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Diagnostic accuracy of 3D magnetic resonance elastography for assessing histologic grade of hepatocellular carcinoma: comparison of three methods for positioning region of interest

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Abstract

Purpose—To assess the influence of region of interest (ROI) placement on the predictive value of 3D MRE in differentiating the histologic grade of HCC.

Methods—85 patients with pathologically confirmed HCCs were analyzed using 3D MRE imaging, two radiologists measured the tumor stiffness with three different ROI positioning methods. Intraclass correlation coefficient (ICC) was expressed in terms of inter- and intra-observer agreements. Kruskal–Wallis rank test or one-way ANOVA was used to compare the difference in MRE stiffness across the three-ROI positioning methods. Receiver operating characteristic curve analysis (ROC) was performed, and the area under curve (AUC) was measured to evaluate the diagnostic performance.

Results—There were 64 (75%) well-or-moderately differentiated HCCs and 21(25%) poorly differentiated HCCs included finally. Almost excellent inter- and intra-observer agreements (all ICC > 0.82) were observed for all three-ROI methods, the volumetric method has the highest values (inter-observer ICC 0.967, intra-observer ICC 0.919, 0.926, respectively). The mean stiffnesses of poorly differentiated HCC obtained by two readers were significantly higher than well-or-moderately differentiated HCC with volumetric method (7.07 ± 1.57 Kpa, 5.00 ± 1.49 Kpa, and 6.85 ± 1.49 Kpa, 4.94 ± 1.48 Kpa, respectively) and three-ROI method (6.14 ± 1.71 Kpa, 4.91 ± 1.56 Kpa and 5.94 ± 1.61 Kpa, 4.84 ± 1.54 Kpa, respectively) but not on single-ROI method ($p > 0.005$), for the diagnostic performance, the highest area under the curve (AUC) with a value of 0.837, 0.812 by using the volumetric method, followed by the three-ROI method (0.713, 0.754) and single-ROI method.

Conclusion—Different ROI positioning methods significantly affect HCC tumor stiffness measurements. The whole tumor volumetric analysis is superior to ROI-based methods for predicting the grade of HCC.

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Weimin Liu and Dailin Rong has contributed equally to this work.

Keywords

Diagnostic imaging; Hepatocellular carcinoma (HCC); Magnetic resonance elastography (MRE); Neoplasm grading

Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver with increasing incidence and mortality and is the fourth cause of cancer-related death worldwide [1]. Histologic differentiation is an important factor affecting patient prognosis [2, 3], as poorly differentiated HCC is often associated with a higher recurrence rate and worse survival than well-or-moderately differentiated HCCs [4]. Therefore, evaluation of histologic differentiation preoperatively is valuable for management decisions [5].

MRE is a phase-contrast MRI technique for quantitatively assessing shear stiffness of biological tissues in vivo [6–8]. 2D MRE is usually adequate to represent the diffuse changes of the whole liver [9]. Some preclinical studies have shown that 3D MRE-based biomarkers represent an improvement over the currently available data obtained from conventional 2D MRE and may provide better spatial resolution to measure focal liver lesions [10, 11]. Recently, researchers have reported that MRE can be useful in predicting the HCC differentiation and thus improve patient management [6, 12]. However, the conclusions on the use of MRE for the grading of HCC is controversial. While some investigators reported that well-or-moderately differentiated HCCs were stiffer than poorly differentiated HCCs [12], others demonstrated that tumor stiffness was higher in poorly differentiated HCCs compared to moderately to well-differentiated HCCs [6]. It is possible that these conflicting findings may be related to different ROI positioning methods used for measuring tumor stiffness in the two studies. Recently, there were two studies about quantifying the heterogeneity of the diffuse liver stiffness (LS) on MRE by different measurement methods. One study showed that LS calculated using ROIs that include the largest part of the liver parenchyma was significantly more reliable than circular ROIs with a radius of 1 cm [13], the other study showed that volumetric segmentation may potentially improve the detection of heterogeneous fibrosis and the accuracy of LS measurement than ROI-based method [14]. The purpose of this study was to evaluate the effect of different ROI positioning methods on the MRE measured tumor stiffness of HCCs, and their performance in differentiating pathologic grade of HCCs.

Materials and methods

Study Subjects

This was a single-center retrospective study. With IRB approval and HIPAA compliance, we consecutively included 343 patients with suspicious HCC who underwent MRE between December 2014 and January 2018. Among them, 258 patients were excluded for several conditions (Fig. 1). A total of 85 patients with surgically confirmed HCCs were finally enrolled. All patients underwent MRE prior to surgery within one month.

MRE scan

All subjects underwent conventional MRI and MRE examinations using a 3.0 T MR system (Discovery MR 750, GE Healthcare, Milwaukee, WI) with an 8-channel, phased array torso coil. Patients were instructed to fast for a minimum of 4 h before the MRI exams to avoid postprandial state effects on stiffness evaluation. 3D MRE was performed using a multislice, flow-compensated, spin-echo echo-planar imaging (SE-EPI), MRE sequence [15]. A passive pneumatic driver was placed over the left or right tumor-containing lobe of the liver at the xiphisternum level and was secured with an elastic belt. Continuous, 60 Hz, mechanical vibrations were generated using an active acoustic driver located outside of the scan room. They were transmitted through polyvinyl chloride tubing to the passive driver to produce shear waves in the liver [10, 16]. The total imaging time for MRE was about 64 s, performed in either three 22-s breath-holds or six 11-s breath-holds. The MRE parameters included: acquisition matrix = 80×80 ; repetition time = 1334 ms; echo time = 52 ms; single shot; field of view = 44.8 cm; number of slices = 32; slice thickness = 3.5 mm, inter-slice gap = 0 mm, superior–inferior spatial saturation bands, and parallel imaging acceleration factor = 2. The MRE phase images were processed using a 3D direct inversion of the Helmholtz wave equations using the curl of the measured wavefield to generate stiffness maps of the liver and tumors (i.e., elastograms) [12].

Image analysis and tumor stiffness measurement

We finally enrolled all the patients with histologic specimens obtained from surgical resection. In patients with multiple tumors, a target tumor with the largest cross-section was analyzed.

The MRE images were interpreted in consensus by a board-certified abdominal radiologist with 26 years of experience and one attending radiologist with 14 years of experience to assess image quality and the reliability of the tumor parameter measurements. The workstation with Func-Tool software (version AW 4.6, GE Healthcare) was used for post-processing. Tumor stiffness was measured independently by two radiologists with 14 or 5 years of experience in liver MRI who were blinded to all clinical and tumor pathology data. By using T2-weighted and contrast-enhanced images as references, regions of interest (ROIs) were manually drawn on the magnitude images as large as possible to include the solid tumor component on every slice while excluding tumor edges (where partial volume effects likely affected the calculated stiffness) [12, 15, 17], areas of significant wave interference, any other artifacts seen on the magnitude and phase images, and regions of liquefactive necrosis, and then the ROIs were copied to 3D MRE stiffness map. Three different ROI positioning methods were used for the measurement: (a) Single-ROI method: One single freehand ROI on the slice with the maximum tumor cross-section; (b) Three-ROI method: The first slice was chosen as the one with maximum tumor cross-section. The other two were adjacent slices above and below the selected slice; (c) Volumetric method: We imported the 3D MRE stiffness and magnitude images (DICOM) format into the ITK-SNAP software (version 3.8.0, Cognitica, Philadelphia, PA, USA) (<https://www.itksnap.org>) to manually draw the tumor boundary slice by slice, the software provided the 3D reconstruction and its volume averaged stiffness value.

The mean liver stiffness based on different methods in kilopascals (kPa) was recorded.

Pathology review

All the surgically resected hepatic specimens (79 patients with surgical resection, while 6 patients with transplantation) were used for the pathological evaluation. An experienced hepatopathologist (21 years of experience) blinded to all clinical data and MRI results reviewed the hematoxylin-and-eosin-stained slides for the histologic grade to the World Health Organization (WHO) classification system [18, 19]. The pathological differentiation grade was subcategorized: poorly differentiated HCC and well-or-moderately differentiated HCC. When various differentiations coexisted within a tumor, the most predominant differentiation of the tumor was used as the histologic grade (> 50%) [20].

Statistical analysis

The continuous variables were described by mean $\pm$ standard deviation (SD). The categorical variables were reported as a percentage. Intraclass correlation coefficient (ICC) was calculated to assess the inter- and intra-observer agreement. We used the Student's *t* test or Mann–Whitney *U* test to compare stiffness values based on different methods between the poorly differentiated HCC and well-or-moderately differentiated HCC groups. The data were tested for normality by the Kolmogorov–Smirnov test and the Shapiro–Wilk test. Receiver operating characteristics (ROC) curve analyses were performed to evaluate the diagnostic performance of each stiffness based on different methods in distinguishing the poorly differentiated HCC from the well-or-moderately differentiated HCC. The cut-off point was selected using the maximized values of Youden indexes, and the sensitivity and specificity at the threshold value for each parameter were determined. Z test was used to compare the area under ROC curves (AUC) in different ROI positioning methods.

Results

Patient characteristics

Eighty-five patients formed the study group. At histology, 64 (75%) had well-or-moderately differentiated HCCs and 21 had (25%) poorly differentiated HCCs. The clinicopathological characteristics of HCC patients are listed in Table 1. There were 20 (95%) male patients in the poorly differentiated HCCs and 59 (92%) male patients in the well-or-moderately differentiated HCCs. The mean age of all the enrolled patients was 49.45 ($\pm$ 12.41) years old. There was no significant difference in the clinicopathological characteristics between the poorly differentiated HCCs and well-or-moderately differentiated HCCs ($p > 0.05$).

Inter- and intra-observer reproducibility

The inter-observer agreements values for single-ROI method, three-ROI method, and volumetric method were 0.829, 0.832, and 0.967, respectively, while the intra-observer agreements values were 0.840, 0.845, 0.919 and 0.851, 0.867, and 0.926, respectively. The inter- and intra-observer ICC values were highest for stiffness measured based on the volumetric method. Detailed results are shown in Table 2.

Diagnostic performance of tumor stiffness for predicting HCC histologic grade based on different ROI methods

The median tumor stiffness values from different ROI methods for the poorly differentiated HCC, and well-or-moderately differentiated HCC groups are summarized in Table 3. The median stiffness values of the poorly differentiated HCC group were higher than the well-or-moderately differentiated HCC group based on volumetric and three-ROI methods (Fig. 2). The volumetric ROI method measured the highest stiffness values for both histologic grade groups ($p < 0.001$).

The receiver operating characteristic curves (ROC) for distinguishing the poorly differentiated HCCs from well-or-moderately differentiated HCC groups of the two readers are shown in Figs. 3 and 4. The highest area under the curve (AUC) value of 0.837, 0.812 of the two readers was obtained by using the volumetric method, followed by 0.713, 0.754 for three-ROI method and 0.624, 0.635 for the single-ROI method. The AUCs of volumetric and three-ROI methods were significantly higher than single-ROI method, however there was no difference between AUC of volumetric method and three-ROI method ($p > 0.005$). Table 4 shows the Diagnostic performance for three different measurements in discrimination of HCC pathological grades.

Discussion

We found that tumor stiffness derived from MRE is a useful method for assessing the histologic grade of HCC, however was affected by different ROI positioning methods. The mean value of stiffness based on the volumetric and three-ROI positioning methods of the poorly differentiated HCC group was significantly higher than that of the well-or-moderately differentiated HCC group. The diagnostic performance of the volumetric method was superior to the three-ROI methods with highest AUC in distinguishing different differentiated HCC groups in all three methods. As the pathological differentiation grade is one of the most important factors to predict the prognosis of HCC patients, the stiffness value derived from the volumetric method may have great clinical importance.

The choice of ROIs also influenced the inter- and intra-observer agreements. Both the inter- and intra-observer agreements showed excellent correlation for the volumetric method (inter-observer ICC 0.967, intra-observer ICC 0.919, 0.926, respectively). The volumetric method resulted in significantly better inter-observer agreement than the other two ROI methods. These results suggest that the MRE analysis with manual selection of the ROI for evaluation of HCC may lead to potential inter-observer variability [21] and that analyzing a larger number of pixels results in more reproducible values, which is similar to apparent diffusion coefficient (ADC) value measurement by using three-ROI methods in a previous study [22]. These findings suggest that volumetric measurements might be a better indicator of tumor heterogeneity and may therefore be more suitable for assessing tumor pathological differentiation grade, but the findings need to be confirmed in a larger study group in the future.

Previous studies on MRE stiffness in the evaluation of pathological differentiation produced conflicting conclusions. Wang J et al. [12] reported that tumor stiffness derived from 3D

MRE and whole tumor volumetric analysis was higher in poorly differentiated lesions than in moderately to well-differentiated lesions, which was consistent with our results. However, Thompson et al. [6] showed that well-or-moderately differentiated HCCs were stiffer than poorly differentiated HCCs using a 2D MRE technique and a single ROI-based method. Our results indicated that the stiffness value derived from the single-ROI method has no statistical significance between the two groups. The capability of stiffness obtained using the volumetric method was superior to the single and three-ROI methods in distinguishing the pathological HCC differentiations. The conflicting results of the previous two studies may be attributed to a different ROI method. A study from Rezvani Habibabadi R et al. [14] about the diagnostic performance of different ROI positioning methods in liver stiffness (LS), indicated that the volumetric method might improve the measurement accuracy of LS, it implies a mean value of tumor stiffness reported by the single-ROI method may fail to detect heterogeneity of HCC, our study echoes this point. Our conclusion is consistent with studies evaluating the effect of ROI methods on other quantitative imaging biomarkers, such as tumor ADC measurements or intravoxel incoherent motion diffusion-weighted imaging (IVIM) metrics for diagnosing HCC histologic grade [23], rectal cancers [22, 24], and thyroid nodules [25]. All the results indicated that the whole tumor volume method is superior to other ROI methods. In the present study, the volumetric method achieved the highest AUC values and Youden index for grading HCC, which may be attributed to intratumoral heterogeneity and reduced sampling error by volumetric imaging. Stiffness value derived from volumetric analysis is an assessable method for evaluating the histologic grade of HCC, it can guide surgical decision making and be a preoperative prognostic factors for postsurgical outcome. However, further multiple-center research is needed to validate these findings.

There were some limitations of our study. It was a retrospective single-center study. Further prospective and comprehensive studies with a larger sample size are needed for investigating the heterogeneity of HCC. The number of poorly differentiated HCCs in this study is smaller raising the question about reproducibility of the study results. Therefore, future studies with larger number are required to validate the conclusions of the study. Second, this is a single-center study with a single MR scanner utilized for the study and hence reproducibility across scanners was not evaluated. This also needs to be addressed in the future studies. Furthermore, most of our HCC patients were HBV-related, the conclusion of the study may not be generalizable to patients with other etiologies as well as population in Europe and Western countries where HBV infection is not the leading risk factor of HCC.

In conclusion, Different ROI positioning methods used significantly affect HCC stiffness measurements. Measurement of MRE stiffness value derived from volumetric analysis is superior to ROI-based methods for evaluating the histologic grade of HCC.

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Fig. 1.

Flowchart shows the patient selection process. *MRE* magnetic resonance elastography, *HCC* hepatocellular carcinoma, *OLT* Orthotopic Liver Transplantation

Fig. 2.

A surgically confirmed, well-or-moderately differentiated HCC, in a 35-year-old man. The 3D elastograms show that the tumor stiffness was 3.80 ± 1.58 kPa, 3.62 ± 1.67 Kpa, 3.46 ± 1.74 Kpa, respectively based on the volumetric method, three-ROI method and single-ROI method. **a** Axial, fat-suppressed, T2WI images of the liver show a slightly hyperintense focal liver lesion. **b** Axial, Magnitude: 32-Slice 3D EPI MRE, shows a freehand ROI drawn as large as possible contains the solid tumor. **c** Axial, RGB Stiffness color: 32-Slice 3D EPI MRE, stiffness colored shows a heterogeneous slightly stiffer focal liver lesion. **d** Axial, Stiffness (Gray Scale): 32-Slice 3D EPI MRE, shows the freehand ROI on which obtained the volumetric stiffness. **e** Coronal, fat-suppressed, T1WI contrast-enhanced images show the whole tumor. **f** Coronal, Magnitude: 32-Slice 3D EPI MRE, shows the volume of interest (VOI) was created by merging all ROIs nearly covering the whole tumor

Fig. 3. ROC curves of MRE stiffness measured by Reader 1 using three different kinds of ROI positioning methods. AUC value of stiffness with volumetric, three-ROI, and single-ROI method were 0.837, 0.713, and 0.624, respectively

Fig. 4.

ROC curves of MRE stiffness measured by Reader 2 using three different kinds of ROI positioning methods. AUC value of stiffness with volumetric, three-ROI, and single-ROI method were 0.812, 0.754, and 0.635, respectively

Table 1

The Characteristics of the study population (n = 85)

Characteristics	All patients (n = 85)	Poorly differentiated HCC (n = 21)	Well-or-moderately differentiated HCC (n = 64)	p value
Demographics				
Age, year	49.45 (± 12.41)	48.46 ± 8.34	50.06 ± 11.39	0.59
Sex (M/F)	78/7	20/1	59/5	0.83
BMI* (kg/m ²)	22(16–30)	22(16–26)	22(17–30)	0.32
Chronic liver disease				1
HBV	80(94%)	20	60	
HCV	3(4%)	1	2	
Alcoholic	2(2%)	0	2	
Child-Pugh				1
A	79 (93%)	19(91%)	60(94%)	
B	6(7%)	2(9%)	4(6%)	
Radiological characteristics				
Number of tumors				0.53
Single	53(62%)	17(81%)	36(56%)	
Multiple	32(37%)	4(19%)	28(44%)	
Tumor size, mm*	54(26–190)	48(30–190)	60(26–158)	0.59
Tumor volume, × 10 ³ mm ³ *	74.83 (8.20–3598.00)	57.30 (16.70–3598.00)	74.37 (8.20–1948.00)	0.71
Surgical treatment				1
Local tumor resection	54(64%)	15(71%)	39(61%)	
Hemihepatectomy	25(29%)	4(19%)	21(33%)	
OLT	6(7%)	2(10%)	4(6%)	

Unless otherwise indicated, data are the mean and standard deviation (SD) or numbers with percentages in parentheses *BMI*/body mass index, *HBV*/hepatitis B virus, *HCV*/hepatitis C virus, *OLT*/Orthotopic Liver Transplantation

* Presented as the median and range

Table 2

Intraclass correlation for inter- and intra- observer variability

	Stiffness values		Inter-observer ICC	95% CI	Intra-observer ICC Reader 1	95% CI	Intra-observer ICC Reader 2	95% CI
	Reader 1	Reader 2						
Single-ROI	4.98 ± 1.73	4.93 ± 1.68	0.829	0.736–0.943	0.840	0.678–0.930	0.851	0.756–0.939
Three-ROI	5.09 ± 1.75	5.07 ± 1.35	0.832	0.739–0.894	0.845	0.763–0.878	0.867	0.789–0.954
Volumetric	5.41 ± 1.92	5.27 ± 1.69	0.967	0.951–0.985	0.919	0.792–0.955	0.926	0.897–0.955

ICC, intraclass correlation coefficient, *MRE* magnetic resonance elastography, *CI* confidence interval

Table 3
The values of stiffness (Kpa) based on three methods of the two different differentiated HCC groups

Methods		Poorly differentiated HCC (<i>n</i> = 21)	Well-or-moderately differentiated HCC (<i>n</i> = 64)	<i>p</i> value
Reader 1	Single-ROI	5.42 ± 1.93	4.77 ± 1.58	0.089
	Three-ROI	6.14 ± 1.71	4.91 ± 1.56	0.004
	Volumetric	7.07 ± 1.57	5.00 ± 1.49	< 0.001
Reader 2	Single-ROI	5.53 ± 1.63	4.76 ± 1.56	0.064
	Three-ROI	5.94 ± 1.61	4.84 ± 1.54	< 0.001
	Volumetric	6.85 ± 1.49	4.94 ± 1.48	< 0.001

MRE Magnetic resonance elastography, *ROI* Region of interest

Diagnostic performance for three different measurements in discrimination of HCC pathological grades

Table 4

Reader	Measurement	AUC	95% CI	Cut-off value (%)	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)	Youden index
Reader 1	Single-ROI	0.624	0.513–0.727	4.78	71.43	57.81	61.1	35.7	86.0	0.2924
	Three-ROI	0.713	0.604–0.806	5.02	80.95	59.38	64.7	39.5	90.4	0.4033
	Volumetric	0.837	0.741–0.908	5.75	85.71	73.44	76.4	51.4	94	0.5915
Reader 2	Single-ROI	0.635	0.524–0.737	5.04	66.67	60.94	62.4	35.9	84.8	0.2760
	Three-ROI	0.754	0.685–0.798	5.19	76.19	64.06	65.8	40.0	88.9	0.4025
	Volumetric	0.812	0.697–0.878	5.68	71.43	75.69	74.1	48.4	84.8	0.5112

ROC Receiver operating characteristic curve, MRE Magnetic resonance elastography, AUC area under curve, PPV positive predictive value, NPV negative predictive value