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Retrospective Study

Radiomic Analysis Based on Multi-phase magnetic resonance imaging **to Predict Preoperatively Microvascular Invasion in Hepatocellular Carcinoma**

MRI Radiomic Analysis Predict HCC MVI

Yueming Li, Yuemin Zhu, Lanmei Gao, Zewen Han, Xiaojie Chen, Chuan Yan, Rongping Ye, Dairong Cao

Abstract

BACKGROUND

The prognosis of hepatocellular carcinoma (HCC) still remains poor and the relapse occurs in more than half of patients within two years after hepatectomy. In terms of recent studies,microvascular invasion (MVI) is one of the potential predictors for recurrence.Accurate preoperative prediction of MVI is potentially beneficial to the optimization of treatment planning.

AIM

The aim of this study is to develop a radiomic analysis model based on pre-operative magnetic resonance imaging (MRI) datato predictMVI in HCC.

METHODS

A total of 113 patients recruited to this study have been diagnosed as HCC with histological confirmation, among whom, 73 were found to have MVI and 40 were not. All the patients received preoperative examination by Gd-enhanced MRI and then curative hepatectomy. We manually delineated the tumor lesion on the largest cross-sectional area of the tumor and the adjacent two images in MRI, namely the regions of interest (ROIs). Quantitative analyses includedmost discriminant factors (MDFs) developed using linear discriminant analysis (LDA) algorithm and histogram analysis by the MaZda software.Independent significant variables of clinical, radiologicalfeaturesand MDFs for the prediction of MVI were estimated and discriminant model was established by univariate andmultivariate logistic regression analysis. Prediction ability of above-mentioned parameters or modelwas then evaluated by Receiver operating characteristic (ROC) curve. 5-fold cross-validation was also applied *via* R software.

RESULTS

The area under the ROC curve (AUC) of the MDF (0.77-0.85) outperformed histogram parameters (0.51-0.74). After multivariate analysis, MDF values of arterial and portal venous phase, peritumoral hypointensity on hepatobiliary phase were independent predictors for MVI (P< 0.05). The AUC value of the model was 0.939 (95%CI 0.893-0.984, standard error 0.023). The result of internal 5-fold cross-validation (AUC: 0.912, 95%CI: 0.841-0.959, standard error: 0.0298) also showed favorable predictive efficacy.

CONCLUSION

Noninvasive MRI radiomic model of MDF values and imaging biomarkers may be useful to make a preoperative prediction of MVI in patients with primary HCC.

Key Words: Hepatocellular carcinoma; Microvascular invasion; Magnetic resonance imaging; Radiomic analysis; imaging biomarkers

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Core Tip: we developed a radiomic analysis model based on pre-operative magnetic resonance imaging (MRI) data to predict microvascular invasion (MVI) in hepatocellular carcinoma (HCC). Quantitative analyses includes most discriminant factors (MDFs) developed using the linear discriminant analysis (LDA) algorithm and histogram analysis by the MaZda software. The AUC value of the model and the result of internal 5-fold cross-validation showed favorable predictive efficacy. A noninvasive radiomic model of MDF values and imaging biomarkers may be useful to make a preoperative prediction of MVI in patients with primary HCC.

INTRODUCTION

As important therapies for HCC, liver resection and transplantation are widely applied in clinic and the techniques have great advances. However, the prognosis still remains poor andthe relapse occursin more than half patients within two years after hepatectomy[1].In terms of recent studies,MVI is one of the potential predictors for recurrence[2, 3]. MVI,only seen under the microscope,is defined as the appearance of tumor cells in smaller vessels inside the liver which include small portal vein, small lymphatic vessels or hepatic artery [4, 5].And MVI can be classified as four subclasses varying from M0 to M3,and higher grade usually indicates the higher invasiveness of HCC and poor survival rate[6].Nonetheless, MVI is diagnosed by post-surgery histological result at present,which is the gold standard. The accurate prediction of MVI before operation can help the anatomic resection with expanding resection margin even for a small tumor[7]. Thus, accurate preoperative prediction of MVI is potentiallybeneficial to the optimization of treatment planning [3, 8].

There have been some studies to preoperatively predictMVIin terms of serum markers,radiological featuresor imaging techniques[9-11]. For example, albumin was independently associated with MVI [9]. Besides, non-smooth tumor marginshadstrong diagnostic power and were of great importance for MVI assessment[10].Moreover, Gd-EOB-DTPA, a special hepatocellular parenchymal contrastagent for MRI,was valuable for MVI predictionas well[11, 12]. However, thelevel of serum markersis instable and likely tobe affected by other diseases,and the imaging characteristics areevaluated subjectively and lack of conformance between observers. Thus,a more reliable biomarker is needed for preoperative prediction of MVI.

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Quantitative analysis may have advantages over subjective analysis in reflecting valuable microscopic image features. Radiomic analysis can quantify the spatial variations in gray-level patterns, image spectral properties and pixel interrelationships which therefore, has attracted great interest[13-15].Usingautomation algorithms based on big data andwith the advantages of noninvasiveness, radiomics analysisprovides a powerful toolfor modern medicine,and it can broadly combine the multiple biomarkers and then guide clinical decision making for patients suspected with cancer [16]. Various

machine-learning methods have been used for radiomic analysisfor MVI prediction,such as support vector machine, random forest[17, 18].To the best of our knowledge, there is not yet radiomics study based on linear discriminant analysis (LDA) algorithmto predict MVI. Additionally, even without spatial information, histogram analysis alone can indicate a gray-level distribution and is used for MVI prediction[19, 20].

Our aim was to identify the histogram parameters alone that were predictive for MVI, and determined the prediction capacity of LDA radiomic modelsbased on multiple phases in pre-operative Gd-enhanced MRI aloneorcombined with the image features for detecting MVI.

MATERIALS AND METHODS

2.1 Patients

Patients were consecutively recruited between June 2019 and November 2021, who underwent Gd-enhanced MRI examination before surgery. The inclusion criteria were: (1) solitary HCC lesion which is resectable or multiple HCC lesions appearing within one liver lobe; (2) no macroscopic vascular invasion; (3) received the examination of Gd-enhanced MRI of the liver (with or without hepatobiliary phase) within 1 mo before surgery; (4) received curative hepatectomy; and (5) verification of MVI by pathological evidence. Exclusion criteria were as follows: (1) other anti-tumor therapies have been performed before surgery; (2) pathological or clinical information is incomplete; (3) The imaging is not enough for analysis as a result of motion artifact; and (4) MRI performed in a different 3.0T MR machine. A total of 113 patients (91 men, 22 women; age ranging from 29–88 years, median age 58 years old)were included.According to pathologic results, HCC patients were allocatedinto MVI-positive (MVI+) and MVI-negative (MVI-) groups. The inclusion and exclusion criteria are shown in the flow diagram (Figure 1). This single-center retrospective cohort study was approved by the Institutional Review Board (No. [2019]283), who determined the requirement for informed consent could be waived.

2.2 *MRI examination*

A 3.0T MR machine (MAGNETOM Verio; Siemens, Healthcare, Erlangen, Germany) with a dedicated phased-array body coil was used for MRI. The standard abdominal MRI protocol included: (1) Axial T2-weighted fat-suppressed turbo-spin-echo (TSE): Repetition time (TR)/echo time (TE), 4700/79msec, slice thickness, 5mm, slice gap, 1mm, FOV, 21x38mm^2; (2) in-phase and out-of-phase axial T1-weighted imaging (T1WI) : TR/TE,133/2.5msec (in-phase), 6.2msec (out-phase), slice thickness, 5mm, slice gap, 1mm, FOV, 21x38mm^2; (3) diffusion-weighted imaging (DWI) (b=50, 800sec/mm^2) performed with a free-breathing single-shot echo-planar technique, TR/TE, 9965/73msec, slice thickness, 5mm, slice gap, 1mm, FOV, 21x38mm^2. MRI system automatically calculated the corresponding ADC maps; and(4) contrast enhanced MRI, a 3D gradient echo sequence with volumetric interpolated breath-hold examination (VIBE) was performed before and after injection of gadobenate dimeglumine (MultiHance; Bracco),ata dose of 0.2 mL/kg andat a rate of 2mL/sec followed by a 20mL saline flush with the following parameters: TR/TE, 3.9/1.4msec, slice thickness 3mm, slice gap, 0.6mm, FOV, 25x38mm^2. Hepatic arterial phase (AP), portal venous phase (PVP), equilibrium phase (EP) and hepatobiliary phase (HBP) images were obtained at 20–30sec, 70–80sec, 180sec and 90min after contrast medium injection, respectively.

2.3 *Radiomic analysis*

MaZda software (version 4.6.0, available at http://www.eletel.p.lodz.pl/mazda/) was used for Radiomic analysis [21], Digital Imaging Transformation and Communications in Medicine (DICOM) format for compatibility with it. Images of MVI+ and MVI- were loaded into the MaZda software; then, ROI was segmented manually by one radiologist, on the largest cross-sectional area and adjacent two images of the tumor or largest lesion (in the case of multiple lesions), which also included cystic necrotic regions. To delineate the tumor, the reference was based on HBP or T2 weighted imaging (in case of artifact) which were first segmented. Subsequently, the ROI was

overlaid onto other phase images as required. If the respiratory movement caused the change of tumor location, the ROI was finely adjusted.

Radiomic analysis were performed by the MaZda package after loading all segmented tumor images on T2-weighted imaging (T2WI)and T1WI+Gd; within each ROI,101 features were generated. Six different statistical image descriptors including gradient features,histogram features,GLCM, RLM,wavelet transformand autoregressive modelwere used to create these radiomic features [21, 22]. In each ROI, Gray-level was normalized to minimize the effect of brightness and contrast variation by the normalization of image intensities in the range $\mu \pm 3\sigma$ (μ gray-level mean, σ standard deviation), which range was quantized to 6 bits/pixel [23, 24].

Dimension reduction is necessary because it is impractical for clinicians to analyze all radiomic features on each patient andcurse of dimensionalitymay happen in the case of too many features. Thus, the useful features were selectedamong 101 features in each sequence using algorithms, i.e., mutual information (MI), Fisher coefficient (Fisher) and classification error probability, which was combined with average correlation coefficients (POE + ACC and PA). These combinations led to the 30 highest discriminative power features in each sequence for further analysis. The statistical B11 radiomic analysis package (a plug-inof Mazda software) was used for these 30 features; a linear discriminant analysis (LDA) model with the lowest misclassification rate was used to calculate the most discriminant factor (MDF) [25], which served as a comprehensive variable for discrimination and represented a linear combination of these input 30 features that achieves the maximum separation for samples between MVI+ and MVI- groups and the minimum separation of samples within each group. Hence, there were six MDFs,i.e., MDF_{T1WI}, MDF_{T2WI}, MDF_{AP}, DMF_{PVP}, MDF_{EP}, MDF_{HBP}.

The values of the 9 histogram features (mean, variance, skewness, kurtosis, percent 1%, percent 10%, percent 50%, percent 90% and percent 99%) previously described (i.e., one of six different statistical image descriptors used for radiomic analysis) were separately saved in addition for the comparison with MDF values. All characteristics of

radiomic analysis were generated as presented in Figure 2 and 3. And a LDA model was used for text feature dimension reduction.

2.4 *Analysis of semantic features*

In each case, an optimal window setting was adjusted to evaluate the preoperative MR images in the Picture Archiving and Communication System (PACS) adjustment. The imaging features for each HCC were evaluated by the two abdominal radiologists independently based on the following criteria: (a) arterial rim enhancement, this definition was based on the image of irregular ring-like enhancement with relatively hypovascular central areas in the arterial phase[26, 27]; (b) arterial peritumoral enhancement, this definition was based on the detectable crescent or polygonal shaped enhancement outside the tumor margin, which broadly contact with the tumor border in the arterial phase, changing to isointense with liver parenchyma background in the delayed phase [28]; (c) tumor margin, also defined as smooth margin, the representative image was nodular tumors with smooth contour, or non-smooth margin presenting as non-nodular tumors with irregular margin that had surrounding budding portion in the transverse and coronal HBP images[10, 28]; (d) radiological capsule, presenting as peripheral edge of smooth hyperenhancement in the portal venous or equilibrium phase[28, 29]; (e) tumor hypointensity on HBP, shown as lower SI than that of the surrounding liver [12, 30] and (f) peritumoral hypointensity on HBP, defined as wedge-shaped or flame-like hypointense area of hepatic parenchyma located outside of the tumor margin on HBP [31]. Two radiologists assessed the features of the HCC imaging or largest lesion (in the case of multiple lesions). The final decision was based on their consensus.

2.5 *Histopathological analysis*

The tumor size, number, and capsule condition was collected and analyzed. The histological type, differentiation grade, lymphocyte infiltration, satellite nodules, MVI status and chronic liver disease was compared [32]. The definition of MVI was the presence of tumor emboli in an endothelial cells-lined vascular space. The experienced

pathologists reported the histopathological results after reviewing the clinical and imaging files.

2.6 Statistical Analysis

SPSS for Windows (version25.0) and Medcalc (Version15.2.2)were used to generate the ROC curves and compare the diagnosis performance for identifying MVI. The areas under the ROC curve (AUCs) were used to assess the predictive efficacy and the optimal cutoff values from the maximum Youden's index were calculated, as well as the corresponding sensitivity and specificity for discriminating between MVI+ and MVI-. Univariate and multivariate logistic regression analysis was performed to confirm the significant variables related to MVI including clinical factors, imaging features and MDFs in different sequences, and then build the discriminant model. Multivariate logistic regression analysis was performed using forward stepwise elimination method to identify the independent predictors. The prediction ability of significant MDF and the discriminant model was evaluated by AUC. The five-fold cross-validation was performed using the "caret" package, and nomogram was used as a graphical representation using the "rms" package (R software version 4.0.2, http://www.r-project.org). Student's t-test or Mann-Whitney U test was used to compare the continuous variables. Fisher's exact test or Pearson's chi-squared test was used to compare the categorical variables. $P< 0.05$ indicates statistical significance.

RESULTS

3.1 Patient characteristics

The patients were divided into two groups according to the histopathological results: The MVI+ group and the MVI- group. Among 113 HCCs, 73 had MVI (4 patients had no images of HBP), while 40 had no MVI (4 patients had no images of HBP). The patients' clinical and radiological characteristics are listed in Table 1 and 2,respectively. There were statistically significantdifferences in alpha-fetoprotein (AFP), pathologic grade,maximum tumor diameter (MTD), arterial rim enhancement, tumor margin and peritumoral hypointensity on HBP between the MVI+ and MVI- groups ($P< 0.050$).

3.2 *Radiomic Analysis*

For the MVI+ and MVI- patients, the values of MDF resulting from the LDA model under B11 analysis were significantly different between the two groups (P< 0.001). The analysis of MDF values by ROC generated an AUC of 0.82 (95%CI, 0.77-0.87) for T1WI; 0.77 (95%CI, 0.72-0.83) for T2WI; 0.84 (95%CI, 0.80-0.88) for AP; 0.85 (95%CI, 0.81-0.90) for PVP; 0.84 (95%CI, 0.79-0.88) for EP and 0.83 (95%CI, 0.78-0.87) for HBP. Cutoff values of -1.38×10^{-3} (T1WI), 4.73×10^{-3} (T2WI), 1.97×10^{-2} (AP), 4.17×10^{-3} (PVP), 2.25×10^{-2} (EP) and 4.30×10^{-4} (HBP) were obtained with corresponding high sensitivities and specificities (T1WI 78%, 78%; T2WI 59%, 80%; AP 87%, 66%; PVP 67%, 90%; EP 68%, 85%; HBP 76%, 79% respectively). The predictive powerof MDFs derived from the radiomics analysis was better than that of all other histogram parameters (AUC: T1WI range from 0.52-0.68, T2WI range from 0.53-0.70, AP range from 0.54-0.69, PVP range from 0.50-0.74, EP range from 0.51-0.74 and HBP range from 0.52-0.65) (Table3-4).The MRI images of four cases with MVI+ and MVI- at AP and PVP were presented, which showed similar histogram features but different MDFs (Figure 4 and Table S1).

3.3 *Association of the most discriminant factor and patient characteristics with microvascular invasion*

We excluded the patients who had no images of HBP. MDF values were derived from the largest cross-sectional area of images for univariate analysis. Univariate analysis showed that MDF_{T1WI} greater than -1.38×10^{-3} (OR = 11.2000, 95%CI 4.346-28.861; P < 0.001), MDF_{T2WI} greater than 4.73×10^{-3} (OR = 6.066, 95%CI 2.334-15.765; P < 0.001), MDF_{AP} greater than 1.97×10^{-2} (OR = 8.552, 95%CI 2.967-24.650; P < 0.001), MDF_{PVP} less than 4.17×10^{-3} (OR = 0.050, 95%CI 0.017-0.143; P< 0.001), MDF_{EP} less than 2.25×10^{-2} (OR = 0.095, 95%CI 0.037-0.244; P< 0.001) and MDF_{HBP} greater than 4.30×10^{-4} (OR = 8.800, 95%CI 3.222-24.032; P < 0.001) were important risk factors related to the existence of MVI. Among patient characteristics, univariate analysis showed that MTD (OR = 1.351, 95%CI 1.146–1.593; P< 0.001), the AFP level (OR = 3.818, 95%CI 1.357–10.605; P = 0.028), arterial rim enhancement (absent *vs* present, OR = 5.683, 95%CI 1.977–16.340; P = 0.001),tumor margin (smooth *vs* non-smooth, OR = 4.024, 95%CI 1.555–10.414; P =

0.004), and peritumoral hypointensity on HBP (absent *vs* present, OR =52.000, 95%CI 11.287–239.569; $P < 0.001$) were significant risk factors associated with the presence of MVI (Table 5).

3.4 Multivariateanalysis of the most discriminant factor values and patient characteristics with microvascular invasion

Multivariate analysis of the above 11 significant parameters showed that only the MDF_{AP} ($\leq 1.97\times10^{-2}$ vs. $>1.97\times10^{-2}$, OR = 7.654, 95%CI 1.860-31.501; $P = 0.005$), MDF_{PVP} ($\leq 4.17\times10^{-3}$vs. $> 4.17\times10^{-3}$,OR = 0.182, 95%CI 0.047-0.705; $P = 0.014$), and peritumoral hypointensity on HBP (absent *vs* present, OR = 37.098, 95%CI 6.861-200.581; $P < 0.001$) were independent predictors related to the existence of MVI (Figure 5).

The risk scores for individual patients based on the final discriminant model were calculated using the following formula: Logit（P）= −4.612 + 3.614 × peritumoral hypointensity on HBP (absent =0, present =1) + 2.035 × MDF_{AP} (≤1.97×10-2 vs. >1.97×10-2, ≤1.97×10-2 = 0, >1.97×10-2 = 1) -1.876 ×MDF_{PVP} (≤ 4.17×10-3 vs. > 4.17×10-3, ≤ 4.17×10-3= 0, >4.17×10-3 = 1). The probabilities of MVI were calculated by the formula (P= e Logit (P)/ 1+ e Logit (P)).

AUC of the final model was 0.939 (95%CI 0.893-0.984, standard error 0.023) and the optimal cutoff value was 0.595881 ≈ 0.60 (specificity: 89%, sensitivity: 90%, Youden's index: 0.788) (Figure 6A). The result of internal 5-fold cross-validation (AUC: 0.912, 95%CI: 0.841-0.959, standard error: 0.0298) also showed favorable predictive efficacy (Figure 6A). The independent predictive factors were integrated into a nomogram by the multivariate logistic regression analysis (Figure 6B).

3.5 Comparison of area under the receiver operating characteristic curve values of MDF values and imaging features

We generated the ROC curves of MDF_{AP} and MDF_{PVP} which were independent predictors. The ROC curves of imaging features which were significantly different were also generated. The results were compared using the Delong test. The MDF_{AP} and MDF_{PVP} had significantly higher AUCs than MTD, arterial rim enhancement, tumor

margin (P< 0.05;Table S2). However, there were no differences in AUCs among MDF_{AP} and MDF_{PVP} and peritumoral hypointensity on HBP (P > 0.05; Table S1). Comparison of ROC curves is shown in Figure 6C.

DISCUSSION

MVI indicates the invasiveness of HCC and poor prognosis[2, 3]. Therefore, the pre-operative prediction of MVIis an important factor for assessing long-term patient survival and treatment optimization (8, 9). The quantification of MRI images by Radiomic analysis can characterize the heterogeneity of tumor and has demonstrated previous success in reflecting histological subtype [33, 34]. To the best of our knowledge, through the analysis of the top 30 parameters in each sequence, an overall discriminator MDF was generated by LDA model, providing better prediction ability to MVI than thehistogram features.

Our study showed the high sensitivity of MDF values from radiomic analysis on preoperative Gd-enhanced MRI images and/or specificity in distinguishing between MVI+ and MVI-. The AUCs of MDF values of six sequences, all of which were more than 0.75, outperformed all histogram parameters and imaging features. The MDF values of AP and PVP had significantly higher AUCs than the most of imaging features. MDF values could provide additional information useful for clinical management decisions. Moreover, MaZda software can be easily used for general clinicians without additional requirement of expertise, easily serving as a potential powerful tool in preoperative prediction of MVI.

LDA has been used in radiomics studies recently[35]. Han et al. found that LDA and support vector machine achieved optimal performance when compared with multiple machine learning methods[35]. In our study, among the LDA models based on various sequences, MDF_{AP} and MDF_{PVP} were significant independent factors for the prediction of MVI, and showed satisfactory predictive efficacy with AUC greater than 0.80.Histogram parameters have been used in quantitative analysis of MVI in clinical studies[19, 20]. Li et al. performed histogram analysis in intravoxel incoherent motion

and the best parameter provided a sensitivity of 81% and a specificity of 85%[19]. It was based on whole tumor volume, but only 41 patients were enrolled. Wang *et al* used computational quantitative measures based on the maximum cross-sectional area to predict MVI of small HCC, but only in HBP images [20]. The AUC, sensitivity, and specificity of 0.91, 87 %, and 80 %, respectively. In our study, the radiomic analysis-based MDF outperformed each individual histogram parameter in predicting the presence of MVI. Therefore, we considered that MDFs on the basis of LDA model that contained more comprehensive information could evaluate the Gd-enhanced MR images and determine MVI status better than histogram analysis alone.

Multivariate analysis of the 11 risk factors identified on univariate analysis found that only peritumoral hypointensity in HCCs on the HBP, MDF_{PVP} and MDF_{AP} were independent predictors of MVI. Pathologically, MVI is usually found in the small portal vein and hepatic artery[4]. It may be detected in the small liver lymphatic vessels. But it is mostly found in small branches of the portal vein. This may explain why the MDF_{PVP} and MDF_{AP} were independent predictors of MDF values in the model that predicted MVI. The MDF_{PVP} whose OR was less than 1 may be a protective factor, which means the higher MDF_{PVP}, the less possible presence of MVI. MVI may affect the biological functions of the canalicular transporter multidrug resistance-associated protein 2 or the organic anion transporting peptides, both of which lead to the elimination of gadoxetate disodium. That may be the reason why peritumoral hypointensity appeared in HCCs on the HBP[12]. The OR of peritumoral hypointensity on HBP was quite high, which may result from relatively small sample size.

It has been reported that MR findings including arterial peritumoral enhancement and non-smooth tumor margin were independent predictors associated with the presence of MVI or indicated the association between the hypointensity of HCCs on HBP images and a higher frequency of MVI [12, 17], which is not consistent with our study. One possible reason for the inconsistence may be in the differences between study populations, as all patients enrolled in that study had a single HCC with diameter ≤ 5 cm. The inherent and technical inconsistencies between the observers in two studies

may also account for the incompatible results. Arterial rim enhancement can predict biological characters of HCCs, including MVI, rapid progression and early recurrence[26, 36]. Our study showed rim enhancement in the arterial phase was not an independent predictor of MVI, the reason may be that rim enhancement in arterial phase is uncommon in HCC but more often seen in mass-forming cholangiocarcinoma or metastasis[37].

However, here are some limitations in this study. First, a selection bias may exist due to the retrospective study. Second, the radiomic analysis was performed only on the largest cross-sectional area and adjacent two images of the tumor. There may be information loss compared to whole tumors. In spite of this, our results showed excellent discriminative efficacy between MVI+ and MVI- groups. Third, different MVI grading indicates a decreasing gradient of overall survival and time to early recurrence, which was not analyzed in the MVI+ group due to the small sample size. Finally, this study was performed at only one institution, causing the sample size small relative to the number of variables. Further multicenter, prospective studies are needed to validate the results of this study.

CONCLUSION

In conclusion, radiomic analysis based on preoperative Gd-enhanced MR images may be feasible for predicting MVI of HCC. Upon the application of MRI findings and radiomic variables in our model, the diagnostic prediction of MVI showed high specificity and sensitivity, showing this method to be a useful tool for clinicians in treatment decision making.

ARTICLE HIGHLIGHTS

Research background

The prognosis of HCC remains poor and the relapse occurs in more than half of the patients within two years after hepatectomy. MVI is one of the potential predictors for recurrence. MVI is defined as the appearance of tumor cells in smaller vessels inside the

liver which include small portal vein, small lymphatic vessels or hepatic arteries. Accurate preoperative prediction of MVI is potentially beneficial to the optimization of treatment planning.

Research motivation

There have been some studies to preoperatively predict MVI in terms of serum markers, radiological features or imaging techniques. However, the level of serum markers is instable and likely to be affected by other diseases, and the imaging characteristics are evaluated subjectively and lack of conformance between observers. Thus, a more reliable biomarker is needed for preoperative prediction of MVI.

Research objectives

The aim of this study is to develop a radiomic analysis model based on pre-operative MRI data to predict MVI in HCC.

Research methods

A total of 113 patients recruited to this study have been diagnosed as HCC with histological confirmation, among whom, 73 were found to have MVI and 40 were not. All the patients received preoperative examination by Gd-enhanced MRI and then curative hepatectomy. We manually delineated the tumor lesion on the largest cross-sectional area of the tumor and the two adjacent images in MRI. Quantitative analyses included MDFs developed using a linear discriminant analysis algorithm and histogram analysis via the MaZda software. Independent significant variables of clinical, radiological features and MDFs for the prediction of MVI were estimated and a discriminant model was established by univariate and multivariate logistic regression analysis. Prediction ability of the above-mentioned parameters or model was then evaluated by the ROC curve, and 5-fold cross-validation was also applied *via* R software.

Research results

The area under the ROC curve of the MDF (0.77-0.85) outperformed the histogram parameters (0.51-0.74). After multivariate analysis, MDF values of the arterial and portal venous phase, and peritumoral hypointensity in the hepatobiliary phase were independent predictors for MVI ($P < 0.05$). The AUC value of the model was 0.939. The result of internal 5-fold cross-validation (AUC: 0.912) also showed favorable predictive efficacy.

Research conclusions

A noninvasive MRI radiomic model of MDF values and imaging biomarkers may be useful to make a preoperative prediction of MVI in patients with primary HCC.

Research perspectives

We believe that models of a noninvasive radiomic model based on pre-operative MRI data have potential to be widely used in clinical fields.

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