologic proof in patient at high risk for HCC

| | |
|---|---|
| If cannot be categorized due to image degradation or omission | **LR-NC** |
| If definite tumor in vein (TIV) | **LR-TIV** |
| If definitely benign | **LR-1** |
| If probably benign | **LR-2** |
| If probably or definitely malignant but not HCC specific (*e.g.*, if targetoid) | **LR-M** |

Otherwise, use CT/MRI diagnostic table below

| | |
|---|---|
| If intermediate probability of malignancy | **LR-3** |
| If probably HCC | **LR-4** |
| If definitely HCC | **LR-5** |

CT/MRI diagnostic table

| Arterial phase hyperenhancement (APHE) | | No APHE | | Non-rim APHE | | |
|---|---|---|---|---|---|---|
| Observation size (mm) | | <20 | ≥20 | <10 | 10-19 | ≥20 |
| Count additional major features: <br> • Enhancing "capsule" <br> • Non-peripheral "washout" <br> • 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 |

**LR-4 / LR-5**: Observations in this cell are categorized based on one additional major feature:
- LR-4 - if enhancing "capsule"
- LR 5 - if non-peripheral "washout" **OR** threshold growth

**B**

Below are management suggestions by AASLD and LI-RADS in consensus

Untreated observations

Multiphase CT or MRI

**No observation** — Categorize each untreated observation detected

| Negative | LR-NC | LR-1 | LR-2 | LR-3 | LR-4 | LR-5 | LR-M | LR-TIV |
|---|---|---|---|---|---|---|---|---|
| Return to surveillance in 6 months | Repeat or alternative diagnostic imaging in ≤3 months | Return to surveillance in 6 months | Return to surveillance in 6 months <br><br> Consider repeat diagnostic imaging in ≤6 months | Repeat or alternative diagnostic imaging in 3-6 months | Multi-disciplinary discussion for tailored workup <br><br> May include biopsy | HCC confirmed <br><br> Multi-disciplinary discussion for consensus management | Multi-disciplinary discussion for tailored workup <br><br> Often includes biopsy | Multi-disciplinary discussion for tailored workup <br><br> May include biopsy |

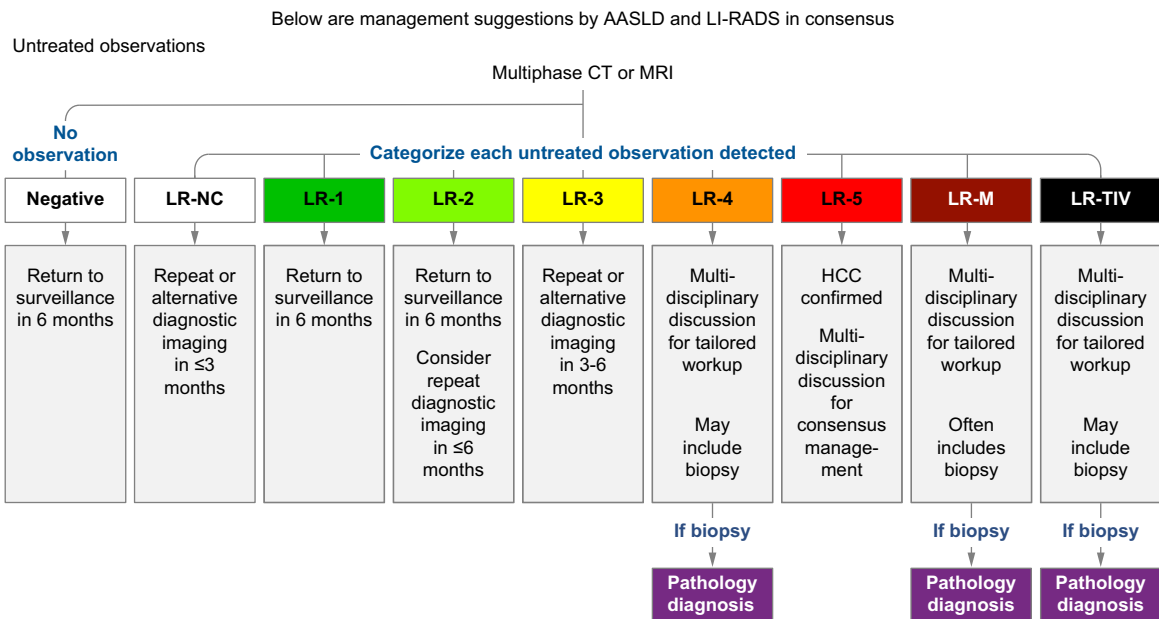**If biopsy** → **Pathology diagnosis** (LR-4, LR-M, LR-TIV)

**Fig. 1. CT/MRI LI-RADS® diagnostic algorithm.** (A) Major features should be reported on high-quality CT or MRI to allow correct LR classification. (B) AASLD 2018 surveillance algorithm. Reproduced with permission *from the American College of Radiology Committee on LI-RADS®. LI-RADS Assessment Categories 2018*. Available at https://www.acr.org/-/media/ACR/Files/RADS/LI-RADS/LI-RADS-2018-Core.pdf. Accessed on March 2023. HCC, hepatocellular carcinoma; LI-RADS, Liver Imaging Reporting and Data System; LR, LI-RADS.
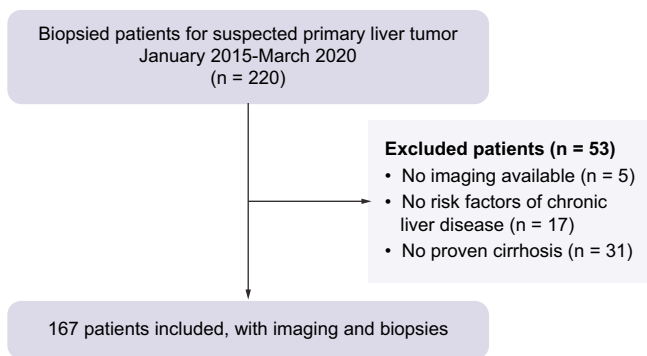
**Fig. 2. Flow diagram of the study population.**

**Table 1. Patients' baseline characteristics.**

| Characteristic | Value |
|---|---|
| Clinical status | |
|   Age, year, range | 72 (65–78) |
|   Male/female, n (%) | 156/11 (93–7) |
| Etiology of liver disease (n = 167) | |
|   Hepatitis B/C, n (%) | 5/32 (3/20) |
|   Alcohol consumption, n (%) | 53 (32) |
|   Metabolic syndrome, n (%) | 13 (8) |
|   Alcohol and metabolic, n (%) | 52 (31) |
|   Other/unknown, n (%) | 9/3 (5/2) |
| Biological status | |
|   Child–Pugh A/B/C, n (%) | 147/19/1 (88/11/1) |
|   MELD score, mean (±SD) | 9 (±2.7) |
|   AFP, median (ng/ml) (IQR) | 8 (4–37) |
|   Patients with AFP serum >9 ng/ml, n (%) | 72 (46) |
| Biopsy (n = 137) | |
|   Nodule location right liver/left liver, n (%) | 95/51 (65/35) |
|   Tumor sample size median; mm (IQR) | 10 (1.75–22.5) |
| HCC characteristics (n = 114) | |
|   Edmonson differentiation grade 1/2/3/4, n (%) | 14/65/25/5 (12/57/22/4) |
|   Unknown, n (%) | 5 (5) |
| Subtypes (n = 114) | |
|   Trabecular, n (%) | 74 (65) |
|   Macrotrabecular, n (%) | 7 (6) |
|   Pseudoglandular, n (%) | 3 (3) |
|   Trabecular + pseudoglandular, n (%) | 11 (9) |
|   Trabecular + macrotrabecular, n (%) | 3 (3) |
|   Other/Unknown, n (%) | 3/13 (3/11) |
| Imaging (n = 167) | |
|   Size of the nodules median; mm (IQR) | 27 (19–51.8) |
|   Imaging study: CT scan/MRI/Both, n (%) | 77/40/50 (46/24/30) |

AFP, alpha-fetoprotein; CT, computed tomography; MELD, model for end-stage liver disease; MRI, magnetic resonance imaging.

with HCC in each LI-RADS category (LR-1 to LR-5, LR-M, LR-TIV) was calculated for each available imaging. Several combinations of categories (LR-4 + LR-5; LR-4 + LR-5 + LR-TIV) were created. The diagnostic performance was assessed based on the sensitivity and specificity of these various categories, as compared with histology. The kappa test was used to determine the agreement between the two radiologists for each item, using the Landis and Koch thresholds. Statistical analyses were performed using Jamovi v.1.8 software (The Jamovi project [2021] https://www.jamovi.org) and R v.4.0 (Core Team, 2021, R Foundation for Statistical Computing, Vienna, Austria).

## Results

### Clinicopathological characteristics
A total of 167 patients with a mean age of 72 years were included. Of these, 93% were men, with alcohol-related cirrhosis as the main etiology (62%). All patients were suspected as having cirrhosis on imaging and biology; histological F3 fibrosis was observed in 32 patients (23%) and F4 was detected in 106 patients (77%) according to the METAVIR classification. Cirrhosis was mostly compensated in 88% patients with a Child–Pugh A status and a median model for end-stage liver disease (MELD) score of 9 (±2.7). Approximately 46% (n = 77) had increased AFP and 13% reported levels greater than 200 ng/ml. Eighty-seven patients (52.1%) had uninodular tumors and 80 patients (47.9%) had multinodular tumors. The median size of the targeted tumors was 27 mm (IQR 19–51.8). The size of the tumor biopsy specimen was greater than 10 mm in 50% of cases. In 114 cases (68.3%), the histological diagnosis was HCC. Of the 114 patients diagnosed with HCC based on biopsy specimens, according to the Edmonson classification, the majority were grade 2 (60%) or grade 3 (23%), and with a trabecular architecture (79%). Following HCC diagnosis, 39% of patients were treated with percutaneous thermo-ablation, 25% with systemic therapy, and 23% with transarterial chemoembolization. At the time of data entry (March 2020), with a median follow-up of 26.9 months, 60% of patients had reported a tumor recurrence. The baseline characteristics of all patients are summarized in Table 1.

### Histological results
Of the 167 biopsied lesions, 137 biopsies (82%) were contributive (Fig. 3). Among the 137 histological diagnoses, 114 (83.2%) patients were confirmed with HCC and 23 (16.8%) had excluded HCC: seven patients had dysplastic nodules (30%); four had

benign lesions (17%) comprising a regenerative macronodule, adenoma, angioma, and an aspecific fibroinflammatory lesion; 12 patients had a malignant (52%) lesion including nine CCAs (75%) and one patient each had hepatocholangiocarcinoma (HCC-CCA) (8.3%); angiosarcoma (8.3%), and colorectal cancer metastasis (8.3%).

In addition, 30 biopsies (18%) were non-contributive, with no tumoral proliferation found but only cirrhosis. Among these 30 biopsies, two nodules (6.7%) were classified as LR-3; 8 (26.7%) as LR-4, 19 (63.3%) as LR-5, and one (3.3%) as LR-TIV. After consulting with the MDT team and based on the subsequent oncological history, a HCC diagnosis was considered for 20 patients (66.6%) with a previous history of histologically-proven HCC (n = 6) or subsequent recurrence or progression during follow up (n = 14), whereas HCC was excluded in 10 patients (33.3%) given the proof of benign lesion with subsequent follow-up (n = 5) or the loss of follow-up (n = 5). Thus, the biopsy was wrongly negative for 20 cases of 167, that is, for 12% of the sample.

The sensitivity and specificity of the biopsies were 85.1% and 100%, respectively, the PPV and NPV were 100% and 62.3%. The median size of the nodules for which the biopsy was negative was 20 mm (IQR 16–27), which was significantly smaller than the median size of the nodules for which the biopsy was positive at 30 mm (IQR = 20-57; $p$ <0.01). The liver segments most represented in negative biopsies were segments IV (32%), VI, and VII (21%), and VIII (21%), according to Couinaud's classification.

### Imaging results
A total of 77 (46%) patients were analyzed using CT alone; 40 (24%) by MRI alone; and 50 (30%) using both imaging modalities.
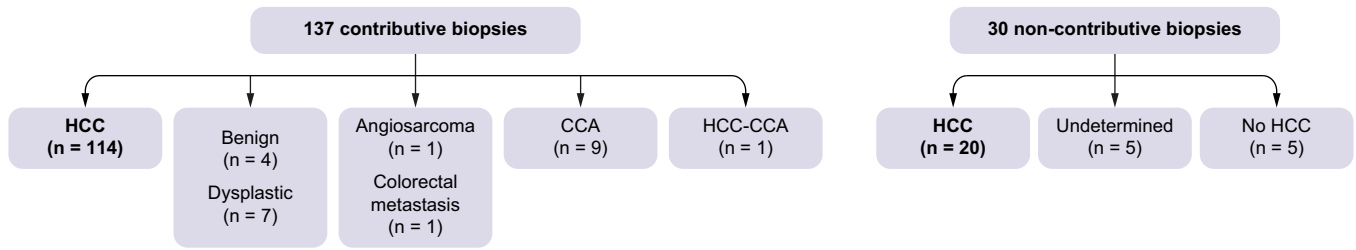
**Fig. 3. Histological findings.** CCA, cholangiocarcinoma; HCC, hepatocellular carcinoma; HCC-CCA; hepatocholangiocarcinoma.

The median size of the nodule analyzed was 27 mm (IQR: 19–51.8). The distribution for each LI-RADS category according to the R1 interpretation was as follows: LR-2 = 1 (0.6%), LR-3 = 7 (4.2%), LR-4 = 27 (16.2%), LR-5 = 100 (60.0%), LR-TIV = 18 (10.8%), LR-M = 11 (6.7%), and LR-NC = 3 (1.8%) (Fig. 4). The median time between imaging and biopsy was 47 days. HCC was diagnosed in zero of one LR-2 lesion (0%), two of seven LR-3 lesions (28.5%), nine of 27 LR-4 lesions (70.4%), 89 of 100 LR-5 lesions (89%), 16 of 18 LR-TIV lesions (88.9%), six of 11 LR-M lesions (54.5%), and in two of three LR-NC lesions (66.7%).

**Diagnostic performance**
The diagnostic performance of the LI-RADS 2018 and AASLD criteria is summarized in Table 2. For the nodules classified as LR-4 (n = 27) and corresponding to the category 'probable HCC', 19 were HCC and eight were not. Among these eight non-HCC lesions, five were considered benign and three were dysplastic nodules (two high-grade dysplastic nodules and one low-grade dysplastic nodule). For nodules classified as LR-5 (n = 100) and corresponding to the category 'definite HCC', 89 lesions were HCC and 11 were not (two high-grade dysplastic nodules, one low-grade dysplastic nodule, two CCAs, one colorectal cancer metastasis, and five benign lesions). For nodules classified as LR-TIV (n = 18), 16 nodules were HCCs, two were CCAs, and none were benign. Finally, among the lesions classified as LR-M (n = 11) and corresponding to the category 'probably or

certainly malignant but not specific for HCC', six lesions were HCC, five were non-HCC malignant lesions (four CCAs and one angiosarcoma), and none were benign.

Of the 109 nodules that met the 2011 AASLD criteria, 98 (89.9%) and 11 (10.1%) were confirmed as HCC or invalidated as HCC, respectively, after biopsy and tumor MDT evaluation. Among the false positives were two CCAs, one colorectal cancer metastasis, and three dysplastic nodules. Conversely, among the 58 nodules without the AASLD criteria, 36 were in fact HCCs (26.9% of the diagnosed HCCs).

The agreement for the LI-RADS 2018 classification between the two radiologists was fair for the LR-5 classification (kappa = 0.380): among the 32 lesions classified as LR-3 by R2, 15 were classified as LR-5 by R1. The agreement was also fair for the LR-4/5/TIV (kappa = 0.212) pooled categories.

**LI-RADS performance according to tumor histology**
Of the 79 tumors with Edmonson grades 1 or 2, that is, very well-to well-differentiated HCC, 23 (29.1%) were not classified as LR-5. Among these 23 tumors, five were classified as LR-TIV and 11 as LR-4, which is a good classification, and seven were misclassified (8.8%). Comparatively, among the 31 tumors with Edmonson grades 3 or 4 (i.e. moderately- and poorly-differentiated HCC), 15 (48.4%) were not classified as LR-5 (p = 0.07). Of these 15 tumors, eight were classified as LR-TIV and three as LR-4 and four were misclassified (12.9%). The combination of LR-4/5/TIV missed 8.9%
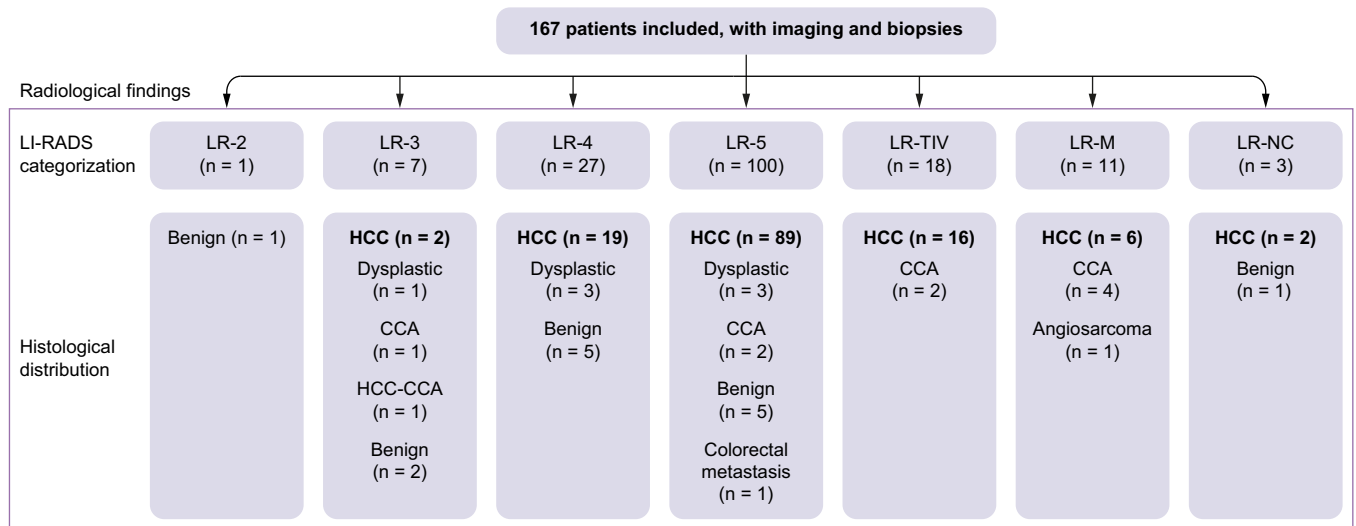


**Fig. 4. Radiological findings.** CCA, cholangiocarcinoma; HCC, hepatocellular carcinoma; HCC-CCA, hepatocholangiocarcinoma; LR-M, LI-RADS-malignant but not HCC; LR-NC, LI-RADS-not categorizable; LR-TIV, LI-RADS-tumor in vein.

**Table 2. Diagnostic performance of LI-RADS classification and AASLD for HCC.**

|  | LR-4 | LR-5 | LR-TIV | LR-M | LR-4/5 | LR-4/5/TIV | AASLD |
|---|---|---|---|---|---|---|---|
| Sensitivity (%) | 14.2 | 66.4 | 11.9 | 4.5 | 80.6 | 92.5 | 73.1 |
| Specificity (%) | 75.8 | 66.7 | 93.9 | 84.8 | 42.4 | 36.4 | 66.7 |
| PPV (%) | 70.4 | 89 | 88.9 | 54.5 | 85 | 85.5 | 89.9 |
| NPV (%) | 17.9 | 32.8 | 20.8 | 10.9 | 35 | 54.5 | 37.9 |

**Diagnostic performance of LI-RADS according to R2.**

|  | LR-4 | LR-5 | LR-TIV | LR-M | LR-4/5 | LR-4/5/TIV | AASLD |
|---|---|---|---|---|---|---|---|
| Sensitivity (%) | 4.4 | 38.5 | 16.3 | 4.4 | 43 | 59.3 | 62.4 |
| Specificity (%) | 93.8 | 84.4 | 87.5 | 87.5 | 78.1 | 65.6 | 77.4 |
| PPV (%) | 75.0 | 91.2 | 84.6 | 60 | 89.2 | 87.9 | 92.7 |
| NPV (%) | 18.9 | 24.5 | 19.8 | 17.8 | 24.5 | 27.6 | 33.8 |

Results superior to 85% in bold type. AASLD, American Association for the Study of Liver Diseases; ALI-RADS, Liver Imaging Reporting and Data System; HCC, hepatocellular carcinoma; NPV, negative predictive value; PPV, positive predictive value; R2, reviewer 2.

of well-differentiated HCC (Edmonson grades 1 + 2) and 12.9% of less-differentiated HCC (Edmonson grades 3 + 4), with $p = 0.414$. Regarding tumor architecture, of the macrotrabecular HCCs, 50% (five/10) were not classified as LR-5 but all (10/10) were classified as LR-4/LR-5/LR-TIV (one LR-4 and four LR-TIV). Among non-macrotrabecular HCC, 31.5% (28/89) were not classified as LR-5 ($p = 0.24$) and 9% (eight/89) were not classified as LR-4/LR-5/LR-TIV ($p = 0.323$).

Among the nine CCAs found in our cohort, four were classified as LR-M (44.4%); two as LR-5 (22.2%); two as LR-TIV (22.2%), and one as LR-3 (11.1%); two were both wash-in and wash-out.

## Discussion

The LI-RADS criteria were established to define the likelihood of a nodule being considered an HCC, according to more specific and reproducible criteria. LR-5 indicates with almost 100% certainty that the observed lesion is HCC,[21] whereas only LR-4, LR-TIV, and LR-M observations should lead to a biopsy (Fig. 4). However, clinical studies showed discrepancies in their performance.[13,15–20,21–24]

In our study including patients, the LI-RADS criteria did not show sufficient diagnostic performance but demonstrated significant improvement in screening, thanks to detailed clinical information. Our key message is that the LI-RADS criteria are not a substitute for biopsy and that only a combination of radiological and histological criteria can avoid missed and misdiagnosis.

In our study, LR-5 demonstrated a sensitivity of 66.4%, a specificity of 66.7%, a PPV of 89%, which was close to 90% of the AASLD criteria, but was far from the 100% expected with the LI-RADS 2018 algorithm; the NPV was 32.8%. One colorectal metastasis and two CCAs were classified as LR-5. This suggests a huge discrepancy in the recently described performance in the meta-analysis by Jin *et al.*[16] with 77% and 82% of sensitivity and specificity, or 67% and 92% in the meta-analysis by Lee *et al.*,[15] or 81% and 91% in the study by Lee *et al.*[25]

The main reason for the poor specificity results observed in this study is our study is a real-life study. First, owing to current recommendations, several biopsies (especially before 2018) were performed only when cases were complex. Several patients with LR-5 unifocal tumors did not undergo biopsy and were not included in the cohort. Second, not all patients had access to an enhanced MRI; the occasional absence of a late time or a very early arterial time on CT led to a loss of accuracy in interpretation. The cited meta-analyses showed a great heterogeneity in the specificity of LR-5: between 70% and 98% in the study by Jin *et al.*[16] and between 77% and 98% in the study by Lee *et al.*[15] In the latter, it

was clear that the parameters were very quickly influenced by the constitution of the cohorts (selective or consecutive enrolment) or by the diagnosis if the certainty was mixed or only histological.[15] Obviously, we never compared the same populations because diagnostic practices differed and these variations were as much a matter of epidemiology as of radiological performance.

LI-RADS 2018 was initially developed to improve specificity.[26] An improvement in specificity has already been shown as a result of the application of LI-RADS 2018.[22,25] In our study, we recorded a good sensitivity rate of 92.5% for the combined LR-4 + 5 + TIV (instead of 66.4% for LR-5 only, or 73.1% for AASLD criteria), demonstrating the significant contribution of the LI-RADS criteria in HCC screening.

Regarding CCA, the diagnostic imaging performance of our cohort was poor. According to the LI-RADS classification, CCA should be classified as LR-M, a lesion that is probably or certainly malignant but not specific to HCC. However, of the nine CCAs in our study, less than half (4 [44.5%]) were correctly labeled as LR-M. The rest were categorized as LR-5 (2 [22.2%]), LR-TIV (2; [22.2%]), and LR-3 (1; [11.1%]). If biopsy had not been performed routinely, at least two CCAs classified as LR-5 would have been 'falsely' diagnosed as HCC, and two CCAs were classified as LR-TIV, which is widely interpreted as HCC in current practice. The LR-3 classified CCA would have lost 3–6 months of radiologic reassessment in the algorithm. It was also demonstrated in a recent study[24] that HCC-CCA, which mimics HCC, simultaneously lowered the sensitivity of the LR-M criteria and the specificity of the LR-5 criteria. The only case of HCC-CCA in our cohort was classified as LR-3.

While macrotrabecular architecture is associated with a poor prognosis,[27] the LI-RADS classification is less efficient for this subtype than for the other architectures. In our study, 50% of macrotrabecular HCCs were not classified as LR-5, compared with 'only' 31.5% for non-macrotrabecular HCCs. Most non-LR-5 macrotrabecular HCCs were classified as LR-TIV (four/five; $p = 0.24$). Similarly, almost half of the moderately to poorly differentiated HCCs were not classified as LR-5, compared with only 29% of the very well-to well-differentiated HCCs, although these were the tumors wherein the tumor growth and therapeutic urgency were paramount.

The interobserver agreement was 'fair' at 0.38 for the LR-5 category, which was similar to that described in other studies evaluating the performance of LI-RADS,[17,21,24,28] but was insufficient for a standardized classification. An explanation is that the LI-RADS criteria include major criteria that must be considered by all radiologists. Conversely, ancillary criteria,[16] which can

modify up to 15% of the findings,[19] are applied at the radiologist's discretion and are more flexible criteria. Therefore, they may enhance performance while altering the reproducibility of the criteria.

In our study, which recorded a sensitivity of 85.1% and a specificity of 100%, liver biopsy remains the gold standard. However, 12% (n = 20) of the 167 biopsies performed returned as 'falsely negative' (NPV = 62.3%). These rates are comparable to those found in the literature.[29–31] The corresponding nodules were located in segments considered to be poorly accessible; and the median size of the nodules involved in biopsy failure was smaller than that of the overall cohort (20 mm *vs.* 27 mm). Within our cohort, three dysplastic nodules were interpreted as LR-5, raising the issue of sampling bias and the question of the continuum between dysplastic nodules and HCC.

The complication rates related to biopsy, which used to be a main concern, do not appear to be an issue today. This is because progress in radiological techniques has allowed a clear regression of these complications, estimated at 0.5% for severe hemorrhages[32] and 0.5–2.7% for the risk of tumor seeding,[33] without a significant difference in overall survival rates.[34] The risk of death after biopsy is estimated to be between 0.06% and 1%.[32,35] Besides its diagnostic impact, biopsy provides information about differentiation grades and cancer subtypes. In the near future, it could describe the presence of molecular signatures that could guide therapeutic management. For instance, a higher rate of recurrence was seen following radiofrequency when cytokeratin 19 was overexpressed.[36] Furthermore, a higher resistance to chemoembolization is observed when cytokeratin 19 and EpCAM are overexpressed.[37] CD133 and CD90 expression could be associated with a poorer response to sorafenib.[38] Furthermore, gene signatures are good predictors of response to immunotherapy.[39,40]

Our findings are consistent with the results of a recent multicenter UK audit[41] in which 240 patients with cirrhosis were prospectively included before sorafenib treatment, which achieved a sensitivity and PPV of the AASLD criteria of 65.4% and 91.4%, respectively. In our study, among the 164 patients who met the AASLD criteria, 11 were not HCC after histology and would have received sorafenib, 30 patients had not been biopsied.

The limitations of our study were its monocentric design; the varied imaging modalities that may be of unsatisfactory quality, as this was a real-life study; and the selection bias of our patients. In fact, some patients underwent a biopsy during a radiofrequency assay, while some patients underwent a biopsy because of the uncertainty of the diagnosis. Although our goal was to perform systematic biopsies for new patients with HCC in the study period, we could not determine the exact number of unbiopsied patients as a result of ascites, low platelets, clotting derangement, or inaccessibility to biopsy or because our delay in biopsy was not deemed acceptable for our patients.

The adoption of LI-RADS is an achievement, as the standardization of terminology is of great significance. In addition, it offers a good assessment of liver lesions, with the possibility of true communication among specialities. However, we argue that LI-RADS alone is not sufficient for diagnosis and stress the need for histological confirmation by biopsy. The inclusion of our standpoint is currently being encouraged in some recommendations, including the 2018 EASL recommendations[42] and the French Le Thésaurus National de Cancérologie Digestive.[43]

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