Value of T1 Mapping on Gadoteric acid-enhanced MRI for Microvascular Invasion of Hepatocellular Carcinoma: A Retrospective Study

chenyi Rao

Nantong University Medical School

Xinquan Wang

Affiliated Hospital of Nantong University

Minda Li

Affiliated Hospital of Nantong University

Guofeng Zhou

Zhongshan Hospital Fudan University

Hongmei Gu (✉ raoxray@126.com)

Affiliated Hospital of Nantong University

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Abstract

Background: To evaluate the utility of non-invasive parameters deriving from T1 mapping on gadoxetic acid-enhanced MRI for predicting microvascular invasion (MVI) of hepatocellular carcinoma (HCC) compared with diffusion-weighted imaging (DWI).

Methods: A total of 94 patients with single HCC undergoing partial hepatectomy was included in the retrospective study, who underwent preoperative gadoxetic acid-enhanced MRI combined with DWI and T1 mapping. Parameters including precontrast, postcontrast and reduction rate of T1 relaxation time and ADC values were measured for differentiating MVI-positive HCCs (n=38) from MVI-negative HCCs (n=56). The receiver operating characteristic curve (ROC) was analyzed to compare the diagnostic performance of the calculated parameters.

Results: The mean value of postcontrast T1 relaxation time were significantly higher in MVI-positive HCCs than MVI-negative HCCs (621.0 vs. 536.5, $P < 0.001$). MVI-positive HCCs demonstrated significantly lower reduction rates of T1 relaxation time and lower ADC values than MVI-negative HCCs (39.4% vs 49.9, $P < 0.001$; $1.495 \times 10^{-3} \text{mm}^2/\text{s}$ vs $1.620 \times 10^{-3} \text{mm}^2/\text{s}$, $P = 0.003$, respectively). The area under receiver operating characteristic curves were 0.587, 0.728, 0.824 and 0.690 for precontrast, postcontrast, reduction rate of T1 relaxation time and ADC, respectively. The reduction rate of T1 relaxation time was the most reliable feature with sensitivity, specificity and accuracy of the cut-off value (44.9%) of 79.0%, 73.2%, 75.5%, respectively.

Conclusions: Reduction rate of T1 relaxation time on gadoxetic acid-enhanced MRI holds promise for evaluating MVI status of HCC.

Background

Hepatocellular carcinoma (HCC) ranks the sixth most frequent cancer and the fourth leading cause of cancer-related death worldwide in 2018 [1]. Liver resection, liver transplantation and radiofrequency ablation are the curative treatment modalities for HCC with different indications [2]. However, early recurrence is a major problem that impairs patient prognosis and microvascular invasion (MVI) of HCC is a critical predictor for early recurrence and poor prognosis after curative treatments [3–5]. Non-invasive evaluation of MVI before surgery is important as it allows for optimal treatment modalities [4, 5].

In clinical practice, MVI is determined by pathologic evaluation on the surgical specimens after liver resection or transplantation. There are some studies that demonstrating promising results for preoperatively predicting MVI of HCC based on qualitative analysis of morphologic MR imaging features [6, 7] and quantitative analysis including apparent diffusion coefficient (ADC) values of diffusion weighted imaging (DWI) [8, 9], kurtosis value of diffusion kurtosis imaging [10] or D value of intravoxel incoherent motion [11]. Recently, a radiomics approach based on radiological images [12] provided satisfactory diagnostic performance for preoperative evaluation of MVI. However, the subjective nature of the evaluation of morphologic features, instable image quality of diffusion weighted/kurtosis images

(i.e., T2 blackout effect, susceptibility artifacts and image distortion) or obscure algorithms of radiomics analysis are challenges for further clinical utility.

Gadoxetic acid-enhanced magnetic resonance imaging (Gd-EOB-DTPA MRI) is accepted widely as a preferred imaging method for detection and stage of hepatic nodules [2], and evaluation of liver function in patients with HCC [13]. The signal intensity (SI) on the hepatobiliary phase (HBP) of gadoxetic acid-enhanced MRI determined by the amount of Gd-EOB-DTPA uptake by HCC was associated with tumor invasiveness and clinical outcome [14, 15]. T1 mapping is an absolute and more reliable value than SI measurement for reflecting the Gd-EOB-DTPA uptake within tissue [16]. Additionally, T1 mapping with high temporal and spatial resolution images could integrate seamlessly into gadoxetic acid-enhanced MRI scan protocol. Previous studies demonstrated that gadoxetic acid-enhanced MRI combined with T1 mapping had potential for predicting histologic grades and recurrence after resection of HCC [17–19]. It supposed that the measurement of T1 relaxation time is expected to predict MVI of HCC.

Thus, the aim of our study was to compare the diagnostic performance between parameters driving from T1 mapping and DWI on gadoxetic acid-enhanced MRI in evaluation of MVI of HCC.

Methods

This study was approved by the Institutional Review Board of Zhongshan Hospital, Fudan University (approval number B2018-236) in accordance with the ethical guidelines of the Declaration of Helsinki. The committee waived the requirement for informed consent because it is a retrospective study.

Patients selection

According to the AASLD guideline, patients with preexisting cirrhosis were at high risk for developing HCC and surveillance program of ultrasound (US) and α -fetoprotein (AFP) were recommended. In our institution, between February 2016 and March 2017, 222 patients underwent gadoxetic acid-enhanced MRI for further evaluation of suspicious HCCs detected during surveillance. Patients with probable benign nodules (i.e., cysts, hemangiomas, arterioportal shunts) screened by US or patients with HCCs having any previous treatments such as transcatheter arterial chemoembolization (TACE) and radiofrequency ablation (RFA) were initially excluded from the study. The inclusive criteria of the patient selection were: (a) single HCC with histology and preoperative gadoxetic acid-enhanced MRI; (b) the interval time between MRI protocol and the operation was less than 2 weeks; (c) patients in Child-Pugh A-B; (d) HCC with qualified MR images. Of the 222 patients, 55 patients were excluded for having two or more HCCs; 8 patients were excluded for Child-Pugh C; 28 were excluded for other types of nodules including intrahepatic cholangiocarcinoma ($n = 15$), combined HCC and cholangiocarcinoma ($n = 1$), dysplastic nodule ($n = 10$) and metastasize ($n = 2$); 16 patients were excluded for more than 2 weeks interval time during follow-up; 21 patients were excluded for lesions on left lobe with susceptibility or respiratory motion artifacts on DW images. Finally, 94 patients with single HCC were included in our study (Fig. 1).

MR Imaging Protocol

All patients enrolled in our study underwent gadoxetic acid-enhanced MRI in a single 1.5-T MR system (MAGNETOM Aera, Siemens Healthcare, Erlangen, Germany), with a 8-channel phased-array receiver coil. Single-spin echo plane DWI for free breathing (3200/56 milliseconds repetition time (TR) / echo time (TE), 84×128 matrix, $380\text{--}400 \times 300\text{--}324$ mm field of view (FOV), 5.5 mm slice thickness) was performed, and corresponding ADC maps were automatically generated with b values of 0 and 500 s/mm^2 . Dynamic contrast-enhanced T1-weighted 3D gradient-recalled echo images (3.47 / 1.36 TR / TE, 320×195 matrix, 10° flip angle, 308×380 mm FOV, 3 mm slice thickness) were obtained after intravenously injection of contrast agent. A dual flip-angle (Flip angle, 2° and 12°) before and at 20 min after injection of gadoxetic acid based on a voxel-by-voxel basis was applied for generating T1 maps with syngo MapIt. The precontrast phase was obtained before a bolus injection of 0.025 mmol/kg of gadoxetic acid (Primovist, Bayer Schering Pharma, Berlin, Germany) at a rate of 1 ml/sec with a subsequent 20 ml saline flush. Subsequent MR images during the arterial phase (automatically triggered when the ascending aorta reached peak enhancement), the portal vein phase (about 14 seconds), the transition phase (about 3 minutes), and the hepatobiliary phase (HBP; 20 minutes) were obtained.

MR images analysis

Two abdominal radiologists (Blinded) independently reviewed the MR images of all the patients. Region of interest (ROI) was outlined around the edge of tumor on each slice on precontrast T1 maps, postcontrast T1 maps and ADC maps, which were copied from ROIs of HCCs that drawn on high flip angle (12°) T1-weighted images and high b value images (500 s/mm^2), respectively (Fig. 2). Precontrast, postcontrast T1 relaxation time and ADC values of the two observers were then calculated. We also calculated the reduction rate ($\Delta\%$) of T1 relaxation time using the following formula: $\Delta\% = 100\% \times (\text{pre T1 value} - \text{post T1 value}) / \text{pre T1 value}$, in which pre T1 and post T1 values representing the T1 relaxation times before and after injection of gadoxetic acid.

Reference standard for MVI

Pathological data including presence of cirrhosis, Edmondson-Steiner grade or microvascular invasion was according to surgical pathologic reports generated by our institutional pathologists specialized in liver histology (each individual with more than 20 years of experience). Microvascular invasion was defined as presence of muscular wall in any vascular space with invasion or adherence of any intravascular tumors to the vessel wall visible microscopically.

Statistical Analysis

Frequencies of categorical variables for differentiating MVI were compared by using Fisher exact test. Difference of quantitative variables including precontrast/postcontrast T1 relaxation time and ADC

values between MVI-positive and MVI-negative groups was compared by using independent sample t test. The interclass correlation coefficient (ICC) of quantitative data between the two observers was calculated (poor: <0.40; fair: 0.40–0.59; good: 0.60–0.74; excellent: 0.75–1.00). Area under receiver operating characteristic curve (AUC) with 95% confidence interval (95% CI) based on receiver operating characteristic curve (ROC) analysis was generated for evaluating the utility of variables to discriminate the status of MVI. Sensitivity, specificity, accuracy, positive predictive value (PPV), negative predictive value (NPV) and likelihood ratio (LR) of appropriate cutoff value corresponding to maximal Youden index by using ROC analysis were presented with 95% CI. All the statistical tests were performed by using statistical software (SPSS version 21, SPSS, Chicago, Ill) and a two-side P value less than 0.05 indicating significance level.

Results

Patients and treatment characteristics

A total of 94 patients (76 men and 18 women; median age: 54 years (range, 24–75 years)) with single HCC were included in the study. Among the 94 patients, 87 of them (92.6%) were hepatitis B virus infected. The mean size of maximal diameter of tumors estimated on HBP was 1.9 cm, ranging from 1.2 to 4.5 cm. All the patients underwent partial hepatectomy for HCC. Fifty-six HCCs were categorized of presence of MVI and 38 HCCs were absence of MVI confirmed by histology. The other main characteristics of patients are shown in Table 1.

T1 relaxation time and ADC measurements

Table 2 shows the mean values of T1 relaxation time (pre-contrast, postcontrast) and ADC of the two readers. The reduction rate was then calculated based on the mean values of the two readers. There was no significant difference for precontrast T1 relaxation time between MVI-negative and MVI-positive groups (Figure 3). The mean values of postcontrast T1 relaxation time of the two readers were significantly higher in MVI-positive HCCs compared with MVI-negative HCCs (621.0ms vs 536.5ms, $P<0.001$). The reduction rates of T1 relaxation time was significantly lower in MVI-positive HCCs than in MVI-negative HCCs (39.4% vs 49.9, $P<0.001$, Figure 4). The mean values ADC value was significantly lower in MVI-positive HCCs than MVI-negative HCCs ($1.495\times 10^{-3}\text{mm}^2/\text{s}$ vs $1.620\times 10^{-3}\text{mm}^2/\text{s}$, $P=0.003$). The agreements between two readers shown in Table 2 were excellent for ADC, precontrast and postcontrast T1 relaxation time (ICC: 0.759, 95%CI: 0.637–0.840; ICC: 0.823, 95%CI: 0.744–0.879; ICC: 0.858, 95%CI: 0.786–0.906, respectively).

Diagnostic performance for evaluating MVI of HCC

The ROC curves with AUC were analyzed to compare the diagnostic performance of the parameters driving from T1 relaxation time and ADC of DWI for evaluation of MVI status of HCC (Figure 5). The corresponding AUC, cutoff value, sensitivity, specificity, +LR, -LR, PPV and NPV with 95% CI are summarized in Table 3. AUCs were 0.587, 0.728, 0.824 and 0.690 for precontrast, postcontrast, reduction

rate of T1 relaxation time and ADC, respectively. Among the parameters of T1 relaxation time and ADC, the reduction rate was the most reliable feature with an AUC of 0.824 (95%CI: 0.732-0.895), and the sensitivity, specificity and accuracy of the cut-off value (44.9%) were 79.0%, 73.2%, 75.5%, respectively. The AUC of reduction rate of T1 relaxation time was significantly higher than that of ADC (0.824 vs 0.690, $P=0.043$).

Discussion

The study demonstrated that HCC with MVI had significantly higher postcontrast and reduction rate of T1 relaxation time than HCC without MVI. The reduction rate of T1 relaxation time demonstrated a better diagnostic performance for predicting MVI status of HCC in comparison with ADC.

Gadoxetic acid-enhanced MRI combined with DWI is a part of the standard workup in detection and characterization of hepatic nodules for better providing clinicians with roadmap of therapeutic strategies in our institution. Considering the pitfalls of DWI sequence and subjective nature of evaluating morphological imaging features on gadoxetic acid-enhanced MRI for assessing MVI, we quantitatively compared parameters deriving from T1 relaxation time of HCC with values of ADC maps that demonstrating good image quality for identifying the MVI status of HCC. Previous studies reported that ADC values based on DWI was useful for evaluation of MVI status of HCC [8, 9, 20]. In line with our study, lower ADC value has been proven helpful for predicting MVI of HCC because it reflects higher tissue cellularity and decreased micro-capillary perfusion [9]. There are several pitfalls of DWI that affect the reliability of the ADC measurement including [21, 22]: (1) limited image quality with poor signal-to-noise ratio and low spatial resolution; (2) more sensitive to motion and air susceptibility, especially for pulsation artifacts in left robe; (3) misregistration artifacts on ADC map; (4) T2 blackout effect mainly refer to fibrotic tissues or calcifications depicting hypointesity on both DW images and ADC maps. Some studies reported that the reproducibility for ADC and IVIM measurement of hepatic nodules was poor [23–25].

T1 mapping on gadoxetic acid-enhanced MRI can be used as an additional protocol included in the routine MR sequences for evaluation of diffuse liver disease [13, 26–27]. Ding [26] et al reported that the measurement of T1 relaxation time parameters was more reproducible compared with the measurement of ADC values for staging hepatic fibrosis. Previous studies also showed T1 mapping on gadoxetic acid-enhanced MRI outperformed DWI for evaluation of liver function in patients with HCC [13] and staging hepatic fibrosis [26, 27].

The reduction rate of T1 relaxation time demonstrated improved diagnostic performance compared with ADC values after excluding the cases that showing moderate to evident artifacts of tumor on DW images. In our institution, the sequence of T1 mapping with Syngo MapIt is routinely performed, which can provide the acquisition of MR images with high resolution 3D-dataset of whole liver. Our results demonstrated that there was no significant value in predicting MVI of HCC by using precontrast T1 relaxation time because it may be affected by some factors such as liver inflammation [28]. Our results

indicated that lower reduction rate of T1 relaxation time was a potential predictor for MVI positive status of HCC. Peng [17] et al reported that the reduction rate in T1 value was the best predictor correlated with degree of differentiation of HCC, and higher histological grade is correlated with MVI positive status of HCC [29]. Wang [18] et al demonstrated that reduction rate of T1 relaxation time was a reliable biomarker for predicting recurrence of HCC (≤ 3 cm) after hepatectomy. The SI of hepatobiliary phase on gadoxetic acid-enhanced MRI has shorten T1 effect that determined by expression levels of the organic anion transporter 1B3 (OATP8) protein in HCC, and was reported to have a strong association with the expression of Wnt/ β -catenin target genes [30]. Additionally, β -catenin gene (CTNNB1) mutations of HCC showed more aggressive tumor biology with increased probability of MVI [31]. Hence, MVI positive HCC may show higher SI on HBP and lower reduction rate of T1 relaxation time.

The present study is limited by its selection bias of retrospective nature. The sample size of the study is relative small. Additionally, we only use two b-values of 0, 500 s/mm² for DW imaging that routinely performed in our institution. The measurement of ADC values based on these two b values was previously applied for evaluating MVI of small HCC with satisfactory diagnostic performance [20]. In our study, to reduce the measurement error, we excluded DW images with moderate to evident artifacts, especially those showing artifacts caused by pulsation artifacts in the left lobe, misregistration and air susceptibility.

Conclusions

Currently, MVI of HCC can only be confirmed by histology and noninvasive approach to MVI status of HCC for guiding tumor management, such as selecting appropriate allocation of liver transplantation [4] and resection margin [5] is limited. So far, there is a large body of evidence that gadoxetic acid-enhanced MRI combined with DWI and T1 mapping can show high accuracy for characterization of focal liver lesions and evaluation of the whole and segmental liver function reserve. ADC value of DWI helps improve the diagnostic accuracy of MVI of HCC [2], however, the reliability of measurement can also be affected by technical factors. Our results suggested that T1 relaxation time measurement on gadoxetic acid-enhanced MRI holds promise to provide additional information for HCC MVI status, which is preliminary and warrants further validation.

Declarations

Ethics approval and consent to participate:

This study was approved by the Institutional Review Board of Zhongshan Hospital, Fudan University (approval number B2018-236) in accordance with the ethical guidelines of the Declaration of Helsinki. The committee waived the requirement for informed consent because it is a retrospective study.

Consent for publication: Not applicable.

Competing interests: no conflict of interest.

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Authors' contributions:

All authors have read and approved the manuscript. HMG designed and supervised the study; CYR, GFZ, XQW collected the patient's clinical and MRI data; MDL, GFZ analyzed the data; CYR drafted the paper.

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Availability of data and materials:

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Abbreviations

MVI: microvascular invasion; HCC: hepatocellular carcinoma;

DWI: diffusion-weighted imaging; ROC: receiver operating characteristic curve;

ADC: apparent diffusion coefficient; DWI: diffusion weighted imaging;

Gd-EOB-DTPA MRI: Gadoxetic acid-enhanced magnetic resonance imaging;

HBP: hepatobiliary phase; US: ultrasound; AFP: a-fetoprotein;

TACE: transcatheter arterial chemoembolization; RFA: radiofrequency ablation;

TR: repetition time; TE echo time; FOV: field of view;

ROI: Region of interest; ICC: interclass correlation coefficient;

AUC: Area under receiver operating characteristic curve;

ROC: receiver operating characteristic curve;

PPV: positive predictive value; NPV: negative predictive value;

LR: likelihood ratio; organic anion transporter: OATP8;

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Tables

Table 1. Baseline characteristics of patients with hepatocellular carcinoma

Characteristics	All patients (n=94)	MVI		<i>P</i>
		Negative (n=56)	Positive (n=38)	
Gender				0.217
Male	88	54	34	
Female	6	2	4	
Age, years (Range)	52 (24-75)	52 (30-73)	53 (24-75)	0.744
Diameter, cm (Range)	1.9 (1.2-4.5)	1.8 (1.2- 3.5)	2.2 (1.4-4.5)	0.078
Etiology				0.190
HBV	87	54	33	
HCV	5	1	4	
Alcohol or others	2	1	1	
AFP >20ng/ml				>0.99
Positive	51	30	21	
Negative	43	26	17	
Child-Pugh				>0.99
A	91	54	37	
B	3	2	1	

HBV: Hepatitis B virus; HCV: Hepatitis C virus; AFP: a-fetoprotein; MVI: microvascular invasion

Table 2. Comparisons of mean values and standard deviations of T1 relaxation time and apparent diffusion coefficient (ADC) value between MVI-negative and MVI-positive groups of hepatocellular carcinoma.

	All (n=94)	MVI		P value	ICC (95% CI)*
		Negative (n=56)	Positive (n=38)		
relaxation time					
re-contrast					0.823 (0.744-0.879)
Reader 1	1040.9	1065.9	1004.2	0.095	
SD	175.6	191.2	144.3		
Reader 2	1079.2	1094.2	1057.1	0.283	
SD	163.5	149.9	181.4		
Mean	1060.1	1080.0	1030.6	0.148	
SD	161.9	163.6	156.9		
postcontrast					0.858 (0.786-0.906)
Reader 1	578.1	548.5	621.7	0.001	
SD	107.9	102.3	102.2		
Reader 2	563.2	524.5	620.3	<0.001	
SD	117.1	103.8	113.3		
Mean	570.6	536.5	621.0	<0.001	
SD	105.4	95.6	99.8		
reduction rate (%) *	45.7	49.9	39.4	<0.001	
SD	9.2	8.0	7.1		
					0.759 (0.637-0.840)
Reader 1	1571.5	1597.4	1533.3	0.134	
SD	194.4	175.6	216.0		
Reader 2	1568.7	1643.9	1457.8	<0.001	
SD	257.1	233.6	252.6		
Mean	1570.1	1620.7	1495.6	0.003	
SD	204.6	194.3	198.8		

MVI: microvascular invasion; SD: standard deviations; CI: confidence intervals;

ICC: interclass correlation coefficient; ADC: apparent diffusion coefficient;

* The ICC was not calculated because reduction rate of T1 relaxation was based on the mean values of precontrast and postcontrast T1 relaxation time of the two readers.

Table 3. Diagnostic performance for T1 relaxation time and ADC value in evaluating MVI-positive HCC by receiver operating characteristic analyses.

	AUC	Cutoff	Sensitivity	Specificity	Accuracy	+LR	-LR	PPV	NPV
1									
relaxation									
me									
Pre-contrast	0.587	1138.4	78.9	44.7	58.5	1.43	0.47	49.2	75.8
95% CI	0.481-0.688		62.7-90.4	31.3-58.5	48.6-68.5	1.1-1.9	0.2-0.9	36.1-62.3	57.7-88.9
postcontrast	0.728	586.7	57.9	75.0	68.1	2.32	0.56	61.1	72.4
95% CI	0.626-0.814		40.8-73.7	61.6-85.6	58.7-77.5	1.4-3.9	0.40-0.80	43.5-76.9	59.1-83.3
Reduction rate (%)	0.824	44.9	79.0	73.2	75.5	2.95	0.29	66.7	83.7
95% CI	0.732-0.895		62.7-90.4	59.7-84.2	66.9-84.2	1.9-4.7	0.2-0.5	51.0-80.0	70.3-92.7
DC	0.690	1553.5	71.1	66.1	68.1	2.09	0.44	58.7	77.1
95% CI	0.586-0.781		51.1-84.6	52.2-78.2	58.7-77.5	1.4-3.2	0.30-0.70	43.2-73.0	62.7-88.0

AUC: area under receiver operating characteristic curve; LR: likelihood ratio; PPV: positive predictive value; NPV: negative predictive value;

CI: confidence intervals; ADC: apparent diffusion coefficient;

Figures

Figure 1

Flow chart of patients selection.

Figure 2

The ROIs of HCC was drawn on the corresponding ADC maps and postcontrast T1 maps. (A) the HCC on right lobe of liver showing hyperintensity on DWI maps of $b=500 \text{ mm}^2/\text{s}$; (B) ROI was drawn on corresponding ADC maps; (C) the HCC on right lobe of liver showing hypointensity on hepatobiliary phase; (D) ROI was drawn on postcontrast T1 maps.

Figure 3

Comparisons of mean values and standard deviation of precontrast and postcontrast T₁ relaxation time between MVI-positive and MVI-negative HCCs.

Figure 4

Comparisons of mean values and standard deviation of reduction rate T_1 relaxation time between MVI-positive and MVI-negative HCCs.

Figure 5

The utility of receiver operating characteristic curve of precontrast, postcontrast and reduction rate of T1 relaxation time and ADC value to discriminate MVI-positive and MVI-negative HCCs. The AUC of reduction rate of T1 relaxation time was 0.801 with the optimal cutoff value of 44.9%.