ORIGINAL ARTICLE

Texture analysis on preoperative contrast-enhanced magnetic resonance imaging identifies microvascular invasion in hepatocellular carcinoma

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Abstract

Background: Radiomic texture analysis quantifies tumor heterogeneity. The aim of this study is to determine if radiomics can predict biologic aggressiveness in HCC and identify tumors with MVI.

Methods: Single-center, retrospective review of HCC patients undergoing resection/ablation with curative intent from 2009 to 2017. DICOM images from preoperative MRIs were analyzed with texture analysis software. Texture analysis parameters extracted on T1, T2, hepatic arterial phase (HAP) and portal venous phase (PVP) images. Multivariate logistic regression analysis evaluated factors associated with MVI.

Results: MVI was present in 52.2% (n = 133) of HCCs. On multivariate analysis only T1 mean (OR = 0.97, 95%CI 0.95–0.99, p = 0.043) and PVP entropy (OR = 4.7, 95%CI 1.37–16.3, p = 0.014) were associated with tumor MVI. Area under ROC curve was 0.83 for this final model. Empirical optimal cutpoint for PVP tumor entropy and T1 tumor mean were 5.73 and 23.41, respectively. At these cutpoint values, sensitivity was 0.68 and 0.5, respectively and specificity was 0.64 and 0.86. When both criteria were met, the probability of MVI in the tumor was 87%.

Conclusion: Tumor entropy and mean are both associated with MVI. Texture analysis on preoperative imaging correlates with microscopic features of HCC and can be used to predict patients with high-risk tumors.

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Introduction

The clinical management of hepatocellular carcinoma (HCC) requires a complex, multi-disciplinary evaluation and is based on the tumor staging at presentation, extent of underlying liver disease, and patient performance status. These factors are critical to determine the ideal treatment strategy given two curative options in liver resection/ablation and liver transplantation. Numerous staging criteria have been developed to help guide the management of these patients with the Barcelona Clinic Liver Cancer staging system being the most widely accepted.[1,2] Tumor staging in this schema is heavily influenced by only the size and number of tumors present.[3] HCCs that fall within these Milan criteria are generally considered for curative therapy. Currently there is no standardized method to assess tumor biology and expected behavior aside from these two characteristics. Only recently has the AJCC staging system begun adopting additional prognostic factors into the staging system in attempts to better stage patients.

Microvascular invasion (MVI) is one of the few established prognostic factors in HCC.[4–8] In the most recent eighth edition,

staging of HCC now uses vascular involvement to stratify solitary tumors. Unlike macrovascular invasion, which can typically be established on preoperative imaging, MVI is largely determined postoperatively from pathologic assessment of the tumor specimen. Determination of MVI status in the preoperative setting would provide insight into disease biology and help guide treatment decisions. Several attempts, including some recent reports, have attempted to identify MVI preoperatively using a variety of clinical data and scoring systems.[9–12] Texture analysis is an emerging radiologic technique that can be applied to any cross-sectional imaging. This technique analyzes and objectifies imaging characteristics on the pixel level providing quantitative data on a number of defined parameters. As this technology continues to grow, we believe this technology will provide an additional level of data for radiologic diagnoses and may provide insight into tumor prognosis/biology. In this current study we examined the nature of MRI texture analysis in hepatocellular carcinoma and its association with microvascular invasion.

Methods

Study cohort

All consecutive patients (n = 255) undergoing resection or ablation with curative intent for HCC from 2009 through 2017 at the University of Pittsburgh Medical Center were considered for study inclusion. At our institution, surgical resection is the preferred curative intervention for HCC when transplantation is not an option. However, for small HCCs (<3 cm) curation treatment with radiofrequency ablation is considered based on a case by case analysis and determined by extent of underlying liver disease and location of tumor. Clinical and pathologic parameters were retrospectively collected from electronic chart review. Microvascular invasion (MVI) was determined by the final pathologic evaluation. These patients represented the entire cohort evaluated in this study. This cohort was used analyze patient, clinical, and pathologic parameters for a large cohort of resected/ablated HCC. Statistical methods are detailed below. Long term oncologic outcomes were evaluated including overall survival, disease-free survival and recurrence patterns. Association of clinical factors with MVI were analyzed. Preoperative magnetic resonance imaging of the entire cohort was reviewed for quality and appropriateness of inclusion based on techniques listed below. Patients with images appropriate for texture analysis were then analyzed as the texture analysis cohort (n = 38). To be included for texture analysis evaluation, magnetic resonance images had to meet the following criteria: multiphasic liver protocol with the administration of equivalent intravenous contrast agent, studies performed within three months of the surgical resection, no significant motion or other imaging artifacts, adequate post-contrast late hepatic arterial phase, and presence of untreated HCC larger than 1 cm. Given the number of outlying hospitals that are part of our health care system, a large number of patients underwent imaging at an outside facility which were either unavailable or inadequate for texture analysis. This study was performed after approval from and in accordance with the University of Pittsburgh Institutional Review Board.

MR imaging technique

MR imaging studies were performed using 1.5 T or 3 T scanners (General Electric, Healthcare, Milwaukee, WI, USA). Liver imaging protocol includes at least the following sequences in all patients: axial T2-weighted single shot fast spin echo, axial T2-weighted fast spin-echo (FSE), axial T1-weighted dual-echo gradient-recalled echo (GRE) and axial T1-weighted three-dimensional (3D) GRE with fat suppression (Liver Acquisition with Volume Acceleration, LAVA) obtained before and after the intravenous administration of 0.1 mmol/kg or maximum 24 ml of Gd-BOPTA (Gadobenate Dimeglumine, MultiHance, Bracco Diagnostics, Princeton, NJ). Post-contrast images were acquired during the late hepatic arterial phase (HAP, obtained with delay of 25–35 s using test-bolus or fluoroscopic-triggering technique), portal venous phase (PVP, delay of 60–70 s), and delayed phases (2 min and 4–5 min after contrast administration). At our institution, the 3D GRE LAVA sequence used in the dynamic study is acquired with the following parameters: slice thickness, 4.6 mm; reconstruction interval, 2.3 mm; TR, 3.9–7.2 ms; TE, 1.8–3.4 ms; Flip Angle, 12.0°. Scanning parameters for T2-weighted FSE sequence are the following: slice thickness, 7.0 mm; reconstruction interval, 9.0 mm; TR, 2000–8000 ms; TE, 77–140 ms; Flip Angle, 90.0°.

Texture analysis

Texture analysis is a mathematical post-processing method for quantification of tissue heterogeneity. This technique is based on analysis of grey level distribution and relationship of pixels within a region of interest (ROI). Texture parameters were extracted using a commercially available research software (TexRAD, version 3.9, Feedback Plc, Cambridge, UK). The analysis was conducted by a single investigator with 4 years of experience in cross-sectional imaging and 6 months of experience in texture analysis, blinded to the histopathological data. In patients with several HCC, information about location of the pathologically-proven lesion was provided before the analysis. A polygonal ROI was manually drawn on the largest cross section of the lesion, avoiding the margins, on pre-contrast T1-weithed, T2-weighted FSE, and post-contrast images acquired during HAP and PVP phases, as described in several prior studies on focal liver lesions.[13–16] An additional 2 cm rounded ROI was placed on the non-lesional right lobe liver parenchyma, avoiding the major vessels.

In each sequence the texture analysis software package automatically extracts the following independent histogram-based texture features: mean pixel intensity (mean), standard deviations (SD), entropy, mean of positive pixels (mpp), skewness, and kurtosis. The mean is the average pixel grey level; SD represents the degree of variation from the mean; the entropy

describes the image inhomogeneity and randomness of pixel co-occurrence based on the formula described in prior studies[17]; mpp is defined as the average intensity of pixels with positive values; skewness measures the asymmetry of the histogram; kurtosis indicates the peakedness of the histogram.[18,19]

Statistical analysis

All statistical analyses were performed using STATA version 15.1 (StataCorp LLC). Continuous variables are listed as mean ± standard deviation for normally distributed variable and median (interquartile range, IQR) for variables non-normally distributed. Multivariable analyses were performed on both cohorts examining the association of clinical and radiographic variables with MVI. Variables with a p value of <0.15 and variance inflation factor less than 5 were included in the final multivariable model. The final multivariable model including the texture analysis variables was analyzed with receiver-operating characteristic (ROC) curve and Youden index J was used to determine optimal cutoff values. Overall survival and disease-free survival were determined from the date of surgical procedure. Survival estimates were determined by Kaplan-Meier analysis with differences between groups determined by log rank

Table 1 Patient demographic and clinical characteristics

Clinicopathologic Characteristics	Entire Cohort	MVI negative	MVI positive	p
Age (median, IQR)	67 (60–75)	68 (61–76)	67 (60–76)	0.85
Sex				0.38
Male	75.3% (192)	77.1% (81)	72.2% (96)	
Female	24.7% (63)	22.9% (24)	27.8% (37)	
Race				0.49
White	83.1% (212)	86.7% (91)	84.2% (112)	
Black	8.6% (22)	6.7% (7)	10.5% (14)	
Asian	3.9% (10)	2.9% (3)	3.8% (5)	
Other	4.3% (11)	3.8% (4)	1.5% (2)	
BMI	27.2 (24.7–31.2)	27.3 (24.2–31.1)	27.2 (24.9–31.4)	0.95
Diabetic	34.9% (87)	38.5% (40)	32.3% (43)	0.32
Insulin Dependent	12.9% (32)	14.4% (15)	12.0% (16)	0.59
Hepatitis B	6.9% (17)	5.8% (6)	6.9% (9)	0.73
Hepatitis C	32.0% (79)	21.2% (22)	38.2% (50)	0.005
Cirrhosis	41.6% (104)	44.8% (47)	36.1% (48)	0.18
Alcohol abuse	31.6% (78)	35.0% (36)	29.3% (39)	0.36
Radiographic Tumor size (cm)	4.5 (2.6–7)	4 (2.3–6)	5.5 (3.5–9)	0.001
Tumor morphology				0.73
Solitary Tumor	79.4% (197)	78.6% (81)	80.5% (107)	
Multifocal (>1 tumor)	20.6% (51)	21.3% (22)	19.5% (26)	
Preoperative AFP	13 (4–119.25)	5 (3.3–17.7)	37 (6–562)	<0.001
Margin of Resection				0.08
R0	80.9% (190)	87.1% (88)	76.3% (100)	
R1	19.1% (45)	12.9% (13)	23.7% (31)	
Background Liver Fibrosis				0.15
None – moderate fibrosis	51.3% (120)	46.9% (46)	56.6% (73)	
Severe fibrosis or cirrhosis	48.7% (114)	53.1% (52)	43.4% (56)	
Tumor Grade				<0.001
well differentiated	25.9% (62)	43.7% (45)	12.2% (16)	
moderately differentiated	64.9% (155)	51.5% (53)	74.8% (98)	
poorly differentiated	9.2% (22)	4.9% (5)	13.0% (17)	
Microscopic vascular invasion				
no	44.1% (105)			
yes	55.9% (133)			

analysis. Statistical significance was determined by a two sided p value of <0.05.

Results

Clinical and pathologic characteristics of HCC, disease-free survival by microvascular status and factors associated with microvascular invasion in the entire cohort

Patient demographics, tumor characteristics and pathologic data for the entire cohort undergoing surgical resection or ablation with curative intent are listed in Table 1. MVI was present in 55.9% (n = 133) of the resected specimens. Median overall survival for the entire cohort was 48.2 mos, 95% CI 36.5–55.5. Based on previous reports, the effect of MVI status on DFS in solitary HCC was evaluated and is shown in Fig. 1. Disease free survival was lower in the MVI-positive group with a median survival of 14.8 mos, 95% CI = 9.8–19.8 compared to MVI-negative HCC with median survival of 28.7 mos, 95% CI = 25.2–32.2 (p = 0.012). The association between preoperative clinical variables and MVI was analyzed with univariate and multivariate logistic regression (Table 2). Based on the final multivariate model only HCV status (OR = 2.73, 95% CI 1.40–5.33, p = 0.003) and tumor size (OR = 1.11, 95% CI 1.02–1.21, p = 0.021) were independently associated with MVI positive HCC. Although preoperative alpha-fetoprotein (AFP) level was included in the multivariate model there was not a statistically significant association (OR = 1.00, 95% 1.00–1.00, p = 0.105).

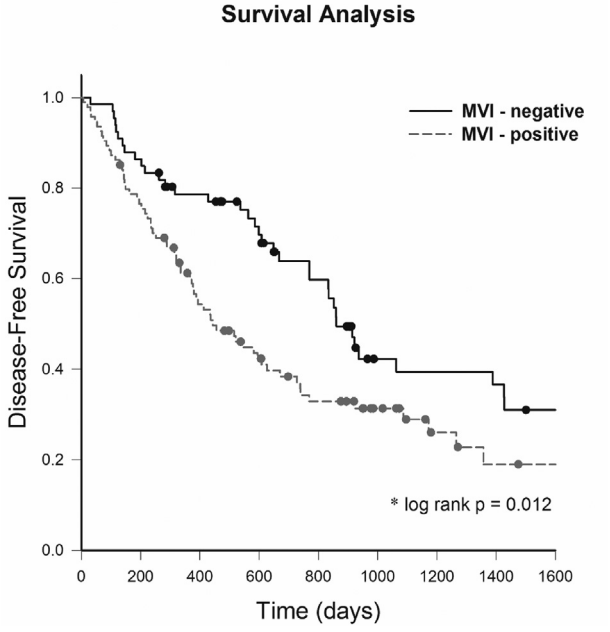

Figure 1 Disease-free survival based on the presence of microvascular invasion (MVI) on final pathology

Texture analysis of HCC on preoperative contrast-enhanced MRI and association with microvascular invasion in HCC

We then performed texture analysis on preoperative imaging of the tumor (at its largest diameter) and background liver for each contrast phase for the texture analysis cohort (Fig. 2a – b). Demographic and clinical data for this cohort on are listed in Table 3. A comparison of the six texture analysis variables between tumor and background liver for each contrast phase is shown in Fig. 2c.

In the texture analysis cohort, 61.1% (n = 22) of patients had MVI-positive tumor. Factors associated with MVI including both clinical and now texture analysis variables were analyzed with logistic regression. Significant variables that included in the final model construction are listed in Table 4. T1 tumor mean and PVP tumor entropy were the only factors independently associated with MVI. Receiver operating characteristic (ROC) curve for this final model is depicted in Fig. 3a. Empirical optimal cutpoint for PVP tumor entropy and T1 tumor mean were 5.73 and 23.41, respectively. At these cutpoint values, sensitivity was

Table 2 Univariate and multivariate analysis of preoperative factors associated with tumor microvascular invasion (MVI)

Clinical Variable	OR	95% CI	p-value	OR	95% CI	p-value
Age	1.00	0.98–1.02	0.895			
Gender	0.97	0.65–1.45	0.879			
BMI	1.00	0.95–1.04	0.864			
Diabetic	0.76	0.45–1.31	0.327			
Chronic Kidney Disease	1.27	0.4–3.99	0.686			
Hepatitis B infection	1.20	0.41–3.5	0.732			
Hepatitis C infection	2.30	1.28–4.14	0.005	2.73	1.40–5.33	0.003
Cirrhotic	0.70	0.41–1.18	0.176			
History of alcohol abuse	0.77	0.45–1.34	0.358			
Radiographic size of tumor	1.12	1.04–1.20	0.04	1.11	1.02–1.21	0.021
Preoperative bilirubin	0.93	0.60–1.45	0.760			
Preoperative albumin	1.41	0.86–2.30	0.171			
Preoperative Creatinine	1.24	0.70–2.18	0.461			
Preoperative Sodium	0.97	0.89–1.05	0.417			
Preoperative INR	0.45	0.12–1.69	0.235			
Preoperative platelet count	1.00	1.00–1.00	0.226			
AFP level	1.00	1.00–1.00	0.057	1.00	1.00–1.00	0.105
Solitary tumor	1.10	0.58–2.09	0.760			

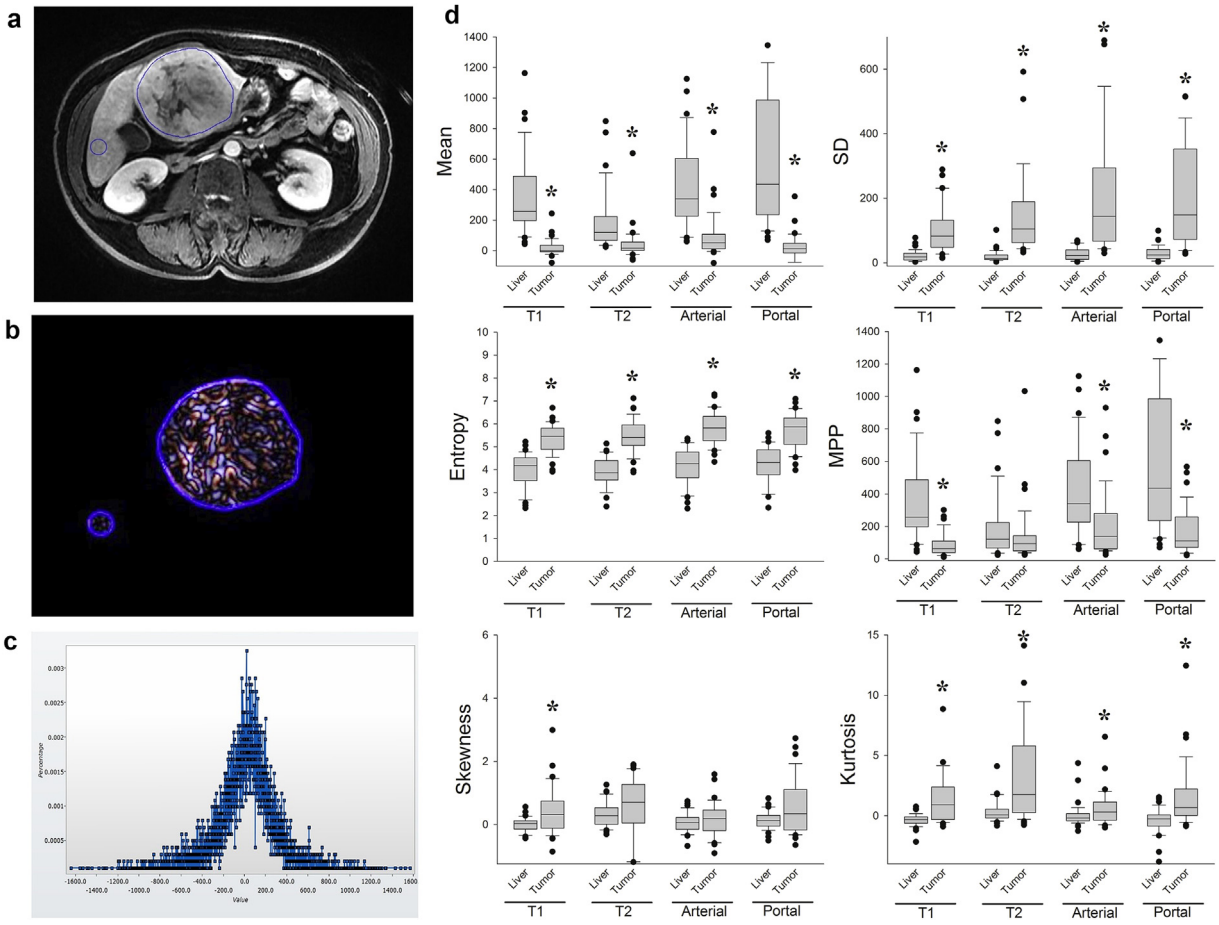

Figure 2 Textures analysis on preoperative magnetic resonance imaging (MRI). a) Representative slice of preoperative contrast-enhanced magnetic resonance imaging used for texture analysis. b) Cross sectional regions of interest (ROI) including the tumor at its largest diameter and a second ROI of uninvolved background liver were analysis with texture analysis software. c) Quantitative analysis of the pixel intensity histogram from the ROI for each patient provided values (d) for mean pixel intensity (mean), standard deviation (SD), entropy, mean of positive pixels (MPP), skewness, and kurtosis. * - $p < 0.05$ for comparison of texture analysis variables between the tumor and background liver (liver) at the specified phase of imaging.

0.68 and 0.5, respectively and specificity was 0.64 and 0.86. Probability of MVI based on the final multivariable model is depicted in Fig. 3b with optimal cutoff points depicted as dashed lines. In the quadrant meeting both cutpoint values, the probability of MVI in the tumor was 87%.

Discussion

In this current study we evaluate the novel role of texture analysis on preoperative imaging and its association with microvascular invasion in hepatocellular carcinoma. The focus of our analysis was to identify factors associated with microvascular invasion as this variable continues to be one the most important prognostic variable in HCC considered for curative treatment. By focusing on preoperative variables our intent was to isolate variables that would identify MVI prior to planned intervention. The novel aspect of this study is that we analyzed first-order MRI-based texture analysis features of HCC and background liver from preoperative imaging and incorporated these variables into a multivariable analysis for identifying MVI. Interestingly, only the texture analysis variables mean pixel intensity and entropy were associated with MVI on final multivariable analysis.

This retrospective review of our institutional series demonstrates the importance of microvascular invasion as a prognostic variable in HCC, consistent with previous reports.[5,7,8] Based on this cohort there were only three clinical variables that were associated with microvascular invasion: hepatitis C infection, tumor size, and preoperative AFP level. These findings are consistent with variables represented in the current literature.[10] We then set out to expand upon this model by introducing texture analysis variables. First, there were notable differences between the tumor and background liver which could be useful

Table 3 Patient demographic and clinical characteristics for the texture analysis cohort

Clinicopathologic Characteristics	Entire Cohort	MVI negative	MVI positive	p
Age (median, IQR)	71 (62–77)	68 (60–76)	73 (66–79)	0.16
Sex				0.55
Male	89.5% (34)	92.9% (13)	86.4% (19)	
Female	10.5% (4)	7.1% (1)	13.6% (3)	
Race				0.44
White	89.5% (34)	85.7% (12)	91% (20)	
Black	7.9% (3)	14.3% (2)	4.5% (1)	
Asian	2.6% (1)	0	4.5% (1)	
BMI	28.1 (25.1–33.6)	30.3 (24.3–37.9)	27.0 (25.2–33.0)	0.29
Diabetic	34.2% (13)	28.6% (4)	40.9% (9)	0.45
Insulin Dependent	13.2% (5)	0	22.7% (5)	0.055
Hepatitis B	5.3% (2)	0	4.5% (1)	0.42
Hepatitis C	23.7% (9)	21.4% (3)	22.7% (5)	0.93
Cirrhosis	55.3% (21)	57.1% (8)	50% (11)	0.67
Alcohol abuse	31.6% (12)	42.9% (6)	27.3% (6)	0.33
Radiographic Tumor size (cm)	4.5 (2.3–6)	2.7 (2–4.9)	5.5 (3.5–7)	0.01
Tumor morphology				0.30
Solitary Tumor	86.8% (33)	78.6% (11)	90.9% (20)	
Multifocal (>1 tumor)	13.2% (5)	21.4% (3)	9.1% (2)	
Preoperative AFP	4.8 (3–19.3)	4.5 (3.8–10.1)	6.9 (1.9–26.5)	0.91
Margin of Resection				0.62
R0	81.6% (31)	78.6% (11)	81.8% (18)	
R1	18.4% (7)	21.4% (3)	18.2% (4)	
Background Liver Fibrosis				0.052
None – moderate fibrosis	43.8% (14)	20% (2)	57.1% (12)	
Severe fibrosis or cirrhosis	56.3% (18)	80% (8)	42.9% (9)	
Tumor Grade				0.16
well differentiated	25.7% (9)	42.9% (6)	14.3% (3)	
moderately differentiated	62.9% (22)	50% (7)	71.4% (15)	
poorly differentiated	11.4% (4)	7.1% (1)	14.3% (3)	
Microscopic vascular invasion				
no	38.9% (14)			
yes	61.1% (22)			

Table 4 Multivariate analysis of factors including texture analysis variables associated with microvascular invasion (MVI) in HCC

Clinical and Texture Analysis Variable	OR	95% CI	p-value	OR	95% CI	p-value
T1 Tumor mean	0.98	0.96–1.00	0.068	0.97	0.95–0.99	0.043
T1 Tumor skewness	3.42	0.88–13.29	0.075			
T1 Tumor kurtosis	1.75	0.95–3.22	0.074			
T2 Tumor entropy	3.80	1.10–13.04	0.034			
HAP Tumor mean	0.99	0.98–1.00	0.12			
PVP Tumor entropy	4.27	1.20–15.13	0.025	4.72	1.37–16.29	0.014
Radiographic size of tumor	1.32	0.96–1.82	0.083			
Tumor grade	3.03	0.83–11.03	0.093			
Extent of liver fibrosis	0.19	0.03–1.11	0.064			

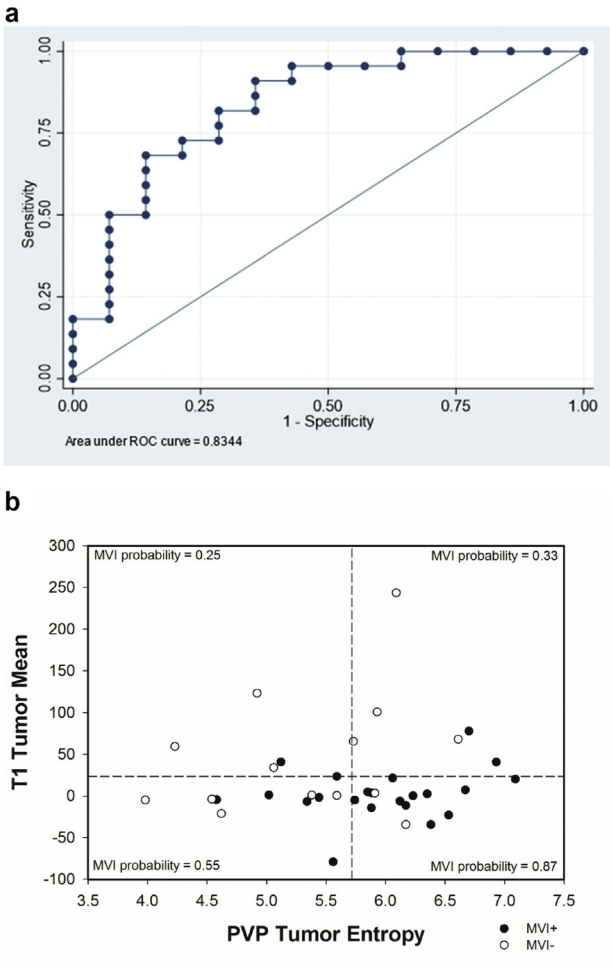

Figure 3 (a) Receiver operating characteristic (ROC) curve for the final multivariate model for prediction of microvascular invasion (MVI) in hepatocellular carcinoma which included two variables: portal venous phase (PVP) tumor entropy and T1 tumor mean (b) Scatter plot showing probability of HCC with MVI based on the final model and optimal cutpoint values (dashed lines)

as diagnostic adjuncts. Additionally, TA factors were found to be associated with microvascular invasion: PVP tumor entropy and T1 tumor mean. When these factors were incorporated into a multivariate model they were the only factors associated with MVI.

The field of radiomics and texture analysis is quickly expanding and becoming an important addition to radiology for solid tumors.[19,20] We believe that one of the strongest aspects regarding this technique is the ability to objectively define quantitative variables for specific image findings. Indeed, texture analysis may be applied to extract additional mathematical data from both prospectively and retrospectively acquired imaging examinations, including CT and MRI with different contrast agents.[21] In our study we performed texture analysis on MR images acquired with Gd-BOPTA, which is the current standard approach for the preoperative evaluation of patients with HCC at our Institution. Other studies have applied texture analysis on liver MRI studies obtained with different extracellular or hepatobiliary[22,23] contrast agents. In this current study one of the most predictive variables was tumor entropy. Entropy is a texture feature that estimate the inhomogeneity and irregularity of the gray-level pixel intensities distributed within a selected region of interest. Higher lesion entropy reflects greater imaging inhomogeneity and it may represent an additional imaging biomarker of histopathological tumor heterogeneity and aggressiveness. Among the wide spectrum of texture features, the entropy has demonstrated to be a potential strong predictor of lesion histological background in focal liver lesions.[15] Moreover, few prior studies have explored the potential of texture analysis on resected hepatocellular carcinoma to predict prognosis and treatment response on contrast-enhanced CT or MRI images.[13,14,16,24–26] Mulé et al.[14] identified the entropy on portal venous phase CT images as independent predictor of overall survival at multivariate analysis in patients with advanced hepatocellular carcinoma treated with Sorafenib. Akai et al.[27] correlated the entropy, along with other 5 texture features, with disease free survival and overall survival of 127 patients with resectable HCC imaged with contrast-enhanced CT. Ahn et al.[28] reported that texture analysis (including entropy on hepatobiliary phase images) added to MRI analysis improved the performance for estimate early recurrence in 179 patients with single HCC images with gadoxetate disodium-MRI. One additional study[26] examined the angle co-occurrence matrix and local binary pattern on preoperative CT imaging and its association with MVI. Their methods were technically challenging, examining only the 10-pixel width region of interest that made up the liver-tumor interface, making broad clinical applicability difficult. This current adds to this data supporting the utility of texture analysis on cross-sectional imaging in identifying MVI in HCC with the advantage of identifying specific variables and cutpoint values that can be easily implemented into clinical practice.

This study is not without its limitations. The retrospective nature of the study cohort in a selected patient population is associated with selection bias. Additionally, the heterogeneity of preoperative imaging resulted in reduced cohort size to maintain consistency in the texture analysis and minimize the differences due to heterogeneous imaging protocols. Although there is not strong recommendation for an ideal MRI protocol for texture analysis, different acquisition parameters may lead to different texture results. Moreover, texture analysis was performed by a single reader and the inter-reader agreement could not be evaluated. Other recently published studies have reported a high reproducibility and inter-reader agreement of texture features extracted from HCC lesions (ICC range of MRI-based texture features reported from 0.64 to 0.99).[22,29,30] Despite these inherent limitations we were able to identify a simplistic model that allows for easy application to identify microvascular invasion

in hepatocellular carcinoma. Thus, the biggest deficiency of this study is the lack of a validation cohort. Without such the immediate clinical applicability of these findings are limited. However, this study is one of the first studies to review texture analysis parameters in a granular fashion with identification of specific numbers and cutpoint values that can be easily applied in a clinical setting. In order to validate these findings a prospective study of patients undergoing evaluation for the treatment of hepatocellular carcinoma should be undertaken. Design and planning of this study is currently ongoing.

In conclusion, MRI-based texture analysis can help identify tumor biology in the form of microvascular invasion. First-order texture analysis variables mean pixel intensity and entropy were associated with MVI on final multivariable analysis. These findings should be validated in a prospective study.

Conflicts of interest

None declared.

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