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Correlation of Qualitative and Quantitative Characteristics of Contrast-Enhanced Dynamic Magnetic Resonance Imaging with Hepatospecific Contrast Agent Gadoxetic Acid (Primovist) and Histopathological Differentiations in Hepatocellular Carcinoma

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Abstract

Objective: The aim of this study was to investigate the correlation between qualitative and quantitative characteristics of contrast-enhanced dynamic magnetic resonance imaging with hepatospecific contrast agent gadoxetic acid (primovist) and histopathological differentiations in hepatocellular carcinoma.

Methods: This study included 32 consecutive naïve patients with needle biopsy-proven hepatocellular carcinoma. All patients were divided into 2 groups: those with well-differentiated tumors and those with moderately/poorly differentiated tumors. Pre-contrast and post-contrast signal intensities, relative signal intensity ratios, and enhancement ratios of tumors were determined during the hepatobiliary phase of magnetic resonance imaging.

Results: There were no significant differences between 2 groups regarding patients' age (P = .657), gender (P = .589), chronic hepatitis etiology (P = .665), α-fetoprotein levels (P = .156), Child-Pugh classes (P = .166), contrast-enhancing pattern (P = .479), visually registered signal intensities (P = .228), and mean pre-contrast relative signal intensity ratios (P = .444). Mean post-contrast relative signal intensity ratios and enhancement ratios of well-differentiated tumors were significantly higher compared to moderately/poorly differentiated tumors' values (P = .017 and P = .014, respectively). The test power of quantitative properties was calculated as good (area under curve for post-contrast relative signal intensity ratio by 0.74, sensitivity by 73%, and specificity by 76%; area under curve for enhancement ratio by 0.71, sensitivity by 82%, and specificity by 76%)).

Conclusion: The quantitative but not qualitative parameters of hepatocellular carcinoma detected during hepatobiliary phase of contrast-enhanced dynamic magnetic resonance imaging with gadoxetic acid (primovist) may provide objective and predictive information in terms of the differentiation between well-differentiated and moderately/poorly differentiated tumors.

Keywords: Contrast agent, gadoxetic acid, primovist, hepatocellular carcinoma, histopathological differentiation, magnetic resonance imaging

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary malignant tumor of the liver and ranks third among cancer-causing cancers.[1] In recent years, with the advances in screening, diagnosis, and treatment methods, the detection frequency of HCC at early stage has increased, and with the application of appropriate treatments, survival times of more than 5 years have been achieved.[2] To predict better treatment results, multivariate statistical analyses were performed and risk factors for possible relapse were investigated. Tumor stage, liver functions, general patient's performance status, tumor biomarkers, and histopathological differentiation of HCC are recognized as main prognostic factors. A needle or surgical biopsy in HCC still provides beneficial information about the morphological variants and subtypes that can serve as important surrogates of tumor behavior for targeted therapies for HCC. Thus, tumor biopsy is being recognized as an invaluable tool for the diagnosis, management, and prognostication of HCC. Moreover, tumor differentiation was included as independent criterion for determining patient selection for liver transplantation in the expanded Toronto criteria.[3] However, currently, tissue biopsies are used less frequently for HCC diagnosis. The main reasons for this tendency are some limitations due to the invasiveness of this procedure such as pain, bleeding, needle tract seeding, possible risk of mortality, and sampling errors along with interpretative errors. On the other hand, HCC is unique among malignancies due to specific tumor characteristics on cross-sectional multiphasic contrast computed tomography (CT) or dynamic magnetic resonance imaging (MRI) that allow for a highly accurate diagnosis of HCC without an invasive biopsy in significant number of patients. Since the histological differentiation of the tumor is widely accepted as important prognostic factor, non-invasive imaging tests are needed to determine the differentiation of the tumor before treatment in HCC patients.

Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA, Primovist; Bayer AG, Leverkusen, Germany) is used in the routine clinical practice in many radiological departments as a liver-specific contrast agent. Gadolinium-ethoxybenzyl-diethy lenetriamine pentaacetic acid , injected intravenously, conjoins in the liver parenchyma with specific organic anion transporting polypeptide (OATP) in the hepatocytes and then excretes through the biliary system and kidney.[4-6] Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid combines futures of dynamic bolus extracellular contrast agent with a delayed hepatobiliary phase;[7] therefore, Gd-EOB-DTPA-enhanced MRI is very sensitive and accurate in the detection of HCC in cirrhotic patients.[8] In MRI examinations performed with Gd-EOB-DTPA contrast agent, the relationships between tumor intensity and histopathological differentiation of the tumor were previously investigated.[9,10] However, these studies are qualitative in their nature and based on visual evaluation.[9,10] Studies with quantitative measurements are few in number, and conflicting results are obtained.[11-15] For this reason, the aim of this study was to investigate the correlation between qualitative and quantitative characteristics of the HCC on dynamic MRI with Gd-EOB-DTPA and histopathological differentiations of the tumors.

METHODS

Study Population

This study was conducted as a single-center retrospective investigation in accordance with the Helsinki Declaration with approval from Çukurova University Medical School Institutional Ethical Committee for Clinical Researches (decision number 7 from April 10, 2020). Written informed consent was obtained from all patients for MRI examination and biopsy before each procedure. This study included 32 consecutive naïve patients (93.7% males, median age 66 years) with HCC histopathologically proven by tru-cut needle biopsy. Inclusion criteria were patient's age above 18 years old, histopathologically proven diagnosis of HCC, and biopsy performed within 1 month after dynamic Gd-EOB-DTPA MRI study. Exclusion criteria were as follows: more than 1-month period between MRI and tissue biopsy, history of previously performed transarterial embolization, thermal ablation therapy or systemic chemotherapy regarding the liver, and reduced iron-laden MRI signal secondary to hemochromatosis or hemosiderin accumulation.

Magnetic Resonance Imaging Protocols

In this study, dynamic MRIs were performed within 1 month before tissue biopsy using 3.0 Tesla scanner (Philips Achieva, Phillips Medical Systems, Best, The Netherlands) with 16-channeled body coil. Dynamic images were obtained as non-contrast phase, arterial phase at 20th second, portal phase at 70th second, equilibrium phase at 180th second, and hepatobiliary phase at 20th minute after injection of contrast agent. Three-dimensional turbo-field-echo images (T1 high-resolution isotropic volume examination) with parameters determined as TR 3.4 ms, TE 1.8 ms, slice thickness 2 mm, slice spacing 2 mm, matrix size 336 × 2060, and field of view 320-380 mm were achieved. The contrast agent was injected with a 22 G intravenous catheter inserted into the antecubital vein with a power injector at a rate of 2 mL/s with a dose of 0.025 mmol/kg. After the contrast agent injection, 20-30 mL of 0.9% saline was injected sequentially, at the same rate.

MAIN POINTS

- The quantitative but not qualitative parameters of hepatocellular carcinoma detected during hepatobiliary phase of gadolinium-ethoxyben zyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced magnetic resonance imaging (MRI) may provide objective and predictive information in terms of the differentiation between well-differentiated and moderately/poorly differentiated tumors.
- Post-contrast relative signal intensity ratio and enhancement ratio on Gd-EOB-DTPA-enhanced MRI provide useful information about histological differentiation of the tumor with high sensitivity and specificity.
- These quantitative metrics can be used in the selection of an optimal candidate for liver transplantation.

ANALYSIS OF IMAGES

Qualitative Analysis

The MR images were evaluated by 2 radiologists unaware of the results of histopathological analysis with 12 and 6 years of experience in the field of abdominal radiology. All disagreements were resolved by consensus. Analysis of all images was performed at IntelliSpace Portal workstation (Phillips Medical Systems).

In the images obtained, signal intensities (SIs) of the tumor and non-tumor liver parenchyma were visually evaluated. Hepatocellular carcinomas that were visible as hyperintense tumors in the arterial phase (so-called wash-in phenomenon) and hypointense in the portal and/or venous phase (wash-out phenomenon) were considered as lesions with typical contrast pattern. On the other hand, tumors that did not show this specific feature of HCC were considered as lesions with an atypical contrast pattern. In the hepatobiliary phase, the SIs of the tumor and non-tumor liver parenchyma were compared visually. All tumors were divided into 2 groups: hypointense or iso/hyperintense tumors by comparison to the non-tumoral sections of the liver parenchyma.

Quantitative Analysis

Signal intensity measurements were performed with operator-defined region of interest (ROI) of the tumor and liver parenchyma on the pre-contrast and hepatobiliary phase images, corresponding to the same place in both sequences. Region of interest locations were selected from image slices outside of heterogeneous areas, vascular/biliary structures, or necrosis area on pre-contrast slices on the T1-weighted sequences with a round ROI with diameter at least of 1 cm[11] (Figure 1). In addition, the measurement locations for the liver parenchyma were determined to be at least 1 cm away from the tumor. The pre-contrast relative SI ratio (pre-contrast relative signal intensity ratio (RSIR)) and the same parameter during hepatobiliary phase (post-contrast RSIR) from the tumor and non-tumor liver parenchyma with the enhancement ratio (ER) were calculated as follows: RSIR = tumor SI/non-tumor liver parenchyma SI and ER = (post-contrast RSIR−pre-contrast RSIR)/pre-contrast RSIR × 100%, respectively.

Laboratory Tests and Histopathological Evaluation

All patients were evaluated by laboratory tests 1 week before tissue biopsy. Child-Pugh scores and α-fetoprotein (AFP) values were recorded. The biopsies were performed with 16 G tru-cut needle under ultrasound guidance and local anesthesia using 2% prilokain solution. A single sample was taken from the tumor because of possible risk of major complications such as bleeding and needle tract seeding. The material obtained by tissue biopsy was evaluated histopathologically by the pathologist with more than 9 years of experience in the field. All tumors were divided into 2 groups as well-differentiated and moderately/poorly differentiated tumors according to Edmondson and Steiner criteria[15] (Figure 1). The main reason for this approach was that distribution between groups regarding tumor differentiation was not equal (n = 19,

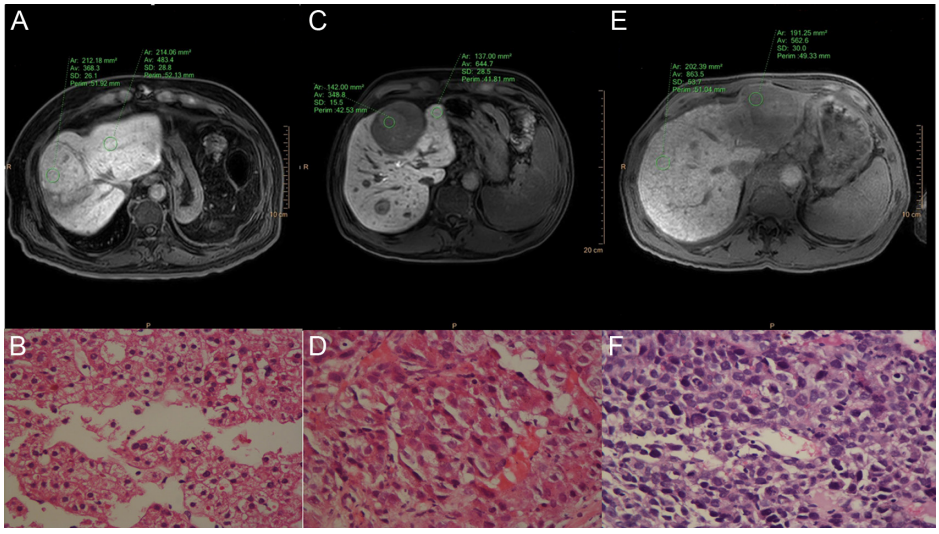

Figure 1. Representative images showing HCC on gadoxetic acid-enhanced dynamic MRI with varied histopathological tumor differentiation. (A) 71-year-old male with well-differentiated HCC. Dynamic MRI shows nodular type of the tumor at the liver segment 8 with post-contrast RSIR 0.75. (B) 71-year-old male with well-differentiated HCC shown on (A). Microscopic imaging shows well-differentiated HCC (hematoxylin and eosin, magnification ×200). (C) 62-year-old male with moderate differentiated HCC. Dynamic MRI shows nodular type of the tumor at the liver segments 4,5, and 8 with post-contrast RSIR 0.53. (D) A 62-year-old male with moderate differentiated HCC shown on (C). Microscopic imaging shows moderate differentiated HCC (hematoxylin and eosin, magnification ×200). (E) 50-year-old male patient with poorly differentiated HCC. Dynamic MRI shows infiltrative type of the tumor at the liver segments 2-4 with post-contrast RSIR 0.63. (F) 50-year-old male patient with poorly differentiated HCC shown on (E). Microscopic imaging shows poorly differentiated HCC (hematoxylin and eosin, magnification ×200). HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging; RSIR, relative signal intensity ratio.

n=9, and n=4 for well-differentiated, moderate, and poor-differentiated HCC, respectively). Provisional performed one-way analysis of variance test with post hoc tests for 3 groups showedn that the group sizes are unequal, and type I error levels are not guaranteed. After splitting all patients into 2 groups, reasonable equality was achieved in terms of the number of patients in this approach (19 patients with well-differentiated vs. 13 patients with moderately/poorly differentiated tumors).

Statistical Analysis

In this study, demographic information and clinical features of patients were expressed with descriptive statistical data. Quantitative data showing normality were presented with mean ± standard deviation, and quantitative data without normality were presented with median and range (minimum–maximum values). Qualitative data were summarized as numbers and percentages. Qualitative features of both groups regarding histopathological differentiation were analyzed with chi-square test with Fischer's exact test, while quantitative parameters were analyzed with Student's *t*-test. Threshold values for quantitative properties were calculated using the receiver operating characteristic curves. *P* value <.05 was accepted as statistically significant. Statistical analyses were performed with SStatistical Package for the Social Sciences version 20.0. (IBM SPSS Corp.; Armonk, NY, USA).

RESULTS

Demographic and Clinical Features of the Study Population

In this study, 32 naïve HCC patients (93.7% males) with a median age of 66 years (range, 50-75) were evaluated. The patients' demographic and clinical features are presented in Table 1. Briefly, all patients

Table 1. Demographic and Clinical Characteristics of the Study Population

Parameters	Well-Differentiated HCC	Moderately/Poorly Differentiated HCC	*P*
Age, years; median (range)	67 (54-74)	65 (50-75)	.657
Sex, n (%)			
Male	13 (86.7)	16 (94.1)	.589
Female	2 (13.3)	1 (5.9)	
Chronic hepatitis etiology, n (%)			
HBV	13 (86.7)	13 (76.5)	.665
HCV	-	3 (17.6)	
Cryptogenic	2 (13.3)	1 (5.9)	
α-fetoprotein, n (%)			
≤ 20 (ng/mL)	9 (60.0)	6 (35.3)	.156
> 20 (ng/mL)	6 (40.0)	11 (64.7)	
Child-Pugh class, n (%)			
A	11 (73.3)	8 (47.1)	.166
B	4 (26.7)	9 (52.9)	

HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus.

Chi-square test with Fischer's exact test.

Table 2. Qualitative Findings of Gadoxetic Acid-Enhanced Dynamic MRI in the Study Population

Parameters	Well-Differentiated HCC	Moderately/Poorly Differentiated HCC	*P*
Tumor size, mm; median (range)	77 (57-97)	83 (64-102)	.649
Enhancement pattern, n (%)			
Typical	7 (58.8)	7 (53.8)	.479
Non-typical	6 (42.2)	6 (47.2)	
Hepatobiliary phase SI, n (%)			
Hypointense	15 (78.9)	12 (92.3)	.228
Iso/hyperintense	4 (21.1)	1 (7.7	

MRI, magnetic resonance imaging; HCC, hepatocellular carcinoma; SI, signal intensity.

Chi-square test with Fischer's exact test.

had clinically proven chronic hepatitis supported by laboratory tests. Chronic hepatitis etiologies included hepatitis B virus (n=26; 81.4%), hepatitis C virus (n=3; 9.3%), and cryptogenic (n=3, 9.3%). At the time of diagnosis, AFP values of 15 (46.9%) patients were ≤20 ng/mL and AFP values of remaining patients (n=17; 53.1%) were >20 ng/mL. Patients were in the Child-Pugh class A or B (n=13; 46.6% and n=19; 53.4%, respectively). As a result of histopathological evaluation of the lesions, 19 (59.3%) well-differentiated and 13 (41.7%) moderately/poorly differentiated tumors were detected.

There were no statistically significant differences between 2 groups regarding patients' age (*P* = .657), gender (*P* = .589), chronic hepatitis etiology (*P* = .665), AFP levels (*P* = .156), and Child-Pugh classes (*P* = .166).

Qualitative Magnetic Resonance Imaging Findings

When contrasting pattern of the tumors was evaluated in contrast-enhanced MRI, typical enhancement pattern (so-called wash-in followed by wash-out) was detected in 11 (58.8%) patients with well-differentiated tumors and atypical enhancement pattern in 8 (42.2%) patients from the same group. On the other hand, 7 (53.8%) patients with the moderately/poorly differentiated tumors had a typical contrast pattern, while remaining 6 (47.2%) patients had the atypical contrast pattern. There was no significant difference between the contrasting pattern of the 2 groups (*P* = .479). When SIs of the tumors and liver parenchyma were compared during the hepatobiliary phase of dynamic MRI, most of the well-differentiated tumors (n=15, 78.9%) had hypointense SIs relative to the liver parenchyma and 4 (21.1%) were iso- or hyperintense. Additionally, SIs of moderately/poorly differentiated tumors were hypointense in 12 (92.3%) patients and iso-or hyperintense in 1 (7.7%) patient compared to adjacent liver parenchyma. There was no statistically significant difference between the SIs during hepatobiliary phase of 2 groups (*P* = .228). Qualitative MRI findings of tumors, contrasting patterns, and SIs at the hepatobiliary phase are summarized in Table 2.

Quantitative Magnetic Resonance Imaging Findings

The mean values of the pre-contrast RSIR of the tumors were 0.76 ± 0.12 for well-differentiated tumors and 0.71 ± 0.22 for moderately/poorly

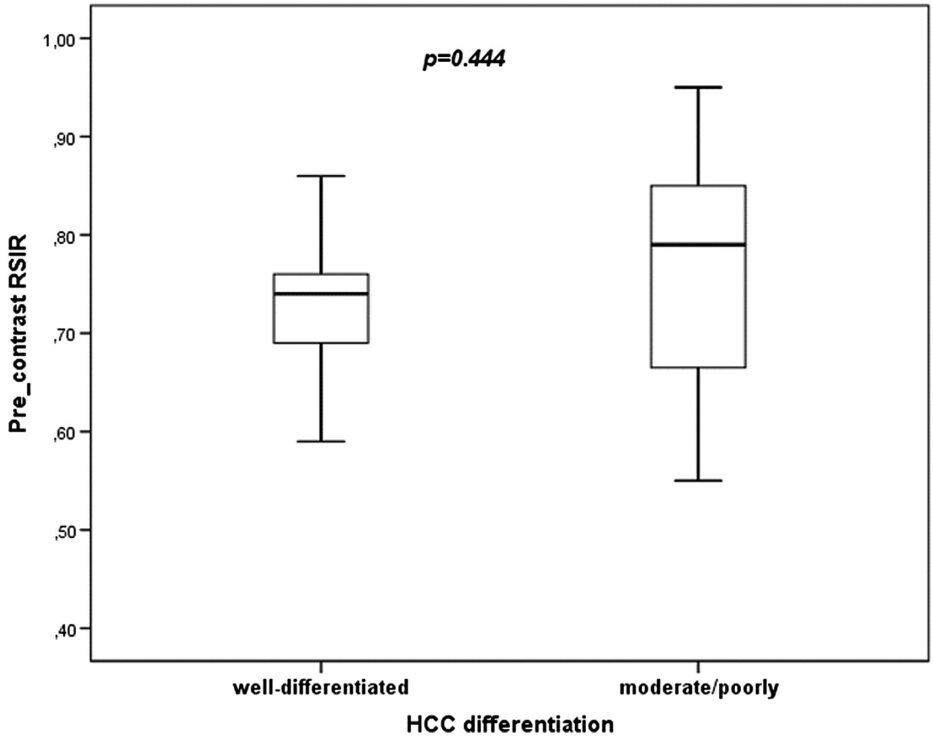

Figure 2. Relationship between pre-contrast RSIR and HCC differentiation in patient population. Student's t-test shows no difference between well-differentiated and moderately/poorly differentiated HCC in study population (P = .444). RSIR, relative signal intensity ratio; HCC, hepatocellular carcinoma.

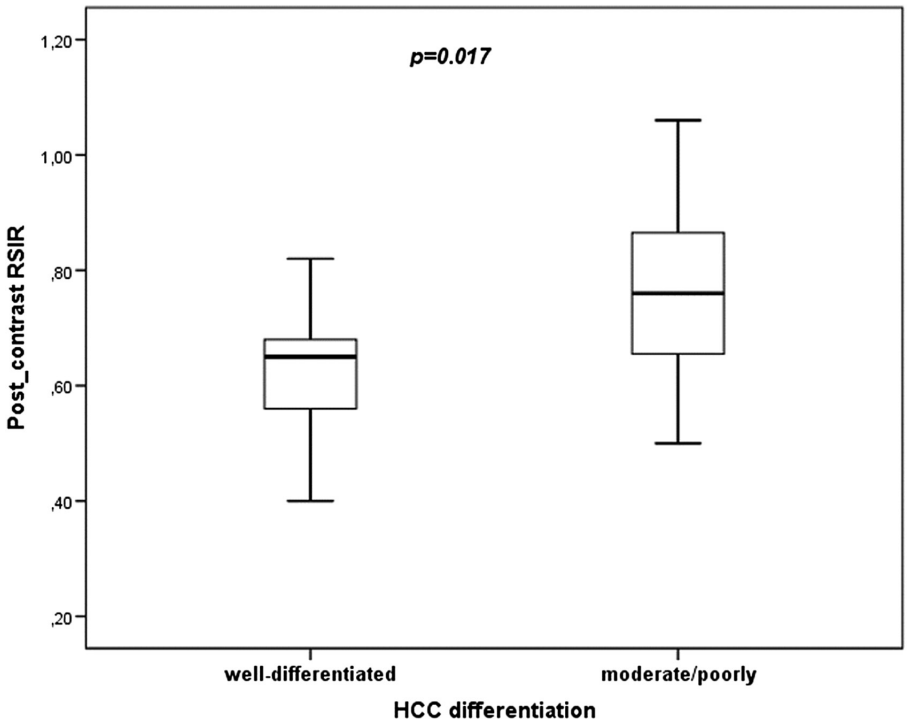

Figure 3. Relationship between post-contrast RSIR and HCC differentiation in patient population. Student's t-test shows statistically significant difference between well-differentiated and moderately/poorly differentiated HCC's post-contrast RSIR values in study population (P = .017). RSIR, relative signal intensity ratio, HCC, hepatocellular carcinoma.

differentiated tumors. There was no significant difference between the mean pre-contrast RSIR values between 2 groups (*P* = .444) (Figure 2). The mean values of the post-contrast RSIRof the tumors were 0.74 ± 0.19 and 0.58 ± 0.17 for well-differentiated tumors and for moderately/poorly differentiated tumors, respectively. Mean ER values of tumors were 89.8 ± 60.55 for well-differentiated tumors and 47.7 ±

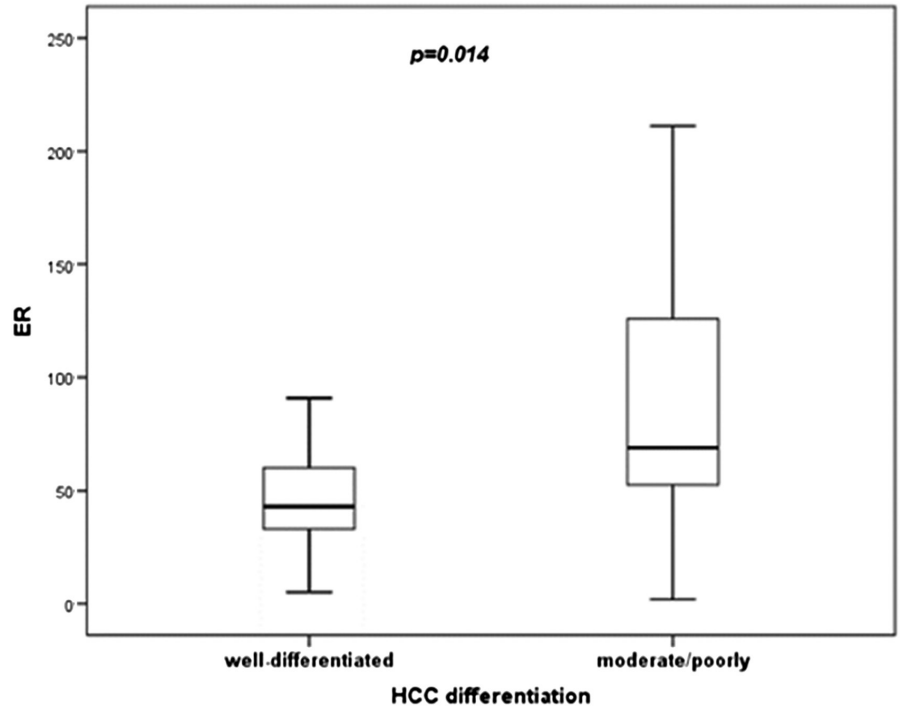

Figure 4. Relationship between ER and HCC differentiation in patient population. Student's t-test shows statistically significant difference between well-differentiated and moderately/poorly differentiated HCC's ER values in study population (P = .014). ER, enhancement ratio, HCC, hepatocellular carcinoma

Table 3. Quantitative Findings on Gd-EOB-DTPA-Enhanced Dynamic MRI in the Study Population

Parameters, Mean ± SD	Well-Differentiated HCC	Moderately/Poorly Differentiated HCC	*P*
Pre-contrast RSIR	0.76 ± 0.12	0.71 ± 0.22	.044
Post-contrast RSIR	0.74 ± 0.19	0.58 ± 0.17	.017
ER	89.8 ± 60.55	47.7 ± 25.8	.014

Gd-EOB-DTPA, gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid; MRI, magnetic resonance imaging; SD, standard deviation; HCC, hepatocellular carcinoma; RSIR, relative signal intensity ratio; ER, enhancement ratio.

Student's *t*-test.

25.8 for moderately/poorly differentiated tumors. Mean post-contrast RSIR and ER valuesof well-differentiated tumors were statistically significantly higher compared to the mean post-contrast RSIR and ER valuesof moderately/poorly differentiated tumors (P = .017 and P = .014, respectively) (Figures 3 and 4, respectively). Quantitative MRI findings, contrasting patterns, and SIs during hepatobiliary phase are summarized in the Table 3.

DISCUSSION

Tumor differentiation of HCC is a well-known independent factor directly representing the prognosis of the disease detected at the time of diagnosis. Tamura et al[16] analyzed the clinicopathological information of 53 patients who underwent liver transplantation due to HCC and found that the risk of recurrence after treatment was directly connected to the tumor differentiation. Later, tumor differentiation was included as an independent criterion for determining patient selection for liver transplantation in the expanded Toronto criteria.[3] In the present study, regarding the histopathological differentiation of HCCs, tumors were divided into 2 groups as well-differentiated and moderately/poorly differentiated due to the fact that moderately/poorly differentiated tumors have much worse prognosis.[17] Qualitative and quantitative characteristics of the 2 groups determined on MRI with Gd-EOB-DTPA at the time of the diagnosis were evaluated. While there was no difference between the qualitative characteristics of the 2 groups with different tumor differentiation, a significant difference between the quantitative features between the values of post-contrast RSIR and ER was detected (P = .017 and P = .014, respectively).

According to the American Association for the Study of Liver Diseases guidelines,[18] in cirrhotic patients, hyperatenuation/hyperintensity during arterial phase, and hypoatenuation/hypointensity during portal and/or venous phase in tumors larger than 1 cm on dynamic CT or MRI is sufficient for the diagnosis of HCC. On the other hand, the sensitivity of this typical contrast enhancement pattern for diagnosis was determined to be variable and limited (33%-81.8%).[2,15] In the study by Leoni et al.[19] 204 HCCs with a pathologically proven <3 cm nodule were evaluated visually in terms of the contrast pattern. Typical contrasting pattern was detected in 47% (47/101) of all HCCs. In addition, moderately and poorly differentiated tumors showed a significantly more frequent typical contrast pattern than well-differentiated tumors (48% (67/141) vs. 13% (8/63)). In this study, 43.7% (14/32) of tumors showed a typical contrast-enhancing pattern and the rates were consistent with the previously published data.[20,21] There was no difference in terms of frequency of showing typical contrast enhancement pattern of well-differentiated and moderately/poorly differentiated tumors (P = .479). This may be because the typical contrast enhancement pattern does not fully reflect tumor differentiation. The relationship between tumor carcinogenesis steps and tumor vascularity of HCCs was previously investigated; it was determined that the tumor has blood supply from the both arterial and portal system in early carcinogenesis stages and that the tumor has blood supply only from the arterial system in the advanced carcinogenesis stages. These changes in the blood supply determine the contrast pattern of the tumor in dynamic CT and MR imaging.[22,23] For this reason, we think that the typical contrast enhancement pattern detected in CT/MRI may be a predictive marker for moderate/poor histological differentiation of tumors, although its sensitivity is limited in HCC patients.

Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid is a paramagnetic liver-specific contrast agent. Previously published studies showed that Gd-EOB-DTPA at the hepatobiliary phase increased the sensitivity of early detection of HCCs compared to other contrast agents. Due to the fact that hepatocytes and HCC cells have different Gd-EOB-DTPA uptakes, tumors during the hepatobiliary phase are detected mostly as hypointense compared to background liver parenchyma. Therefore, HCCs can be easily detected visually in the hepatobiliary phase.[24,25] However, in later studies, it was found that all HCCs were not hypointense in the hepatobiliary phase, and some tumors showed iso- or hyperintense features. In the systematic review by Erra et al.[26] 13% (418/3110) of pathologically proven HCCs detected in MRI with Gd-EOB-DTPA showed iso- or hyperintense properties. In the study by Choi et al.[6] it was determined that in the tumors detected during hepatobiliary phase as hypointense, histological differentiation was poor and the risk of recurrence was higher. Chang et al[27] found that low post-contrast RSIR values on MRI performed with Gd-EOB-DTPA are predictive markers for poor histological differentiation of the tumor. In the study by Jin et al.[28] in the hepatobiliary phase on MRI with Gd-EOB-DTPA, ER values of well-differentiated tumors were significantly higher compared to moderately/poorly differentiated tumors (P < .01).

In this study, in the visual (qualitative) evaluation performed in the hepatobiliary phase, no difference between the signal intensity characteristics of the well-differentiated and moderately/poorly differentiated tumors was detected. However, there was a significant difference between the quantitative parameters of the well-differentiated and moderately/poorly differentiated tumors (P = .017 for post-contrast RSIR and P = .014 for ER). Gadolinium-ethoxybenzyl-diethylenet riamine pentaacetic acid is taken into hepatocytes through specific OATP-8 proteins located in the cell membranes. In the study by Kitao et al.[29] it was determined that as the HCC tumor carcinogenesis steps progress, OATP-8 expression in the cell membrane decreases. Therefore, moderately and poorly differentiated tumors show lower signal characteristics in MRI with Gd-EOB-DTPA than well-differentiated tumors. We think that the qualitative assessment made in MRI with Gd-EOB-DTPA is open to errors because of its subjective nature. Moreover, post-contrast RSIR and ER value differences in HCC during hepatobiliary phase lead to conclusion that quantitative evaluation could be an objective predictive marker for tumor differentiation. Our findings are in accordance with results of the study of Chang et al.[27]

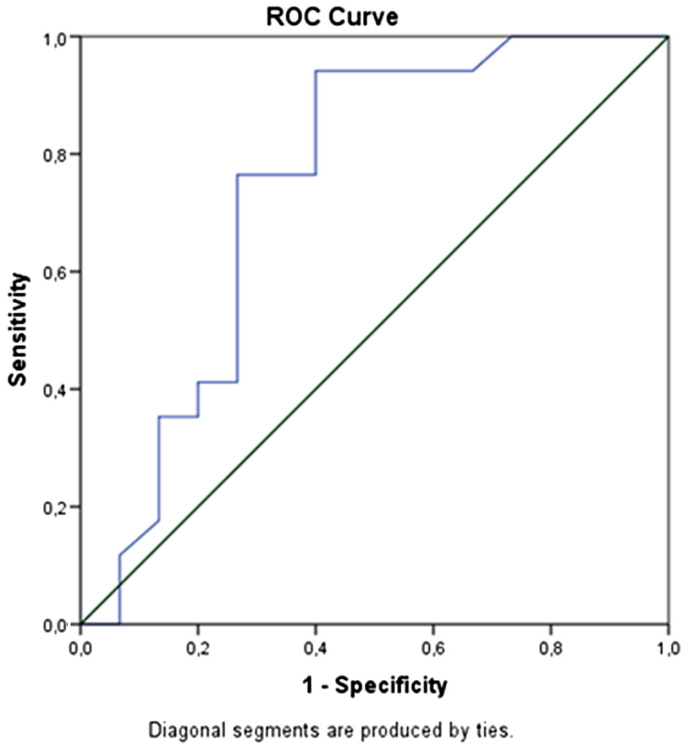

Figure 5. Area under curve for post-contrast RSIR in study population. ROC analysis shows good test power of post-contrast RSIR for the separation of well-differentiated and moderate/poorly differentiated tumors (area under curve 0.74, sensitivity 73%, and specificity 76%). RSIR, relative signal intensity ratio.

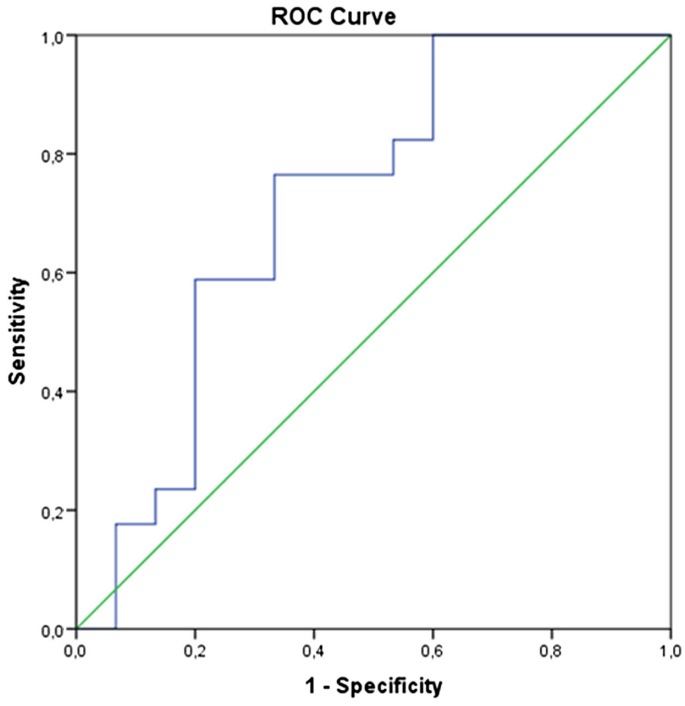

Figure 6. Area under curve for ER in study population. ROC analysis shows good test power of ER for the separation of well-differentiated and moderate/poorly differentiated tumors (area under curve for ER 0.71, sensitivity 82%, and specificity 76%). ER, enhancement ratio.

which determined post-contrast RSIR threshold values to differentiate other tumors from poorly differentiated tumors; sensitivity was 81.4% and specificity was 93.9% for this test. In this study, the test power of quantitative properties for the threshold values determined for the separation of well-differentiated and moderately/poorly differentiated tumors was calculated as good (area under curve for post-contrast RSIR = 0.74, sensitivity = 73%, and specificity = 76%; area under curve for ER = 0.71, sensitivity = 82%, and specificity = 76%) (Figures 5 and 6, respectively).

There were some important limitations in this study. First, this investigation was conducted retrospectively although we included all consecutive patients with histologically proven HCC in the study. Since this study was a retrospective, sufficient sample size was not calculated. Another important limitation is due to the relatively small number of patients because routine biopsies unfortunately are not commonly done due to possible complications of this procedure. Nevertheless, the number of patients is not significantly less compared to many other published studies. In order for the number of tumors examined in groups to be similar, moderately and poorly differentiated tumor diffraction was handled within the same group, but it may have affected study results. Another important limitation is that histopathological examinations were performed on the single specimen obtained by tru-cut biopsy. Thus, the presence of different tumor diffraction sites in the investigated tumor was ignored. Although there were no patients with Child-Pugh Class C in the groups, the effect of impaired liver function on the enhancement pattern and amount of contrast agent involvement was neglected in cirrhotic patients.

In conclusion, the quantitative but not qualitative parameters of HCC detected during hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI may provide objective and predictive information in terms of the differentiation between well-differentiated and moderately/poorly differentiated tumors. Post-contrast RSIR and ER on Gd-EOB-DTPA-enhanced MRI provide useful information about histological differentiation of the tumor with high sensitivity and specificity. These quantitative metrics can be used in the selection of an optimal candidate for liver transplantation. Further studies with standardized quantitative protocols and pre-calculated sample size are needed to clarify the exact threshold values for tumor differentiation in HCC.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Çukurova University School of Medicine (Date: April 10, 2020, Decision No:07).

Informed Consent: Written informed consent was obtained from all patients for MRI examination and biopsy before each procedure.

Peer-review: Externally peer-reviewed.

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Declaration of Interests: The authors declare that they have no conflicts ofinterest.

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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(6):394-424. [CrossRef]
2. Kudo M, Izumi N, Sakamoto M, et al. Survival Analysis over 28 years of 173,378 Patients with Hepatocellular Carcinoma in Japan. *Liver Cancer*. 2016;5(3):190-197. [CrossRef]
3. Sapisochin G, Goldaracena N, Laurence JM, et al. The extended Toronto criteria for liver transplantation in patients with hepatocellular carcinoma: A prospective validation study. *Hepatology*. 2016;64(6):2077-2088. [CrossRef]
4. Schuhmann-Giampieri G, Schmitt-Willich H, Press WR, Negishi C, Weinmann HJ, Speck U. Preclinical evaluation of Gd-EOB-DTPA as a contrast agent in MR imaging of the hepatobiliary system. *Radiology*. 1992;183(1):59-64. [CrossRef]
5. Vogl TJ, Kümmel S, Hammerstingl R, et al. Liver tumors: comparison of MR imaging with Gd-EOB-DTPA and Gd-DTPA. *Radiology*. 1996;200(1): 59-67. [CrossRef]
6. Narita M, Hatano E, Arizono S, et al. Expression of OATP1B3 determines uptake of Gd-EOB-DTPA in hepatocellular carcinoma. *J Gastroenterol*. 2009;44(7):793-798. [CrossRef]
7. Frericks BB, Loddenkemper C, Huppertz A, et al. Qualitative and quantitative evaluation of hepatocellular carcinoma and cirrhotic liver enhancement using Gd-EOB-DTPA. *AJR*. 2009;193(4):1053-1060. [CrossRef]
8. Baird AJ, Amos GJ, Saad NF, Benson MD. Retrospective audit to determine the diagnostic accuracy of Primovist-enhanced MRI in the detection of hepatocellular carcinoma in cirrhosis with explant histopathology correlation. *J Med Imaging Radiat Oncol*. 2013;57(3):314-320. [CrossRef]
9. Lee MH, Kim SH, Park MJ, Park CK, Rhim H. 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*. 2011;197(5):W868 -W875. [CrossRef]
10. Kobayashi S, Matsui O, Gabata T, et al. Relationship between signal intensity on hepatobiliary phase of gadolinium ethoxybenzyl diethylene triaminepentaacetic acid (Gd-EOB-DTPA)-enhanced MR imaging and prognosis of borderline lesions of hepatocellular carcinoma. *Eur J Radiol*. 2012;81(11):3002-3009. [CrossRef]
11. 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(10):2405-2413. [CrossRef]
12. Okada M, Imai Y, Kim T, et al. Comparison of enhancement patterns of histologically confirmed hepatocellular carcinoma between gadoxetate- and ferucarbotran-enhanced magnetic resonance imaging. *JMRI*. 2010;32(4):903-913. [CrossRef]
13. Choi JY, Kim MJ, Park YN, et al. Gadoxetate disodium-enhanced hepatobiliary phase MRI of hepatocellular carcinoma: correlation with histological characteristics. *AJR*. 2011;197(2):399-405. [CrossRef]
14. Kim HY, Choi JY, Kim CW, et al. Gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging predicts the histological grade of hepatocellular carcinoma only in patients with Child-Pugh class A cirrhosis. *Liver Transpl*. 2012;18(7):850-857. [CrossRef]
15. Edmondson HA, Steiner PE. Primary carcinoma of the liver: a study of 100 cases among 48,900 necropsies. *Cancer*. 1954;7(3):462-503. [CrossRef]
16. Tamura S, Kato T, Berho M, et al. Impact of histological grade of hepatocellular carcinoma on the outcome of liver transplantation. *Arch Surg*. 2001;136(1):25-30. [CrossRef]
17. Choi JW, Lee JM, Kim SJ, et al. Hepatocellular carcinoma: imaging patterns on gadoxetic acid-enhanced MR Images and their value as an imaging biomarker. *Radiology*. 2013;267(3):776-786. [CrossRef]
18. Sherman M. The radiological diagnosis of hepatocellular carcinoma. *Am J Gastroenterol*. 2010;105(3):610-612. [CrossRef]
19. Leoni S, Piscaglia F, Golfieri R, et al. The impact of vascular and nonvascular findings on the noninvasive diagnosis of small hepatocellular carcinoma based on the EASL and AASLD criteria. *Am J Gastroenterol*. 2010;105(3):599-609. [CrossRef]
20. Yoon SH, Lee JM, So YH, et al. Multiphasic MDCT enhancement pattern of hepatocellular carcinoma smaller than 3 cm in diameter: tumor size and cellular differentiation. *AJR*. 2009;193(6):W482-W489. [CrossRef]
21. Lee JH, Lee JM, Kim SJ, et al. Enhancement patterns of hepatocellular carcinomas on multiphasic multidetector row CT: comparison with pathological differentiation. *Br J Radiol*. 2012;85(1017):e573-e583. [CrossRef]
22. Honda H, Tajima T, Kajiyama K, et al. Vascular changes in hepatocellular carcinoma: correlation of radiologic and pathologic findings. *AJR*. 1999;173(5):1213-1217. [CrossRef]
23. Liu GJ, Xu HX, Lu MD, et al. Correlation between enhancement pattern of hepatocellular carcinoma on real-time contrast-enhanced ultrasound and tumour cellular differentiation on histopathology. *Br J Radiol*. 2007;80(953):321-330. [CrossRef]
24. Golfieri R, Renzulli M, Lucidi V, Corcioni B, Trevisani F, Bolondi L. Contribution of the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI to Dynamic MRI in the detection of hypovascular small (≤ 2 cm) HCC in cirrhosis (</=2 cm) HCC in cirrhosis. *Eur Radiol*. 2011;21(6):1233-1242. [CrossRef]
25. Inoue T, Kudo M, Komuta M, et al. Assessment of Gd-EOB-DTPA-enhanced MRI for HCC and dysplastic nodules and comparison of detection sensitivity versus MDCT. *J Gastroenterol*. 2012;47(9):1036-1047. [CrossRef]
26. Erra P, Puglia M, Ragozzino A, et al. Appearance of hepatocellular carcinoma on gadoxetic acid-enhanced hepato-biliary phase MR imaging: a systematic review. *Radiol Med*. 2015;120(11):1002-1011. [CrossRef]
27. 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(6):1202-1212. [CrossRef]
28. Jin YJ, Cho SG, Lee KY, Kim JM, Lee JW. Association between relative liver enhancement on gadoxetic acid enhanced magnetic resonance images and histologic grade of hepatocellular carcinoma. *Medicine*. 2017;96(30):e7580. [CrossRef]
29. Kitao A, Matsui O, Yoneda N, et al. Gadoxetic acid-enhanced MR imaging for hepatocellular carcinoma: molecular and genetic background. *Eur Radiol*. 2020;30(6):3438-3447. [CrossRef]