Original Article | Gastrointestinal Imaging

eISSN 2005-8330
https://doi.org/10.3348/kjr.2020.1341
Korean J Radiol 2021;22(10):1628-1639

Korean Journal of Radiology
KJR

Should Threshold Growth Be Considered a Major Feature in the Diagnosis of Hepatocellular Carcinoma Using LI-RADS?

Jae Hyon Park, Yong Eun Chung, Nieun Seo, Jin-Young Choi, Mi-Suk Park, Myeong-Jin Kim

All authors: Department of Radiology, Yonsei University College of Medicine, Seoul, Korea

Objective: Based on the Liver Imaging Reporting and Data System version 2018 (LI-RADS, v2018), this study aimed to analyze LR-5 diagnostic performance for hepatocellular carcinoma (HCC) when threshold growth as a major feature is replaced by a more HCC-specific ancillary feature, as well as the frequency of threshold growth in HCC and non-HCC malignancies and its association with tumor size.

Materials and Methods: This retrospective study included treatment-naive patients who underwent gadoxetate disodium-enhanced MRIs for focal hepatic lesions and surgery between January 2009 and December 2016. The frequency of major and ancillary features was evaluated for HCC and non-HCC malignancies, and the LR-category was assessed. Ancillary features that were significantly more prevalent in HCC were then used to either replace threshold growth or were added as additional major features, and the diagnostic performance of the readjusted LR category was compared to the LI-RADS v2018.

Results: A total of 1013 observations were analyzed. Unlike arterial phase hyperenhancement, washout, or enhancing capsule which were more prevalent in HCCs than in non-HCC malignancies (521/616 vs. 18/58, 489/616 vs. 19/58, and 181/616 vs. 5/58, respectively; $p < 0.001$), threshold growth was more prevalent in non-HCC malignancies than in HCCs (11/23 vs. 17/119; $p < 0.001$). The mean size of non-HCC malignancies showing threshold growth was significantly smaller than that of non-HCC malignancies without threshold growth (22.2 mm vs. 42.9 mm, $p = 0.040$). Similar results were found for HCCs; however, the difference was not significant (26.8 mm vs. 33.1 mm, $p = 0.184$). Additionally, Fat-in-nodule was more frequent in HCCs than in non-HCC malignancies (99/616 vs. 2/58, $p = 0.010$). When threshold growth and fat-in-nodule were considered as ancillary and major features, respectively, LR-5 sensitivity (73.2% vs. 73.9%, $p = 0.289$) and specificity (98.2% vs. 98.5%, $p > 0.999$) were comparable to the LI-RADS v2018.

Conclusion: Threshold growth is not a significant diagnostic indicator of HCC and is more common in non-HCC malignancies. The diagnostic performance of LR-5 was comparable when threshold growth was recategorized as an ancillary feature and replaced by a more HCC-specific ancillary feature.

Keywords: *Liver neoplasms; Magnetic resonance imaging; Liver; Diagnosis*

INTRODUCTION

Imaging studies play a crucial role in the diagnosis of hepatocellular carcinoma (HCC) since pathologic confirmation is not always necessary before instituting treatment [1-3]. To standardize the use of imaging to diagnose HCC in high-risk patients, the Liver Imaging Reporting and Data System (LI-RADS) was developed and recently integrated with the American Association for the Study of Liver Disease 2018 HCC clinical practice guidelines [4]. Since the first LI-RADS was developed (v2014), five major features, including arterial phase

Received: November 17, 2020 **Revised:** February 22, 2021 **Accepted:** April 7, 2021
Yong Eun Chung received faculty research grant of Yonsei University College of Medicine (No. 6-2019-0118).
Corresponding author: Yong Eun Chung, MD, PhD, Department of Radiology, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea.
• E-mail: yelv@yuhs.ac

Korean Journal of Radiology
KJR

hyperenhancement (APHE), washout, enhancing capsule, diameter, and threshold growth, have been established as major features for the initial categorization, which is later adjusted according to ancillary features. Among the major features, APHE has consistently showed high sensitivity for progressed HCC as it indicates the presence of an increased intranodular arterial supply during hepatocarcinogenesis [5-7]. Likewise, washout is also considered a strong predictor of HCC, as it indicates decreased portal supply accompanied by a progression in the histologic grade of the tumor [7,8]. Taken together, these two features show a high specificity for HCC in patients with cirrhosis or other risk factors for HCC [9,10]. In addition, enhancing capsule, while less sensitive, is reported to be specific for HCC, as it is directly correlated with either the tumor capsule in progressed HCC or a pseudocapsule consisting of mixed fibrous tissue and dilated sinusoids [11,12].

These three major features have a strong pathophysiological basis in the hepatocarcinogenesis of HCC, are well-established in the context of HCC diagnosis, and are included in all major imaging-based HCC diagnostic algorithms [13-16]. In contrast, the latest LI-RADS version 2018 (v2018) limits the definition of threshold growth to ≥ 50% increase in diameter in ≤ 6 months, which is arbitrary and based mainly on expert opinion and an attempt to be consistent with the Organ Procurement and Transplantation Network (OPTN) algorithm [17]. In addition, although interval growth is an important feature for radiologists to consider in the diagnosis of any neoplasm, the growth rate of HCC can vary widely depending on the initial tumor size or histologic differentiation of the lesion [18-20]. Furthermore, while threshold growth may be useful in reducing false-positive diagnoses by differentiating slow-growing benign entities, it has limited value in diagnosing growing hepatic malignancies, including intrahepatic mass-forming cholangiocarcinoma (IMCC) or combined HCC-cholangiocarcinoma (HCC-CCA), which can also occur in patients at high-risk for HCC. Indeed, the reported HCC tumor doubling time [18,19] overlaps significantly with that of IMCC [21]. In a previous study, the removal of threshold growth as a major feature was found to cause a significant proportion (about 9%) of LR-5 observations to be downgraded to LR-4 [22]; however, no study has yet evaluated whether replacing threshold growth with an ancillary feature would have a similar impact on the LI-RADS categorization.

Thus, we analyzed LR-5 diagnostic performance when the threshold growth as a major feature was replaced by a more HCC-specific ancillary feature. Additionally, the frequency of threshold growth and associated tumor size in HCC and non-HCC malignancies were analyzed.

MATERIALS AND METHODS

Study Population

This study was approved by our Institutional Review Board (IRB No. 2020-3696-001), and the requirement for written informed consent was waived due to the retrospective study design. Using electronic medical records, patients with underlying liver cirrhosis or chronic hepatitis B viral infection who underwent gadoxetate disodium-enhanced MRI between January 2009 and December 2016 for the evaluation of focal hepatic observations were identified. Patients who 1) underwent surgical resection within 3 months of the MRI examination, 2) had not received treatment for hepatic lesions prior to the MRI examination, and 3) were pathologically diagnosed via surgical specimen were included. Likewise, patients who 1) had underlying congestive hepatopathy or iron-deposition liver disease, 2) had > 3 hepatic observations, and 3) did not have all required MRI protocol imaging were excluded from the analysis. For patients with more than one observation, the largest observation and its corresponding histopathologic diagnosis were used for the analysis [23].

MRI Techniques

All patients underwent MRI examinations using a 3T Magnetom Trio Tim (Siemens Medical Solutions), Intera Achieva or Ingenia (Philips Medical Systems), or Discovery MR750w (GE Medical Systems) MRI scanner [24]. Dynamic MRI studies of the liver were performed using 10 mL of intravenous gadoxetate disodium (Primovist; Bayer AG) at a rate of 1 mL/sec, followed by 20 mL of 0.9% saline chaser at the same rate (Spectris Solaris MR Injection System; Medrad). T1-weighted three-dimensional gradient-echo imaging was performed before contrast injection and in the arterial phase (18 seconds after aortic enhancement using the bolus tracking method), portal venous phase (60 seconds), delayed phase (90 seconds) transitional phase (150 seconds), and hepatobiliary phase (20 minutes after contrast agent injection).

Other MRI sequences included an axial dual-echo T1-weighted breath-hold gradient echo sequence for acquisition of in-phase and out-of-phase images, an axial respiratory-

 https://doi.org/10.3348/kjr.2020.1341

triggered turbo spin-echo T2-weighted sequence with fat saturation, an axial half-Fourier acquisition single-shot turbo spin-echo T2-weighted sequence with fat saturation, and diffusion-weighted imaging with respiratory-triggered single-shot echo planar imaging sequences with b values of 0, 50, 400, and 800 sec/mm^2 or 50, 400, and 800 sec/mm^2.

MRI Analysis and the LI-RADS Category Assignment

MR images were randomized and reviewed together by two board-certified radiologists with 12 years and 16 years of experience in hepatic imaging. If multiple lesions were present in one patient, the largest lesion was analyzed. However, for surgically confirmed patients, the largest lesion, excluding benign LR-1 or LR-2 lesions, was analyzed. All MRIs were retrieved and reviewed using a picture archiving and communication system (Centricity Radiology RA 1000; GE Healthcare). The reviewers analyzed each hepatic observation according to the LI-RADS v2018 [25]. For the LR-M criteria, both targetoid mass features and non-targetoid mass features (i.e., infiltrative appearance, marked diffusion restriction, necrosis or severe ischemia, and other features considered a non-HCC malignancy by a qualified radiologist) were used in the analysis [25]. For observations with documented threshold growth, reviewers determined the qualifying threshold growth criteria (≥ 50% increase in diameter in ≤ 6 months) by retrospectively reviewing, measuring and comparing the longest diameter of observation on current and prior exams in either the transitional or hepatobiliary phase for liver dynamic MRIs and the portal venous phase or delayed phase for liver CT.

Adjustment of Major and Ancillary Features in the LI-RADS v2018

Ancillary features with greater frequency in HCC compared to non-HCC malignancies in the univariable analysis (i.e., χ^2 test or Fisher's exact test) were considered possible candidates for new major features. After the relevant ancillary features replaced or were added to the major features, the final LR-category was then re-evaluated.

The final diagnosis of the hepatic observation and the status of the adjacent non-tumor liver parenchyma were obtained from the pathology report. For HCC, tumor grade was categorized as I, II, III, and IV based on the nuclear grading scheme proposed by Edmondson and Steiner [26]. Benign diagnoses were confirmed by surgical pathology (n = 3), typical imaging features, or stable imaging for at least 2 years (n = 336) [27]. The fibrosis stage of non-tumor liver parenchyma was determined according to the Batts-Ludwig scoring system (from F0, no fibrosis to F4, cirrhosis) [28].

Statistical Analysis

The patients' baseline characteristics were compared using the χ^2 test or the Fisher's exact test for categorical variables and the Student's *t* test or Wilcoxon signed-rank test for continuous variables. Continuous variables are expressed as medians and interquartile ranges. Imaging feature endpoints were evaluated on a per-patient basis since one hepatic observation for each patient was selected for imaging analysis [1]. Estimates and 95% confidence intervals (CIs) of diagnostic performance, including sensitivity, specificity, positive predictive value, negative predictive value, and accuracy, were calculated. The diagnostic performance of the adjusted LR-5 was then calculated and compared to that of the original LR-5 using the McNemar's test. The Fisher's exact test was used to evaluate the correlation between threshold growth and the Edmondson grade of HCC, and the Cochran-Armitage trend test was used to evaluate whether the Edmondson grade was higher with or without threshold growth. Statistical significance was defined as a two-sided p value < 0.05. All statistical analyses were performed using MedCalc (version 19.0.7; MedCalc Software) and SPSS version 25 (IBM Corp.).

RESULTS

Patient Characteristics and Pathologic Findings

Of the 1017 patients who were identified based on the inclusion and exclusion criteria, four with tumor in vein were excluded, resulting in a total of 1013 patients who were included in the final analysis (Fig. 1). The clinicopathologic characteristics of these 1013 patients (775 male and 238 female; median age, 56 years) are summarized in Table 1. A total of 677 underwent surgery (99 underwent wedge resection, 256 and 291 underwent segmentectomy and lobectomy, respectively, and 31 underwent liver transplantation).

Of the 1013 hepatic observations evaluated, 616 were HCCs, 58 were non-HCC malignancies (29 IMCC; 24 cHCC-CCA; 4 metastases from ovarian epithelial cancer, pancreatic adenocarcinoma, and colon adenocarcinoma; and 1 sarcomatoid cHCC-CCA), and 339 were benign tumors (222 hemangioma, 63 dysplastic or regenerative nodules, 32 focal nodular hyperplasia-like nodules, 16 eosinophilic infiltrations, 4 focal fat depositions, 1 focal fat sparing and

https://doi.org/10.3348/kjr.2020.1341

Korean Journal of Radiology
KJR

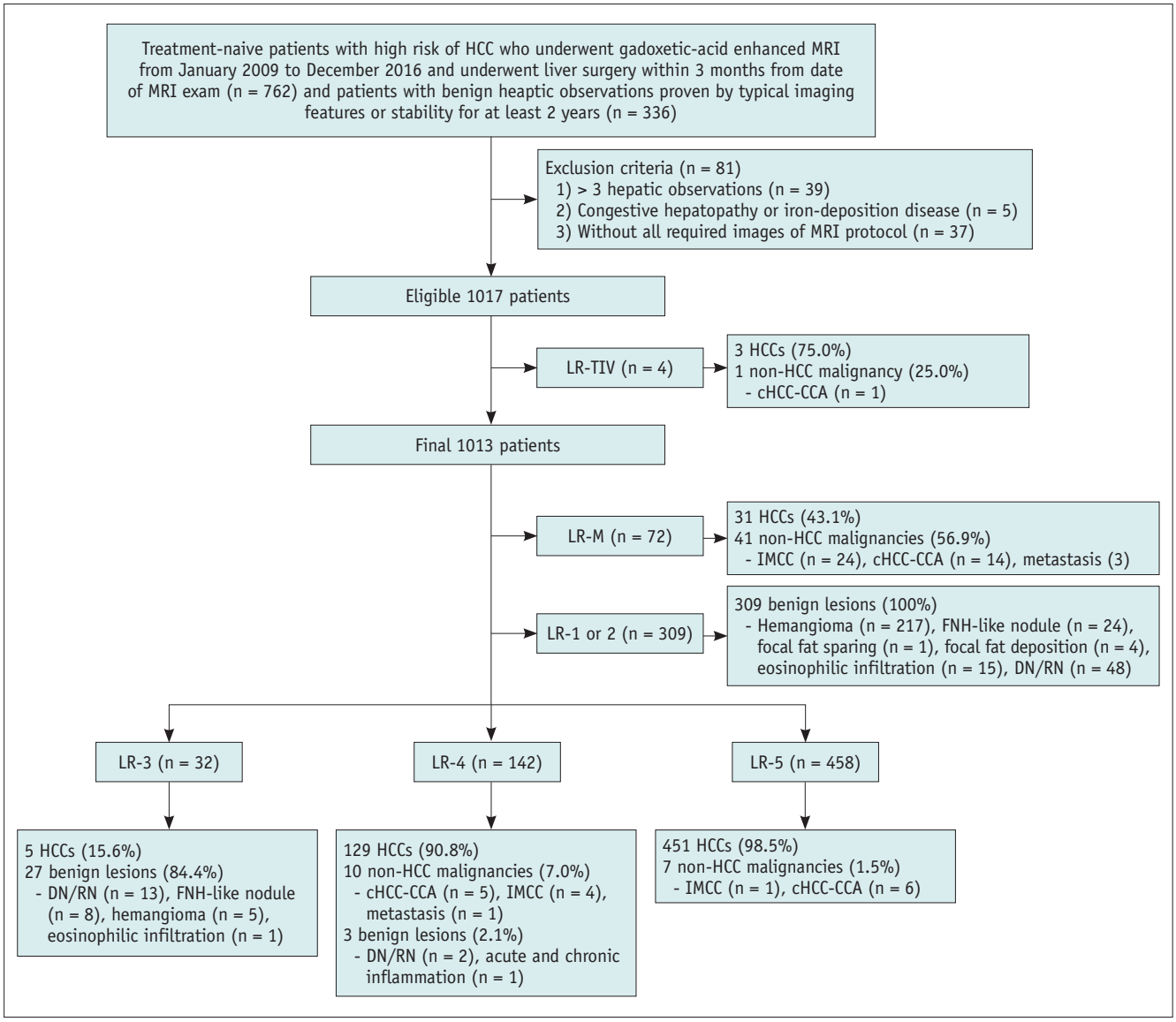

Fig. 1. Inclusion and exclusion criteria and original final LR-categories of the study population based on LI-RADS v2018. cHCC-CCA = combined HCC-choangiocarcinoma, DN = dysplastic nodule, FNH = focal nodular hyperplasia, HCC = hepatocellular carcinoma, IMCC = intrahepatic mass-forming cholangiocarcinoma, LI-RADS = Liver Imaging Reporting and Data System, RN = regenerative nodule, TIV = tumor-in-vein

1 acute and chronic inflammatory lesion). The median sizes of HCC and non-HCC malignancies were 29.3 mm and 36.2 mm, respectively. In addition, of the 405 patients who had liver cirrhosis, 230, 173, and 2 had Child Pugh class A, B, and C, respectively.

Frequency of Threshold Growth and Correlation to Size of Hepatic Observation

A total of 674 patients had hepatic malignancies. Of the 58 patients with non-HCC malignancy and the 616 with HCCs, 23 (39.7%) and 119 (19.3%) had examinations within 6 months of the MRI, respectively (Table 2). Of the 142 patients with prior examinations, 15 had an exam within 1 month of the MRI, 92 had one within 1–3 months of the MRI, and 35 had prior exams 3–6 months before the MRI. All the patients with exams within 1–6 months of the MRI underwent a follow-up MRI to determine the change in interval size, while most of the patients who underwent an examination within 1 month of the MRI underwent MRI following prior CT for further characterization. Among the patients with prior exams, threshold growth was more frequent in non-HCC malignancies than in HCCs ($p < 0.001$) (Table 3).

The mean size of non-HCC malignancies with threshold

https://doi.org/10.3348/kjr.2020.1341

Table 1. Clinical-Pathologic Characteristics of Patients and Hepatic Observations

Characteristics	Value
Patients (n = 1013)	
Median age, year*	56 (50–63)
Sex	
Male	775 (76.5)
Female	238 (23.5)
Cause of liver disease	
Hepatitis B virus	875 (86.4)
Alcohol	78 (7.7)
Hepatitis C virus	34 (3.4)
NASH	8 (0.8)
Autoimmune	1 (0.1)
Unknown	17 (1.7)
Number of observations per patient	
1	825 (81.4)
2	99 (9.8)
3	89 (8.8)
Lesions (n = 1013)	
Median size, mm*	24.1 (14.0–35.9)
HCC	29.3 (21.8–42.9)
Non-HCC malignancies	36.2 (24.0–46.6)
Benign lesions	11.0 (10.0–18.0)
Size subgroup, mm	
< 10	82 (8.1)
10–19	315 (31.1)
20	616 (60.8)
Final diagnosis	
HCC	616 (60.8)
Non-HCC malignancies	58 (5.7)
IMCC	29 (50.0)
cHCC-CCA	24 (41.4)
Metastasis	4 (6.9)
Sarcomatoid cHCC-CCA	1 (1.7)
Benign tumors	339 (33.5)
Hemangioma	222 (65.5)
Dysplastic or regenerative nodule	63 (18.6)
FNH-like nodule	32 (9.4)
Eosinophilic infiltration	16 (4.7)
Focal fat deposition	4 (1.2)
Focal fat sparing	1 (0.3)
Inflammatory pseudotumor	1 (0.3)
Pathologically confirmed liver fibrosis (n = 677)	
Cirrhosis (grade 4)	405 (59.8)
Septal fibrosis (grade 3)	134 (19.8)
Periportal fibrosis (grade 2)	102 (15.1)
Portal fibrosis (grade 1)	36 (5.3)
Median time interval between MRI and pathologic diagnosis, day*	13 (7–22)

Unless stated otherwise, data are number of patients or observations with the percentage in parentheses. *Data are presented as median (interquartile range). cHCC-CCA = combined HCC-choangiocarcinoma, FNH = focal nodular hyperplasia, HCC = hepatocellular carcinoma, IMCC = intrahepatic mass-forming cholangiocarcinoma, NASH = non-alcoholic steatohepatitis

growth (22.2 ± 14.2 mm; range, 9.0–48.6 mm) was significantly smaller than the mean size of non-HCC malignancies without threshold growth (42.9 ± 28.2 mm; range, 12.4–120.4 mm) (p = 0.040). There was no significant correlation between the size of non-HCC malignancies (i.e., < 10 mm, 10–19 mm, and ≥ 20 mm) and threshold growth (p = 0.090). For HCC, the mean size of HCC with threshold growth (26.8 ± 12.9 mm; range, 11.7–60.7 mm) was also smaller than the mean size of HCC without threshold growth (33.1 ± 18.6 mm; range, 7.0–140.0 mm); however, this difference was not statistically significant (p = 0.184). Furthermore, smaller HCCs did not trend toward greater threshold growth, as there was no significant correlation between HCC size and threshold growth (p = 0.607) (Table 2, Fig. 2).

Changes to Final LR-Category before and after Follow-Up Exam

Of the 142 patients with prior exams, the final LR category changed in 11 (7.7%) patients (Supplementary Table 1). Four patients (patients #1–#4) showed threshold growth on MRI and had their LR categories changed due to the added major criterion. In the case of patient #3, the presence of threshold growth allowed the final LR-category to be upgraded to LR-5 on follow-up MRI, even though the pathology was later confirmed to be combined hepatocellular cholangiocarcinoma, a non-HCC malignancy (Fig. 3). The LR categories of six patients (patients #5–10) were upgraded since the tumor size had increased ≥ 20 mm on MRI. One patient (patient #11) had their LR-category upgraded from LR-3 to LR-4 due to ancillary features such as transitional phase hypointensity and hepatobiliary phase hypointensity on MRI, which could not be assessed in prior CT examinations.

Frequency of Major and Ancillary Features in HCC and Non-HCC Malignancy

As expected, APHE, washout, and enhancing capsule were more frequently observed in HCC than in non-HCC malignancies with a significant difference (p < 0.001) (Table 3).

Concerning the ancillary features, targetoid mass features and corona enhancement were significantly more common in non-HCC malignancies. Of the ancillary features favoring HCC in particular, transitional phase hypo-intensity and fat-containing nodules were more frequently observed in HCC.

https://doi.org/10.3348/kjr.2020.1341

Korean Journal of Radiology
KJR

Table 2. Correlation between Observation Size and Theshold Growth

	# of Patients with 6 Months CT/MR (%)	Threshold Growth (+) (%)	Threshold Growth (-) (%)	P*	P†
HCC, mm (n = 616)					
< 10	3/8 (37.5)	0/3 (0.0)	3/3 (100.0)	0.360	0.607
10–19	27/114 (23.7)	6/27 (22.2)	21/27 (77.8)		
20	89/494 (18.0)	11/89 (12.4)	78/89 (87.6)		
Non-HCC malignancies, mm (n = 58)					
< 10	3/3 (100.0)	3/3 (100.0)	0/3 (0.0)	0.199	0.090
10–19	4/6 (66.7)	2/4 (50.0)	2/4 (50.0)		
20	16/49 (32.7)	6/16 (37.5)	10/16 (62.5)		

*Fisher's exact test, †Cochran-Armitage's trend test. HCC = hepatocellular carcinoma

Table 3. Frequency of Major and Ancillary Features in Non-HCC Malignancies and HCC

	Data Available	Non-HCC Malignancies (n = 58) (%)	HCC (n = 616) (%)	P*
Major features				
APHE	674	18 (31.0)	521 (84.5)	< 0.001
WO	674	19 (32.7)	489 (79.3)	< 0.001
Enhancing capsule	674	5 (8.6)	181 (29.4)	< 0.001
Threshold growth	142	11/23 (47.8)	17/119 (14.2)	< 0.001
Ancillary features				
Subthreshold growth	53	5/7 (71.4)	36/46 (78.3)	0.704
Targetoid mass features	674	32 (55.2)	27 (4.4)	< 0.001
Corona enhancement	674	22 (37.9)	134 (21.8)	0.005
Fat sparing in solid mass	674	1 (1.7)	13 (2.1)	0.844
Restricted diffusion	674	55 (94.8)	585 (95.0)	0.963
Mild to moderate T2 hyperintensity	674	53 (91.4)	579 (94.0)	0.431
Iron sparing in solid mass	674	0 (0)	3 (0.5)	> 0.999
TP hypointensity	674	47 (81.0)	562 (91.2)	0.012
HBP Hypointensity	674	54 (93.1)	574 (93.2)	0.982
Nonenhancing capsule	674	2 (3.4)	27 (4.4)	> 0.999
Nodule-in-nodule	674	0 (0)	7 (1.1)	> 0.999
Mosaic architecture	674	2 (3.4)	50 (8.1)	0.203
Fat-in-nodule	674	2 (3.4)	99 (16.1)	0.010
Blood product	674	2 (3.4)	56 (9.1)	0.217

*χ^2 test or Fisher's exact test. APHE = (nonrim) arterial phase hyperenhancement, HBP = hepatobiliary phase, HCC = hepatocellular carcinoma, TP = transitional phase, WO = washout

Diagnostic Performance of Adjusted LR-5 after Modifying Major Features Using Ancillary Features

The final LR categories of the 1013 patients based on the LI-RADS v2018 were as follows: 72 LR-M, 309 LR-2, 32 LR-3, 142 LR-4, and 458 LR-5 (Fig. 1). Based on these categorizations, LR-5 had a sensitivity of 73.2% and a specificity of 98.2% for HCC (Table 4).

Although transitional phase hypointensity was significantly different between non-HCC malignancy and HCC (p = 0.012), this finding was high in both non-HCC malignancies (47/58, 81.0%) and HCC (562/616, 91.2%) and was therefore not considered a useful imaging feature for the differential diagnosis of HCC. Since fat-in-nodule were significantly more frequent in HCCs than in non-HCC malignancies (p = 0.010) and were only seen in 3.4% of non-HCC malignancies, it was selected as a possible major feature.

After adding fat-in-nodule as a major feature, four LR-4 observations were upgraded to LR-5 and the LR-5 sensitivity increased non-significantly to 73.9% (p = 0.125), while no change was noted for the specificity (Table 4).

When threshold growth was replaced by fat-in-nodule as

 https://doi.org/10.3348/kjr.2020.1341

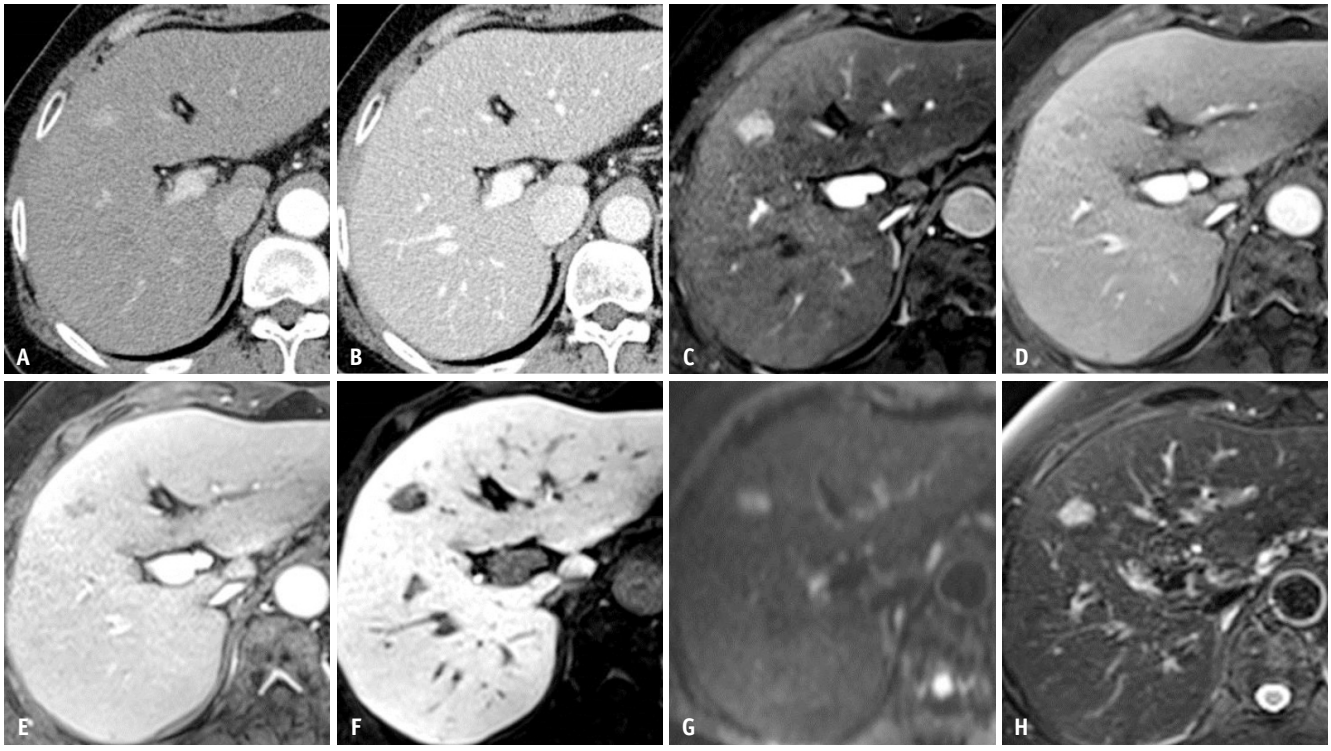

Fig. 2. A 61-year-old female with Edmonson grade II hepatocellular carcinoma is presented.
A-H. A liver dynamic CT **(A, B)** taken on January 2, 2009 with **(A)** non-rim APHE in the arterial phase and **(B)** washout in the portal venous phase. A gadoxetate-enhanced liver dynamic MRI **(C-H)** taken on February 27, 2009 (about 2 months after the prior exam) with **(C)** APHE in the late arterial phase, **(D)** washout with capsular enhancement in the portal venous phase, **(E)** transitional phase hypointensity, **(F)** hepatobiliary phase hypointensity, **(G)** diffusion restriction in diffusion-weighted imaging and **(H)** moderate T2 hyperintensity in T2-weighted imaging. This observation's longest diameter measured 12 mm on liver dynamic CT and 15 mm on gadoxetate-enhanced MRI and thus threshold growth was not present. APHE = (nonrim) arterial phase hyperenhancement

a major feature and threshold growth was considered an ancillary feature, seven LR-4 observations were upgraded to LR-5, while three LR-5 observations were downgraded to LR-4. Under these conditions, LR-5 sensitivity and specificity were 73.9% (p = 0.289) and 98.5% (p > 0.999), respectively.

Correlation between Observation Size and Edmondson Grade of HCC and Threshold Growth

No significant correlation was found between threshold growth and Edmondson grade of HCC (p = 0.364), and no trend was found in threshold growth for either low or high Edmondson grade of HCC (p = 0.637) (Table 5).

DISCUSSION

The results of our study indicate that when fat-in-nodule replaced threshold growth as a major feature, both LR-5 specificity and sensitivity were slightly improved, although there was no statistically significant difference. When fat-in-nodule was added as an additional major feature, the sensitivity of LR-5 was slightly higher without affecting the specificity. The presence of threshold growth was higher in non-HCC malignancies than in HCC, and non-HCC malignancies with threshold growth were smaller in size than those not exhibiting threshold growth.

Intuitively, the presence of threshold growth could be affected by the initial tumor size because the definition of ≥ 50% increase in diameter in ≤ 6 months can be more easily achieved by smaller observations than larger observations. Previous results have also shown that smaller HCCs usually increase in size faster than larger ones, although there are many other factors related to the growth rate of HCC [18,19]. In our study, this trend was more dominant in non-HCC malignancies, although the difference was not statistically significant. However, when excluding HCCs < 10 mm in size, threshold growth was also more frequent in smaller HCCs (10–19 mm) than in larger HCCs (≥ 20 mm), although this difference was also not significant. A possible reason for this result could be the

https://doi.org/10.3348/kjr.2020.1341

Korean Journal of Radiology
KJR

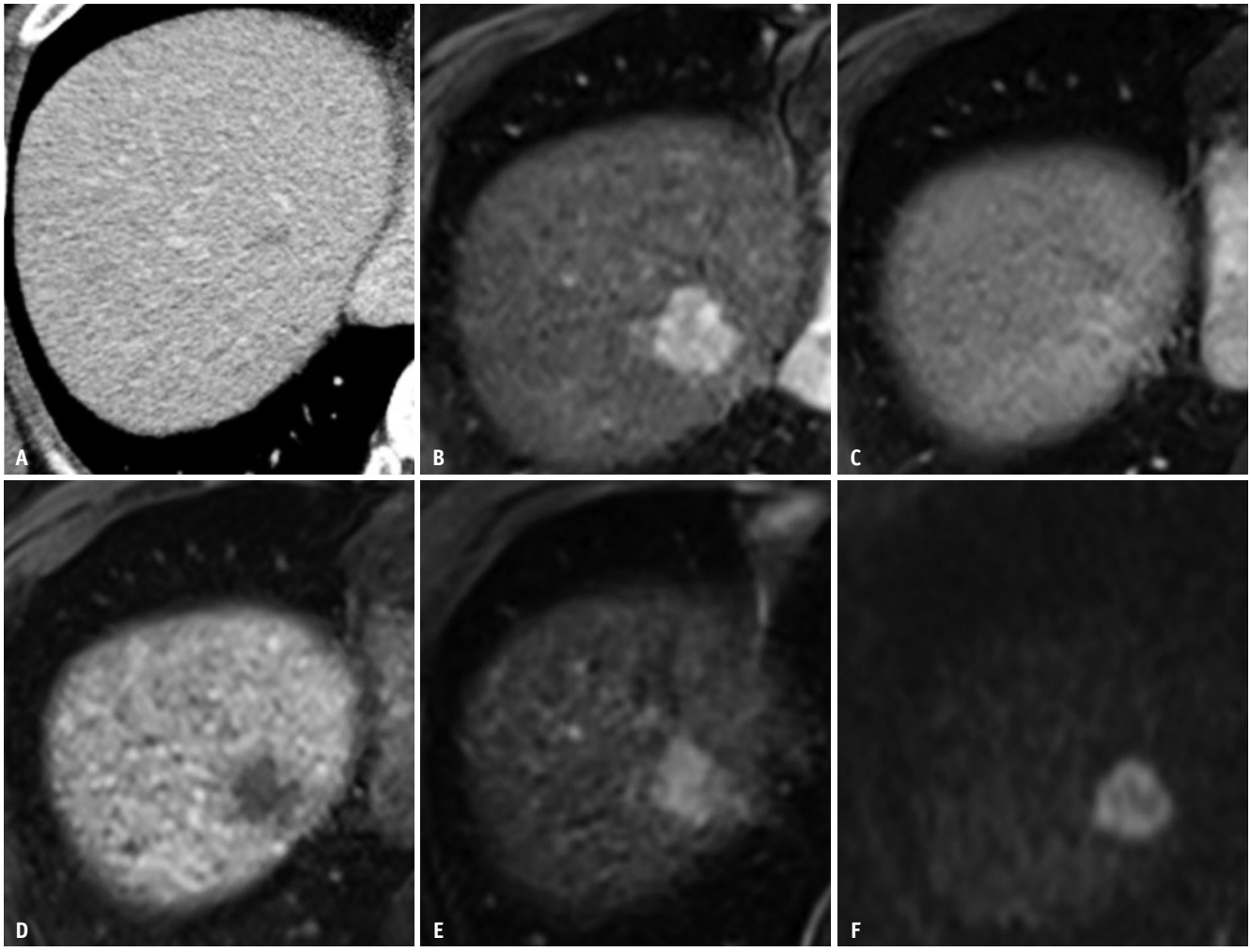

Fig. 3. A 34-year-old male with combined hepatocellular-cholangiocarcinoma is presented.
A-F. An abdominal CT in the portal venous phase **(A)** obtained on December 27, 2008 shows a focal hypodense lesion measuring < 1 cm at its longest diameter. A gadoxetate-enhanced MRI taken on June 7, 2009 (less than six months after the prior exam) in the late arterial phase **(B)**, portal venous phase **(C)**, and hepatobiliary phase **(D)**, and with T2-weighted imaging **(E)** and diffusion-weighted imaging **(F)**. This observation shows non-rim enhancement in the arterial phase without definite washout, hepatobiliary phase hypointensity, moderate T2 hyperintensity and diffusion restriction. This observation measured 2.3 cm at its longest diameter on gadoxetate-enhanced MRI, thus showing the presence of threshold growth and was categorized as LR-5 on MRI.

low proportion (n = 82, 8.1%) of observations < 10 mm in size, thus explaining the low statistical power. Additionally, the proportion of small HCCs (< 10 mm) was less than the proportion of small non-HCC malignancies (< 10 mm), since many of the small HCCs were treated using non-surgical methods such as radiofrequency ablation and transarterial chemoembolization.

Fatty metamorphosis in HCCs has been reported in approximately 16–18% of HCC cases [29], which is consistent with our results (16.1% in HCC), and it was more frequently observed in HCC than in non-HCC malignancies (3.4%). In our study, fat-in-nodule were a more HCC-specific feature than threshold growth, and the diagnostic performance of LR-5 for HCC when fat-in-nodule replaced threshold growth as a major feature was comparable to that obtained using the current LI-RADS v2018. However, our results showed that when fat-containing nodules replaced threshold growth as a major feature, neither LR-5 sensitivity nor specificity were significantly higher than those of the original LR-5. Similarly, when fat-in-nodule was added as a major feature, no reduction in LR-5 specificity was noted, while the LR-5 sensitivity increased non-significantly by approximately 0.7%. However, fatty metamorphosis occurs more frequently in early-stage HCCs, especially in those < 15 mm in size [30]. Thus, the proportion of early- and progressed HCCs in the study population could have

https://doi.org/10.3348/kjr.2020.1341

Table 4. Sensitivity, Specificity, Accuracy, PPV and NPV of HCC Under Various Adjustment of Major and Ancillary Features in LI-RADS v2018

	Sensitivity	Specificity	PPV	NPV	Accuracy	$P^{\dagger}$	$P^{\ddagger}$
LI-RADS v2018							
LR-5	73.2 (451/616) [69.5, 76.7]	98.2 (390/397) [96.4, 99.3]	98.5 (451/458) [96.9, 99.3]	70.3 (390/555) [67.5, 72.9]	83.0 (841/1013) [80.6, 85.3]		
Fat- in-nodule as an additional major feature							
LR-5	73.9 (455/616) [70.2, 77.3]	98.2 (390/397) [96.4, 99.3]	98.5 (455/462) [96.9, 99.3]	70.8 (390/551) [68.0, 73.5]	83.4 (845/1013) [81.0, 85.7]	0.125	> 0.999
Fat-in-nodule replaces threshold growth as major feature*							
LR-5	73.9 (455/616) [70.2, 77.3]	98.5 (391/397) [96.7, 99.4]	98.7 (455/461) [97.2, 99.4]	70.8 (391/552) [68.0, 73.5]	83.5 (846/1013) [81.1, 85.8]	0.289	> 0.999

Data are percentages with the number of lesions in parentheses. Numbers in brackets are the 95% confidence intervals. *Threshold growth was considered as an ancillary feature, $^{\dagger}p$ value after comparing sensitivity to sensitivity of original LR-5 using McNemar's test, $^{\ddagger}p$ value after comparing specificity to specificity of original LR-5 using McNemar's test. HCC = hepatocellular carcinoma, LI-RADS = Liver Imaging Reporting and Data Systems, NPV = negative predictive value, PPV = positive predictive value

Table 5. Correlation between Edmondson Grade of Hepatocellular Carcinoma and Threshold Growth

	Edmonson Grade (%)				P^{*}	$P^{\dagger}$
	1	2	3	4		
Threshold growth	3 (17.7)	10 (58.8)	4 (23.5)	0 (0)	0.364	0.637

*Fisher's exact test, †Cochran-Armitage's trend test.

affected the prevalence of fat-containing nodules.

Regardless, our findings demonstrate a diagnostic performance comparable to the original LR-5 when threshold growth is replaced by a more HCC-specific ancillary feature, which raises the question of whether threshold growth has enough scientific evidence to remain a major feature. One significant limitation of threshold growth is that it cannot be applied in the diagnosis of HCC when previous CT or MRI examinations are not available [2]. In our study, 43.2% (438/1013) of all patients had prior exams, of which 29.3% (142/483) had hepatic malignancies, and 19.7% (28/142) showed threshold growth. In the case of HCC, 19.3% (119/616) had prior exams, wherein 14.2% (17/119) showed threshold growth, which was close to the reported 14.7% in a previous study where prior exams were available in 66.4% of all patients (n = 489 observations) [22]. However, Chernyak et al. [22] acknowledged that their study period was too short to include many first-time patients, thus explaining the relatively larger proportion of patients with prior exams, acknowledging this might have inflated the importance of threshold growth. However, the small proportion of observations with the LI-RADS categorization changes due to threshold growth was similar between the studies.

Previously, it has been suggested that removing threshold growth as a major feature would lead to the under-diagnosis of aggressive, rapidly growing HCCs, which, if left untreated, would be the most harmful to patients [22]. While the histological differentiation of HCC is often heterogeneous, tumor doubling time is reported to correlate significantly with histological differentiation of HCC, with more rapid tumor growth reported in poorly differentiated HCCs [20,31,32]. However, our results showed no significant correlation between Edmondson grade of HCC and the presence of threshold growth. Moreover, our results showed that HCCs with threshold growth were not correlated with higher Edmondson grade tumors compared to those without threshold growth. Thus, removing threshold growth as a major feature and incorporating it into ancillary features alongside subthreshold growth may have a marginal impact on the exclusion of rapidly growing HCCs. Although threshold growth can be useful for differentiating benign observations, such as dysplastic or regenerative nodules and focal nodular hyperplasia-like nodules from primary hepatic malignancy, it has a limited role in differentiating other hepatic malignancies from HCC [33-35]. However, benign lesions (i.e., LR-1 and LR-2) are

https://doi.org/10.3348/kjr.2020.1341

Korean Journal of Radiology
KJR

often excluded before categorizing a hepatic observation as LR-3, -4, or -5 based on the LI-RADS v2018 algorithm; therefore, the presence of threshold growth may have a limited role in the diagnosis of HCC. In our study, two of the 63 (3.2%) dysplastic or regenerative nodules showed threshold growth and were categorized as LR-4, while the other nodules were categorized as LR-2 or LR-3. However, both nodules would still have been categorized as LR-4 via upgrade using threshold growth as an ancillary feature. By keeping threshold growth as an ancillary feature, LR-3 observations can still be upgraded to LR-4, which improves the diagnostic performance of LR-4 while also preventing non-HCC malignancies from being assigned to LR-5, thus allowing for high LR-5 specificity for HCC.

This study has several limitations. First, there may have been selection bias due to the retrospective study design and the inclusion of hepatic malignancies histopathologically confirmed through surgical resection. While only surgically resected hepatic malignancies were included in this study, pathological confirmation was necessary to accurately evaluate the prevalence of both major and ancillary features, especially threshold growth, between HCCs and non-HCC malignancies since some LR-4 and/or LR-5 non-HCC malignancies may have been categorized as HCCs using imaging findings alone. Second, imaging analysis was performed by two radiologists in consensus; thus, no interobserver agreement was determined. Third, slightly more than half of all included observations did not have prior exams since this study was conducted in a tertiary hospital, and the number of patients with prior exams was smaller than that reported in a previous study [22]. Fourth, fat-in-nodule noted on MRI were not confirmed by pathology since only fatty changes at the cellular level were reported. Lastly, while we used fat-in-nodule as an example to show that similar diagnostic performance can be obtained when an ancillary feature is added to or replaces threshold growth, further investigation is required before the actual application of fat-in-nodule as a major feature, as it may not be the most appropriate HCC-specific feature. Moreover, various factors, including the possibility of over-categorizing hypervascular tumors with fatty components such as hepatic adenoma or angiomyolipoma, and benign entities, such as dysplastic or regnerative nodules, must be considered before recognizing fat-in-nodules as a major feature.

In conclusion, while threshold growth can occur in both HCC and non-HCC malignancies, it is more common in non-HCC malignancies and can be affected by the initial tumor size. Radiologists should be cautious when upgrading LR-4 observations to LR-5 using threshold growth as the sole determining factor. When threshold growth was considered an ancillary feature and a different ancillary feature more specific to HCC was added or replaced threshold growth as a major feature, no significant reduction in LR-5 diagnostic performance was observed compared to the LI-RADS v2018.

Supplement

The Supplement is available with this article at https://doi.org/10.3348/kjr.2020.1341.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Jae Hyon Park, Yong Eun Chung. Data curation: Jae Hyon Park, Yong Eun Chung, Jin-Young Choi. Formal analysis: Jae Hyon Park, Yong Eun Chung, Jin-Young Choi. Funding acquisition: Yong Eun Chung. Investigation: Yong Eun Chung. Methodology: Yong Eun Chung. Project administration: Yong Eun Chung. Resources: Yong Eun Chung. Software: Jae Hyon Park, Yong Eun Chung. Supervision: Yong Eun Chung, Mi-Suk Park, Myeong-Jin Kim. Validation: Yong Eun Chung, Jin-Young Choi, Nieun Seo, Mi-Suk Park, Myeong-Jin Kim. Visualization: Jae Hyon Park, Yong Eun Chung. Writing—original draft: Jae Hyon Park, Yong Eun Chung. Writing—review & editing: Yong Eun Chung, Jin-Young Choi, Nieun Seo, Mi-Suk Park, Myeong-Jin Kim.

ORCID iDs

Jae Hyon Park
https://orcid.org/0000-0002-7626-194X
Yong Eun Chung
https://orcid.org/0000-0003-0811-9578
Nieun Seo
https://orcid.org/0000-0001-8745-6454
Jin-Young Choi
https://orcid.org/0000-0002-9025-6274
Mi-Suk Park
https://orcid.org/0000-0001-5817-2444
Myeong-Jin Kim
https://orcid.org/0000-0001-7949-5402

REFERENCES

1. Kim YY, Kim MJ, Kim EH, Roh YH, An C. Hepatocellular carcinoma versus other hepatic malignancy in cirrhosis: performance of LI-RADS version 2018. *Radiology* 2019;291:72-80
2. Kim YY, Choi JY, Sirlin CB, An C, Kim MJ. Pitfalls and problems to be solved in the diagnostic CT/MRI liver imaging reporting and data system (LI-RADS). *Eur Radiol* 2019;29:1124-1132
3. Elsayes KM, Kielar AZ, Chernyak V, Morshid A, Furlan A, Masch WR, et al. LI-RADS: a conceptual and historical review from its beginning to its recent integration into AASLD clinical practice guidance. *J Hepatocell Carcinoma* 2019;6:49-69
4. Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology* 2018;67:358-380
5. Efremidis SC, Hytiroglou P. The multistep process of hepatocarcinogenesis in cirrhosis with imaging correlation. *Eur Radiol* 2002;12:753-764
6. Choi JW, Lee JM, Kim SJ, Yoon JH, Baek JH, Han JK, et al. Hepatocellular carcinoma: imaging patterns on gadoxetic acid-enhanced MR images and their value as an imaging biomarker. *Radiology* 2013;267:776-786
7. Choi JY, Lee JM, Sirlin CB. CT and MR imaging diagnosis and staging of hepatocellular carcinoma: part II. Extracellular agents, hepatobiliary agents, and ancillary imaging features. *Radiology* 2014;273:30-50
8. Matsui O, Kobayashi S, Sanada J, Kouda W, Ryu Y, Kozaka K, et al. Hepatocelluar nodules in liver cirrhosis: hemodynamic evaluation (angiography-assisted CT) with special reference to multi-step hepatocarcinogenesis. *Abdom Imaging* 2011;36:264-272
9. Forner A, Vilana R, Ayuso C, Bianchi L, Solé M, Ayuso JR, et al. Diagnosis of hepatic nodules 20 mm or smaller in cirrhosis: prospective validation of the noninvasive diagnostic criteria for hepatocellular carcinoma. *Hepatology* 2008;47:97-104
10. Kim TK, Lee KH, Jang HJ, Haider MA, Jacks LM, Menezes RJ, et al. Analysis of gadobenate dimeglumine-enhanced MR findings for characterizing small (1-2-cm) hepatic nodules in patients at high risk for hepatocellular carcinoma. *Radiology* 2011;259:730-738
11. Ishigami K, Yoshimitsu K, Nishihara Y, Irie H, Asayama Y, Tajima T, et al. Hepatocellular carcinoma with a pseudocapsule on gadolinium-enhanced MR images: correlation with histopathologic findings. *Radiology* 2009;250:435-443
12. Lim JH, Choi D, Park CK, Lee WJ, Lim HK. Encapsulated hepatocellular carcinoma: CT-pathologic correlations. *Eur Radiol* 2006;16:2326-2333
13. Korean Liver Cancer Association, National Cancer Center. 2018 Korean Liver Cancer Association-National Cancer Center Korea Practice Guidelines for the management of hepatocellular carcinoma. *Gut Liver* 2019;13:227-299
14. Omata M, Cheng AL, Kokudo N, Kudo M, Lee JM, Jia J, et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. *Hepatol Int* 2017;11:317-370
15. Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, 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
16. European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2018;69:182-236
17. Rosenkrantz AB, Campbell N, Wehrli N, Triolo MJ, Kim S. New OPTN/UNOS classification system for nodules in cirrhotic livers detected with MR imaging: effect on hepatocellular carcinoma detection and transplantation allocation. *Radiology* 2015;274:426-433
18. Kim JK, Kim HD, Jun MJ, Yun SC, Shim JH, Lee HC, et al. Tumor volume doubling time as a dynamic prognostic marker for patients with hepatocellular carcinoma. *Dig Dis Sci* 2017;62:2923-2931
19. An C, Choi YA, Choi D, Paik YH, Ahn SH, Kim MJ, et al. Growth rate of early-stage hepatocellular carcinoma in patients with chronic liver disease. *Clin Mol Hepatol* 2015;21:279-286
20. Shingaki N, Tamai H, Mori Y, Moribata K, Enomoto S, Deguchi H, et al. Serological and histological indices of hepatocellular carcinoma and tumor volume doubling time. *Mol Clin Oncol* 2013;1:977-981
21. De Rose AM, Cucchetti A, Clemente G, Ardito F, Giovannini I, Ercolani G, et al. Prognostic significance of tumor doubling time in mass-forming type cholangiocarcinoma. *J Gastrointest Surg* 2013;17:739-747
22. Chernyak V, Kobi M, Flusberg M, Fruitman KC, Sirlin CB. Effect of threshold growth as a major feature on LI-RADS categorization. *Abdom Radiol (NY)* 2017;42:2089-2100
23. Park JH, Chung YE, Seo N, Choi JY, Park MS, Kim MJ. Gadoxetic acid-enhanced MRI of hepatocellular carcinoma: diagnostic performance of category-adjusted LR-5 using modified criteria. *PLoS One* 2020;15:e0242344
24. Lee S, Kim SS, Chang DR, Kim H, Kim MJ. Comparison of LI-RADS 2018 and KLCA-NCC 2018 for noninvasive diagnosis of hepatocellular carcinoma using magnetic resonance imaging. *Clin Mol Hepatol* 2020;26:340-351
25. American College of Radiology. CT/MRI LI-RADS® v2018. Acr.org Web site. https://www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/LI-RADS/CT-MRI-LI-RADS-v2018. Accessed November 6, 2020
26. Edmondson HA, Steiner PE. Primary carcinoma of the liver: a study of 100 cases among 48,900 necropsies. *Cancer* 1954;7:462-503
27. Lee S, Kim MJ, Kim SS, Shin H, Kim DY, Choi JY, et al. Retrospective comparison of EASL 2018 and LI-RADS 2018 for the noninvasive diagnosis of hepatocellular carcinoma using magnetic resonance imaging. *Hepatol Int* 2020;14:70-79
28. Batts KP, Ludwig J. Chronic hepatitis. An update on terminology and reporting. *Am J Surg Pathol* 1995;19:1409-

https://doi.org/10.3348/kjr.2020.1341

1417
29. Cerny M, Chernyak V, Olivié D, Billiard JS, Murphy-Lavallée J, Kielar AZ, et al. LI-RADS version 2018 ancillary features at MRI. *Radiographics* 2018;38:1973-2001
30. Cho ES, Choi JY. MRI features of hepatocellular carcinoma related to biologic behavior. *Korean J Radiol* 2015;16:449-464
31. Cucchetti A, Vivarelli M, Piscaglia F, Nardo B, Montalti R, Grazi GL, et al. Tumor doubling time predicts recurrence after surgery and describes the histological pattern of hepatocellular carcinoma on cirrhosis. *J Hepatol* 2005;43:310-316
32. Ebara M, Hatano R, Fukuda H, Yoshikawa M, Sugiura N, Saisho H. Natural course of small hepatocellular carcinoma with underlying cirrhosis. A study of 30 patients. *Hepatogastroenterology* 1998;45 Suppl 3:1214-1220
33. An C, Rakhmonova G, Choi JY, Kim MJ. Liver imaging reporting and data system (LI-RADS) version 2014: understanding and application of the diagnostic algorithm. *Clin Mol Hepatol* 2016;22:296-307
34. Cerny M, Bergeron C, Billiard JS, Murphy-Lavallée J, Olivié D, Bérubé J, et al. LI-RADS for MR imaging diagnosis of hepatocellular carcinoma: performance of major and ancillary features. *Radiology* 2018;288:118-128
35. Borzio M, Fargion S, Borzio F, Fracanzani AL, Croce AM, Stroffolini T, et al. Impact of large regenerative, low grade and high grade dysplastic nodules in hepatocellular carcinoma development. *J Hepatol* 2003;39:208-214

 https://doi.org/10.3348/kjr.2020.1341