Published in final edited form as:

Magn Reson Imaging. 2017 April ; 37: 41–45. doi:10.1016/j.mri.2016.11.005.

MR Elastography of Hepatocellular Carcinoma: Correlation of Tumor Stiffness with Histopathology Features—Preliminary Findings

Scott M. Thompson, M.D., PhD.^a, Jin Wang, M.D., Ph.D.^a, Vishal S. Chandan, M.B.B.S.^b, Kevin Glaser, Ph.D.^a, Lewis R Roberts, M.B., Ch.B., Ph.D.^c, Richard L. Ehman, M.D.^a, and Sudhakar K. Venkatesh, M.D.^a

^aDepartment of Radiology, College of Medicine, Mayo Clinic, 200 1st St SW, Rochester, MN 55905, United States of America

^bDepartment of Laboratory Medicine and Pathology, College of Medicine, Mayo Clinic, 200 1st St SW, Rochester, MN 55905, United States of America

^cDivision of Gastroenterology and Hepatology, Department of Medicine, College of Medicine, Mayo Clinic, 200 1st St SW, Rochester, MN 55905, United States of America

Abstract

Purpose—To determine if tumor stiffness by MR Elastography (MRE) is associated with hepatocellular carcinoma (HCC) pathologic features.

Material and Methods—A retrospective review was undertaken of all patients with pathologically confirmed HCC who underwent MRE prior to locoregional therapy, surgical resection or transplant between 1/1/2007 to 12/31/2015. An independent observer measured tumor stiffness (kilopascals, kPa) by drawing regions of interest (ROI) covering the HCC and in the case of HCCs with non-enhancing/necrotic components, only the solid portion was included in the ROI. HCC tumor grade (WHO criteria), vascular invasion and tumor encapsulation were assessed from retrievable pathology specimens by an expert hepatobiliary pathologist. Tumor stiffness was compared by tumor grade, size, presence of capsule and vascular invasion using student's t-test (or Exact Mann-Whitney test).

Results—21 patients were identified who had pathologically confirmed HCC and tumor MRE data. 17 patients (81.0%) had underlying chronic liver disease. The mean±SD tumor size (cm) was 5.3±3.9 cm. The mean±SD tumor stiffness was 5.9±1.4 kPa. Tumors were graded as well differentiated (N=2), moderately differentiated (N=11) and poorly differentiated (N=8). There was a trend toward increased tumor stiffness in well/moderately differentiated HCC (6.5k±1.2 kPa; N=13) compared to poorly differentiated HCC (4.9±1.2 kPa; N=8) (p<0.01). There was no significant correlation between tumor stiffness and liver stiffness or tumor size. There was no

Corresponding Author: Sudhakar Venkatesh, M.D., Department of Radiology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, Phone 507-284-1728, Fax 507-284-2405, Venkatesh.Sudhakar@mayo.edu.

Conflict of Interest

The authors report no conflicts of interest related to the content of this manuscript

significant difference in tumor stiffness by presence or etiology of chronic liver disease, vascular invasion or tumor encapsulation.

Conclusion—Preliminary data suggest that tumor stiffness by MRE may be able to differentiate HCC tumor grade.

Keywords

MR Elastography; MRE; Hepatocellular Carcinoma; HCC; Tumor Grade

1. INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common malignancy and second most frequent cause of cancer related death worldwide [1]. The global incidence of HCC is increasing with non-alcoholic fatty liver disease (NAFLD) as an emerging major cause of chronic liver disease in the United States [1–3]. The overall survival of patients with HCC remains very poor with a five-year survival of < 15% [4]. Previous studies have identified poor tumor differentiation and microvascular invasion as negative prognostic factors for outcomes after surgical resection and liver transplantation for HCC while tumor encapsulation has been associated with a better prognosis [5–8]. However, as noted by Dhanasekaran et al., “One of the main challenges faced by clinicians managing patients with HCC is the heterogeneity of this cancer, both at an epidemiologic and at a molecular level” [9]. Numerous candidate prognostic and therapeutic serum and tissue biomarkers for HCC are under active investigation and may hopefully aid in both the stratification of HCC patients and the selection of personalized therapies based on individual tumor biology [10].

However, HCC is a unique malignancy in that it does not require histologic confirmation but rather is primarily diagnosed by cross-sectional imaging [11–13]. As such, imaging biomarkers may provide important surrogate HCC tumor biologic, pathologic and ultimately prognostic information for patient stratification in clinical trials and clinical practice [14]. Various imaging features by CT, MRI and PET have been proposed as imaging biomarkers for HCC but none have been translated into routine clinical practice or clinical trials for HCC [15–20]. Magnetic resonance elastography (MRE) is a noninvasive MRI based technique for quantitatively assessing the mechanical properties of tissues and has been used clinically most extensively in the liver as a quantitative tool for diagnosing and staging liver fibrosis [21,22]. Moreover, MRE has been shown to be feasible for measuring liver tumor stiffness (kPa) and is more accurate than diffusion-weighted imaging (DWI) for differentiating benign and malignant focal liver lesions [23,24]. However, it is not known if tumor stiffness by MRE can differentiate HCC tumor pathologic features.

The aim of the present study was to determine if tumor stiffness by MRE is associated with HCC pathologic features.

2. MATERIAL AND METHODS

2.1 Patient Selection

After receiving approval from the Institutional Review Board and obtaining a waiver of informed consent, a HIPAA-compliant, retrospective review was undertaken using the comprehensive electronic medical records of all patients with pathologically confirmed HCC who underwent MRE prior to locoregional therapy, surgical resection or transplant from January 1, 2007 to December 31, 2015. 155 patients with a clinical and imaging diagnosis of HCC were identified from the MRE database of 4254 liver MRE exams during the indicated time period. Of those 155 patients, 72 patients had a pathologic diagnosis of HCC from surgical resection, transplant or biopsy. Fifty-one patients were excluded for the following reasons: 1) MRE performed after surgical resection, liver transplant and/or locoregional therapy, 2) the MRE did not include at least one slice through the tumor or 3) pathology specimens were not available for review. 21 patients formed the final study group.

2.2 Magnetic Resonance Elastography Technique

Two-dimensional liver MRE was performed as previously described [21,22]. MRE was performed for evaluation of chronic liver disease. The MRE was performed at standard 60Hz with four slices through the widest cross-section of the liver. The slice selection was done by the operating technologist at the time of clinically indicated scan. The MRI parameters were as follows: Time to repeat (TR) = 50ms; Time to echo (TE)=20msec, slice thickness 10mm, interslice gap 0, flip angle=30, bandwidth=32kHz, matrix= 256 × 96 and acceleration factor 2. Each slice of MRE was obtained with 12–18 second breath hold depending on patient size. MRE sequence was completed in 1–2 minutes. MRE sequence was performed either before or after intravenous contrast. On the scanner, an inversion algorithm automatically processed the raw data and produced gray and color scale stiffness maps (elastograms).

2.3 Tumor Stiffness Evaluation from MRE Elastograms

Tumor stiffness (kPa) was measured by an independent observer blinded to the clinical and tumor pathologic data as previously described [23,24]. Regions of interest (ROI) were drawn on the elastograms covering the HCC and in the case of HCCs with non-enhancing/necrotic components, only the solid portion was included in the ROI. Pseudocapsule was excluded from the ROIs.

ROIs were also drawn on the non-tumor bearing liver parenchyma away from the HCC for clinical purposes. This was performed by a trained technologist at the time of MRI exam and reported.

2.4 Tumor Pathology Review

HCC tumor grade, vascular invasion and tumor encapsulation were assessed from retrievable pathology specimens by an experienced hepatobiliary pathologist blinded to the clinical and MRE data. Tumors were graded as well, moderately or poorly differentiated types according to WHO criteria [25].

2.5 Statistical Methods

Data were analyzed using JMP 11.0 (SAS, Cary, NC) and Prism 5.0 (GraphPad Software, Inc, La Jolla, CA). Descriptive statistics were generated. Tumor stiffness was compared by tumor grade, presence of capsule, vascular invasion and clinical variables using a *t* test (or Exact Mann-Whitney test). $P < .05$ was considered statistically significant.

3. RESULTS

3.1 Patient and tumor characteristics

21 patients were identified who had pathologically confirmed HCC and tumor MRE data. 17 patients (81.0%) had underlying chronic liver disease. The mean $\pm$ SD tumor size (cm) was 5.3 $\pm$ 3.9 cm. Tumors were graded as well differentiated (N=2), moderately differentiated (N=11) and poorly differentiated (N=8). The mean $\pm$ SD tumor stiffness was 5.9 $\pm$ 1.4 kPa. Demographic, clinical, tumor stiffness and pathologic data are summarized in Table 1.

3.2 Correlation of tumor stiffness by MRE with pathologic and clinical variables

There was a trend toward increased tumor stiffness in well/moderately differentiated HCC (6.5k $\pm$ 1.2 kPa; N=13; Figure 1) compared to poorly differentiated HCC (4.9 $\pm$ 1.2 kPa; N=8; Figure 2) ($p < 0.01$; Figure 3). There was no significant correlation between tumor stiffness and liver stiffness ($r^2 = 0.07$; $p = 0.26$) or tumor size ($r^2 = 0.12$; $p = 0.14$). There was no significant difference in tumor stiffness by presence or etiology of chronic liver disease ($p = 0.92$), vascular invasion ($p = 0.94$) or tumor encapsulation ($p = 0.20$).

4. DISCUSSION

Our preliminary experience show that well and moderately differentiated HCC are approximately 28% more stiff than poorly differentiated HCC (6.5 kPa v. 4.9kPa, respectively), thereby suggesting that tumor stiffness by MRE may be a candidate imaging biomarker to differentiate HCC tumor grade. The differences in stiffness between well and moderately HCC and poorly differentiated HCC are not well understood. Poorly differentiated HCCs may often have more necrosis and reduced vascularity, which may account for reduced stiffness. However, in the present study only the solid, enhancing portion of the tumor was included in the region of interest for tumor stiffness calculation. One hypothesis is that well and moderately differentiated HCCs by definition have a more organized trabecular pattern of tissue architecture than poorly differentiated HCCs which lose their trabecular pattern [26]. Of note, there was no significant association between tumor stiffness and liver stiffness, tumor size, presence or etiology of chronic liver disease, vascular invasion or tumor encapsulation. However, given the small sample size, further investigation is needed to identify additional associations between tumor stiffness and clinical and pathologic features of HCC.

Numerous imaging features have been described as candidate imaging biomarkers in HCC. A recent study by Bailly et al. showed that increased FDG uptake at ^{18}F -FDG PET is associated with higher HCC tumor grade and microvascular invasion [18]. However, ^{18}F -FDG PET is not routinely used in the clinical evaluation of HCC. Choi et al. have shown that

HCCs with atypical enhancement pattern and iso-to-hyperintensity on contrast-enhanced MRI were associated with lower tumor grade and better prognosis after surgical resection [16]. Moreover, a recent meta-analysis showed that diffusion-weighted imaging (DWI) has a high diagnostic accuracy in the preoperative prediction of well and poorly differentiated HCC (AUC = 0.93 and 0.85, respectively) [20]. Venkatesh et al. have shown that MRE is feasible for measuring liver tumor stiffness (kPa) and is more accurate than diffusion-weighted imaging (DWI) for differentiating benign and malignant focal liver lesions [23,24]. Taken together, tumor stiffness by MRE adds to the growing list of candidate imaging biomarkers for HCC tumor grade. Given that multiparametric liver MRI and MRE are now routinely used in the evaluation of chronic liver disease, the addition of routine liver tumor MRE may be clinically feasible.

There are limitations to this study. This was a retrospective review of only 21 patients with both pathologically confirmed HCC and tumor MRE data. While lack of histologic confirmation of HCC was one of the main reasons for exclusion, a number of patients with histologic confirmation were excluded because the MRE was performed for liver stiffness measurements and did not include at least one slice through the tumor. At our institution we are currently in the process of incorporating both liver and tumor into the routine liver MRE protocol in order to maximize data acquisition. Furthermore, there were only two cases of well-differentiated HCC in the current study. Therefore no preliminary conclusions can be drawn regarding tumor stiffness differences between well and moderately differentiated HCC. As such, the well and moderately differentiated HCC cases were grouped together for analysis, which is often the case in clinical practice in which pathologists often grade non-poorly differentiated HCC as well to moderately differentiated HCC. Nonetheless, the range of stiffness between the two groups overlapped suggesting there may be a range of stiffness within tumor grades that warrants further investigation. Additionally, there is a known risk of sampling error in cases of biopsy as previous studies have identified frequent grading heterogeneity in HCC tumors obtained at biopsy versus surgical resection [27]. While there were five HCCs from biopsy specimens in the current study, future prospective radiologic-pathologic prospective studies would ideally obtain HCCs from surgical resection specimens to minimize the problems associated with biopsy and the potential longer time intervals with liver transplant. Additionally, the MRE images and pathology specimens were reviewed by a single radiologist and pathologist. Future prospective multi-reader studies will be needed to determine the inter- and intra-rater reliability of tumor stiffness calculated by MRE and pathologic features of HCC. Additionally, previous studies have shown MRE to be a highly reproducible method for quantifying liver stiffness [28,29]. Similar studies will be needed in the validation of MRE for measuring HCC tumor stiffness. Lastly, with the current slice thickness of 1cm with two-dimensional MRE, tumors less than 1cm may not be accurately measured with MRE. Three-dimensional MRE may provide better spatial resolution to more accurately measure focal liver lesions.

5. CONCLUSION

In summary, the present data suggest that tumor stiffness by MRE may be useful to differentiate well and moderately differentiated HCC from poorly differentiated HCC. With this encouraging preliminary observation, the question remains is tumor stiffness by MRE an

independent predictor of HCC pathologic or molecular features, prognosis or therapeutic response? Prospective studies are needed to systematically investigate the MRE-HCC radiologic-pathologic correlates in order to determine the role of tumor stiffness by MRE as an HCC imaging biomarker.

Acknowledgments

Contract grant sponsor: National Institutes of Health; Contract grant number: EB01981. The National Institutes of Health did not have a role in the study design, collection, analysis or interpretation of data, the writing of the manuscript or the decision to submit the manuscript for publication.

References

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015; 136(5):E359–386. [PubMed: 25220842]
2. Younossi ZM, Otgonsuren M, Henry L, et al. Association of nonalcoholic fatty liver disease (NAFLD) with hepatocellular carcinoma (HCC) in the United States from 2004 to 2009. *Hepatology*. 2015; 62(6):1723–1730. [PubMed: 26274335]
3. Everhart JE, Ruhl CE. Burden of digestive diseases in the United States Part III: Liver, biliary tract, and pancreas. *Gastroenterology*. 2009; 136(4):1134–1144. [PubMed: 19245868]
4. Peery AF, Dellon ES, Lund J, et al. Burden of gastrointestinal disease in the United States: 2012 update. *Gastroenterology*. 2012; 143(5):1179–1187. e1171–1173. [PubMed: 22885331]
5. Poon RT, Fan ST, Ng IO, Lo CM, Liu CL, Wong J. Different risk factors and prognosis for early and late intrahepatic recurrence after resection of hepatocellular carcinoma. *Cancer*. 2000; 89(3):500–507. [PubMed: 10931448]
6. Klintmalm GB. Liver transplantation for hepatocellular carcinoma: a registry report of the impact of tumor characteristics on outcome. *Ann Surg*. 1998; 228(4):479–490. [PubMed: 9790338]
7. Tamura S, Kato T, Berho M, et al. Impact of histological grade of hepatocellular carcinoma on the outcome of liver transplantation. *Arch Surg*. 2001; 136(1):25–30. discussion 31. [PubMed: 11146770]
8. Jonas S, Bechstein WO, Steinmuller T, et al. Vascular invasion and histopathologic grading determine outcome after liver transplantation for hepatocellular carcinoma in cirrhosis. *Hepatology*. 2001; 33(5):1080–1086. [PubMed: 11343235]
9. Dhanasekaran, R., Venkatesh, SK., Torbenson, M., Roberts, LR. *J Hepatol*. 2015. Clinical Implications of Basic Research in Hepatocellular Carcinoma; p. 1-31.
10. Chaiteerakij R, Addissie BD, Roberts LR. Update on Biomarkers of Hepatocellular Carcinoma. *Clin Gastroenterol Hepatol*. 2015; 13(2):237–245. [PubMed: 24275343]
11. European Association for Study of L, European Organisation for R, Treatment of C. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *Eur J Cancer*. 2012; 48(5):599–641. [PubMed: 22424278]
12. Bruix J, Sherman M. American Association for the Study of Liver D. Management of hepatocellular carcinoma: an update. *Hepatology*. 2011; 53(3):1020–1022. [PubMed: 21374666]
13. Venkatesh SK, Chandan V, Roberts LR. Liver Masses: A Clinical, Radiologic, and Pathologic Perspective. *Clin Gastroenterol Hepatol*. 2014; 12(9):1414–1429. [PubMed: 24055987]
14. Llovet JM, Di Bisceglie AM, Bruix J, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. *J Natl Cancer Inst*. 2008; 100(10):698–711. [PubMed: 18477802]
15. Banerjee S, Wang DS, Kim HJ, et al. A computed tomography radiogenomic biomarker predicts microvascular invasion and clinical outcomes in hepatocellular carcinoma. *Hepatology*. 2015; 62(3):792–800. [PubMed: 25930992]
16. Choi JW, Lee JM, Kim SJ, et al. Hepatocellular carcinoma: imaging patterns on gadoteric acid-enhanced MR Images and their value as an imaging biomarker. *Radiology*. 2013; 267(3):776–786. [PubMed: 23401584]

17. Okada M, Imai Y, Kim T, et al. Comparison of enhancement patterns of histologically confirmed hepatocellular carcinoma between gadoxetate- and ferucarbotran-enhanced magnetic resonance imaging. *J Magn Reson Imaging*. 2010; 32(4):903–913. [PubMed: 20882621]
18. Bailly M, Venel Y, Orain I, Salame E, Ribeiro MJ. 18F-FDG PET in Liver Transplantation Setting of Hepatocellular Carcinoma: Predicting Histology? *Clin Nucl Med*. 2016; 41(3):e126–129. [PubMed: 26545024]
19. Cho ES, Choi JY. MRI features of hepatocellular carcinoma related to biologic behavior. *Korean J Radiol*. 2015; 16(3):449–464. [PubMed: 25995679]
20. Chen J, Wu M, Liu R, Li S, Gao R, Song B. Preoperative evaluation of the histological grade of hepatocellular carcinoma with diffusion-weighted imaging: a meta-analysis. *PLoS One*. 2015; 10(2):e0117661. [PubMed: 25658359]
21. Venkatesh SK, Yin M, Ehman RL. Magnetic resonance elastography of liver: technique, analysis, and clinical applications. *J Magn Reson Imaging*. 2013; 37(3):544–555. [PubMed: 23423795]
22. Venkatesh SK, Ehman RL. Magnetic resonance elastography of liver. *Magn Reson Imaging Clin N Am*. 2014; 22(3):433–446. [PubMed: 25086938]
23. Venkatesh SK, Yin M, Glockner JF, et al. MR Elastography of Liver Tumors: Preliminary Results. *AJR Am J Roentgenol*. 2008; 190(6):1534–1540. [PubMed: 18492904]
24. Hennemig TP, Hallinan JTPD, Leung FP, et al. Comparison of magnetic resonance elastography and diffusion-weighted imaging for differentiating benign and malignant liver lesions. *Eur Radiol*. 2015:1–9.
25. Hamilton, SR., Aaltonen, LA., editors. *Pathology and Genetics of Tumours of the Digestive System*. IARC Press; Lyon: 2000. World Health Organization Classification of Tumours.
26. Paradis V. Histopathology of hepatocellular carcinoma. *Recent Results Cancer Res*. 2013; 190:21–32. [PubMed: 22941011]
27. Pawlik TM, Gleisner AL, Anders RA, Assumpcao L, Maley W, Choti MA. Preoperative assessment of hepatocellular carcinoma tumor grade using needle biopsy: implications for transplant eligibility. *Ann Surg*. 2007; 245(3):435–442. [PubMed: 17435551]
28. Hines CD, Bley TA, Lindstrom MJ, Reeder SB. Repeatability of magnetic resonance elastography for quantification of hepatic stiffness. *J Magn Reson Imaging*. 2010; 31(3):725–731. [PubMed: 20187219]
29. Shire NJ, Yin M, Chen J, et al. Test-retest repeatability of MR elastography for noninvasive liver fibrosis assessment in hepatitis C. *J Magn Reson Imaging*. 2011; 34(4):947–955. [PubMed: 21751289]

Figure 1.

A 57-year-old male with chronic hepatitis C and a 3.0 cm moderately differentiated HCC in right hepatic lobe. HCC shows arterial phase (A) hyperenhancement (arrow) with no definite washout on portal venous (B) or delayed phase (C) and restricted diffusion (D). Stiffness map from 2D-MRE (E) demonstrates a mean tumor stiffness of 6.4 kPa (dotted white line) and a background liver stiffness of 6.0 kPa (range 5.6 to 6.8 kPa). Photomicrograph (F) of H&E stained section from explanted liver at transplant shows moderately differentiated HCC with cystic changes due to chemoembolization performed after MRE.

Figure 2.

A 65-year-old female with non-alcoholic fatty liver disease and a 3.2 cm poorly differentiated HCC. The mass is T2 hyperintense (arrow) (A), hypointense on T1-weighted image (B) and shows mild arterial phase enhancement (C) and washout with a pseudocapsule in delayed phase (D). Stiffness map (E) shows a mean tumor stiffness of 3.4 kPa (dotted white line) and an elevated background liver stiffness of 6.9 kPa (range 5.6 to 8.4). Photomicrograph (F) of histopathology from surgical resection specimen shows poorly differentiated HCC.

Figure 3.
Box and whisker plot of HCC tumor stiffness (kPa) by tumor grade

Table 1

Demographic, clinical, tumor stiffness and pathologic data (N=21)

Age (years) (mean±SD)	59.5±10.3
Gender	
Female	5 (23.8)
Male	16 (76.2)
Chronic Liver Disease *	
HCV	9 (42.9)
HBV	1 (4.8)
NAFLD	4 (19.0)
Alcoholic	4 (19.0)
PSC	1 (4.8)
Hemochromatosis	1 (4.8)
Cardiac cirrhosis	1 (4.8)
Cryptogenic	1 (5.3)
None	4 (15.8)
Childs Score	
A	15 (71.4)
B	6 (28.6)
Tumor Stiffness (kPa)	
	5.9±1.4
Pathology Source	
Surgical Resection	8 (38.1)
Liver Explant at Transplant	8 (38.1)
Biopsy	5 (23.8)
Pathologic Features	
Tumor Size	5.3±3.9 cm.
Tumor Grade (WHO criteria)	
Well	2 (9.5)
Moderately	11 (52.4)
Poor	8 (38.1)
Vascular Invasion	4 (25.0) †
Tumor Encapsulation	7 (43.8) †

* Does not add up to 21 because some patients had more than one etiology for chronic liver disease

† Assessed in 16 patients with pathology specimens from surgical resection or transplant

Data are presented as N (%) or mean±SD. HCV = hepatitis C; HBV = hepatitis B; NAFLD = non-alcoholic fatty liver disease; PSC = primary sclerosing cholangitis; WHO = world health organization; kPa = kilopascal