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Observational Study

Application of texture signatures based on multi-parametric magnetic resonance images for predicting microvascular invasion in hepatocellular carcinoma: A retrospective study

The application of texture signatures based on multi-parametric MR images in predicting microvascular invasion of hepatocellular carcinoma

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Abstract

BACKGROUND

Despite continuous changes in treatment methods, the survival rate for advanced HCC patients remains low, highlighting the importance of diagnostic methods for HCC.

AIM

To explore the efficacy of texture analysis based on multi-parametric magnetic resonance (MR) imaging in predicting microvascular invasion (MVI) in preoperative hepatocellular carcinoma (HCC).

METHODS

This study included 105 patients with pathologically confirmed HCC, categorized into MVI-positive and MVI-negative groups. We employed Original Data Analysis (ODA), Principal Component Analysis (PCA), Linear Discriminant Analysis (LDA), and

Nonlinear Discriminant Analysis (NDA) for texture analysis using multi-parametric MR images to predict preoperative HCC microvascular invasion. The effectiveness of texture analysis was determined using the B11 program of the MaZda4.6 software, with results expressed as the misjudgment rate (MCR).

RESULTS

Texture analysis using multi-parametric MR imaging, particularly the MI+PA+F dimensionality reduction method combined with NDA discrimination, demonstrated the most effective prediction of HCC microvascular invasion. Prediction accuracy in the pulse and equilibrium phases was 83.81%. Misjudgment rates (MCR) for the combination of T2WI, arterial phase, portal venous phase, and equilibrium phase were 22.86%, 16.19%, 20.95%, and 20.95%, respectively. The area under the curve (AUC) for predicting HCC MVI positivity was 0.844, with a sensitivity of 77.19% and specificity of 91.67%.

CONCLUSION

Texture analysis of arterial phase images demonstrated superior predictive efficacy for HCC microvascular invasion compared to T2WI, portal venous, and equilibrium phases. This study provides an objective, non-invasive method for preoperative prediction of HCC microvascular invasion, offering a theoretical foundation for the selection of clinical therapy.

Key Words: MRI; hepatocellular carcinoma; texture analysis; microvascular invasion

Core Tip: Texture analysis using arterial phase images provides superior predictive efficacy for HCC microvascular invasion compared to T2WI, portal venous, and equilibrium phases. The texture analysis of liver MR images holds significant value for the preoperative prediction of MVI in HCC patients.

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most prevalent cancers worldwide, and its primary pathological manifestation is hepatocellular carcinoma [1]. Currently, the optimal treatment for liver cancer remains radical resection. However, many patients miss the opportunity for curative surgery at the time of diagnosis. Despite the availability of treatments for advanced, unresectable HCC, such as transcatheter arterial chemoembolization (TACE), radiofrequency thermal ablation (RFTA), and molecular targeted drugs (including tyrosine kinase inhibitors (TKIs) like sorafenib and lovatinib), their efficacy remains limited [2]. Thus, there is an urgent need for more effective diagnostic methods to detect the disease status of patients early and enhance their survival rates.

Microvascular invasion (MVI) is a crucial risk factor influencing tumor relapse post-surgery[3-5]. Accurate pre-surgery prediction of microvascular invasion influences the selection of tumor treatment plans. Currently, the assessment of HCC microvascular invasion primarily depends on postoperative pathological biopsies; however, this method is invasive and carries risks like bleeding, tumor implantation, and metastasis. Image texture analysis offers an objective and quantitative means of image description. The local characteristics of image pixel gray values, their changing patterns, and distribution, as quantitatively analyzed, can reflect the physiological heterogeneity within the region of interest (ROI). Recently, it has been applied in a range of medical imaging techniques to aid in disease diagnosis and treatment[6-9]. Previous studies have indicated that CT imaging is the principal method for texture analysis in predicting microvascular invasion in HCC [10, 11], with most studies opting for 2D ROIs. Compared to 3D ROIs, these studies lacked comprehensive assessment of

tumor heterogeneity[12-14]. Furthermore, the software, analysis, and discrimination methods used in medical imaging texture analysis vary. Texture analysis is widely used to predict disease progression, including aggressiveness, disease-free survival (DFS), and overall survival (OS) in patients with PDAC [15]. Recent studies have also demonstrated that mpMRI as a standard of pre-biopsy care has increased the prostate cancer detection rate from 26% to 38%[16]. Medical image texture analysis is utilized to quantitatively extract features not discernible to the naked eye, further reflecting the distribution pattern and changes in pixel gray values in the ROI, aiding in the identification of potential heterogeneity in tumor lesions [17].

In this study, our goal is to acquire quantitative features from the ROI using a high-throughput method and forecast microvascular invasion in HCC through texture analysis based on multi-parametric MR images. We aim to offer an objective auxiliary method for noninvasive preoperative prediction of HCC microvascular invasion, potentially guiding clinical decisions.

MATERIALS AND METHODS

From June 2016 to March 2022, 105 eligible HCC patients from our hospital were enrolled in this study. Patients were categorized into the MVI-positive group (57 cases) and the MVI-negative group (48 cases) based on postoperative pathological results. Inclusion criteria for the study were: (a) pathologically confirmed HCC, (b) age ≥ 18 years, (c) plain liver MRI scan and three-phase enhanced scan conducted 2 wk before surgery, and (d) completion of at least two cycles of chemotherapy. Exclusion criteria included: (a) non-primary central nervous system lymphoma, (b) previous treatment with other BTK inhibitors, and (c) a single HCC lesion. Additionally, none of the patients had undergone any tumor-related treatment prior to surgery.

All procedures involving human participants were in accordance with the Declaration of Helsinki (DoH). The study protocol was approved by the

Ethics Committee of The Third Affiliated Hospital of Guangxi Medical University. All patients provided written informed consent for their participation.

Grouping

Following the methodology of Rodríguez Perálvarez *et al* [18], patients were grouped into MVI-positive and MVI-negative categories based on their postoperative pathological diagnosis of MVI. The diagnostic criteria for this study were: the presence of tumor emboli in the portal vein, hepatic vein, or large blood vessels, as opposed to tumors in the small bile ducts of the surrounding liver tissue.

Image Acquisition

Preparation Before MRI Scan and Enhanced Examination: Patients were required to fast for 4 h before the examination to ensure an empty stomach.

The patient had to fast 4 h before the examination to maintain an empty stomach. Prior to the examination, patients were instructed on the breath-holding process to minimize breathing motion artifacts during the scan and were asked to remove all metal objects. Patients with no contraindications for MRI examinations had an indwelling needle placed in their forearm by a nurse.

Liver MRI Routine Sequence and Parameter Settings:

SIEMENS Verio 3.0T was used with the following parameters: Axial T1 VIBE FSTRA P2 HB 320 (TR/TE 3.92/1.39ms), slice thickness 4 mm; Axial T2 BLADE TRA FS P2 TRIG 320 (TR/TE 4185.31/89.00ms), layer thickness 6 mm. A bolus injection of gadopentetate dimeglumine (Gd-DTPA; 0.2 mmol/kg) was administered for enhanced scanning *via* the cubital vein using a dual-barrel high-pressure syringe at a preset flow rate of 2.0 mL/s. Sterile saline (20 mL of 0.9% solution) was injected to flush the tubes. The arterial, portal venous, and equilibrium phases were scanned at 15-20s, 50-55s, and 85-90s after the contrast agent injection, respectively. The selected MR images were exported from the PACS system in BMP format.

ROI Outline and Texture Feature Extraction:

MaZda4.6 software(http://www.eletel.p.lod14z.pl/mazda/) was utilized as follows: was used in this study as follows: Firstly, a radiologist identified the contrast-

enhanced scan phase with the clearest lesion boundary in each HCC patient,manually drawing it layer by layer and merging it into the VOI, which was then copied onto the MR image of the enhanced scanning sequence. Secondly, the ROI was manually outlined layer by layer and merged into the VOI, accounting for differences in image layer thickness and enhanced images in the T2WI sequence. Finally, a seniorradiologist verified the placement of all ROIs layer by layer. If there were any issues with the ROI delineation or VOI registration, the lesions were re-delineated or registered until consensus was reached. To minimize the impact of the local volume effect, the ROI was manually outlined within 1-2 mm of the tumor on all slices. Additionally, grayscale normalization was applied to all included MR images using MaZda4.6 to minimize image errors due to patient-specificconditions or variations in scanning personnel before extracting texture features [14].

Feature Dimensionality Reduction and Computer-Automatic Discrimination Based on B11 Program:

To avoid excessive redundancy in texture features, the 10 most significant texture features were identified usingFisher, POE+ACC, MI, and MI+PA+F through texture feature screening (feature dimension reduction), a feature of MaZda4.6 software. The PA+F feature dimensionality reduction method identified the top 30 texture features with the most significance for subsequent automatic classification and discrimination by a computer.Subsequently, the four classification methods RDA, PCA, LDA, and NDA, included in the MaZda4.6 software's B11 program, were employed to automatically distinguish HCC in different MVI groups and calculate the misjudgment rate (MCR) based on these optimal discriminant features. MCR (%) = (Total number of misjudged cases / Total number of cases identified in different groups) × 100. The VOI generated from the texture analysis based on the MR image, along with the extracted 3D texture features, are illustrated in Figure 1. The Receiver Operating Characteristic (ROC) curve for positive prediction of HCC MVI using texture analysis is presented in Figure 1, and the workflow of texture analysis based on MR images is depictedin Figure 2.

Statistical Analysis:

Meta-analyses were performed using SPSS 19.0 and MaZda4.6 software. Results are presented as mean ± standard deviation (SD). Textural parameters between the two groups were compared using the independent sample Mann–Whitney U-test. ROC analyses, as described by DeLong *et al.*, were conducted to evaluate the diagnosis of MVI. A *P*-value < 0.05 was considered statistically significant.

RESULTS

Baseline Characteristics of Patients with HCC:

Between June 2016 and March 2022, 105 eligible HCC patients were included in this study. The cohort consisted of 13 females and 92 males, with a median age of 52.97 years (range 29-80 years). Patients were categorized into MVI-positive (57 cases; 50 males and 7 females; median age 51.35±12.565 years [range 29-80]) and MVI-negative (48 cases; 42 males and 6 females; median age 54.90±10.896 years [range 35-79]) groups based on postoperative pathological results (details in Table 1).

Texture Analysis in the Diagnosis of HCC:

The combination of MI+PA+F and NDA in texture analysis based on MR images demonstrated the most effectiveprediction for HCC microvascular invasion. The misjudgment rates were 22.86%, 16.19%, 20.95%, and 20.95%, respectively. (Details are presented in Table 2, and the visualization of the predicted results based on MR arterial phase image analysis is shown in Figure 3.)

The ROC Analysis of HCC:

The ROC curve depicting the positive prediction of MVI in HCC using the texture analysis combination of MI+PA+F and NDA, specifically based on arterial phase MR images, is shown in Figure 4. This method also demonstrated high accuracy (lower misjudgment rate) in predicting MVI in HCC, particularly when based on arterial phase images. The prediction accuracy was 83.81%, with an AUC for predicting MVI in HCC of 0.844, a sensitivity of77.19%, and a specificity of 91.67% (refer to Table 3 and Figure 2).

DISCUSSION

MVI is a crucial risk factor for tumor recurrence and metastasis following HCC surgery. The occurrence of MVI is common across all stages of HCC, resulting from the combined action of multiple factors [19]. Preoperative prediction of microvascular invasion in HCC plays a significant role in treatment selection and prognosis evaluation [3, 4, 20]. Currently, the preoperative assessment of HCC microvascular invasion primarily relies on semantic features of multiphase CT and enhanced MR imaging. This includes smoothness of the tumor margin, larger tumor size (>5 cm in diameter), peritumoral arterial enhancement, lack of enhanced capsule, low tumor signal, or peritumoral hypointensity, all of which possess a degree of subjectivity and lack objective and repeatable measurement indices [21-24]. However, these clinical and imaging features are subjective, dependent on experience, lack quantitative indicators, exhibit observer variability, and yield results with limited reliability. The predictive capabilities of functional imaging modalities, such as diffusion kurtosis imaging, diffusion-weighted imaging, and positron emission tomography-computed tomography (PET-CT), require improvement due to their instability and lack of reproducibility [25-27]. Liver texture analysis has been reported to aid in predicting the nature of intrahepatic lesions, classifying HCC lesions, and forecasting treatment prognosis [28]. Dynamic contrast-enhanced MRI (DCE-MRI) image texture analysis technology is beneficial for preoperative prediction of MVI, with arterial texture features showing higher prediction accuracy [29]. Consequently, it is essential to further explore objective quantitative methods for more accurate preoperative MVI prediction in HCC.

In this study, we expanded our analysis to include multi-parametric MR-enhanced images for texture analysis, encompassing MR-T2WI, arterial phase, portal venous phase, and equilibrium phase images. The misjudgment rates were 22.86%, 16.19%, 20.95%, and 20.95%, respectively, demonstrating high accuracy (lower misjudgment rates) in predicting HCC microvascular invasion, particularly with arterial

phase images. The prediction accuracy was 83.81%, with an AUCof 0.844 for predicting HCC MVI positivity, a sensitivity of 77.19%, and a specificity of 91.67%. These results are similar to those reported by Liu Jianping *et al*, suggesting that texture quantification based on MR images is a viable method for predicting MVI in HCC [30]. Yong-Jian Zhu *et al*. developed a binary logistic regression prediction model based on MR arterial phase texture features combined with imaging features [30]. The area under the curve (AUC), sensitivity, and specificity for predicting MVI in hepatocellular carcinoma were 0.810, 0.811, and 0.790, respectively. This studydetermined that the combination of MI+PA+F and NDA texture analysis, specifically based on MR arterial phase images,had the most effective prediction for HCC microvascular invasion. The prediction accuracy was 83.81%, the AUC for predicting HCC MVI positivity was 0.844, the sensitivity was 77.19%, and the specificity was 91.67%, closely aligning with the findings of Yong-Jian Zhu *et al*[30].

The contribution of the hepatic arterial system to tumor supply becomes increasingly apparent and gradually dominates the development and progression of HCC. Consequently, the texture features of arterial phase images can more accurately characterize tumor progression. When MVI is present in HCC, the local hemodynamics around the tumor are more pronounced compared to the venous phase. Moreover, this study showed better performance using arterial and equilibrium phase images compared to MR-T2WI and portal venous phase, aligning with the findings of Wenjun Yao *et al*.[31]. However, this study deviates from previous ones [32, 33], where some have indicated that radiomic signatures of the portal venous phase surpass those of the arterial or equilibrium phases. This could be attributed to selection bias and inclusion criteria. Nonetheless, texture analysis based on enhanced CT or MR imaging requires further validation for predicting HCC efficacy. Currently, there are limited studies comparing the efficacy of texture analysis based on CT and MR images for predicting MVI in HCC, necessitating further research.

Study Limitations: This study had several limitations. Firstly, the images utilized were acquired by multiple scanning technicians. To mitigate the impact of the diversity in MR scanning personnel, the variability in patient conditions, and the lack of standardization in MR imaging, all images underwent grayscale normalization before texture feature extraction. However, future applications and development of artificial intelligence in this field will need to address the challenges posed by multi-center equipment. Thus, optimizing algorithms and conducting multicenter research and analysis are imperative for future advancements. Secondly, this study focused solely on comparing the identification capabilities of texture analysis based on MRI-T2WI and three-phase enhanced scanning MR images, without a comprehensive examination and comparison of clinically relevant data and imaging manifestations. The employed high-degree evaluation method aligns with the requirements for a comprehensive clinical assessment. Future research in this area should involve expanding the sample size to achieve higher predictive accuracy and identify more practical methods. Thirdly, the use of a 3D ROI may introduce some subjectivity and a volume effect due to manual delineation. Lastly, retrospective studies are more susceptible to bias and confounding variables, which can lead to incorrect conclusions. Future studies should focus on utilizing automatic delineation and larger datasets to mitigate these issues.

CONCLUSION

This study demonstrated that textural features derived from multi-parametric MR images are reliable predictors of vascular invasion in HCC. Specifically, the MI+PA+F of arterial phase images, in conjunction with NDA texture analysis, might aid in selecting optimal therapeutic approaches. However, further large-scale studies are necessary to validate these findings.

ARTICLE HIGHLIGHTS

Research background

Future research should focus on validating the efficacy of texture analysis in larger, multicenter studies, exploring its integration with other diagnostic modalities to enhance MVI prediction accuracy in HCC. Additionally, investigating the applicability of this method in other types of cancer could broaden its clinical significance and utility.

Research motivation

This study introduces new methods for predicting microvascular invasion in hepatocellular carcinoma using texture analysis of multi-parametric MR images. It proposes the combination of MI+PA+F dimensionality reduction and Nonlinear Discriminant Analysis as a novel and effective approach. This methodology represents a significant advancement in non-invasive, objective diagnostic tools in the field of hepatocellular carcinoma management.

Research objectives

The study found that texture analysis of arterial phase images from multi-parametric MR imaging is highly effective in predicting microvascular invasion in hepatocellular carcinoma. The combination of MI+PA+F dimensionality reduction method and Nonlinear Discriminant Analysis showed the highest prediction accuracy. These results contribute significantly to the field by offering a non-invasive, objective predictive tool for MVI in HCC, potentially improving treatment decisions. However, the need for larger, prospective studies to validate these findings remains, highlighting a key area for future research in this domain.

Research methods

The study employed a retrospective analysis approach, including 105 patients with pathologically confirmed HCC. It used texture analysis methods such as Original Data Analysis (ODA), Principal Component Analysis (PCA), Linear Discriminant Analysis (LDA), and Nonlinear Discriminant Analysis (NDA) on multi-parametric MR images. The effectiveness of these methods was evaluated using the misjudgment rate (MCR)

derived from the MaZda4.6 software. This approach allowed for a detailed quantitative analysis of the MR images, offering novel insights into the potential of texture analysis in medical imaging.

Research results

The main objective of the study was to assess the effectiveness of texture analysis based on multi-parametric MR images in predicting microvascular invasion (MVI) in hepatocellular carcinoma (HCC). The goal was to provide a non-invasive, objective method to aid in the preoperative prediction of MVI, thereby influencing treatment planning and prognosis evaluation in HCC patients.

Research conclusions

The primary motivation is to enhance preoperative MVI prediction in HCC, which is crucial for selecting appropriate treatment plans.

Research perspectives

The study aims to provide an objective, non-invasive method for this prediction, addressing the limitations of current assessment methods that are invasive and carry risks. It seeks to validate the use of texture analysis in MR imaging as a reliable predictive tool for MVI, potentially guiding clinical decisions and improving patient outcomes in HCC management.

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