Observational Study

Medicine®

OPEN

Association between relative liver enhancement on gadoxetic acid enhanced magnetic resonance images and histologic grade of hepatocellular carcinoma

Young-Joo Jin, MD, PhD[a], Soon Gu Cho, MD, PhD[b,*], Kun Young Lee, MD, PhD[c], Joon Mee Kim, MD, PhD[d], Jin Woo Lee, MD, PhD[a]

Abstract

We evaluated the association between histologic grade of hepatocellular carcinoma (HCC) and degree of HCC enhancement on Gd-EOB-DTPA (Gadoxetic acid, Primovist)-enhanced magnetic resonance images (MRI) in HCC patients.

A total of 121 patients who underwent curative surgical resection for HCC at our institution between January 2012 and March 2015 were retrospectively analyzed. Gadoxetic acid enhanced MRI was performed in all patients before surgery. Signal intensities of HCC and peri-HCC areas were measured using regions of interest. Relative intensity ratios of HCC lesions versus the surrounding non-HCC areas on unenhanced images (precontrast ratio) and on hepatobiliary phase images (postcontrast ratio) were calculated. Relative liver enhancement (RLE) ratios (post-contrast ratio/pre-contrast ratio) were also calculated. The Edmondson–Steiner (E-S) grading system was used to histologically grade HCC.

E-S grades I, II, III, and IV were observed in 2 (1.7%), 14 (11.6%), 54 (44.6%), and 51 (42.1%) of the patients, respectively. For E-S grades I/II (n = 16), III (n = 54), and IV (n = 51), mean RLE (%) were 85.5, 84.9, and 71.2, respectively ($P = .01$), and for E-S grades I-III (n = 70) and IV (n = 51), mean RLE (%) were 85.1 and 71.2, respectively ($P < .01$). Barcelona Clinic Liver Cancer (BCLC) stage A (vs 0) (odds ratio 4.38, $P = .03$) and mean RLE (odds ratio 0.05, $P < .01$) were found to predict E-S grade IV.

E-S grade IV was associated with a low level mean RLE in the gadoxetic acid enhanced MR images of HCC patients.

Abbreviations: AASLD = American Association for the Study of Liver Diseases, AUC = area under the curve, BCLC = Barcelona Clinic Liver Cancer, CI = confidence interval, CT = computed tomography, DN = dysplastic nodule, E-S = Edmondson and Steiner, HCC = hepatocellular carcinoma, MR = magnetic resonance, MRI = magnetic resonance image, OR = odds ratios, RFA = radiofrequency ablation, RLE = relative liver enhancement, ROI = region-of-interest, SI = signal intensity, SR = surgical resection, TACE = transarterial chemoembolization.

Keywords: gadoxetic acid enhanced magnetic resonance imaging, hepatocellular carcinoma, histologic grade, relative liver enhancement

1. Introduction

Surgical resection (SR) remains the treatment of choice for hepatocellular carcinoma (HCC), and contributes to improve the prognosis of HCC patients.[1–3] However, even after surgery, patient's prognoses remain to be poor, and not all patients can underwent SR.[4,5] Several preoperative factors have been reported to predict the outcome of SR, but their associations with patient's prognosis are tenuous.[6,7] In addition to tumor stage, liver function, and general performance status, HCC differentiation has been shown to be associated with prognosis,[8–12] but degrees of differentiation are usually determined in postoperative specimens. Although differentiation degree can often be determined by liver biopsy before treatment,[12] biopsies are inherently invasive. Furthermore, in patients treated by radiofrequency ablation (RFA) or transarterial chemoembolization (TACE), histologic specimens are not available after treatment. Therefore, we hypothesized that the determination of HCC differentiation before treatment would considerably aid treatment decision making and post-treatment follow-up assessments.

Recent advances in magnetic resonance (MR) imaging (MRI) based on the use of the hepatocyte-specific MR contrast agent, gadolinium-ethoxybenzyl-diethylenetriamine (Gd-EOB-DTPA, Gadoxetic acid, Primovist; Bayer-Schering, Berlin, Germany)

Editor: King-Wah Chiu.

YJJ is the first author of this study.

Authorship: YJJ and SGC were responsible for the concept and design of the study, the acquisition, analysis, and interpretation of the data, and the drafting of the manuscript. JWL, JMK, KYL helped with the acquisition of the data.

Funding/support: This study was supported by an Inha University Research grant. The statistical analysis was consulted by the Department of Biostatistics of the Catholic Research Coordinating Center, Catholic Medical Center, South Korea.

The authors have no conflict of interest to declare.

[a] Department of Internal Medicine, [b] Department of Radiology, [c] Department of Surgery, [d] Department of Pathology, Inha University Hospital, Inha University School of Medicine, Incheon, South Korea.

[*] Correspondence: Soon Gu Cho, Department of Radiology, Inha University Hospital, Inha University School of Medicine, Incheon, South Korea, 27 Inhang-ro, Jung-gu, Incheon 400-711, South Korea (e-mail: soongucho@inha.ac.kr).

Medicine (2017) 96:30(e7580)

Received: 28 February 2017 / Received in final form: 27 June 2017 / Accepted: 29 June 2017

http://dx.doi.org/10.1097/MD.0000000000007580

allow liver function to be quantitatively assessed.[13–15] Gadoxetic acid is uptaken by normal hepatocytes and excreted through the biliary tract and kidneys. However, HCC cells cannot uptake gadoxetic acid contrast agent, and thus, they are observed as hypointense nodules on the hepatobiliary phase of gadoxetic acid enhanced MR image. Using this concept, previous studies have been conducted to quantitatively evaluate HCC using enhancement patterns obtained on the hepatobiliary phase of gadoxetic acid enhanced MRI.[16,17] However, these studies were limited by small number of HCCs,[16,17] or by the enrollment of patients with dysplastic nodules (DNs).[16] Furthermore, the association between histologic grade of HCC with the degree of HCC enhancement has not been fully elucidated.

Therefore, we undertook to assess the relationship between the grade of HCC enhancement and histologic grade using gadoxetic acid enhanced MR images, and to identify factors predictive of the presence of poorly differentiated HCC.

2. Patients and methods

2.1. Study subjects

Between January 2012 and April 2015, 583 patients initially diagnosed as having HCC on liver dynamic computed tomography (CT) at our institution were retrospectively analyzed. In these patients, those satisfying the following criteria were excluded; those with a ruptured HCC, no gadoxetic acid-enhanced MRI examination, or HCC of BCLC stage B, C, or D. Moreover, to obtain surgical tissue of HCC, those who received treatments other than surgery, and those lost to follow-up before surgery were also excluded (Fig. 1). Finally, 121 patients were recruited for our retrospective cohort,[18] and medical records of these patients retrospectively analyzed. The study was approved by Institutional Review Board at Inha University Hospital (Approval number: INHAUH 2015-10-019-001).

2.2. Preoperative gadoxetic acid enhanced MRI evaluations

HCC was diagnosed by gadoxetic acid enhanced MRI when liver dynamic CT produced atypical radiologic images of HCC, or was performed to detect HCCs not detected by liver dynamic CT. HCC was diagnosed according to the guidelines issued by the American Association for the Study of Liver Diseases (AASLD).[19] Tumor sizes and numbers, tumor type, and the presence of vascular invasion were recorded. Maximum tumor size was determined by measuring the longest lesion diameter on hepatobiliary phase of gadoxetic acid enhanced MRI. HCCs were staged using the BCLC staging system.[20] The method of acquisition used to obtain gadoxetic acid enhanced MR images was as described in our previous study.[18] Briefly, MR images (3.0-Tesla MRI) were acquired using gadoxetic acid (the liver-specific hepatocyte-directed MRI contrast agent). Gadoxetic acid solution (0.025 mmol/kg body weight dose 0.25 mol/L) was intravenously infused at a speed of 2 mL/s through an antecubital vein, and this was followed by a 20-mL 0.9% normal saline flush. Before injecting the contrast agent, T2- and T1-weighted MR images were obtained. The T2-weighted fast spin-echo (FSE)/turbo spin-echo (TSE) sequence [≥3000/90–120 (repetition time in ms/echo time in ms), 90° flip angle, 320 × 250 matrix, 6 mm slice thickness, 1 mm gap], and a T1-weighted gradient recalled echo (GRE) sequence with chemically selective fat suppression (FS) and without FS using a 160 to 192 × 250 matrix, 15° flip angle, 6 mm slice thickness, and a 1 mm gap. After commencing contrast injection, dynamic images were obtained in the arterial, portal, and transitional phases at 30 seconds, 60 to 70 seconds, and 3 minutes, respectively, and hepatobiliary phase images were acquired at 20 minutes.

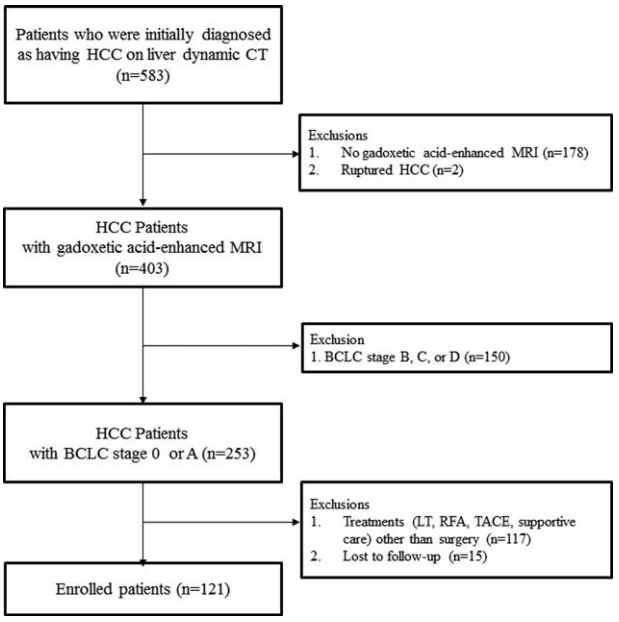

Figure 1. Study subjects. A total of 121 patients were enrolled in the study.

2.3. Quantitation of enhancement degree of liver parenchyma in MR images

Enhancement degrees of liver parenchyma were quantified using signal intensities (SIs) of MR images. SIs of liver parenchyma were measured by a radiology specialist (SG. Cho) with 20 years of experience at interpreting MR images, blinded to clinical information but aware of radiologic findings. The SIs of HCCs and surrounding non-HCC areas were measured by placing (1–2 cm^2) regions-of-interest (ROIs). ROI for HCC was placed in the center of tumor. ROI for surrounding non-HCC was placed in the center of each segment, but vascular structures, artifacts, and focal liver lesions including HCC were avoided. Mean SIs were calculated by averaging value of each segment. Relative SI ratios of HCC lesions to surrounding non-HCC areas on unenhanced images (precontrast ratio) and those on hepatobiliary phase images (postcontrast ratio) were calculated, respectively. Subsequently, relative liver enhancement (RLE) ratios (defined as postcontrast ratio/precontrast ratio) was calculated in each patient.

2.4. Histologic grading of HCC

All surgical liver specimens were obtained within 4 weeks after acquisition of gadoxetic acid enhanced MRI in all patients, and fixed in 10% neutral-buffered formalin. Sections were slicely cut at 3 to 4 μm thickness. Neoplastic lesion was stained with hematoxylin-eosin, or hepatocyte and cytokeratin 19 if needed. Non-neoplastic background liver was routinely stained with hematoxylin-eosin, reticulin, Masson trichrome, Prussian blue, and periodic acid Schiff after diastase (DPAS). If the tumors did not demonstrate characteristic finding of HCC, additional immunohistochemical staining was performed (e.g., Hepar-1, cytokeratin19, c-kit, etc). Histologic findings were retrospectively reviewed by 1 expert pathologist (JM Kim) unaware of RLE

results of the patients. Histologic HCC grading was performed using the Edmondson and Steiner (E-S) grading system,[21,22] and the worst histologic grade was used. E-S grades of 1 or 2, 3, and 4 were defined as well, moderately, and poorly differentiated, respectively.[12,21]

2.5. Statistical analyses

Means (standard deviations), medians (ranges), or frequencies were used to describe patient baseline characteristics. The Chi-square test, Fisher exact test, or the Student *t* test were used to determine differences between categorical or continuous variables. Analysis of variance (ANOVA) test with Turkey multiple comparison test was used determine the significances of differences among 3 or more groups. Multivariate analysis was used to identify significant predictors of E-S grade IV, and logistic regression analysis to calculate odds ratios (ORs) and 95% confidence intervals (CIs). The optimal cut-off mean RLE for predicting the presence of E-S grade IV was determined using the Youden index, and area under the curve (AUC) analysis for prediction of E-S grade IV was also calculated. Two-tailed *P* values of <.05 were considered statistically significant, and the statistical analysis was performed using SPSS v18.0 (SPSS Inc, Chicago, IL).

Table 1

Baseline patient characteristics.

Variables	Total
N (%)	121 (100)
Age, y*	56 (31–78)
Gender (male), n (%)	104 (86.0)
Etiology, HBV/HCV/alcohol/others, n (%)	88/7/16/10 (72.7/5.8/13.2/8.3)
Liver cirrhosis, presence, n (%)	74 (61.2)
CTP class, A/B/C, n (%)	119/2/0 (98.3/1.7/0)
AFP, ng/mL*	13.7 ($0.8–4.8 \times 10^4$)
Tumor size, cm	2.8 (1–14)
Tumor number, 1/2/3, n (%)	106/12/3 (87.6/9.9/2.5)
Tumor type, nodular/infiltrative n (%)	121 (100)
Within Milan criteria, n (%)	101 (83.5)
BCLC stage, 0/A, n (%)	22/99 (18.2/81.8)
Capsule infiltration, n (%)	65 (53.7)
Septum formation, n (%)	81 (66.9)
MVI, n (%)	48 (39.7)
E-S grade, I/II/III/IV, n (%)	2/14/54/51 (1.7/11.6/44.6/42.1)
Mean RLE (%)	79.22 ± 23.53

AFP = alpha-fetoprotein, BCLC = Barcelona Clinical Liver Cancer, CTP = Child–Turcotte–Pugh classification, E-S = Edmonson–Steiner grade, HBV = hepatitis B virus, HCV = hepatitis C virus, MVI = microvascular invasion.
* Median (range).

3. Results

3.1. Baseline characteristics of patients

A flowsheet of the enrollment procedure is shown in Fig. 1, and the baseline characteristics of patients are summarized in Table 1. Median patient age was 56 years (range, 31–78 years), and 104 (86.0%) of the 121 patients were male. The most common etiology of HCC was hepatitis B virus infection (72.7%), and 74 (61.2%) patients had liver cirrhosis. Most patients had good reserve liver function of CTP class A (98.3%). Median AFP level was 13.7 ng/mL (range, $0.8–4.8 \times 10^4$ ng/mL). Median tumor size was 2.8 cm (range, 1–14 cm) and most patients (87.6%) had a single HCC. The majority (83.5%) were within Milan criteria, and 22 (18.2%) and 99 (81.8%) patients had BCLC 0 or A stage HCC, respectively. Histologically, capsule infiltration and septum formation were found in 65 (53.7%) and 8 (66.9%) patients, respectively. In addition, microvascular invasion (MVI) was observed in 48 (39.7%) patients. E-S grades I, II, III, and IV were found in 2 (1.7%), 14 (11.6%), 54 (44.6%), and 51 (42.1%) patients, respectively. Mean RLE (%) for all patients was 79.22 (standard deviation, ±23.53)

3.2. Mean RLE (%) according to E-S grade

On the basis of the E-S grading system, mean RLE was significantly different among patients with E-S grade I, II, III, or IV (Fig. 2A, $P = .01$). Due to the small number of patients with E-S grade I, E-S grades were categorized into 3 groups, that is, E-S grades I-II, III, and IV, and these 3 groups had significantly different mean RLE values (Fig. 2B, $P < .01$).

3.3. Comparison of clinical parameters for Edmonson–Steiner grades I–III versus grade IV

To determine the significance of mean RLE for poorly differentiated HCC, E-S grade was dichotomized into E-S grades

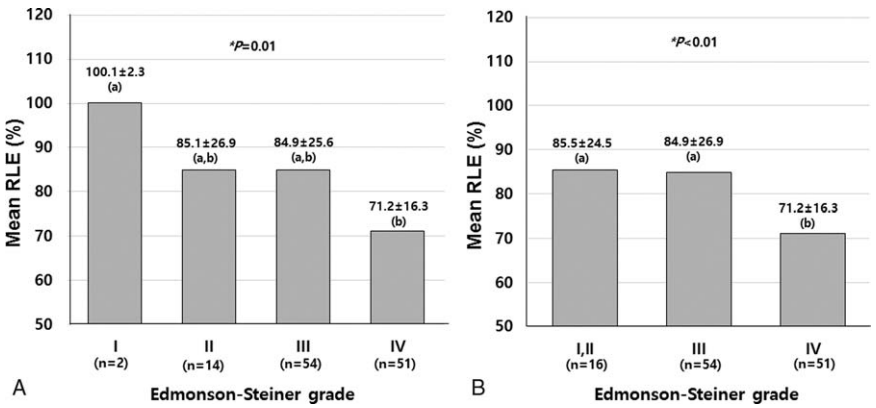

Figure 2. Relative liver enhancement (RLE) of histologic grade based on the Edmonson–Steiner (E-S) grading system. Among 4 groups of E-S grade I, II, II, and IV, mean RLE values were significantly different (A, $P = .01$). When E-S grades were categorized into 3 groups, that is, E-S grades I-II, III, or IV, the 3 groups had significantly different mean RLE values as determined by ANOVA (B, $P < .01$). Same letters (A or B) indicate nonsignificant difference between groups by Turkey multiple comparison test.

Table 2

Comparison of clinical parameters of Edmonson–Steiner grade I-III versus IV.

Variables	E-S grade I-III	E-S grade IV	P†
Total, n (%)	70 (57.9)	51 (42.1)	
Age, y*	56 (31–74)	54 (39–78)	.84
Gender (male), n (%)	59 (84.3)	45 (88.2)	.61
Etiology, n (%)			
HBV/HCV/alcohol/others	49/2/14/5 (70.0/2.9/20.0/7.1)	39/5/2/5 (76.5/9.5/3.9/9.8)	.04
Liver cirrhosis, presence	43 (61.4)	31 (60.8)	1.00
CTP class, A/B, n (%)	69/1 (98.6/1.4)	50/1 (98.0/2.0)	1.00†
AFP, ng/mL*	10.4 (0.8–4.0x10^4)	17.0 (1.6–4.8x10^4)	.17
Tumor size, cm	2.6 (1–12.5)	3.3 (1–14.0)	.04
Tumor number, 1/2/3, n (%)	64/6/0 (91.4/8.6/0)	42/6/3 (82.4/11.8/5.9)	.09†
Tumor type, n (%)			1.00†
nodular/infiltrative	70/0 (100/0)	51/0 (100/0)	
Within Milan criteria, n (%)	62 (88.6)	39 (76.5)	.08
BCLC stage, 0/A, n (%)	19/51 (27.1/72.9)	3/47 (6.0/94.0)	<.01†
Capsule infiltration, n (%)	34 (48.6)	31 (60.8)	.18
Septum formation, n (%)	44 (62.9)	37 (72.5)	.26
MVI, n (%)	21 (30.0)	27 (52.9)	.01
Mean RLE (%)	0.81 (0.38–2.10)	0.72 (0.43–1.13)	<.05

AFP = alpha-fetoprotein, BCLC = Barcelona Clinical Liver Cancer, CTP = Child–Turcotte–Pugh classification, E-S = Edmonson–Steiner, HBV = hepatitis B virus, HCV = hepatitis C virus, MVI = microvascular invasion, RLE = relative liver enhancement.

* Median (range).

† Fisher exact test.

I-III and grade IV (Table 2). Tumor size, frequency of BCLC stage A, and the presence of MVI were significantly higher in patients with E-S grade IV (Table 2, $P < .05$), and mean RLE (%) of patients with E-S grade IV was significantly lower than that of those with E-S grade I-III (Table 2 and Fig. 3, $P < .01$, respectively).

3.4. Significant predictors of Edmonson–Steiner grade IV

Univariate analysis showed that BCLC stage A (OR 5.84, $P < .01$), positive MVI (OR 2.63, $P = .01$), and mean RLE (OR 0.04, $P < .01$) were significant predictive factors of E-S grade IV. Multivariate analysis of these factors revealed that BCLC stage A (OR 4.38, $P = .03$) and mean RLE (OR 0.05, $P < .01$) independently predicted E-S grade IV (Table 3). The optimal cut-off of mean RLE value for predicting E-S grade IV was 74.47, and the AUC (95% CI) of this cut-off was 0.76 (range: 0.62–0.89).

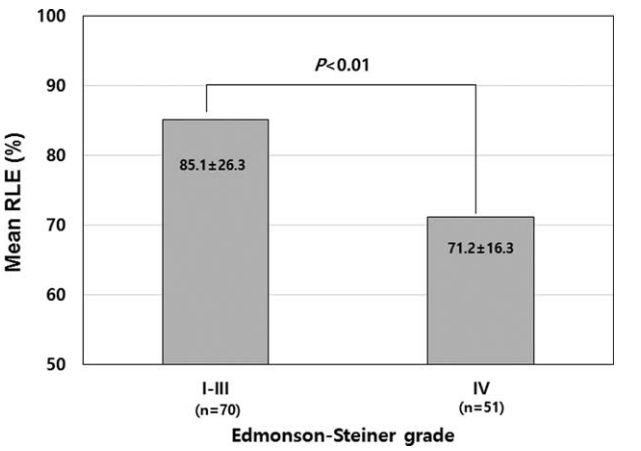

Figure 3. Relative liver enhancements (RLEs) of Edmonson–Steiner (E-S) grades I-III and grade IV Mean RLE was significantly lower for tumors of E-S grade IV than for those of E-S grade I-III ($P < .01$).

4. Discussion

In this study, we found that mean RLE of E-S grade IV HCC patients was significantly lower than that of patients with E-S grade I-III, and mean RLE was found to predict E-S grade IV significantly in HCC patients. Despite the small number of patients with E-S grade I in the present study, mean RLE was also significantly different for E-S grade I, II, III, and IV. Previous studies have reported that histologic grading may be estimated using the hepatobiliary phase of gadoxetic acid enhanced MRI,[16,23] but these studies had some limitations. First, numbers of subjects were small and patients with DNs were also enrolled. Second, some histologic specimens were obtained by preoperative needle biopsy, and thus, histologic grades of HCC were probably underestimated because of reported discordance between final histologic grades and needle core biopsy results.[12,24] On the contrary, only HCC patients were enrolled in the present study, and the cohort was substantively larger than in previous studies. Furthermore, all surgical specimens were assessed histologically in the present study, and we specifically focused on the ability of gadoxetic acid enhanced MRI to predict poorly differentiated HCC by evaluating the association between quantitative enhancement degree on gadoxetic acid enhanced MRI and HCC differentiation.

Poorly differentiated HCCs are associated with poor prognosis[11,25–27]; in the E-S grading system, grade IV is considered indicative of poorly differentiated HCC.[12,21] For this reason, E-S grade IV HCC should be treated with curative intent and closely monitored for early recurrence after treatment. Accordingly, in HCC patients with grade IV, the prediction of tumor differentiation, especially of poor differentiation, would be of considerable utility when determining therapeutic strategy. Therefore, in this study, we focused on how to predict the tumor differentiation using gadoxetic acid enhanced MRI.

Table 3

Significant predictive factors of Edmonson–Steiner grade IV.

Variables	Univariate analysis*			Multivariate analysis*		
	OR	95% CI	P	OR	95% CI	P
Age, y	1.00	0.97–1.04	.84	—	—	—
Gender (male)	1.39	0.48–4.07	.54	—	—	—
AFP, ng/mL	1.00	1.00–1.01	.20	—	—	—
Tumor number, 2–3 vs 1	1.98	0.64–6.12	.23	—	—	—
Tumor size, cm	0.88	0.58–1.32	.53	—	—	—
Milan criteria, within	0.42	0.16–1.12	.08	—	—	—
Liver cirrhosis, presence	0.97	0.46–2.04	.94	—	—	—
BCLC stage, A vs 0	5.84	1.62–21.00	<.01	4.38	1.15–16.73	.03
Capsule infiltration, positive	1.64	0.79–3.41	.19	—	—	—
Septum formation, positive	1.56	0.71–3.42	.27	—	—	—
MVI, positive	2.63	1.24–5.56	.01	2.08	0.91–4.75	.08
Mean RLE,%	0.04	0.01–0.37	<.01	0.05	0.01–0.41	<.01

Subjects, n = 121; event, patient with Edmonson–Steiner grade IV (n = 51).

AFP = alpha-fetoprotein, BCLC = Barcelona Clinical Liver Cancer, CI = confidence interval, MVI = microvascular invasion, OR = odds ratio, RLE = relative liver enhancement.

* Logistic regression model.

In the present study, we evaluated the association between RLE (%) as determined by preoperative gadoxetic acid enhanced MRI and HCC differentiation, and found that poorly differentiated HCC may be preoperatively distinguished from well or moderately differentiated HCCs. Pre-treatment needle biopsy can be used to assess HCC differentiation, but the technique is invasive and unnecessary for all HCC patients being considered for SR.[28] In addition, preoperative gadoxetic acid enhanced MRI is now used to reduce the risk of missing HCC lesions, and thus, of early recurrence postoperatively, and to improve patients' prognosis.[29,30] Given the noninvasiveness of RLE measurements by gadoxetic acid enhanced MRI, the results of the present study may be clinically useful and provide a basis for the routine addition of a gadoxetic acid enhanced MRI examination in HCC patients scheduled for SR.

Godoxetic acid is a hepatocyte specific contrast agent, and allows the acquisition of hepatobiliary phase images, and thus, it is frequently performed in the clinical setting. The enhancement degree of liver on hepatobiliary phase of gadoxetic acid enhanced MRI can be influenced by the severity of liver cirrhosis,[15] which suggests potential confounding in the present study. However, most of the cirrhotic patients (98.3%) recruited had CTP class A liver function, which suggests that liver cirrhosis severity did not have a confounding effect, as evaluated by multivariate analyses. Furthermore, RLE was found to significantly predict E-S grade IV, regardless of cirrhosis in HCC patients, which means that RLE provides a useful tool for the preoperative prediction of poorly differentiated HCC in patients being considered for SR.

In the present study, tumor size was not associated with E-S grade IV, whereas in the previous study,[31] tumor size was found to predict histologic grade of HCC, and tumors larger than 5 cm HCC were associated with poor prognosis due to high rates of poorly differentiated HCC and MVI. This apparent difference was probably caused by the enrollment of surgical candidates in the present study with a median tumor size of 2.8 cm.

The present study has some limitations that warrant mention. First, the number of patients with E-S grade I was small (1.7%). Although the statistical significance of mean RLE was obtained for patients with E-S grades I to IV, the clinical implications of our finding regarding mean RLE for patients with E-S grade I should be approached cautiously, as larger scale studies are required on the topic. Second, no comparative quantitative evaluation of benign lesions, such as, dysplastic or regenerative nodules, versus HCC lesions was performed. Further study is required to enable benign lesions to be distinguished from HCC using quantitative enhancement on gadoxetic acid enhanced MR images. Third, this study is limited by its retrospective nature, and thus, inherent selection bias was unavoidable.

In conclusion, this study shows that E-S grade IV tumors have a lower mean RLE level than E-S grade I-III tumors on the gadoxetic acid enhanced MR images of HCC patients. Given that E-S grade IV is considered to indicate the presence of poorly differentiate HCC, measurements of RLE of HCC by gadoxetic acid enhanced MRI before SR may provide useful information regarding the presence of poorly differentiated HCC. Furthermore, these measurements might be helpful for treatment decision making and post-treatment follow-up in HCC patients. However, well-designed RCTs are required to confirm our findings.

References

[1] Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. Hepatology 1999;30:1434–40.

[2] Grazi GL, Ercolani G, Pierangeli F, et al. Improved results of liver resection for hepatocellular carcinoma on cirrhosis give the procedure added value. Ann Surg 2001;234:71–8.

[3] Arii S, Yamaoka Y, Futagawa S, et al. Results of surgical and nonsurgical treatment for small-sized hepatocellular carcinomas: a retrospective and nationwide survey in Japan. The Liver Cancer Study Group of Japan. Hepatology 2000;32:1224–9.

[4] Bruix J, Llovet JM. Prognostic prediction and treatment strategy in hepatocellular carcinoma. Hepatology 2002;35:519–24.

[5] Bruix J, Sherman M, Llovet JM, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol 2001;35:421–30.

[6] Hoekstra LT, de Graaf W, Nibourg GA, et al. Physiological and biochemical basis of clinical liver function tests: a review. Ann Surg 2013;257:27–36.

[7] Lam CM, Fan ST, Lo CM, et al. Major hepatectomy for hepatocellular carcinoma in patients with an unsatisfactory indocyanine green clearance test. Br J Surg 1999;86:1012–7.

[8] Han DH, Choi GH, Kim KS, et al. Prognostic significance of the worst grade in hepatocellular carcinoma with heterogeneous histologic grades of differentiation. J Gastroenterol Hepatol 2013;28:1384–90.

[9] Jonas S, Bechstein WO, Steinmuller T, et al. Vascular invasion and histopathologic grading determine outcome after liver transplantation for hepatocellular carcinoma in cirrhosis. Hepatology 2001;33:1080–6.

[10] Kim SH, Lim HK, Choi D, et al. Percutaneous radiofrequency ablation of hepatocellular carcinoma: effect of histologic grade on therapeutic results. AJR Am J Roentgenol 2006;186:S327–333.
[11] Lauwers GY, Terris B, Balis UJ, et al. Prognostic histologic indicators of curatively resected hepatocellular carcinomas: a multi-institutional analysis of 425 patients with definition of a histologic prognostic index. Am J Surg Pathol 2002;26:25–34.
[12] Pawlik TM, Gleisner AL, Anders RA, et al. Preoperative assessment of hepatocellular carcinoma tumor grade using needle biopsy: implications for transplant eligibility. Ann Surg 2007;245:435–42.
[13] Wibmer A, Prusa AM, Nolz R, et al. Liver failure after major liver resection: risk assessment by using preoperative Gadoxetic acid-enhanced 3-T MR imaging. Radiology 2013;269:777–86.
[14] Bickelhaupt S, Studer P, Kim-Fuchs C, et al. Gadoxetate uptake as a possible marker of hepatocyte damage after liver resection-preliminary data. Clin Radiol 2013;68:1121–7.
[15] Tamada T, Ito K, Higaki A, et al. Gd-EOB-DTPA-enhanced MR imaging: evaluation of hepatic enhancement effects in normal and cirrhotic livers. Eur J Radiol 2011;80:e311–6.
[16] Kogita S, Imai Y, Okada M, et al. Gd-EOB-DTPA-enhanced magnetic resonance images of hepatocellular carcinoma: correlation with histological grading and portal blood flow. Eur Radiol 2010;20: 2405–13.
[17] Frericks BB, Loddenkemper C, Huppertz A, et al. Qualitative and quantitative evaluation of hepatocellular carcinoma and cirrhotic liver enhancement using Gd-EOB-DTPA. AJR Am J Roentgenol 2009;193: 1053–60.
[18] Jin YJ, Lee SH, Cho SG, et al. Prediction of postoperative liver failure using gadoxetic acid-enhanced magnetic resonance imaging in patients with hepatocellular carcinoma. J Gastroenterol Hepatol 2016;31: 1349–56.
[19] Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology 2011;53:1020–2.
[20] Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet 2003;362:1907–17.
[21] Edmondson HA, Steiner PE. Primary carcinoma of the liver: a study of 100 cases among 48,900 necropsies. Cancer 1954;7:462–503.
[22] Zhou L, Rui JA, Ye DX, et al. Edmondson-Steiner grading increases the predictive efficiency of TNM staging for long-term survival of patients with hepatocellular carcinoma after curative resection. World J Surg 2008;32:1748–56.
[23] Lee MH, Kim SH, Park MJ, et al. Gadoxetic acid-enhanced hepatobiliary phase MRI and high-b-value diffusion-weighted imaging to distinguish well-differentiated hepatocellular carcinomas from benign nodules in patients with chronic liver disease. AJR Am J Roentgenol 2011;197: W868–875.
[24] Pirisi M, Leutner M, Pinato DJ, et al. Reliability and reproducibility of the edmondson grading of hepatocellular carcinoma using paired core biopsy and surgical resection specimens. Arch Pathol Lab Med 2010;134:1818–22.
[25] Decaens T, Roudot-Thoraval F, Badran H, et al. Impact of tumour differentiation to select patients before liver transplantation for hepatocellular carcinoma. Liver Int 2011;31:792–801.
[26] Marelli L, Grasso A, Pleguezuelo M, et al. Tumour size and differentiation in predicting recurrence of hepatocellular carcinoma after liver transplantation: external validation of a new prognostic score. Ann Surg Oncol 2008;15:3503–11.
[27] Zavaglia C, De Carlis L, Alberti AB, et al. Predictors of long-term survival after liver transplantation for hepatocellular carcinoma. Am J Gastroenterol 2005;100:2708–16.
[28] Bruix J, Sherman M. American Association for the Study of Liver DManagement of hepatocellular carcinoma: an update. Hepatology 2011;53:1020–2.
[29] Jin YJ, Nah SY, Lee JW, et al. Utility of adding Primovist magnetic resonance imaging to analysis of hepatocellular carcinoma by liver dynamic computed tomography. Clin Gastroenterol Hepatol 2013;11:187–92.
[30] Kim HD, Lim YS, Han S, et al. Evaluation of early-stage hepatocellular carcinoma by magnetic resonance imaging with gadoxetic acid detects additional lesions and increases overall survival. Gastroenterology 2015;148:1371–82.
[31] Chang WC, Chen RC, Chou CT, et al. Histological grade of hepatocellular carcinoma correlates with arterial enhancement on gadoxetic acid-enhanced and diffusion-weighted MR images. Abdom Imaging 2014;39:1202–12.