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Value of three phase enhanced CT histogram parameters in preoperative prediction of clinicopathological grade of hepatocellular carcinoma

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Abstract: Objective: Preoperative noninvasive prediction of histological grade of hepatocellular carcinoma remains a challenge. Tumor perfusion is closely related to the occurrence and invasion of hepatocellular carcinoma. Here, the aim of this study was to evaluate the role of quantitative perfusion parameters, corresponding histogram parameters, and tumor density (represented by CT values) in predicting the histological grade of hepatocellular carcinoma by traditional three-phase dynamic contrast-enhanced CT scanning.

Methods: A total of 80 cases of pathologically confirmed hepatocellular carcinoma were included in this retrospective study. According to the presence or absence of poorly differentiated hepatocellular carcinoma, patients were divided into two groups: 55 cases with poorly differentiated hepatocellular carcinoma; Twenty-five cases were not poorly differentiated, including well-differentiated hepatocellular carcinoma and moderately differentiated hepatocellular carcinoma. The CT values of tumors at different scanning phases were measured, and the hepatic artery blood supply coefficient (HAC), portal vein blood supply coefficient (PVC) and arterial enhancement fraction (AEF) of tumor tissues and surrounding normal tissues were calculated by CT images. Then the heterogeneity of tumors was analyzed by histogram parameters. The relationship between CT perfusion parameters and histogram parameters and different histological grades of tumors was analyzed and receiver operating characteristic curve analysis was used to determine the best parameters for predicting tumor histological grade.

Results: The difference of AEF histogram parameters in the moderate-high HCC group was higher than that in the poorly differentiated HCC group ($P < 0.05$). The difference between total tumor blood flow and total liver blood flow and the relative blood flow (rHF = AHF/HFllver) in the medium-high hepatocellular carcinoma group were significantly higher than those in the poorly differentiated hepatocellular carcinoma group ($P < 0.05$). There was no significant difference in other hepatic perfusion parameters and related histogram parameters between the two groups. The CT values of the poorly differentiated hepatocellular carcinoma group S were significantly lower than those of the moderate-high hepatocellular carcinoma group S in the plain scan phase (TAu), portal vein phase (TAp) and equilibrium phase (TAe) ($P < 0.05$).

Conclusion: The tumor perfusion parameters, corresponding histogram parameters, tumor CT values at different scanning phases and the difference of tumor CT values at different phases of HCC based on three-phase enhanced CT scan are helpful to predict the differentiation degree of HCC noninvastively before surgery.

Keywords: Hepatocellular carcinoma; Perfusion; Histological grade; Histogram; Computed tomography (ct) scan
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1. Introduction

In recent years, the theory that conventional three-phase CT scan can be used as a simple model for tumor perfusion has been developed and verified. The linear combination of aorta and portal vein enhancement curves can be used to calculate the hepatic artery and portal vein blood supply coefficients of tumors. This has proved to be a simple predictive model for hepatic perfusion. AEF can be used to evaluate the arterial perfusion level of liver tumors. Many past studies have also attempted to analyze whether some clinical, radiological or serological parameters can predict histological grade [1]. A number of studies have shown that different grades of hepatocellular carcinoma show different enhancement patterns in the third-stage enhanced liver scan, and it has been reported that the enhancement pattern of hepatocellular carcinoma is correlated with tumor grade [2]. However, the detection and prediction of tumor differentiation still face great challenges. In most cases, information about histological grade comes from tumor pathology after surgical resection or liver transplantation. Therefore, accurate preoperative prediction of the histological grade of HCC is an effective method to develop treatment strategies and predict prognosis.

2. Materials and Methods

2.1 Research Objects

This retrospective study was approved by the hospital ethics committee. Informed consent was obtained from each patient. From January 2018 to January 2022, 80 patients with hepatocellular carcinoma confirmed by liver resection or liver biopsy in our hospital were selected. The inclusion criteria were as follows :(1) the pathological diagnosis of hepatocellular carcinoma was based on pathological reports; (2) The interval between enhanced CT scan and operation was 1 month; (3) No previous history of RAF, TACE or other treatments. Exclusion criteria :(1) enhancement in arterial phase of

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tumor was too small to characterize; (2) Receiving other combined antitumor therapy, such as TACE, targeted therapy, radiotherapy, etc. (3) Patients with portal vein thrombosis; Patients with more than three intrahepatic lesions of the same type. The study group included 36 men and 44 women, aged 40-80 years; Fifty-six patients were positive for hepatitis virus markers. All patients were considered to have cirrhosis based on histology, CT imaging, or clinical diagnosis.

2.2 Multi-phase enhanced CT examination

The SOMATOM Siemens Force 128-slice spiral CT machine was used for plain and three-phase enhanced CT scan of the upper abdomen. The supine position was adopted, and breathing training was performed before scanning. The head was advanced, and the arms were raised. Scanning parameters: tube voltage 120 K V, tube current 150 m A, pitch 0.800, layer thickness 5 mm, layer spacing 5 mm, matrix 512×512. Scan range: top of diaphragm to lower margin of right lobe of liver. The contrast agent iohexol (350 mg/m L) was injected through the median cubital vein with a high pressure syringe at a rate of 3 m L/s. After contrast injection, the arterial phase (30-35s), portal phase (60-70s) and delayed phase (180s) were scanned. Scanning parameters are as follows: collimation 128x0.625mm, tube voltage 80-120kV, effective tube current 200mAs, and pitch 1.375.

2.3 Image post-processing and parameter measurement

The DICOM raw data were imported into CT syngo. via software. For each case, the region of interest (ROI) was drawn on the tumor region, portal vein and aorta positions on the image images, and then a series of liver perfusion parameters were calculated. HAC, PVC, and AEF were included. AEF was defined as the ratio of the absolute enhancement increase in the hepatic arterial phase to the absolute enhancement increase in the portal venous phase of ROI. From pixel-by-pixel HAC, PVC, and AEF values, software was used to generate histogram data (median, mean, standard deviation, 10-90th percentile, variance, skewness, kurtosis) for each lesion.

2.4 Statistical Methods

SPSS 19.0 and MedCalc 11.4.2.0 software packages were used to analyze the data. Kolmogorov-smirnov method was used for normal distribution and Levene method was used for homogeneity test of variance. When normal distribution was satisfied, the parameters were expressed as mean ± standard deviation. The receiver operating characteristic curve (ROC) was used to evaluate the diagnostic efficiency of HCC classification, and the optimal diagnostic threshold of this quantitative parameter was calculated according to the maximum Youden index, and the area under the ROC curve, sensitivity and specificity were obtained. Delong test was used to compare AUC.

3. Results

3.1 Liver perfusion parameters and corresponding histogram parameters Perfusion parameters of each group

The difference between total tumor blood flow and total liver parenchyma blood flow (AHF = HFtumor-Hfliver) and relative liver blood flow (rHF = AHF/HFliver) in the poorly differentiated HCC group were significantly lower than those in the moderate-high HCC group ($P < 0.05$). The difference of portal vein blood supply between tumor and surrounding normal liver parenchyma (APVC) and relative portal vein blood supply (rPVC) in poorly differentiated HCC group were significantly lower than those in moderate-high HCC group ($P < 0.05$). There were no significant differences in other perfusion parameters between the two groups. Table 1 and Figure 1.

HF, total tumor blood flow; AHF, the difference between

Table 1 Comparison of liver perfusion parameters between poorly differentiated hepatocellular carcinoma and non-poorly differentiated hepatocellular carcinoma

Group	Poorly differentiated HCC	Moderate-well differentiated HCC	T	P
HF_{tumor}	0.231±0.050	0.268±0.05	0.443	0.452
△ HF	-0.112±0.034	-0.046±0.087	-3.221	0.035
rHF	-0.254±0.221	-0.132±0.234	-3.112	0.034
△ HAC	-0.034±0.043	-0.034±0.053	0.442	0.876
rHAC	-0.643±1.211	-8.222±3.232	-0.887	0.453
△ PVC	-0.123±0.043	-0.087±0.043	-3.331	0.035
rPVC	-0.341±0.123	-0.242±0.332	-2.343	0.025
△ AEF	0.054±0.033	0.035±0.045	-0.153	0.454
rAEF	0.923±0.112	0.112±0.156	-0.564	0.564

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Table 2 Comparison of histogram parameters between patients with and without poorly differentiated hepatocellular carcinoma

Group	Poorly differentiated HCC	Moderate-well differentiated HCC
HAC-Median	-0.022±0.034	-0.003±0.012
HAC-Mean	0.023±0.034	0.004±0.035
HAC-Std	0.016±0.013	0.016±0.003
HAC-Variance	0.003±0.011	0.001±0.007
HAC-Skewness	0.078±0.0043	1.221±0.033
HAC-Kurtosis	3.998±0.056	1.889±0.045
PVC-Median	0.267±0.055	0.289±0.062
PVC-Mean	0.231±0.034	0.253±0.044
PVC-Std	0.057±0.086	0.055±0.014
PVC-Variance	0.006±0.012	0.003±0.045
PVC-Skewness	0.012±0.034	4.221±0.452
PVC-Kurtosis	3.444±0.054	5.331±0.776
AEF-Median	0.444±0.563	0.631±0.173
AEF-Mean	0.444±0.234	0.634±0.123
AEF-Std	0.067±0.076	0.087±0.05
AEF-Variance	0.005±0.044	0.024±0.034*
AEF-Skewness	1.234±0.564	1.654±0.341
AEF-Kurtosis	53.345±14.112	45.221±13.141

total tumor blood flow and hepatic blood flow (HF_{tumor} — HF_{liver}); RHF, relative total tumor blood flow (AHF/HFHver); The difference of hepatic arterial blood supply coefficient between AHAC tumor and normal liver parenchyma (HAC > R-Hach stomach); RHAC, relative hepatic arterial blood supply coefficient (AHAC/HAGiVer); delta PVC, month of tumor and normal hepatic portal vein coefficient difference (wide PVCtumo PVCliver); rPVC, relative portal blood supply coefficient (APVC/PVCliver); AAEF, difference between tumor and normal parenchymal artery enhancement fraction (AEFT_R-AEFLlver); RAEF, relative arterial enhancement fraction (AAEF/AEFu).

3.2 Comparison of histogram parameters between poorly differentiated hepatocellular carcinoma and non-poorly differentiated hepatocellular carcinoma

The difference of AEF histogram parameters in patients with moderate-high hepatocellular carcinoma group S was higher than that in patients with poorly differentiated hepatocellular carcinoma group ($P < 0.05$). There was no significant difference in other histogram parameters between the poorly differentiated HCC group and the moderate-high HCC group, as shown in Table 2.

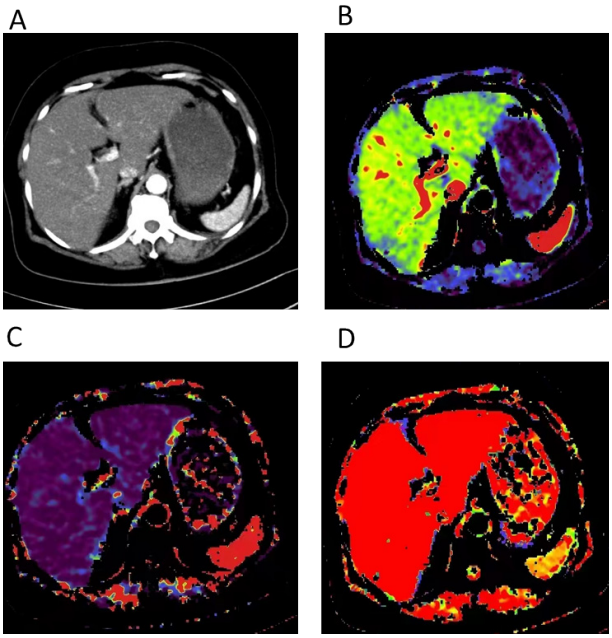

Fig. 1 Plain and enhanced CT images of A patient with hepatocellular carcinoma (A) The original image showed A huge lesion in the right lobe of the liver with significantly uneven enhancement. (B) HAC images showed heterogeneous hyperperfusion. (C) PVC images showed hypoperfusion. (D) AEF images showed heterogeneous hyperperfusion throughout the lesion.

Notes: * represents statistical difference between the two groups ($P < 0.05$), HAC represents hepatic artery blood supply coefficient; PVC represents portal vein blood supply coefficient; AEF represents the arterial enhancement fraction (%).

3.3 Predictive ability of perfusion parameters and corresponding histogram parameters for histopathological grade of hepatocellular carcinoma

ROC analysis was used to evaluate the discriminative ability of variables with significant statistical differences in all hepatic perfusion parameters and histogram parameters between the two groups ($P < 0.05$), as shown in Table 3

4.Discuss

Hepatocellular carcinoma is the fifth most common tumor type and the third leading cause of cancer-related death in China. The treatment of hepatocELLULAR carcinoma includes liver transplantation, surgical resection, radiofrequency ablation, transcatheter arterial chemoembolization and tumor targeted therapy. Surgical resection is the most effective way of treatment of

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Table 3 ROC analysis of △ HF, rHF, △ PVC, rPVC and AEFvariance parameters of hepatocellular carcinoma with different histological grades

	AUC	Sensitivity	Specificity	Cutoff Value
△ HF	0.654	76.3	88.3	-0.045
rHF	0.674	53.3	88.5	-0.123
△ PVC	0.681	87.3	58.4	-0.132
rPVC	0.687	87.3	58.4	-0.345
$AEF_{variance}$	0.543	68.3	64.4	0.003

liver cancer, however, the recurrence rate is still high. Poorly differentiated HCC has a higher recurrence rate, worse prognosis and lower survival rate than moderately differentiated HCC and well-differentiated HCC. In current treatment guidelines, RFA is not recommended for the treatment of poorly differentiated HCC due to tumor dissemination and metastasis and poor prognosis. In addition, due to the high recurrence rate and low survival rate, poorly differentiated HCC is liver transplantation contraindications to [4]. Therefore, accurate preoperative evaluation of tumor grade, especially poorly differentiated hepatocellular carcinoma, has positive significance in the development of treatment strategy and prognosis assessment, and has attracted more and more attention.Histological grade is a reliable predictor of survival or recurrence in patients with hepatocellular carcinoma. A growing number of studies have explored the use of imaging analysis for preoperative noninvasive assessment of histological grade of hepatocellular carcinoma, such as the hemodynamic patterns of diffusion-weighted magnetic resonance imaging, CT arteriography, and CT arterio-portal venography [5-6]. The blood supply source of different histological grade tumors is different. Several studies have evaluated the role of hemodynamic patterns in the histological grade of hepatocellular carcinoma. Foreign scholars believe that the number of tumor vessels in poorly differentiated hepatocellular carcinoma group is significantly lower than that in moderately differentiated hepatocellular carcinoma and well-differentiated hepatocellular carcinoma [7]. Some scholars have reported that with the increase of malignancy of hepatocellular carcinoma, the number of accumulated arteries in the tumor increases [8]. The pattern of tumor enhancement is qualitative rather than quantitative, and is usually judged subjectively by researchers [9]. Therefore, it is unscientific to predict the blood supply of hepatocellular carcinoma with different histological grades using enhancement patterns alone.

Arterial blood supply and neovascularization increase during the progression of hepatocellular carcinoma from low-grade dysplastic nodules to advanced hepatocellular carcinoma [10-11]. Therefore, the quantification of blood vessels in tumors is of great significance for the evaluation of tumor progression. CT perfusion is a promising functional angiography technology, which can obtain a series of images and analyze the temporal changes of tumor hemodynamics [12]. Therefore, it can be used to quantitatively measure patients with hepatocellular carcinoma [13-15]. Liver CT perfusion imaging can provide accurate blood flow parameters for hepatocellular carcinoma and surrounding normal liver parenchyma, and quantitatively evaluate the changes of HAC, PVC and AEF values associated with the disease. However, due to the high radiation dose, liver CT perfusion is rarely used in clinical practice. In recent years, standard three-phase enhanced liver scanning has become a new method to assess the blood supply status of the liver [16-18]. We hypothesized that perfusion parameters may have higher diagnostic performance in predicting the histological grade of HCC. However, tumor perfusion parameters are usually expressed as mean values. Mean values do not account for inhomogeneity of tumor perfusion and are therefore not optimal for pre-or post-treatment response assessment. Histogram analysis of acquired imaging data is a new method to evaluate tumor heterogeneity. The description of CT perfusion heterogeneity by histogram analysis has obvious advantages in tumor grading, tumor recurrence, and predicting overall survival of glioma, cervical cancer and colorectal cancer [19-21]. Therefore, we hypothesized that histogram analysis would improve diagnostic performance in predicting histological grade of HCC.

Our study confirmed that the CT values of tumors at different phases of traditional three-stage enhanced liver scanning, liver perfusion parameters based on three-stage enhanced CT scanning and corresponding histogram parameters have important application value in predicting the histological grade of hepatocellular carcinoma. The results of this study can provide guidance for noninvasive preoperative prediction of the differentiation degree of HCC.

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