



Quantitative Evaluation of the Relationship between Magnetic Resonance Elastic Value and Pathological Grade of Hepatocellular Carcinoma by Magnetic Resonance Elastography

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Abstract

Objectives: To try another non-invasive method to evaluate the relationship between Magnetic Resonance (MR) elastic value and pathological grade of Hepatocellular Carcinoma (HCC) using Magnetic Resonance Elastography (MRE).

Methods: Forty-seven HCC patients underwent MR Imaging (MRI), elastography in the upper abdomen. The elastic value of the lesion area was measured, and that of the normal liver tissue was measured adjacent to the lesion area at the same level. The Mann-Whitney U test was used to compare the difference in elasticity between the lesion area and normal area, and the difference between the low and middle-high differentiation groups. The Receiver Operating Characteristic Curve (ROC) of the lesion area and normal area in the complete case group and different differentiation groups were used to determine the diagnostic cut-off value to distinguish the lesion area from the normal area in each group.

Results: (1) There was a significant difference in elasticity between the normal area and HCC area ($p < 0.001$). The diagnostic cut-off value was 4842 Pa. (2) There was a significant difference in elasticity between the low-and middle-high differentiation groups ($p < 0.001$). The diagnostic cut-off value was 10456 Pa. (3) There was a statistically significant correlation between the elastic value on MRE and degree of pathological differentiation of HCC in the two groups ($p < 0.001$).

Conclusion: The elastic value of HCC measured using MRE can be used to evaluate the degree of pathological differentiation of HCC. MRE may be a non-invasive and reliable method for evaluating the pathological grade of HCC.

Keywords: Magnetic resonance elastography; Liver fibrosis; Hepatocellular carcinoma; Pathological grading

Abbreviations

HCC: Hepatocellular Carcinoma; MR: Magnetic Resonance; MRE: Magnetic Resonance Elastography; MRI: Magnetic Resonance Imaging; ROC: Receiver Operating Characteristic Curve

Introduction

Hepatocellular Carcinoma (HCC) is the fifth most common malignant tumor in the world, and its

fatality rate ranks third among malignant tumors [1]. The occurrence of HCC is closely related to liver cirrhosis. Surgery is one of its most effective treatments. The degree of pathological differentiation of HCC is an important factor in predicting recurrence and survival after surgery [2,3]. The World Health Organization (WHO) classification is commonly used in the pathological grading of HCC, which divides HCC into high, middle, and low differentiation [4]. Puncture biopsy of the tumor tissue is considered the gold standard for the diagnosis of pathological grade. However, this method has several shortcomings. First, if the examination is invasive, the patient is at risk of complications. Second, due to the heterogeneity of malignant tumors, there is a risk of inaccurate sampling. Third, different pathologists may have different diagnoses.

Magnetic Resonance Elastography (MRE) is a safe, non-invasive, and repeatable examination method that can avoid these risks. MRE can quantitatively evaluate the relationship between liver elasticity and the degree of liver cirrhosis. There have been many reports of related research. However, the literature on the quantitative evaluation of pathological differentiation of HCC using MRE has not been reported.

The purpose of this study was to quantitatively evaluate the correlation between MR elasticity of the liver and pathological grade of HCC using MRE, and to provide a new method for clinical non-invasive diagnosis of pathological grade of HCC.

Materials and Methods

Participants

This study was a prospective study approved by the institutional review board. All patients or their next of kin signed a consent form before the MRE examination. From May 2019 to November 2020, 50 patients with primary malignant tumors of the liver were diagnosed using MRI, including 47 patients with pathologically confirmed primary HCC (excluding two cases of cholangiocarcinoma and one case of neuroendocrine tumor). There were 38 men and nine women. The average of participants was 54.55 ± 12.23 years (range, 29 to 80 years; median, 55 years). Case inclusion criteria were as follows: (1) newly diagnosed HCC patients were confirmed by pathology and pathological differentiation grade, including 13 cases of poor differentiation, 32 cases of moderate differentiation, and two cases of high differentiation; and (2) MRE examination of satisfactory quality for assessment. The exclusion criteria were patients in whom the MRE image quality was unsatisfactory and in whom the elastic value could not be accurately measured.

MRI Protocol

All patients underwent conventional and enhanced MR scans of the upper abdomen. A GE 3.0-T Discovery 750-W superconducting MR imaging system with an exogenous elastic drive system (resonant acoustic wave generator) was used. The body coils were a 16-channel phased-array. The scanning sequences included plain axial T1-Weighted Imaging (T1WI), T2-Weighted Imaging (T2WI), Diffusion-Weighted Imaging (DWI), MRE, and coronal T1WI, T2WI, three-phase dynamic enhanced T1WI, and coronal T1WI enhanced scans. The scan parameters of each phase of the enhanced scan were the same as those of the plain T1WI scan. All patients were trained to hold their breath before scanning and hold their breath for 16 s after exhaling. The scan was performed during breath-holding after exhaling. The scanning parameters were as follows:

- (T1WI) Liver Acquisition with Volume Acceleration

(LAVA), Repetition Time (TR), 4.6 ms; echo time (TE), 1.6 ms, fractional anisotropy, 15°; slice thickness, 4 mm; layer spacing, 2 mm; and matrix, 288×208

- (T2WI) turbo spin echo (TSE); TR, 8000-9000 ms; TE, 98.4 ms; layer thickness, 5 mm; layer spacing, 1 mm; and matrix 320×320
- (DWI) TR, 9000-13000 ms; TE, 62.6 ms; layer thickness, 5 mm; layer spacing, 1 mm; and matrix, 128×128 .
- (MRE) 2D SE EPI sequence; TR, 1000 ms; TE, Min Full; NEX, 1; phase time difference, 4; slice thickness, 5 mm; layer spacing, 1 mm; matrix, 64×64 ; and vibration frequency, 60 Hz.

Image process

Image analysis was performed using the workstation FUNCTOOL of GEAW version 4.6. The lesions were observed using the fusion of the elastogram and original image. A Region of Interest (ROI) was placed on the larger layer of the lesion on the elastic image, which included the whole lesion. Three consecutive adjacent layers were selected to measure the elastic value, and the average value was recorded. The ROI was then placed adjacent to the lesioned area at the same level to measure the elastic value. The ROI was placed to avoid the large blood vessels of the liver as much as possible. The elasticity value is represented by different colors, with red indicating the highest elasticity value, followed by yellow, green, and blue in decreasing value (Figure 1).

Statistical analysis

All analyses were performed using R software (version 4.0.2) (R Development Core Team, 2015, R Foundation for Statistical Computing, Vienna, Austria). The Mann-Whitney U test was used to compare the difference in elasticity between the lesion area and normal area, as well as the difference between the low and middle-high differentiation groups. The Receiver Operating Characteristic (ROC) curve of the elastic value of the lesion area and normal area of the complete case group was drawn, the Area under the Curve (AUC) was calculated, and the diagnostic cut-off value to differentiate the lesion area from the normal area was calculated. The same process was repeated to determine the diagnostic cut-off value to differentiate between the low and middle-high differentiation groups. The Mann-Whitney U test was used for univariate analysis of the relationship between elasticity and age, sex, and tumor differentiation grade. Logistic linear regression analysis was used for the multivariate analysis of the relationship between elasticity and tumor differentiation grade. Statistical significance was set at $p < 0.05$.

Results

Comparison of elastic value between the lesion area and normal area in all cases

In 47 patients, elastic values were measured in 47 corresponding lesion areas and 47 normal areas at the same level. The difference between the two groups was statistically significant ($p < 0.001$). The statistical results are shown in Table 1.

The ROC curve of the elastic value of the tumor area and normal area in all cases is shown in Figure 2.

Figure 2 shows that the critical cut-off elasticity for distinguishing between lesion and normal areas was 4842 Pa. According to this standard, the area under the curve AUC was 96.00%, sensitivity was 97.87%, and specificity was 95.74%. The accuracy of the prediction was 96.00%; 97.87% of elasticity values in lesion areas were greater

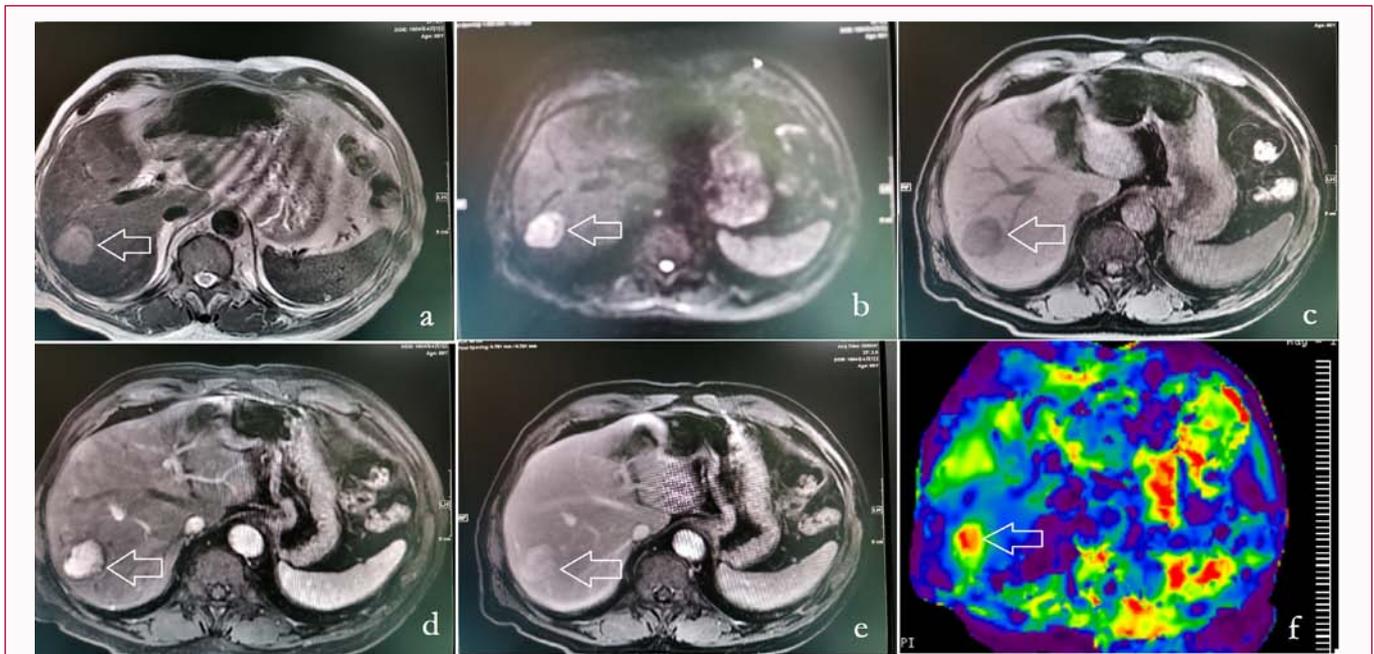


Figure 1: A 66-year-old male with highly differentiated HCC (Arrows). a, b) A 3.6 cm x 3.0-cm mass in S6/7 with high signal intensity on T2WI and DWI. c) Mass shows a low signal intensity on T1WI. d) The mass shows arterial phase hyper enhancement. e) The mass shows washout on the portal venous phase, confirming the radiologic diagnosis of HCC. f) MR Elastogram color map. The stiffness of the HCC stiffness is higher, as indicated by the increased red color in the lesion area. g) Wave propagation in a similar image slice.

Table 1: Comparison of the mean elastic value between the tumor area and normal area.

| | Lesion area (n=47) | Normal area (n=47) | p-value |
|--------------------|--------------------|--------------------|---------|
| Elastic value (Pa) | 9757 ± 4164 | 3862 ± 3256 | <0.001 |

Table 2: Comparison of the mean elastic value of groups with different degrees of differentiation in tumor areas.

| | Low differentiation (n=13) | Middle-high differentiation (n=34) | p-value |
|--------------------|----------------------------|------------------------------------|---------|
| Elastic value (Pa) | 13494 ± 4473 | 8329 ± 3048 | <0.001 |

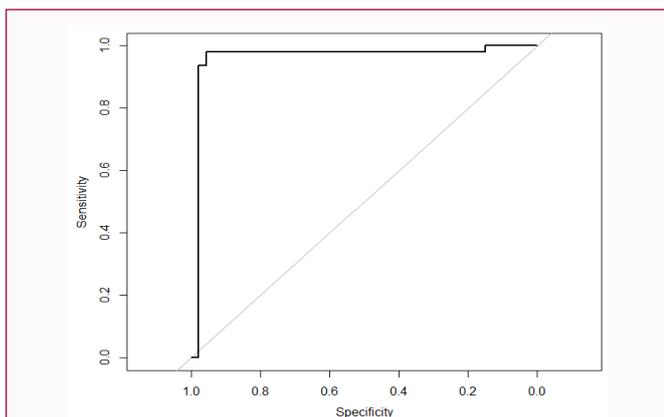


Figure 2: The ROC curve for elastic value to distinguish between the tumor area and normal area in all participants.

than this threshold, and 95.74% of elasticity values in normal areas were less than this threshold.

Comparison of elastic value among groups in the tumor area

Forty-seven patients with HCC were divided into three groups according to the degree of pathological differentiation. There were

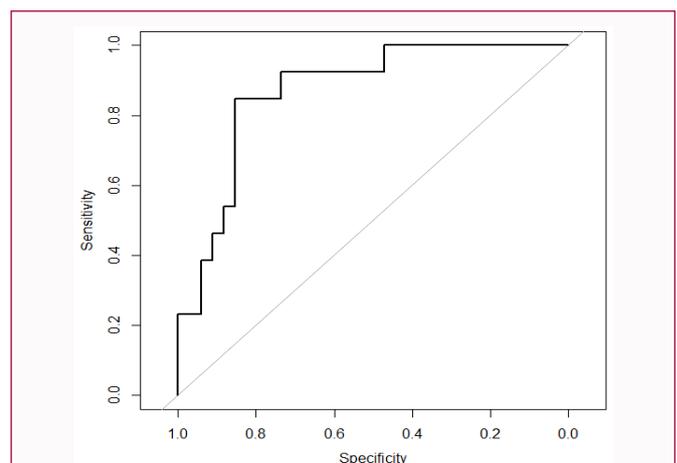


Figure 3: The ROC curve for elastic value to distinguish between the low differentiation group and middle-high differentiation group.

13 cases in the low differentiation group, 32 cases in the middle differentiation group, and two cases in the high differentiation group. Because of the low number of cases in the high differentiation group, they were merged with the middle differentiation group for statistical analysis. The results showed that there was a significant difference in elasticity between the low and the middle-high differentiation groups ($p < 0.001$). The statistical results are shown in Table 2.

The ROC curve of the elasticity of the low and middle-high differentiation groups is shown in Figure 3.

Figure 3 shows that the critical cut-off elasticity for distinguishing between the low differentiation group and middle-high differentiation group is 10456 Pa. According to this standard, the area under the curve AUC is 86.90%, sensitivity is 84.62%, and specificity is 85.29%. The accuracy of prediction is 86.90%; 84.62% of elasticity values in the

low differentiation group were greater than this threshold and 85.29% of elasticity values in the middle-high differentiation group were less than this threshold.

Relationship between the elasticity of MRE and degree of tumor differentiation

Univariate analysis showed that there was no significant correlation between patient age and elasticity ($p=0.297$). There was no positive or negative correlation between them. In addition, there was no significant difference in the median elasticity of the tumor area between men and women ($p=0.199$). Include the degree of differentiation into linear regression model, the Mann-Whitney U test showed that the elastic value of the low differentiation area was greater than that of the middle-high differentiation area, and the difference was statistically significant ($p<0.001$).

The degree of differentiation was included in the linear regression model with the low differentiation group defined as N1 and the middle-high differentiation group defined as N2. The results showed that the difference was statistically significant ($p<0.001$). Compared with the low differentiation degree, the elastic value of the lesion area in the middle-high differentiation group was 5164 Pa lower.

Discussion

MRE is a phase contrast MR multi-phase cinematography technique that can qualitatively or quantitatively evaluate the mechanical properties of tissue, such as elasticity. Many diseases can cause changes in the mechanical properties (hardness) of human tissues. Liver fibrosis, liver cirrhosis, and malignant tumors can increase the hardness of the liver parenchyma and make it exceed that of normal liver parenchyma to varying degrees. The application of MRE in chronic hepatitis, liver fibrosis, liver cirrhosis, and other diseases has been reported in many studies [5-7] and its value has been fully affirmed. There are few reports on the application of MRE in the study of HCC, and its application value remains to be validated by further research. He et al. [8] reported that the elasticity of malignant liver tumors was significantly higher than that of benign tumors ($p<0.001$). Their results showed that the diagnostic threshold of elasticity for benign and malignant liver tumors was 5.08 kPa. Our results showed that there was a significant difference in elasticity between normal liver tissue and HCC ($p<0.001$), with a critical elasticity to distinguish between the lesion and normal areas of 4.842 kPa. The results of the two studies were very similar.

The pathological grade of HCC is an important risk factor for the treatment of HCC [9]. Clinically, liver biopsy is often used to diagnose the pathological HCC grade. However, this method has several limitations. First, this method is invasive and poorly repeatable. Second, the patients are at risk of complications, and the heterogeneity within the malignant tumor leads to the variability of tissues at different puncture sites. Third, different pathologists may have different diagnoses. However, the method used in this study was a non-invasive examination with great repeatability. The comparison of the elastic value between the normal area and tumor area showed an accuracy of 96.00%, sensitivity of 97.87%, and specificity of 95.74%, all of which were very close to the pathological results. In the comparison of the elastic values between low and middle-high differentiation groups, the accuracy, sensitivity, and specificity were 86.90%, 84.62%, and 85.29%, respectively. The diagnostic efficiency is higher than that of the imaging examination method reported in the literature [10].

To the best of our knowledge, the quantitative evaluation of pathological differentiation of HCC using MRE has not been reported. Routine MR Scans also have value in the evaluation of pathological differentiation grade of HCC according to morphological manifestations such as size, edge, internal density, necrosis, and bleeding. The contrast agent in three-phase enhanced MRI scans has the characteristic manifestation of 'fast in and fast out' in HCC, which correlates with the degree of pathological differentiation of the tumor. Highly differentiated HCC may present with 'biphasic enhancement'; because the portal vein system in the tumor tissue has not been completely destroyed, the tumor is still supplied by both the hepatic artery and portal vein. However, most poorly differentiated HCC are 'fast in and fast out' because the portal vein system in the tumor is completely destroyed and only the hepatic artery supplies the tumor. MRI DWI sequences have been widely used in the diagnosis of and research on HCC. It has been reported that DWI has an advantage in the detection and characterization of HCC when the b value is 800-1000 s/mm^2 [11]. Studies have shown that the average ADC value of poorly differentiated HCC decreases significantly, while that of highly and moderately differentiated HCC overlaps [11,12]. The average ADC value is thought to not accurately reflect the degree of differentiation of the tumor because malignant tumors have obvious heterogeneity, and internal bleeding, necrosis, and other factors that will also affect the ADC value.

In conclusion, a multimodal MR technique is helpful for evaluating the pathological grade of HCC. However, factors affecting the quality of MR imaging are complicated, and there is currently no standard scanning approach. The diagnosis depends on the subjective judgment of the imaging doctors with no quantitative evaluation parameters. This study suggests quantitative indicators for evaluation, which can avoid the aforementioned shortcomings.

Ultrasound diagnosis technology has also been widely used in the diagnosis of liver fibrosis, including real-time tissue elastography, instantaneous elastography, and single point shear wave velocity measurement elastography. Among them, ultrasonic instantaneous elastography is currently the most widely used [13-15]. However, ultrasonic diagnosis has its own inherent shortcomings, such as operator dependence and difficulty in measuring obese patients or patients with ascites. It has been reported that MRE is superior to ultrasound elastography in terms of diagnostic accuracy and measurement of failure rate in evaluating the degree of liver cirrhosis [16-19]. Hyo et al. [20] reported that the liver cirrhosis grade assessed using MRE was an independent predictor of early recurrence in patients with HCC after complete remission according to the Milan criteria. The study by Aliya et al. [21] showed that early changes in tumor hardness as evaluated using MRE may be a response index for immunotherapy in patients with advanced liver cancer. Our study also suggests that using MRE to measure the elasticity of the normal area of the liver and HCC can effectively distinguish benign and malignant tumors of the liver and evaluate the pathological grade of HCC.

This study had some limitations. First, it was only a preliminary study, and the number of cases was relatively small. In particular, there are only two cases in the highly differentiated group which had to be incorporated into the moderately differentiated group for analysis; therefore, the grouping is not sufficiently detailed enough. Second, there is no unified standard for the scanning parameters and methods of MRE. Therefore, the effectiveness of using MRE to quantitatively

evaluate the pathological grading of HCC needs to be validated in a large number of patients, in a long-term, multi-centre study.

In conclusion, the elastic value of HCC as measured using MRE correlates well with the pathological differentiation of HCC. MRE may become another reliable, non-invasive, and reproducible method to evaluate the pathological grade of HCC and provide new pathways for the precise diagnosis and treatment of HCC.

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