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# LI-RADS version 2018 in Patients with Prior History of Hepatocellular Carcinoma: Are LR4 Observations Enough for the Diagnosis of Recurrent HCC?

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## Original Article

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**Purpose:** We evaluated the diagnostic performance of LI-RADS version 2018 using gadoxetic acid enhanced MRI for recurrent but untreated HCC in patients with prior history of HCC.

**Materials and Methods:** We enrolled 50 consecutive patients who 1) prior history of treatment of HCC, 2) underwent liver surgery for radiological/clinical diagnosis of new HCC between 2013 to 2018, 3) had gadoxetic acid enhanced MRI within one month before surgery, and 4) did not have more than five HCCs or infiltrative tumors only. Two radiologists reviewed MRI and determined the presence of LR3, LR4 and LR5 observations except previously treated tumors based on LI-RADS version 2018 in consensus. We sub-classified LR4 into LR4m (LR4 with major features only) and LR4u (LR4 upgraded from LR3 by ancillary features). LR4u were further sub-classified into LR4ua (with arterial phase hyperenhancement) and LR4un (without arterial phase hyperenhancement).

**Results:** PPV for LR5, LR4 and LR3 observations for recurrent HCC were 100%, 61.5% and 25.0%, respectively. 100% (3/3) of LR4m were HCC. However, PPV of LR4u was 56.5%. PPV of LR4ua and LR4un were 73.3% and 25.0%, respectively. Sensitivity of LR5 and LR5+LR4 observations as a diagnostic threshold were 32.1% and 89.3%, respectively. Sensitivity for LR5+LR4m+LR4ua observations for diagnosis of HCC were 83.7% and significantly superior to that of LR5 without significant deterioration of specificity (75.0%).

**Conclusion:** In patients with prior history of HCC, LR4 observations by major features or with APHE may be regarded as recurrent HCCs given high sensitivity and comparable specificity/PPV to LR5 observations.

**Keywords:** Liver; Hepatocellular carcinoma; Recurrence; Magnetic resonance Imaging; Diagnosis

## INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide, and primary liver cancer is the fourth most common cause of cancer death (1, 2). Unlike many other solid cancers such as lung cancer, colon cancer, or pancreatic ductal adenocarcinoma, HCC can be diagnosed based on non-invasive imaging features without histopathological confirmation. Therefore, imaging studies play an important role in diagnosis of HCC. Great effort has been made in establishing diagnostic criteria by international scientific societies such as the American Association for the Study of Liver Disease (AASLD), the European Association for the Study of the Liver and the European Organization for Research and Treatment of Cancer (EASL-EORTC), the Asian Pacific Association for the Study of the Liver (APASL), and the Korean Liver Cancer Association and the National Cancer Center (KLCA-NCC) (3-6). The Liver Imaging Reporting and Data System (LI-RADS), endorsed by the American College of Radiology (ACR), has been widely used for the diagnosis and reporting of HCC among high-risk patients. The recent AASLD guidelines adopted diagnostic criteria from CT/MRI LI-RADS version 2018 for HCC in high risk patients (7).

However, existing guidelines except LI-RADS have focused primarily on diagnosing initial HCCs in HCC-naive patients rather than recurrent HCC. Furthermore, LI-RADS only deals with recurrent HCCs at previously treated sites by locoregional therapy and the appropriate diagnostic criteria for imaging recurrent tumors remote from previously noted HCCs remain uncertain (7). Risk of new HCC development is higher in patients with previous histories of HCC than HCC-naive patients because both de novo HCC development in background cirrhotic liver and intrahepatic metastasis of previous HCC are possible (8, 9). Therefore, more generous criteria for imaging diagnoses of HCC could be applied to patients with a previous history of HCC. To our knowledge, no previous studies have dealt with the imaging diagnosis of recurrent HCC remote from previously noted HCCs. Therefore, we designed and performed a study to evaluate the diagnostic performance of LI-RADS version 2018 for new, recurrent HCCs using gadoxetic acid-enhanced MRI in patients with prior histories of HCC.

## MATERIALS AND METHODS

### Patient Selection

This retrospective cohort study was performed with the approval of the Institutional Review Board of our institute and the requirement for informed consent was waived because of the retrospective nature of the study. We searched through our institutional electronic databases for data from May 2013 to April 2018.

The inclusion criteria for this study were 1) patients with previous histories of locoregional treatment of HCC, such as transarterial chemoembolization (TACE), radiofrequency ablation (RFA), radiation therapy, and hepatic resection, 2) patients who underwent liver transplantation or any type of hepatic resection for HCC under radiological or clinical diagnosis of new HCC, and 3) patients who underwent gadoxetic acid-enhanced liver MRI within one month before surgery. The exclusion criteria were 1) patients with more than five HCCs, to avoid the difficulty of lesion-by-lesion matching and 2) patients with infiltrative HCC only. A total of 216 patients who underwent liver surgery for HCC and also had gadoxetic acid-enhanced liver MRI taken within one month before surgery. Among them, 65 patients had previously treated HCC and 15 patients were excluded because they had more than five HCCs (n = 12) or infiltrative type HCCs only (n = 3). Finally, a total of 50 patients (M:F = 39:11; mean age, 56.8 ± 8.2 years old) were included in the final study sample (Fig. 1). Of these, 29 patients were treated by TACE for original HCCs, 16 patients by RFA, 3 patients by TACE+RFA, one patient by TACE+RFA+radiation therapy, and one patient by hepatic resection.

We reviewed patient medical records to determine the causes of chronic liver disease, presence of liver cirrhosis, total bilirubin level, and Child-Pugh score. Liver cirrhosis was diagnosed by morphological findings: 1) typical imaging findings of the liver (surface nodularity, left hemiliver or caudate lobe hypertrophy, blunted contour) and 2) indirect signs of portal hypertension (splenomegaly, variceal vessels, and large amount of ascites). The demographic, clinical, and tumor characteristics of the study are summarized in Table 1.

### Liver MRI Protocol

All liver MRIs were performed with a 3-Tesla MRI scanner (VERIO, Siemens Healthineers, Erlangen, Germany) with an 8-channel phased-array torso coil. Unenhanced respiratory triggering fast spin-echo and breath hold fat-suppressed single-shot fast spin-echo T2-weighted imaging and

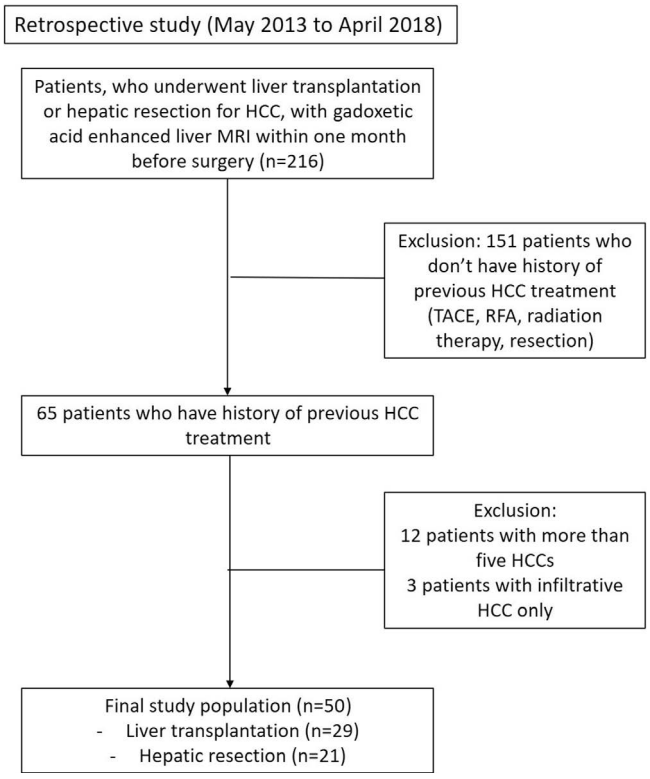


**Fig. 1.** Flowchart showing enrollment of patients.

gradient echo T1-weighted imaging with in-phase and opposed-phase sequences were obtained. Dynamic contrast-enhanced images were obtained after injecting patients with 0.025 mmol/kg of gadoxetic acid (Primovist or Eovist, Bayer Pharma, Leverkusen, Germany) at a rate of 1 mL/s by an automated infusion system followed by a 20-mL saline flush. T1- weighted 3D gradient-recalled echo (CAIPIRINHA, Siemens Healthineers, Erlangen, Germany) images were obtained during the arterial phase (30- to 35-second delay with the bolus-tracking technique), portal venous phase (65- to 80-second delay), transitional phase (180-second delay), and hepatobiliary phase (20-minute delay). DWI sequence was obtained with echo-planar imaging applying b values of 0, 50, 500, and 800 s/mm$^2$. Liver MRI sequence parameters are summarized in Table 2.

### Image Analysis

Two radiologists with 17 and 6 years of experience in abdominal imaging reviewed all preoperative MRI studies in consensus. We adopted consensus reading to minimize bias from reader mistakes. Readers were blinded to the final postoperative histopathologic diagnosis. Readers identified LR3, LR4, LR5, and LR-M observations visible on gadoxetic acid-enhanced MRI according to LI-RADS version 2018, and recorded the size, location, and LI-RADS category of each observation. Previously treated HCCs were excluded for analysis because the purpose of our study is evaluating the performance of LI-RADS version 2018 for new, recurrent HCC rather than local tumor progression. Readers adopted not only major features but also ancillary features to categorize observations. When there were one or more ancillary features favoring HCC or malignancy in general, we upgraded the LI-RADS category. In addition, when there were one or more ancillary features favoring benign status,

**Table 1. Demographic, Clinical, and Tumor Characteristics of the Study Population**

| | |
|---|---|
| Age (years), mean ± SD | |
| Mean ± SD | 56.8 ± 8.2 |
| Median (range) | 55 (33-76) |
| Sex, n (%)‡ | |
| Male | 39 (78.0) |
| Female | 11 (22.0) |
| Underlying liver disease, n (%)‡ | |
| Chronic HBV | 35 (70.0) |
| Chronic HCV | 3 (6.0) |
| Alcoholic liver disease | 8 (16.0) |
| NASH | 2 (4.0) |
| Other | 2 (4.0) |
| Liver cirrhosis, n (%) | 33 (66.0) |
| Serum total bilirubin, mean ± SD | 1.27 ± 1.87 |
| Child-Pugh score, n (%)‡ | |
| A | 42 (84.0) |
| B | 6 (12.0) |
| C | 2 (4.0) |
| Number of recurrent HCCs per patient, n (%) | |
| 0 tumor | 31 (62.0) |
| 1 tumor | 12 (24.0) |
| 2 tumors | 6 (12.0) |
| 3 tumors | 0 (0.0) |
| 4 tumors | 1 (2.0) |
| HCC size, n (%) | |
| < 1.0 cm | 2 (100.0) |
| ≥ 1.0 cm, < 1.9 cm | 16 (50.9) |
| ≥ 2.0 cm, < 4.0 cm | 10 (48.1) |

Numbers in parentheses are percentiles.
HCC = hepatocellular carcinoma; SD = standard deviation

**Table 2.** Liver MRI Sequence Parameters

| Parameters | T2 weighted HASTE with breath hold | T2 weighted turbo spin echo with respiratory triggering | T1 weighted in/ opposed phase | Diffusion weighted imaging | T1 3D gradient echo |
|---|---|---|---|---|---|
| TR (msec) | 600-1000 | 2000-6000 | 170-220 | 3500-4200 | 3.6-4.2 |
| TE (msec) | 80-140 | 100-140 | 2.6 / 1.3 | 40-50 | 1.2-1.4 |
| Flip angle (°) | 138 | 150-160 | 50-70 | 90/180 | 11/14* |
| Slice thickness (mm) | 6 | 6 | 6 | 8 | 3 |
| Reconstruction interval (mm) | 6 | 6 | 6 | 8 | 3 |
| Acquisition matrix | 320-400 × 150-180 | 380-450 × 180-220 | 250-300 × 120-170 | 140-160 × 90-120 | 256-380 × 166-218 |
| Signal averages | 1 | 1 | 1 | 5 | 1 |
| b-values (s/mm$^2$) | n/a | n/a | n/a | 0, 500, 800 | n/a |

HASTE = half Fourier acquisition single shot turbo spin echo; TE = echo time; TR = repetition time

*Hepatobiliary phase

we downgraded the LI-RADS category. We sub-classified LR4 observations into LR4m and LR4u, with LR4m defined as LR4 observations with major features only and LR4u as LR4 observations that were upgraded from LR3 by ancillary features (Fig. 2). LR4u observations were further sub-classified into LR4ua and LR4un depending on the presence of non-rim arterial phase hyperenhancement (APHE), with LR4ua observations showing APHE and LR4un not showing APHE (Figs. 3-5).

### Reference Standards

Final diagnoses of HCC were made via histopathological reports of surgical specimens obtained from liver transplantation or surgical resections. Pathology department of our institute reports the size and location (hepatic segment) of viable HCCs and therefore, we can match observations on MRI and tumors described in the pathology reports lesion-by-lesion. To avoid mismatch, we excluded patients who have more than 5 HCCs as described above.

### Statistical Analysis

Positive predictive value (PPV) was calculated for each LI-RADS categorization and sub-categorization. Then, we evaluated the diagnostic performances of different thresholds of LI-RADS categorization for HCC diagnosis. We adopted four thresholds for the diagnosis of HCC: 1) LR5 only, 2) LR5 and LR4, 3) LR5 and LR4m, and 4) LR5, LR4m and LR4ua. Sensitivity, specificity, PPV, and negative predictive values (NPV) were calculated for each threshold of combined LI-RADS categorization.

McNemar tests were used to compare sensitivity and specificity, whereas Fisher's exact test was adopted to compare PPV and NPV. For all statistical tests, P-values of $< 0.05$ were considered statistically significant. All statistical analyses were performed using commercially available software (MedCalc version 19.6, MedCalc software, Belgium).

## RESULTS

### Histopathological Diagnosis

Among 50 patients, 19 had 28 viable HCCs other than previously treated tumors in histopathological examinations of liver transplants (16 HCCs in 10 patients) or resected livers (12 HCCs in 9 patients). Twelve patients had single HCCs other than treated tumors, 6 patients had two HCCs and one patient had four HCCs other than previously treated tumors. The mean size of HCCs other than previously treated tumors was 1.5 ± 0.8 cm.

### LI-RADS Categorization and Positive Predictive Value of HCC

A total of 44 observations of LI-RADS 3, 4, or 5 were recognized in the preoperative MRIs; nine (20.5%) observations were categorized as LR5, 26 (59.1%) as LR4, 8 (18.2%) as LR3, and one as LR-M (2.3%). Number of observations (n = 44) was smaller than number of patients (n = 50) because some patients only had hepatic tumors which were previously treated. Of these 44 observations, 28 lesions were confirmed as HCCs on histopathological reports. PPV for viable HCCs of LR5, LR4, and LR3 observations were 100% (9/9), 61.5% (16/26), and 25.0% (2/8), respectively.

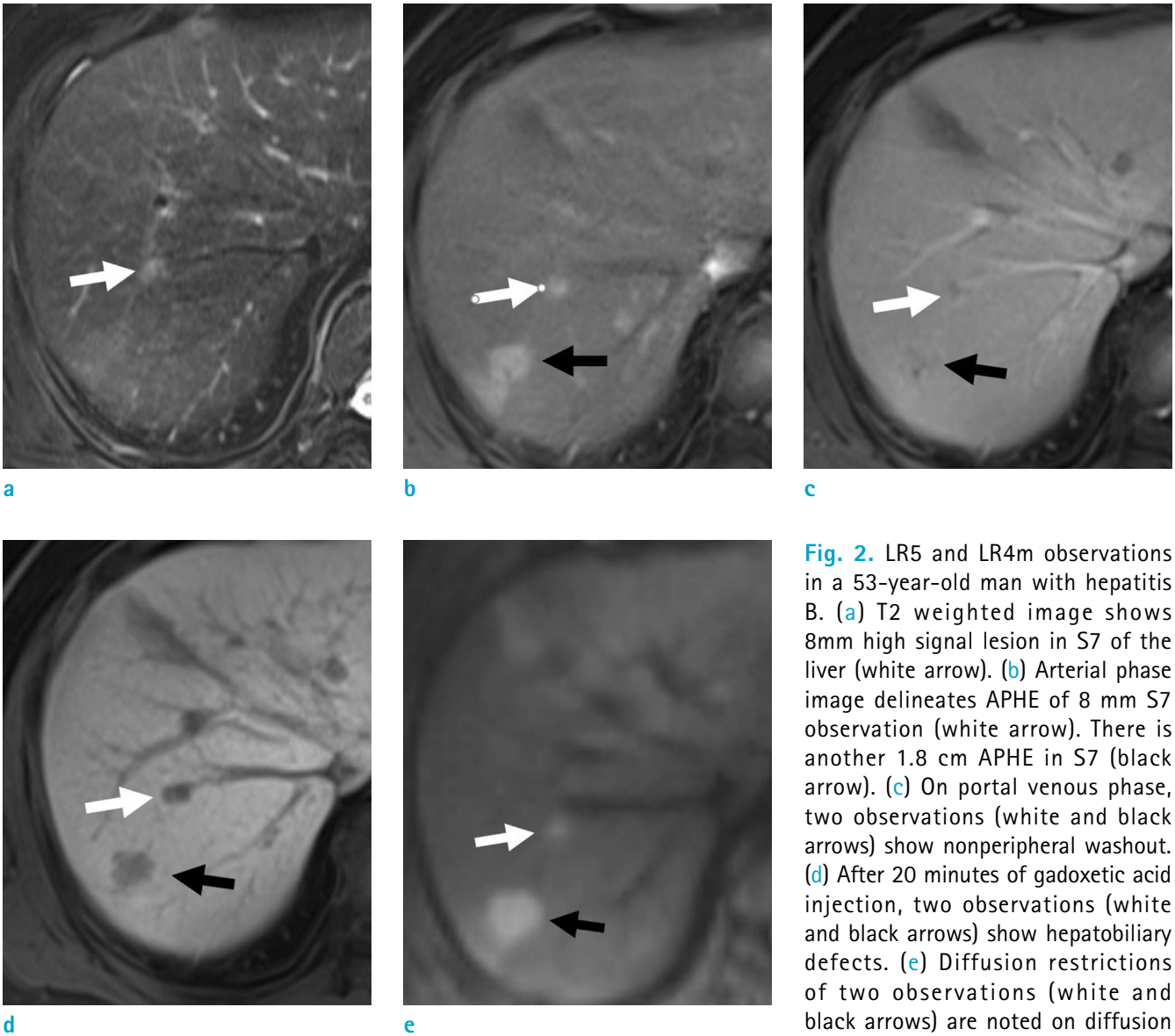


**Fig. 2.** LR5 and LR4m observations in a 53-year-old man with hepatitis B. (a) T2 weighted image shows 8mm high signal lesion in S7 of the liver (white arrow). (b) Arterial phase image delineates APHE of 8 mm S7 observation (white arrow). There is another 1.8 cm APHE in S7 (black arrow). (c) On portal venous phase, two observations (white and black arrows) show nonperipheral washout. (d) After 20 minutes of gadoxetic acid injection, two observations (white and black arrows) show hepatobiliary defects. (e) Diffusion restrictions of two observations (white and black arrows) are noted on diffusion weighted images. The larger lesion is the LR5 observation and the smaller lesion is the LR4m observation. Both observations were confirmed as HCCs.

Among LR4 subgroups, 100% (3/3) of LR4m observations were HCCs while PPV of LR4 observations upgraded from LR3 (LR4u)was 56.5% (13/23). In addition, PPV of LR4ua and LR4un were 73.3% (11/15) and 25.0% (2/8), respectively. PPV of LR4m and LR4u were not significantly different (P = 0.2615). However, PPV of LR4ua and LR4un were significantly different (P = 0.0393). PPV of each LI-RADS category is summarized in Table 3.

### Diagnostic Performance of LI-RADS with Different Thresholds

We evaluated diagnostic performance of different thresholds for recurrent HCCs (Table 4). When only LR5 observations were considered as recurrent HCC, sensitivity and specificity were 32.1% (9/28) and 100.0% (16/16), respectively. Sensitivity and specificity of LR5+LR4 and LR5+LR4m were 89.3% (25/28), 37.5% (6/16), and 42.9% (12/28), 100.0% (16/16), respectively. With a threshold of LR5+LR4m+LR4ua, sensitivity and specificity were

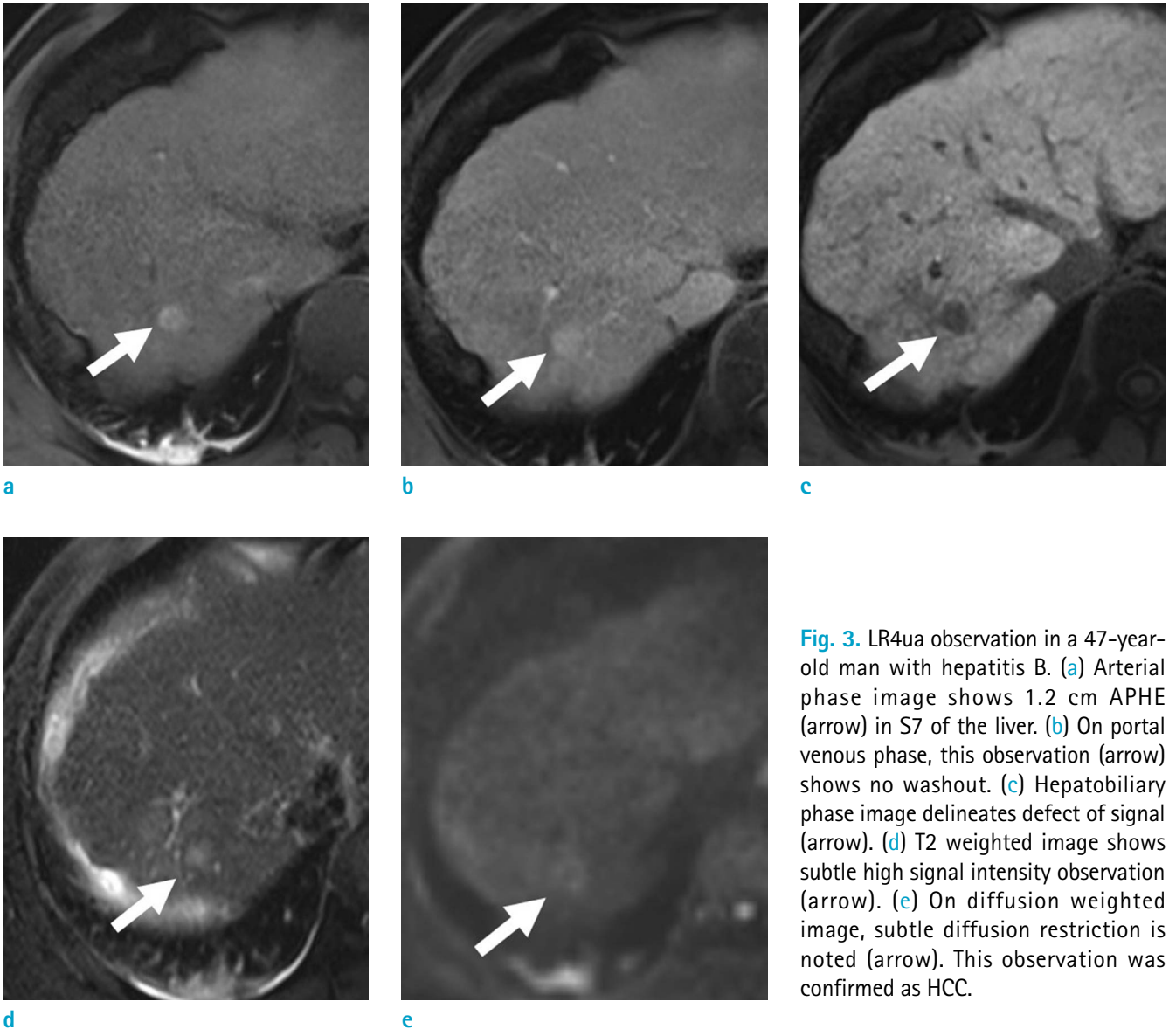


**Fig. 3.** LR4ua observation in a 47-year-old man with hepatitis B. (a) Arterial phase image shows 1.2 cm APHE (arrow) in S7 of the liver. (b) On portal venous phase, this observation (arrow) shows no washout. (c) Hepatobiliary phase image delineates defect of signal (arrow). (d) T2 weighted image shows subtle high signal intensity observation (arrow). (e) On diffusion weighted image, subtle diffusion restriction is noted (arrow). This observation was confirmed as HCC.

89.3% (25/28) and 75.0% (12/16), respectively. When comparing LR5 and LR5+LR4m as thresholds of recurrent HCC, sensitivity (P = 0.2500) and NPV (P = 0.4860) were not significantly different. When comparing LR5 and LR5+LR4m+LR4ua as thresholds, sensitivity (P < 0.0001) and NPV (P = 0.0325) of LR5+LR4m+LR4ua were significantly better than LR5 with comparable specificity (P = 0.1250) and PPV (P = 0.5545).

## DISCUSSION

In patients with prior history of HCC, intrahepatic recurrence of HCC may be caused by both *de novo* multicentric occurrence or intrahepatic metastasis of previous tumors (8, 9). Intrahepatic metastasis is defined as HCC developing from tumor cells spread via the portal vein, and multicentric occurrence refers to new HCC developing due to chronic liver disease. Therefore, risk of HCC development is higher in patients with previous histories of HCC, and the incidence of recurrence of HCC after curative resection is 44-77% (10-15). The importance of earlier identification of recurrent tumors, which allows clinicians to select from more treatment options offering better prognosis, should not be underestimated.

However, diagnostic criteria for imaging diagnosis of HCC

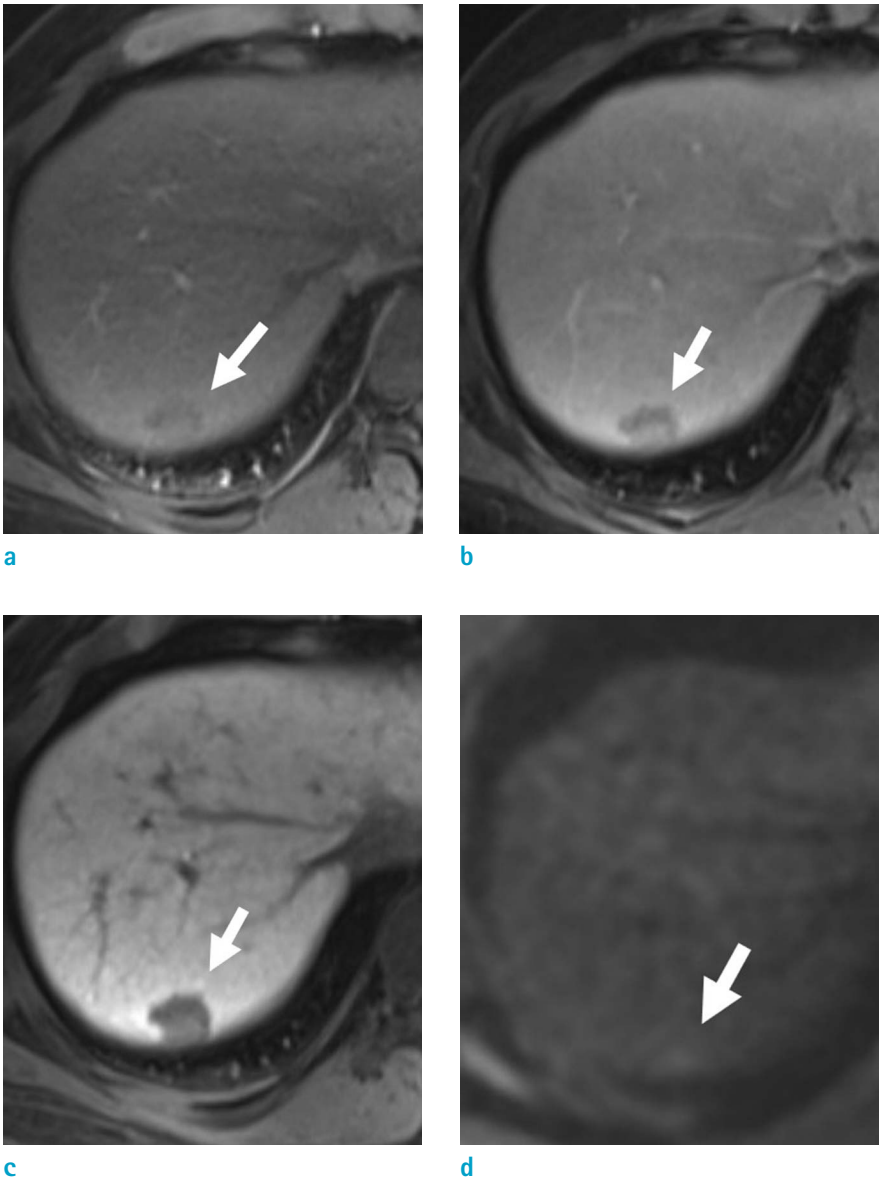

**Fig. 4.** LR4un observation in a 40-year-old man with hepatitis B. (a) On arterial phase, there is a 2.1 cm hypovascular observation (arrow) without APHE in S7. (b) On portal venous phase, this observation (arrow) shows nonperipheral washout. (c) Hepatobiliary defect (arrow) is noted in the hepatobiliary phase. (d) Subtle diffusion restriction is present in this observation (arrow). This observation was confirmed as HCC.

published by the major scientific bodies except LI-RADS only can be applied to HCC-naive patients even if they have higher risk for recurrent HCC (3-6). Therefore, these criteria may not be appropriate for patients with previous histories of HCC and may be too strict. In CT/MRI LI-RADS Version 2018, LI-RADS treatment response (LR-TR) has been proposed as an algorithm to assess treated observations, defining LR-TR viable as any of the following three: arterial phase hyperenhancement, washout appearance, or enhancement similar to pretreatment (7). Nonetheless, the application of LR-TR is confined to observations of patients who have been treated by locoregional therapies, and the appropriate diagnostic criteria for recurrent tumors remote from previously noted HCCs were not defined. KLCA-NCC suggests that for patients with histories of HCC, high sensitivity in diagnosing tumor recurrence should be pursued using ancillary features (4). However, to our knowledge, there have been no investigations of the performance of imaging in the diagnosis of recurrent HCCs which were not previously treated. Based on these concepts, we assembled variable threshold combinations of observations using CT/MRI LI-RADS version 2018 and examined their diagnostic performance.

In the present investigation, 100% (9/9) of LR5 observations were confirmed as HCCs. Meanwhile, only 61.5% (16/26) of LR4 observations were HCCs, and PPV

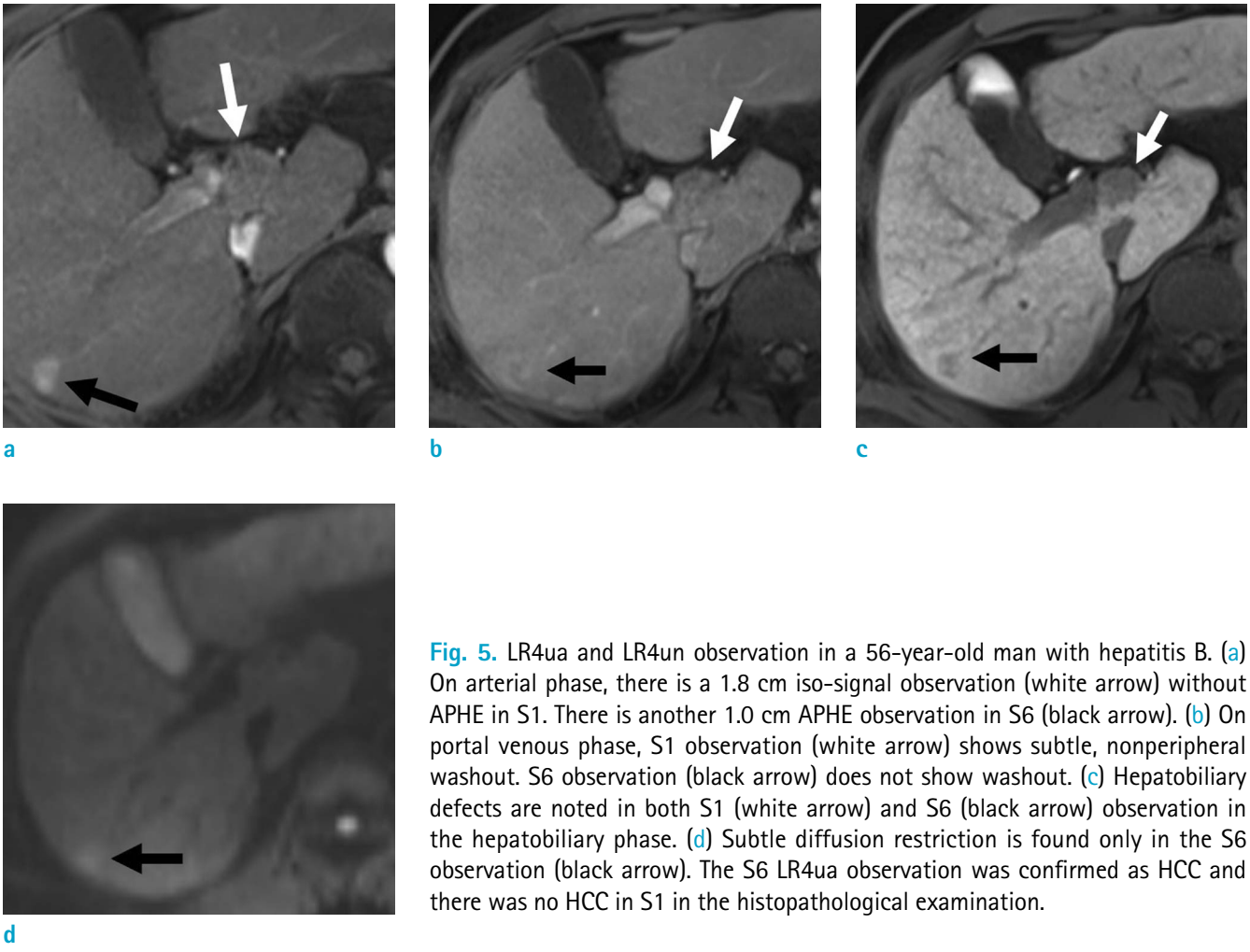

Fig. 5. LR4ua and LR4un observation in a 56-year-old man with hepatitis B. (a) On arterial phase, there is a 1.8 cm iso-signal observation (white arrow) without APHE in S1. There is another 1.0 cm APHE observation in S6 (black arrow). (b) On portal venous phase, S1 observation (white arrow) shows subtle, nonperipheral washout. S6 observation (black arrow) does not show washout. (c) Hepatobiliary defects are noted in both S1 (white arrow) and S6 (black arrow) observation in the hepatobiliary phase. (d) Subtle diffusion restriction is found only in the S6 observation (black arrow). The S6 LR4ua observation was confirmed as HCC and there was no HCC in S1 in the histopathological examination.

**Table 3. LI-RADS Categorization and Positive Predictive Value of HCC**

| LI-RADS categorization | | HCC | Benign lesions | Positive predictive values |
|---|---|---|---|---|
| LR5 | | 9 | 0 | 100.0% |
| LR4 | All LR4 | 16 | 10 | 61.5% |
| | LR4m | 3 | 0 | 100.0% |
| | LR4u | 13 | 10 | 56.5% |
| | LR4ua | 11 | 4 | 73.3% |
| | LR4un | 2 | 6 | 25.0% |
| LR3 | | 2 | 6 | 25.0% |
| LR-M | | 1 | 1 | 100.0% |

HCC = hepatocellular carcinoma; LI-RADS = Liver Imaging Reporting and Data System; LR4m = LR4 by major features only; LR4u = LR4 upgraded by ancillary features; LR4ua = LR4 upgrade by ancillary features with arterial phase hyperenhancement; LR4un = LR4 upgrade by ancillary features without arterial phase hyperenhancement

of LR4 observations is lower than that observed previous reports: 74% in CT/MRI LI-RADS core (5). However, PPV of LR4 observations categorized by major features only (LR4m) was 100% (3/3). In addition, among LR4 observations upgraded from LR3 by ancillary features, observations with APHE (LR4ua) had PPV of 73.3%, higher than that (25.0%) of upgraded LR4 without APHE (LR4un). Based on these results, we compared the diagnostic performances of LI-RADS categorization at different thresholds to identify the best combination with both high sensitivity and PPV. The LR5 only threshold showed the highest PPV (100%) and lowest sensitivity (32.1%). Using LR5+LR4 as a threshold significantly improved sensitivity (89.3%) compared with LR5 only, but with a significant trade-off in PPV (71.4%). LR5+LR4m threshold was not sufficient to achieve satisfying results, resulting in statistically insignificant increases in sensitivity. When LR4ua observations were additionally included, both high sensitivity (89.3%) and PPV (86.2%)

**Table 4. Diagnostic Performance of LI-RADS Categorizations with Different Thresholds**

| LI-RADS categorization thresholds | HCC | Benign lesions | Missed HCC | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|---|---|---|
| LR5 | 9 | 0 | 19 | 32.1 (15.8-53.4) | 100.0 (79.4-100.0) | 100.0 (100.0-100.0) | 45.7 (39.5-52.1) |
| LR5+LR4 | 25 | 10 | 3 | 89.3 (71.8-97.7) | 37.5 (15.2-64.6) | 71.4 (61.6-78.9) | 66.7 (36.6-87.4) |
| LR5+LR4m | 12 | 0 | 16 | 42.9 (24.5-62.8) | 100.0 (79.4-100.0) | 100.0 (100.0-100.0) | 50.0 (42.1-58.0) |
| LR5+LR4m+LR4ua | 25 | 4 | 3 | 89.3 (71.8-97.7) | 75.0 (47.6-92.7) | 86.2 (72.6-93.7) | 80.0 (57.0-92.4) |

Sensitivity, specificity, PPV, and NPV are percentiles and the numbers in the parentheses are 95% confidence intervals.
HCC = hepatocellular carcinoma; LI-RADS = Liver Imaging Reporting and Data System; LR4m = LR4 by major features only; LR4u = LR4 upgraded by ancillary features; LR4ua = LR4 upgrade by ancillary features with arterial phase hyperenhancement; LR4un = LR4 upgrade by ancillary features without arterial phase hyperenhancement; NPV = negative predictive value; PPV = positive predictive value

were achieved. Sensitivity and NPV of the LR5+LR4m+LR4ua threshold were significantly better than those of LR5 only thresholds without significant deterioration of specificity and PPV.

Our results are consistent with those of previous studies regarding the initial diagnosis of HCCs in HCC-naive patients, in that LR4 observations according to major features resulted in higher PPV (90.0%) than upgraded LR4 observations (72.5%) (16). Considerable differences in PPV were noted between LR4ua and LR4un observations. As mentioned above, the diagnostic performances of LR5 only and LR5+LR4m thresholds were similar because the number of LR4m observations was small (n = 3). The low number of LR4m observations might be explained by lack of "nonperipheral washout", which can be recognized only in the portal venous phase when gadoxetic acid is used as contrast in liver MRI. We hypothesized that some LR4ua observations could have been re-categorized into LR4m if extracellular contrast agent (ECA) had been injected. Several authors reported that gadoxetic acid-enhanced liver MRI is inferior to MRI with ECA when LI-RADS is applied as diagnostic criteria (17, 18). In this condition, APHE, another major feature used for HCC diagnosis in CT/MRI LI-RADS, became important for improving diagnostic performance. LR4 observations upgraded from LR3 without APHE (LR4un) resulted in only 25.0% of PPV for the final diagnosis of HCC.

However, previous studies and meta-analyses suggested that gadoxetic acid-enhanced MRI is better than MRI with ECA for the detection of HCC (19-21). In these studies, washout was widely adopted in the transitional phase or even in the hepatobiliary phase. Because of the unique features of gadoxetic acid, including lower dosage compared to ECA, more frequent motion artifacts, and background liver parenchyma enhancement, major features of LI-RADS such as APHE, washout appearance, and the enhancing capsule may be more difficult to detect than ECA-enhanced MRI (22). Therefore, to maximize the performance of gadoxetic acid-enhanced MRI, active upgrades of LI-RADS categorization using ancillary features and close observations of APHE are mandatory.

Early and late recurrence of HCC is a major risk factor affecting survival after hepatectomy (13, 14, 23). Therefore, early identification of tumor recurrence would help clinicians in planning additional therapeutic strategies. To achieve this goal, diagnostic criteria with higher sensitivity are necessary, and the application of strict diagnostic criteria for HCC-naive patients to patients with previous history of HCC might not be appropriate. In this situation, LR4 observations with APHE could be more generous diagnostic threshold for the definition of "strongly suspected recurrent HCC". Also, addition of LI-RADS category for recurrent HCCs can be suggested. For example, similar to LR-TR categorization, we can suggest LR-R recurrence for definite recurrent tumors and LR-R equivocal for strongly suspected, but not definite recurrence. We hope our study will be of little help to this kind of improvement of future LI-RADS.

Our study has several limitations. First, the retrospective nature of this study and the evaluation of only histopathologically confirmed HCCs might have resulted in selection bias. We included only patients who underwent resection or transplantation, and this considerably increases the pretest probability of HCC in the study population. Even though our purpose was to evaluate the performance imaging diagnosis criteria, this potential bias cannot be avoided. Second, the number of patients was small and there were only 3 LR4m observation. This is the major limitation of this study and why the results of this study is underpowered. Some differences in sensitivity, specificity, PPV, and NPV were therefore not statistically significant.

Further investigations including multi-center studies are mandatory to verify the results of our initial investigation. Third, this study was performed in a hepatitis B viral-endemic area, and 70% of the patients included had chronic hepatitis B. The risk of *de novo* hepatocarcinogenesis may differ in patients with other risk factors such as hepatitis C, alcohol abuse, or non-alcoholic steatohepatitis. Therefore, the results of our study may not be generalizable to other regions of the world. Fourth, our study sample underwent gadoxetic acid-enhanced MRI, and the evaluation of major features of CT/MRI LI-RADS is somewhat limited using this method compared to ECA-enhanced MRI even though LI-RADS version 2018 includes gadoxetic acid-enhanced MRI as a diagnostic tool. Fifth, histopathological diagnosis of benign observations was not described because at our institute the pathological reports of surgical specimens from liver surgery usually do not include benign focal lesions such as hemangiomas or dysplastic nodules. Therefore, it was not possible to conduct a false positive analysis.

In conclusion, the sensitivity of LR5 observations for detection of recurrent HCC using gadoxetic acid-enhanced MRI in patients with prior histories of HCC treatment was low. Defining LR4 observations with major features or APHE as HCC may improve sensitivity without significant deterioration of specificity and PPV.

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## REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424
2. Global Burden of Disease Liver Cancer Collaboration; Akinyemiju T, Abera S, et al. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level: results from the global burden of disease study 2015. JAMA Oncol 2017;3:1683-1691
3. European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2018;69:182-236
4. Korean Liver Cancer Association (KLCA); National Cancer Center (NCC). 2018 Korean Liver Cancer Association-National Cancer Center Korea practice guidelines for the management of hepatocellular carcinoma. Korean J Radiol 2019;20:1042-1113
5. Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the study of liver diseases. Hepatology 2018;68:723-750
6. Omata M, Cheng AL, Kokudo N, et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol Int 2017;11:317-370
7. Radiology ACo. CT/MRI LI-RADS v2018 core. Available via https://www.acr.org/-/media/ACR/Files/RADS/LIRADS/ LI-RADS-2018-Core.pdf?la=en. Accessed December 30, 2020
8. Chen PJ, Chen DS, Lai MY, et al. Clonal origin of recurrent hepatocellular carcinomas. Gastroenterology 1989;96:527-529
9. Cha C, Fong Y, Jarnagin WR, Blumgart LH, DeMatteo RP. Predictors and patterns of recurrence after resection of hepatocellular carcinoma. J Am Coll Surg 2003;197:753-758
10. Cucchetti A, Piscaglia F, Caturelli E, et al. Comparison of recurrence of hepatocellular carcinoma after resection in patients with cirrhosis to its occurrence in a surveilled cirrhotic population. Ann Surg Oncol 2009;16:413-422
11. Huang ZY, Liang BY, Xiong M, et al. Long-term outcomes of repeat hepatic resection in patients with recurrent hepatocellular carcinoma and analysis of recurrent types and their prognosis: a single-center experience in China. Ann Surg Oncol 2012;19:2515-2525
12. Taura K, Ikai I, Hatano E, Fujii H, Uyama N, Shimahara Y. Implication of frequent local ablation therapy for intrahepatic recurrence in prolonged survival of patients with hepatocellular carcinoma undergoing hepatic resection: an analysis of 610 patients over 16 years old. Ann Surg 2006;244:265-273
13. Lee EC, Kim SH, Park H, Lee SD, Lee SA, Park SJ. Survival analysis after liver resection for hepatocellular carcinoma: a consecutive cohort of 1002 patients. J Gastroenterol Hepatol 2017;32:1055-1063
14. Minagawa M, Makuuchi M, Takayama T, Kokudo N. Selection criteria for repeat hepatectomy in patients with recurrent hepatocellular carcinoma. Ann Surg 2003;238:703-710
15. Chung YE, Park JY, Choi JY, Kim MJ, Park MS, Seong J. Noninvasive biomarker for predicting treatment response to concurrent chemoradiotherapy in patients with hepatocellular carcinoma. Investig Mag Reson Imaging 2019;23:351-360
16. Choi SH, Byun JH, Kim SY, et al. Liver Imaging Reporting

and Data System v2014 with gadoxetate disodium-enhanced magnetic resonance imaging: validation of LI-RADS category 4 and 5 criteria. Invest Radiol 2016;51:483-490
17. Kim YC, Min JH, Kim YK, et al. Intra-individual comparison of gadolinium-enhanced MRI using pseudo-golden-angle radial acquisition with gadoxetic acid-enhanced MRI for diagnosis of HCCs using LI-RADS. Eur Radiol 2019;29:2058-2068
18. Min JH, Kim JM, Kim YK, et al. Magnetic resonance imaging with extracellular contrast detects hepatocellular carcinoma with greater accuracy than with gadoxetic acid or computed tomography. Clin Gastroenterol Hepatol 2020;18:2091-2100 e2097
19. Semaan S, Vietti Violi N, Lewis S, et al. Hepatocellular carcinoma detection in liver cirrhosis: diagnostic performance of contrast-enhanced CT vs. MRI with extracellular contrast vs. gadoxetic acid. Eur Radiol 2020;30:1020-1030
20. Lee YJ, Lee JM, Lee JS, et al. Hepatocellular carcinoma: diagnostic performance of multidetector CT and MR imaging-a systematic review and meta-analysis. Radiology 2015;275:97-109
21. Hanna RF, Miloushev VZ, Tang A, et al. Comparative 13-year meta-analysis of the sensitivity and positive predictive value of ultrasound, CT, and MRI for detecting hepatocellular carcinoma. Abdom Radiol (NY) 2016;41:71-90
22. Hope TA, Fowler KJ, Sirlin CB, et al. Hepatobiliary agents and their role in LI-RADS. Abdom Imaging 2015;40:613-625
23. Park IK, Yu JS, Cho ES, Kim JH, Chung JJ. Pseudoglandular formation in hepatocellular carcinoma determines apparent diffusion coefficient in diffusion-weighted MRI. Investig Mag Reson Imaging 2018;22:79-85