Tumor Stiffness Measurements of Single Nodular Hepatocellular Carcinomas on MR Elastography for Predicting Survival

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이 논문을 석사 학위논문으로 제출함

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박세진의 석사 학위논문을 인준함

2019 년 1 월

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ABSTRACT

Tumor Stiffness Measurements of

Single Nodular Hepatocellular

Carcinomas on MR Elastography

for Predicting Survival

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Objective: To determine whether tumor stiffness (TS) or liver stiffness (LS) obtained using MR elastography (MRE) is associated with overall survival or recurrence-free survival (RFS) in patients with single nodular HCCs after curative intention treatments.

Materials and Methods: A total of 167 patients who underwent MRE prior to hepatic resection (HR) or radiofrequency ablation (RFA) between July 2011 and February 2014 were retrospectively enrolled. MRE images were acquired using the 3D echo-planar imaging technique on 1.5T MRI at a vibration frequency of 60 Hz. TS and LS values were measured on elastograms. Overall survival/RFS analyses were performed using Kaplan-Meier analyses and Cox multivariate models.

Results: In the patients with underwent HR, TS was demonstrated to significantly correlate with the % of tumor necrosis on histopathology

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and the tumor grade. The mean TS value of poorly－differentiated HCCs was significantly lower than in well－ or moderately－ differentiated HCCs. In the HR group, LS was the only significant prognostic factor of overall survival while tumor size and TS were significant prognostic factors of RFS. In the RFA group, there were no predictive factors related to overall survival but rim enhancement, peritumoral enhancement and TS were shown to be significant factors of RFS.

Conclusions: TS was demonstrated to significantly correlate with the % of tumor necrosis and tumor grade, and to be a significant predictive factor of RFS along with tumor size after both RFA and HR.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third leading cause of cancer-related deaths worldwide [1]. For the management of HCCs, surgical resection has traditionally been considered the most reliable option, but radiofrequency ablation (RFA) has recently emerged as a promising alternative treatment option for the cirrhotic liver and for single HCCs smaller than 3 cm in diameter, demonstrating favorable overall survival (OS) outcomes [2-4]. Yet, despite the proven capabilities of both hepatic resection (HR) and RFA for the eradication or complete ablation of small HCCs, HCC recurrence after treatment is still common, contributing to lower survival rates [5]. Thus, many investigators have sought to identify factors able to predict OS or RFS after curative loco-regional treatment including high serum AFP levels, tumor differentiation, advanced Child-Pugh class, and presence of portal hypertension [4, 6-8]. However, at present, pre-treatment predictive factors of tumor recurrence after curative loco-regional therapies for HCC are not yet established.

Magnetic resonance elastography (MRE) is a phase contrast-based MRI technique for the quantitative measurement of the propagation of mechanical shear waves in human tissue [9]. The diagnostic potential of MRE derives from the fact that normal and diseased tissue often differ significantly in terms of their intrinsic mechanical properties such as tissue stiffness [9-11]. Previous investigators have thus attempted to determine whether tumor stiffness (TS) and liver stiffness (LS) measured using MRE can be utilized as a prognostic factor of hepatocellular carcinoma, [12, 13] and found that TS may be associated with necrosis [12] or other mechanical properties such as cellularity, extracellular matrix, or the interstitial pressure change of the tumor's internal components which may help predict the response to treatment [12, 14, 15]. Furthermore, other studies have shown that TS values were associated with characteristics such as gene mutation or tumor grade, and suggested that this noninvasive measurement may be utilized as an imaging biomarker for the prediction of prognosis [16, 17]. Yet, despite all of the research surrounding this issue, it is still not known whether TS values measured at MRE have any correlation with the recurrence of tumors or survival in patients with HCCs.

Therefore, the purpose of this study is to determine whether stiffness values of the tumor or liver measured with MRE are related to overall survival or recurrence-free survival of patients with HCCs after curative loco-regional treatment.

MATERIALS AND METHODS

This study was approved by the institutional review board (IRB No. 1803-063-929) of our institution, with a waiver of the requirement for informed consent. The images used in this study were generated for clinical purposes using the routine protocol of our hospital.

Patient selection

A search of the database maintained by the Department of Radiology of our institute between July 2011 and February 2014 revealed 225 consecutive patients who underwent liver MR including MRE prior to treatment of HCCs. The inclusion criteria were: 1) a single nodular HCC which was diagnosed with LI-RADS LR-5 criteria, 2) RFA or HR within three months after MRE, 3) no previous treatment history for HCC prior to MRE, and 4) technically successful MRE acquisition with the possibility of TS measurement. Among the 225 patients, 58 patients were excluded from this study for the following reasons: technical failure of MRE (n=4); patients' tumor stiffness was not measurable (n=15); patients underwent other

treatment (n=14); or patients had multiple HCCs (n=25). Finally, a total of 167 patients (in HR group, n=95; in RFA group, n=72) comprised our study population (Fig. 1).

MRE technique

All examinations including MRE were obtained at 1.5-T (Signa Hdx; GE Healthcare, Milwaukee, WI, USA) using an 8-channel torso phased-array coil. The protocol of the spin-echo echo-planar imaging (SE-EPI) MRE used in this study has been described in previous studies [18]. In brief, imaging was obtained in the supine position with an acoustic pressure-activated passive driver placed on the body wall adjacent to the liver. The cylindrical passive driver transmitted 60 Hz vibrations generated by the active acoustic generator into the right lobe of the liver, which were synchronized with the imaging sequence. Thereafter, MRE magnitude and phase images were processed using the 3D direct inversion algorithm for SE-EPI MRE to generate quantitative images of tissue stiffness [19].

For 3D EPI MRE, the EPI sequence was performed to capture shear waves along the x-, y-, and z-directions for a single phase offset. Data acquisition was performed during one breath-hold and then repeated at the three different phase offsets. The acquisition parameters were as follows: 32 axial slices to cover most of the liver, 3.5 mm thickness; TR, 1283.7 ms; TE, 51.3 ms; FA, 90 degrees; matrix, 96× 96; FOV, 430 × 430 mm; bandwidth ±250 kHz.

Tissue stiffness measurements at MRE

To measure TS values, regions of interest (ROIs) were drawn freehand around the focal lesion on magnitude images and copied to stiffness maps by an independent observers (observer 1; observer 2; with four and four years of experience in liver MR, respectively) [16, 20, 21] (Fig. 2). To assess intra-observer variability, observer 1, repeated the TS measurement after a two-week interval. In large tumors, measurements were made on the sections containing the most tumor sites. To measure liver stiffness values, four central slices among 32 EPI MRE slices were selected using visual anatomical landmarks, with the ROIs drawn freehand in the right lobe of

the liver to include as large an area as possible while taking care to avoid fissures and

large hepatic vessels [22]. Mean LS values were obtained as the average of all single

pixel stiffness data in kilopascals (kPa).

Tumor characteristics in MRI findings

The imaging findings, previously known as the prognostic factor of HCC such as rim

enhancement, peritumoral enhancement, intratumoral fat and T1 hyperintensity, were

analyzed [4, 30, 40, 41].

A total of four findings were analyzed and inter-observer variability was also obtained

as in these findings. At this time, consensus reading was performed when there were

discrepancies between independent observers.

RFA and HR procedures and follow-up after treatment

All patients who underwent RFA for treatment of HCC had undergone MR imaging

prior to RFA. RFA procedures were done percutaneously under real-time ultrasound

guidance using moderate sedation (fentanyl citrate [Hana Pharm, Seoul, South Korea],

midazolam [Hana Pharm], and ketamine [Huons; Hwaseong, Kyunggi, South Korea]) by one of four radiologists with 11-20 years of clinical experience in RFA. Hepatic resections were carried out under general anesthesia by one of three experienced surgeons with 14-25 years of clinical experience in the hepatobiliary system. Decisions regarding the type and extent of resection were made using the location of the tumor, underlying liver function of the patients, and their medical condition. Patients were instructed to stay in the hospital until their hepatic function reached normal levels and their complications had disappeared. Complications associated with treatment and duration of their hospital stay were recorded.

One-month follow-up examination after RFA or surgical resection included contrast-enhanced dynamic CT or MRI and laboratory tests such as the liver function test and serum alpha-fetoprotein (AFP) levels to assess the effectiveness of the procedure. In cases where no residual tumor was observed, imaging studies and biochemical tests were followed-up every three months in the first year and every three to six months in the second year. If tumor recurrence did not occur, their follow-up schedules were maintained at the same frequency as that of the surveillance program for cirrhosis [23]

Histopathologic examinations

One experienced pathologist (13 years of experience in liver pathology) assessed tumor characteristics including tumor differentiation, % of necrosis, and vascular invasion from the resected pathology specimens. Tumor differentiation was graded according to a modified version of the Edmonson-Steiner classification [24]: G1–G2, well-differentiated (WD); G3: moderately-differentiated (MD), and G4: poorly-differentiated (PD).

Statistical analysis

Continuous variables were compared using the independent sample T-test for univariate analysis. Spearman correlation coefficient analysis was conducted to determine the correlation TS values according to % of tumor necrosis and tumor size. And to compare TS values and % of tumor necrosis according to tumor grade, one way ANOVA analyses were performed. Inter-observer and intra-observer reproducibility were assessed by using the intraclass correlation coefficient (ICC). A

value less than 0.5, 0.5 to 0.75, 0.75 to 0.9 and a value greater than 0.90 indicates

poor, moderate, good and excellent reliability, respectively [25]. Overall survival,

defined as the interval between treatment and death or the last date of the follow-up

visit, was estimated using the Kaplan-Meier method in both the RFA and HR treated

groups. To determine predictive factors of overall survival after treatment, univariate

and multivariate analyses were performed. For univariate analyses, the prognostic

factors which were conducted in previous studies were selected [26-30]. Additionally,

TS and LS value were selected and for histopathology analysis such as tumor grade,

tumor necrosis and vascular invasion were also inserted. Recurrence-free survival,

defined as the interval between treatment and the recurrence date on follow-up CT,

was also estimated using the Kaplan-Meier method. The predictive factors for

recurrence were selected in previous studies including histopathology analysis [29-

33]. After a univariate Cox proportional hazards model was applied to each variable,

all variables determined to be significant affecting factors of recurrence with a P value

less than 0.05 at univariate analysis were used as input variables for multivariate

logistic regression analysis to reassess their value as independent predictors of

recurrence. All statistical analyses were performed using commercially available

software (MedCalc version 18.2.1, MedCalc software, Mariakerke, Belgium) with P-values less than 0.05 considered indicating a statistically significant difference.

RESULTS

Baseline characteristics of the study population

Demographics of the study population are shown in Table 1. Mean ± SD tumor size was 3.50 ± 2.8 cm, and average focal tumor stiffness was 2.31 ± 0.8 kPa. TS values ranged between 0.78 to 4.97 kPa, and the median value was 2.26 kPa. Stiffness values of the liver parenchyma ranged from 0.78 to 6.62 kPa with a mean ± SD of 2.85 ± 1.00 kPa. When we divided the patients according to their treatment method, there were no differences in sex, TS values, and age between the two groups. However, tumor size was significantly smaller in the RFA group (mean ± SD of 1.87 ± 0.58 cm) than in the HR group (4.73 ± 3.17 cm) (p-value <0.001). Liver stiffness was also significantly different between the two groups; 3.24 ± 1.04 kPa in the RFA group vs. 2.56 ± 0.86 kPa in the HR group (p-value <0.001).

Inter-observer and intra-observer reproducibility

The intraclass correlation coefficient for inter-observer reproducibility was 0.758 and for intra-observer reproducibility was 0.960 for the observer 1. These values

demonstrate good for inter-observer and excellent for intra-observer reproducibility. These findings also were shown in the interobserver reproducibility about MRI findings (in rim enhancement: 0.900, in peritumoral enhancement: 0.832, in intratumoral fat: 0.911, and in T1 hyperintensity: 0.927).

Histopathologic findings of 95 HCCs after hepatic resection

In the HR group, there were 28 WD-, 33 MD- and 34 PD-HCCs. In the WD/MD-HCC subgroup, mean ± SD tumor size was 4.69 ± 3.31 cm, and the % of tumor necrosis ranged from 0% to 40% with a mean ± SD of 4.11 ± 8.53%. LS was 2.59 ± 0.91 kPa and vascular invasion in pathology was 26.2 % (16/61). In the PD-HCC subgroup, mean ± SD tumor size was 4.68 ± 2.94 cm, and the % of tumor necrosis ranged from 0% to 80% with a mean ± SD of 14.18 ± 19.44 %. LS was 2.50 ± 0.78 kPa and vascular invasion in pathology was 64.7% (22/34). Detailed characteristics according to tumor grade are shown in Table 2.

Tumor stiffness in the hepatic resection group, and its correlation with histopathology

The mean ± SD TS value was 2.59 ± 0.77 kPa (range, 1.3 – 4.97 kpa; median value, 2.39 kPa) in the WD/MD-HCC subgroup. In the PD-HCC subgroup, the mean ± SD TS value was 1.86 ± 0.57 kPa (range, 0.86-3.05 kpa; median value, 1.86 kPa). TS values significant decreased along with tumor grade (WD, 2.71 kPa; MD, 2.49 kPa; PD, 1.86 kPa, respectively) (p-value <0.001) (Fig. 3), while tumor necrosis showed significant increase in WD/MD-HCCs compared to PD-HCCs (p-value, 0.002) (Fig. 4). There was a significant correlation in TS values according to the % of tumor necrosis (p-value, 0.04; correlation coefficience, -0.2116) (Fig. 5). And there was a correlation in TS value according to the tumor size (p-value, 0.023; correlation coefficience, 0.2335) (Fig. 6).

Overall survival outcome

Seventeen patients (17/95, 17.9%) died in the HR group and nine patient (9/72, 12.5 %) died during the follow-up period in the RFA group. The estimated 1-, 3- and

5- year overall survival rates for the HR and RFA groups were 95.7%, 86.9%, and

80.8%, and 100%, 94.4%, and 86.5%, respectively. LS values measured at MRE were

demonstrated to be a significant predictive factors of overall survival in the HR group

(p-value, 0.0269). No significant affecting factors were observed in the RFA group

(Table 3).

Recurrence outcomes

Thirty-eight patients (38/95, 40%) developed recurrence during the study period in

the HR group, and forty-three patients (43/72, 59.7%) developed recurrence in the

RFA group. There was a significant difference in RFS between the two groups (p-

value, 0.047). The corresponding RFS rates for the 2 groups were 71%, 63.1%, and

58.5% after HR and 72.3%, 44.8%, and 37.9% after RFA. Prognostic factors affecting

recurrence-free survival after treatment for HCC are summarized in Table 4. In the

HR group, rim enhancement, peritumoral enhancement, AFP level, % of tumor

necrosis, tumor size, TS values, and vascular invasion in pathology were significant

affecting factors at univariate analysis (p-value, 0.0005; 0.0156; 0.0154; 0.0135;

0.0037; 0.0262; 0.0005, respectively). On subsequent multivariate analysis, tumor size and TS values were shown to be significant factors (p-value, 0.0202; 0.0084, respectively). In the RFA group, rim enhancement, peritumoral enhancement, albumin level, gender, tumor size, and TS values were shown to be significant predictive factors on univariate analysis (p-value, 0.0176; 0.0012; 0.0399; 0.0126; 0.0056; 0.0003, respectively), whereas rim enhancement, peritumoral enhancement and TS values were demonstrated to be significant factors according to multivariate analysis (p-value, 0.039; 0.009; 0.006, respectively).

DISCUSSION

Our study demonstrated that TS values were significantly correlated with the % of tumor necrosis on histopathologic examinations and that the mean TS value of PD-HCCs was substantially lower than that of WD- or MD-HCCs. In addition, TS values measured using MRE was shown to be a significant affecting factor for RFS after both HR and RFA for single nodular HCCs. Our study results are in good agreement with the results of a previous study in which the stiffness of PD-HCCs was reported to be lower than that of WD- or MD-HCCs [16]. Although the exact reason for this finding has not yet been clarified, several studies have suggested the low stiffness of necrosis in the tumor as a potential reason [12, 14]. Previous research also has suggested that lower stiffness values of PD-HCCs were related to the more progressive extent of necrosis in PD–HCCs than in WD- or MD-HCCs [16]. Furthermore, we also found in the HR group that higher grade tumors demonstrated higher progression of % necrosis, which also contributed to lower TS values. Considering that tumor grades is a well-known prognostic marker after curative locoregional treatments of HCC, we may suggest that noninvasive measurement of

TS using MRE may be utilized as an imaging biomarker for the prediction of prognosis.

Many previous studies have already explored the diagnostic value of LS values obtained from MRE for the assessment of diffuse liver diseases [11, 13, 20, 34], while others have evaluated the degree of hepatic fibrosis through the analysis of LS or how it may affect the prognosis of patients with chronic liver diseases [13, 35, 36]. However, until now, only a limited number of studies have dealt with MRE for the evaluation of focal liver lesions [16, 20, 37]. As small-sized tumors < 2 cm cannot be accurately measured by two-dimensional gradient-echo MRE with a slice thickness of 1 cm, conducting a study for these lesions may have proven quite difficult. In our study, however, we used the SE-EPI sequence with 3D reconstruction for the evaluation of the liver parenchyma and HCCs. This technique was able to provide better spatial resolution and higher signal-to-noise ratios compared with 2D-GRE-based MRE techniques [38], allowing evaluation of tissue stiffness of focal liver lesions in our study. Furthermore, SE-EPI MRE using a shorter echo time may help overcome the signal loss from susceptibility in all but the most severely iron-

overloaded patients, which would not generally have been possible with 2D GRE-MRE techniques [39].

In terms of overall survival, the estimated 1-, 3- and 5- year overall survival rates for the HR and RFA groups were similar: 95.7%, 86.9%, and 80.8% in the HR group and 100%, 94.4%, and 86.5% in the RFA group, respectively. In the HR group, LS value was demonstrated to be a significant predictors of OS. Predicting effect of LS on OS is in good accordance with the results of a previous study which reported that LS values can predict the development of liver failure after post-hepatectomy [13]. RFS, on the other hand, was shown to be significantly different between the two groups: 71%, 63.1%, and 58.5% for the HR group and 72.3%, 44.8%, and 37.9% for the RFA group, respectively. In the HR group, tumor size and TS values were shown to be significant factors of RFS, while in the RFA group, rim enhancement, peritumoral enhancement and TS values were revealed to be significant factors of RFS. Rim enhancement, peritumoral enhancement and tumor size have already been well-known recurrence factors after curative treatment of HCCs [4, 30, 40, 41]. However, our study revealed for the first time that TS values obtained from MRE may also be able to predict recurrence.

Specifically, we found that lower TS values in HCCs prior to treatment resulted in a significant association with tumor recurrence in our study. Our study results are in good agreement with a previous experimental study on elastography which explored the relationship between TS of resected tumors and recurrence and metastasis in mice with breast tumors [42]. In their study, it was shown that tumors with higher compliance promoted invasion, vascular intravasation, and extravasation of malignant cells more frequently than relatively stiff tumors, ultimately resulting in local recurrence and distant metastasis. Furthermore, other previous studies have also suggested that in the soft environment of tumor cells including HCC cells, the properties of tumor-initiating cells become more proliferative, resulting in higher local recurrence and metastasis [43-45], which also support our findings. One recent study, however, reported opposite results, suggesting that a higher TS value in HCC prior to treatment would result in a significant association with tumor recurrence [37]. However, the previous study had a small study population (n=14) and underwent non-surgical combined loco-regional treatment such as transarterial chemoembolization (TACE) and RFA. Nonetheless, considering that many factors constitute tumor stiffness including cellularity, increased vessel density, and interstitial fluid pressure

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[46, 47], and that HCCs have heterogeneous biological behavior, histopathology and pathogenesis [48], further studies are warranted to more confirmatively determine the relationship between tumor stiffness and tumor recurrence.

There are several limitations in this study that should be mentioned. First, the measurement of TS values was sometimes challenging in small tumors < 2 cm which showed poor contrast on magnitude images. However, we performed ROI measurements with great care using the copy and paste function on the PACS program after drawing ROIs on conventional MR images which have the most excellent contrast. Furthermore, ICC values showed good inter-observer reproducibility for small tumors ranging in size from 1 to 3 cm. Second, there was significant differences in tumor size and LS values between the HR and RFA groups, which were influenced by HCC management guidelines [23]. Despite these limitations, however, we believe that this study would be useful in predicting prognosis through measurement of TS values.

Conclusion

TS values measured using MRE were shown to be correlated with the % of tumor

necrosis on histopathologic examinations, and to be a significant predictive factor of

RFS after curative treatment for single nodular HCCs.

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Tables

Table 1. Demographics of the study population

Category	N, (%)	RFA	HR	p-value
Sex				
Male	128 (76.6)	51 (70.8)	77 (81.1)	0.382
Female	39 (23.4)	21 (29.2)	18 (18.9)	
Age (years)	63.8±10.3	63±9.58	64.4±10.87	0.132
Origin of liver cirrhosis				
Hepatitis B virus-related	123	53	70	
Hepatitis C virus-related	21	12	9	
Alcoholism	8	5	3	
Coinfection of hepatitis B and C virus-related	2	0	2	
NBNC	5	2	3	

Unknown	8	0	8
Child-Pugh class			
Class A	163(97.3)	68 (94.4)	95
Class B	4 (2.4)	4 (5.6)	0
Tumor segment			
Lt. lobe	45 (26.9)	9 (12.5)	36 (37.9)
Rt. lobe	122 (73.1)	63 (87.5)	59 (62.1)
Tumor size (cm)	3.50±2.8	1.87±0.58	4.73±3.17	<0.001
Range (cm)	1-17	1-3.5	1-17
Tumor stiffness (kPa)	2.31±0.8	2.3±0.82	2.33±0.78	0.784
Range (kPa)	0.78-4.97	0.78-4.7	0.86-4.97
Liver stiffness (kPa)	2.85±1.0	3.24±1.04	2.56±0.86	<0.001
Range (kPa)	0.78-6.62	1.88-6.62	0.78-5.61
Duration of hospital stay	9.47±5.71	4.64±2.43	13.13±4.67

Note. − RFA = radiofrequency ablation, HR = hepatic resection, NBNC = hepatitis B surface antigen and hepatitis C antibody negative

Table 2. Detailed characteristics according to tumor grade

Category	WD/MD-HCC	PD-HCC	p-value
Total number	61	34	
Tumor size	4.69±3.31	4.68±2.94	0.918
Range (cm)	1-17	1.1-13.1	
Origin of liver cirrhosis			
Hepatitis B virus-related	45	25	
Hepatitis C virus-related	4	5	

Alcoholism	2	1	
Coinfection of hepatitis B and C virus-related	1	1	
NBNC	3	0	
Unknown	6	2	
Tumor necrosis (%)	4.11±8.53	14.18±19.44	0.007
Range (kPa)	0-40	0-80	
Tumor stiffness (kPa)	2.59±0.77	1.86±0.57	<0.001

Range (kPa)	1.3-4.97	0.86-3.05	
Liver stiffness (kPa)	2.59±0.91	2.50±0.78	0.604
Range (kPa)	0.78-5.61	1.46-3.92	
Vascular invasion in pathology (%)	26.2 % (16/61)	64.7 % (22/34)	<0.001

Note. − WD = well-differentiated, MD = moderately-differentiated, PD = poorly-differentiated, HCC= hepatocellular carcinoma, NBNC= non-B non-C

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Table 3. Prognostic factors of overall survival

| Characteristics | RFA group | | | | HR group | | | |
| | Univariate | Multivariate | | | Univariate | Multivariate | | |
	p-value	Hazard ratio	95% CI	p-value	p-value	Hazard ratio	95% CI	p-value
Rim enhancement	0.8599				0.0007	2.10	0.48-9.30	0.3275
Peritumoral enhancement	0.9570				0.0090	3.97	0.91-17.25	0.066
Intratumoral fat	0.3977				0.4724			

T1 hyperintensity	0.0542				0.1209			
AFP	0.3404				0.0478	1.00	1.00-1.00	0.754
Age	0.1060				0.2261			
Albumin	0.0060	0.1863	0.027-1.292	0.089	0.1911			
INR	0.0347	0.8127	0.002-303.8	0.813	0.3934			
Sex	0.5798				0.3905			

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T. bilirubin	0.4691	0.6262		
Tumor size	0.1697	0.0020	1.08	0.94-1.24	0.2790
Tumor stiffness	0.2364	0.5433		
Liver stiffness	0.1690	0.0007	1.96	1.08-3.56	0.0269
Tumor grade	N/A	0.6178		
Tumor necrosis	N/A	0.0033	1.01	0.98-1.04	0.5229

Vascular invasion N/A	0.0211	1.50	0.42- 0.5351
			5.37

Note. − RFA= radiofrequency ablation, HR= hepatic resection, AFP = alpha-fetoprotein, INR = international

normalized ratio, T. bilirubin = total bilirubin, CI = confidence interval.

Table 4. Prognostic factors of recurrence-free survival

Characteristics	RFA group				HR group			
	Univariate	Multivariate			Univariate	Multivariate		
	p-value	Hazard ratio	95% CI	p-value	p-value	Hazard ratio	95% CI	p-value
Rim enhancement	0.0176	2.34	1.05-5.25	0.039	0.0005	1.73	0.78-3.85	0.1776
Peritumoral enhancement	0.0012	2.61	1.27-5.35	0.009	0.0156	2.32	0.85-6.35	0.1019
Intratumoral fat	0.9728				0.4757			

T1 hyperintensity	0.5195				0.7077			
AFP	0.4589				0.0154	1	1.00-1.00	0.3656
Age	0.1310				0.2212			
Albumin	0.0399	0.88	0.37-2.08	0.774	0.2959			
INR	0.0835				0.4681			
Sex	0.0126	2.28	0.99-5.22	0.505	0.8749			

T. bilirubin	0.0910				0.9239			
Tumor size	0.0056	1.63	0.839-3.18	0.149	0.0135	1.13	1.02-1.26	0.0202
Tumor stiffness	0.0003	0.50	0.31-0.82	0.006	0.0037	0.54	0.32-0.84	0.0084
Liver stiffness	0.6765				0.3222			
Tumor grade					0.1072			
Tumor necrosis					0.0262	1.00	0.97-1.02	0.8145

Vascular invasion	0.0005	2.03	0.97- 0.0601
			4.26

Note. − RFA= radiofrequency ablation, HR= hepatic resection, AFP = alpha-fetoprotein, INR = international

normalized ratio, T. bilirubin = total bilirubin, CI = confidence interval
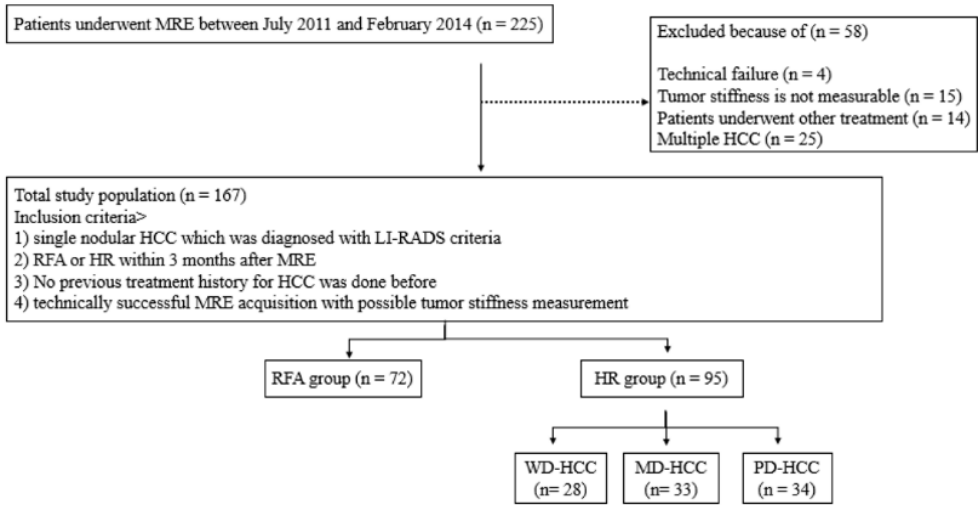
Figure Legends

Fig. 1—Flow diagram of the study population

Fig. 2—64-year-old male with chronic hepatitis B and HCC. A 3.4 cm HCC can be seen in the right hepatic lobe. This HCC appears as a low signal intensity lesion on hepatobiliary phase image (A), and as a hyperintense lesion on the magnitude image (B). On elastogram (C), the lesion shows higher stiffness values (3.22 kPa) than the surrounding liver parenchyma (2.41kPa) (C).

Fig. 3—Tumor stiffness values according to tumor grade

Fig. 4—% of tumor necrosis according to WD-, MD- and PD-HCCs

Fig. 5—Tumor stiffness values according to % of tumor necrosis

Fig. 6—Tumor stiffness values according to tumor size

Figures

Fig. 1—Flow diagram of the study population

Fig. 2—64-year-old male with chronic hepatitis B and HCC. A 3.4 cm HCC can be seen in the right hepatic lobe. This HCC appears as a low signal intensity lesion on hepatobiliary image (A), and as a hyperintense lesion on the magnitude image (B). On elastogram (C), the lesion shows higher stiffness values (3.22 kPa) than the surrounding liver parenchyma (2.41kPa) (C).
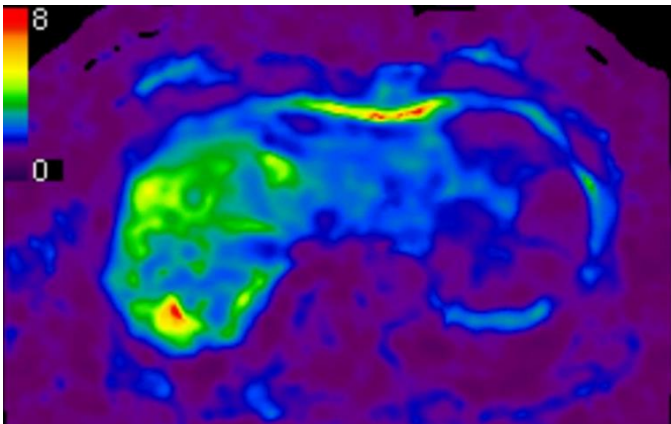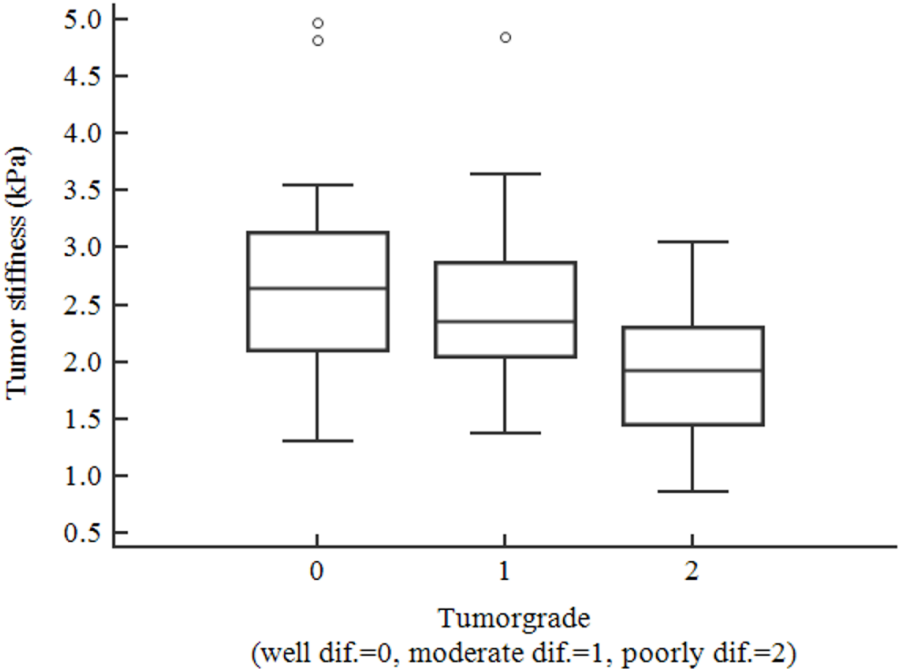
(A)
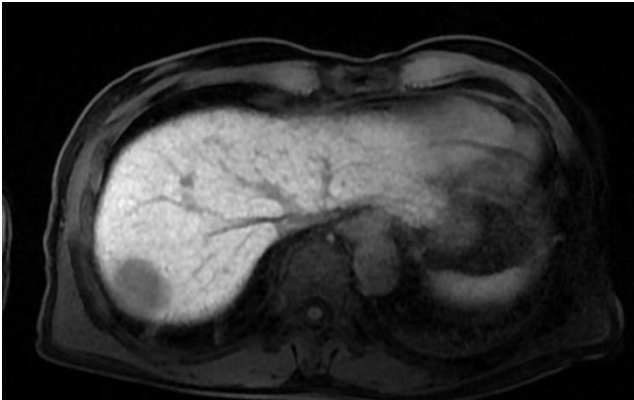
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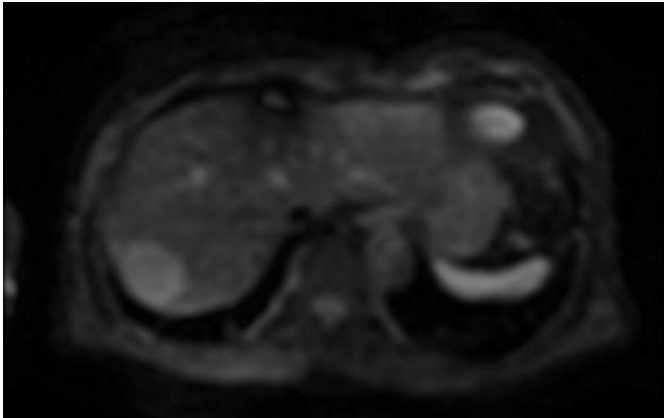
Fig. 3—Tumor stiffness values according to tumor grade (p-value <0.001)

Fig. 4—% of tumor necrosis according to WD-, MD- and PD-HCCs (p-value, 0.002)
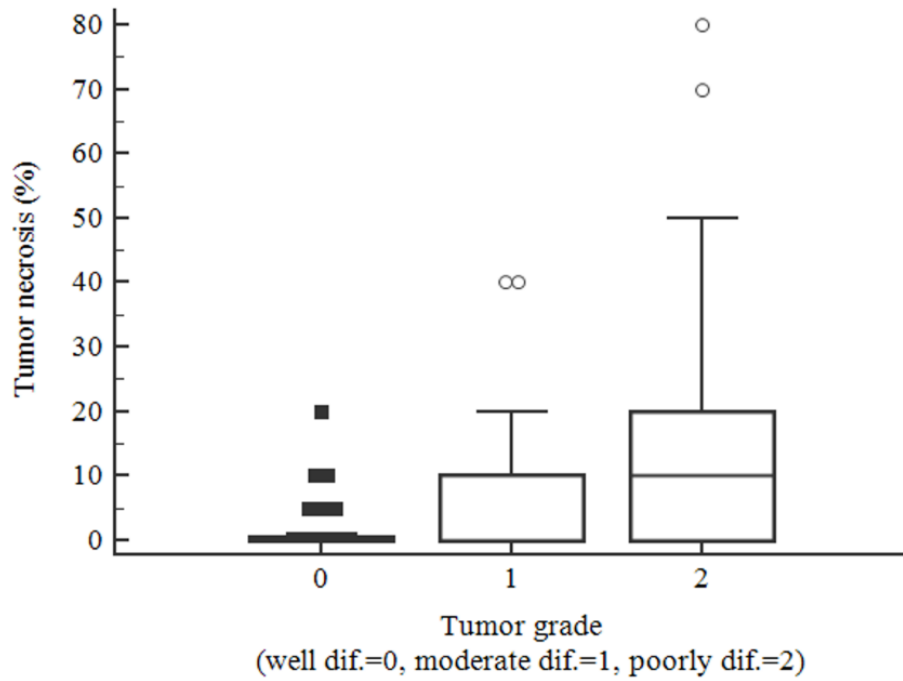
Fig. 5—Tumor stiffness values according to % of tumor necrosis (p-value, 0.04; correlation coefficience, -0.2116)
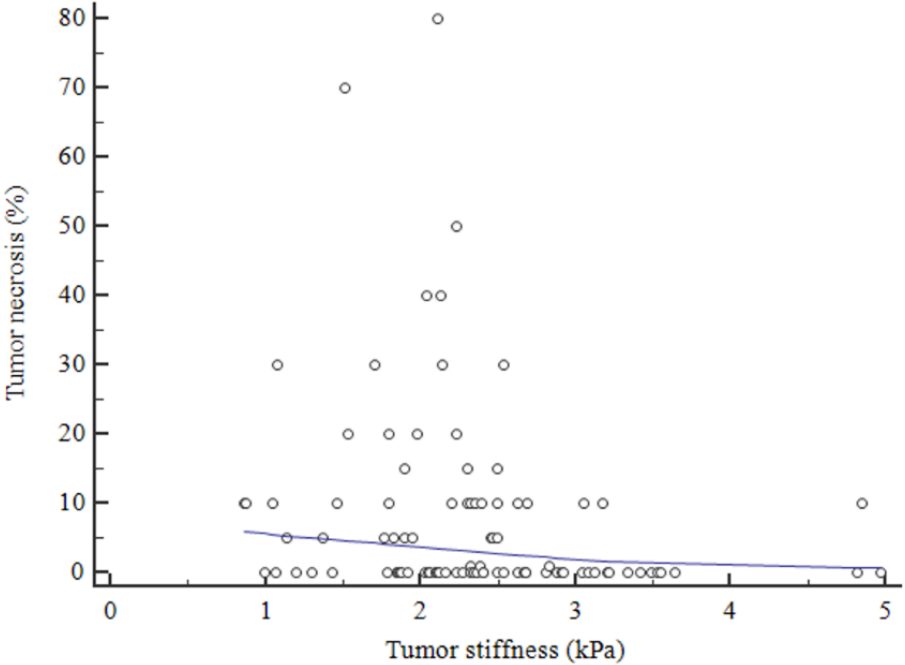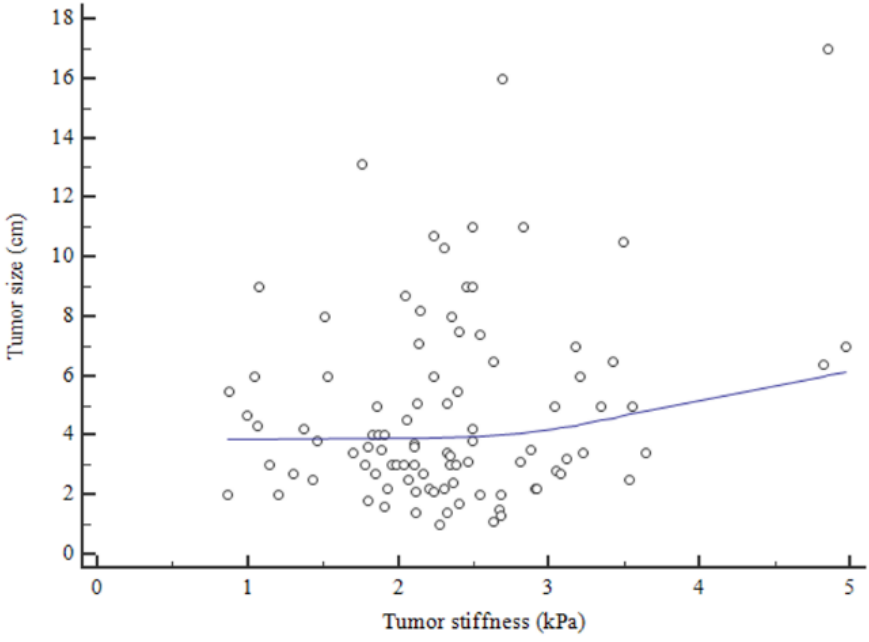
Fig. 6—Tumor stiffness values according to tumor size (p-value, 0.023; correlation coefficience, 0.2335)

요약(국문초록)

자기 공명 탄성영상을 이용하여 측정한 단일 결정 간세포암과 간

실질의 강도가 간절제술이나 고주파열치료술을 받은 환자에게서

전반적인 생존율이나 무재발 생존과 관련이 있는지를 알아보는

것이 이 논문의 목적이다.

2011 년 7 월부터 2014 년 2 월사이에 간절제술과 고주파 열치료술을

받은 적 있는 167 명의 환자를 후향적으로 모집하였다.

자기공명탄성영상은 1.5 테슬라의 자기공명장치에서 진동주파수

60Hz 로 3D EPI 기법을 이용하여 얻을 수 있었다.

전반적인 생존율이나 무재발 생존분석은 Kaplan-Meier 분석과 Cox

multivariate model 을 활용하였다.

결과적으로 간절제술을 받은 환자에게서 간세포암의 강도는

간세포암의 괴사정도와 간세포암의 등급과 밀접한 관련이 있었다.

분화도가 안 좋은 간세포암의 평균적인 강도는 분화도가 좋은

간세포암의 강도보다 통계적으로 의미있게 낮았다. 또한,

간실질강도는 전반적인 생존율에 의미있게 영향을 미치는 유일한

인자였다. 반면에 무재발생존에 영향을 주는 요인은 간세포암의

크기와 강도였다.

고주파열치료술을 받은 그룹에서는 전반적인 생존율에 의미있게

영향을 미치는 인자들은 없었다. 하지만, 무재발 생존에 의미있게

영향을 주는 인자로는 림 조영증강, 암주위 조영증강, 그리고

간세포암의 강도였다.

이를 종합하여서 보았을 때, 자기공명 탄성영상에서 측정한

간세포암의 강도는 간세포암의 괴사정도와 등급에 의미있게

연관이 될 수 있었고, 간절제술과 고주파열치료술 모두에서

간세포암의 크기와 더불어서 의미있는 예측인자가 될 수 있을

것으로 예상한다.