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ORIGINAL ARTICLE

Retrospective Cohort Study

Computed tomography perfusion imaging evaluation of angiogenesis in patients with pancreatic adenocarcinoma

Wen Liu, Bo Yin, Zong-Hui Liang, Yang Yu, Na Lu

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Abstract

BACKGROUND

Pancreatic adenocarcinoma is one of the most common malignant tumors of the digestive system. More than 80% of patients with pancreatic adenocarcinoma are not diagnosed until late stage and have distant or local metastases.

AIM

To investigate the value of computed tomography (CT) perfusion imaging in the evaluation of angiogenesis in pancreatic adenocarcinoma patients.

METHODS

This is a retrospective cohort study. Patients with pancreatic adenocarcinoma and volunteers without pancreatic diseases underwent CT perfusion imaging from December 2014 to August 2017 in Huashan Hospital, Fudan University Shanghai, China.

RESULTS

A total number of 35 pancreatic adenocarcinoma patients and 33 volunteers were enrolled. The relative blood flow (rBF), and relative blood volume (rBV) were significantly lower in patients with pancreatic adenocarcinoma than in the control group ($P < 0.05$). Conversely, the relative permeability in patients with pancreatic adenocarcinoma was significantly higher than that in controls ($P < 0.05$). In addition, rBF, rBV, and the vascular maturity index (VMI) were significantly

lower in grade III-IV pancreatic adenocarcinoma than in grade I-II pancreatic adenocarcinoma ($P < 0.05$). Vascular endothelial growth factor (VEGF), CD105-MVD, CD34-MVD, and angiogenesis rate (AR) were significantly higher in grade III-IV pancreatic adenocarcinoma than in grade I-II pancreatic adenocarcinoma ($P < 0.05$). Significant correlations between rBF and VEGF, CD105-MVD, AR, and VMI ($P < 0.01$) were observed. Moreover, the levels of rBV were statistically significantly correlated with those of VEGF, CD105-MVD, CD34-MVD, and VMI ($P < 0.01$).

CONCLUSION

Perfusion CT imaging may be an appropriate approach for quantitative assessment of tumor angiogenesis in pancreatic adenocarcinoma.

Key Words: Pancreatic adenocarcinoma; Perfusion computed tomography; Angiogenesis; Evaluation; Imaging; Quantitative assessment

Core Tip: A total of 35 pancreatic adenocarcinoma patients and 33 volunteers were enrolled in the study. The relative blood flow, relative blood volume, and relative peak enhancement were significantly lower in patients with pancreatic adenocarcinoma than in the control group ($P < 0.05$). Conversely, the relative permeability in patients with pancreatic adenocarcinoma was significantly higher than that in controls ($P < 0.05$).

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INTRODUCTION

Pancreatic adenocarcinoma is one of the most common malignant tumors of the digestive system. The prognosis of pancreatic adenocarcinoma is poor, with 5-year survival rates lower than 5%[1]. Importantly, more than 80% of patients with pancreatic adenocarcinoma are not diagnosed until late stage and have distant or local metastases[1,2]. Therefore, early detection of pancreatic adenocarcinoma is critical for improving prognosis outcomes.

Accumulating evidence indicates that vascularity is crucially involved in the tumorigenesis and drug responsiveness of pancreatic adenocarcinoma[3,4]. Thus, the evaluation of angiogenesis in pancreatic adenocarcinoma is of considerable significance for the diagnosis, treatment, and prognosis[5-8]. Computed tomography (CT) perfusion imaging provides information on tissue hemodynamics, which facilitates the more effective characterization and identification of pancreatic adenocarcinoma[9-11]. For instance, perfusion CT imaging has been widely applied in brain tumors, and the perfusion parameters have been proven to be of great significance in brain disease diagnosis[12-15]. However, relative perfusion parameters in pancreatic adenocarcinoma diagnosis have not yet been reported.

Therefore, in the present study, we performed perfusion CT imaging to explore the correlations between CT perfusion parameters and immunohistochemical angiogenesis indices, and their application for evaluating their diagnostic value in pancreatic adenocarcinoma.

MATERIALS AND METHODS

Study design and subjects

This retrospective cohort study was conducted in Fudan University from December 2014 to August 2017. Subjects with pancreatic ductal adenocarcinoma and volunteers without pancreatic diseases were enrolled. Pancreatic adenocarcinoma patients with other pancreatic diseases were excluded. This study protocol was approved by the Institutional Review Board of Fudan University, Shanghai, China (2014-04-02). Written informed consent was obtained from each participant.

Procedures

Perfusion CT imaging was performed using a 64-slice spiral CT scanner (SOMATOM Sensation 64, Siemens Medical Solutions, Forchheim, Germany). The baseline unenhanced CT acquisition provided

wide coverage of the whole organ of interest. The field of view of perfusion CT imaging was positioned to include the maximum visible area of the tumor and a relevant arterial vessel. The abdominal aorta was used as an arterial input. An abdominal bandage was utilized to reduce the artifacts caused by respiratory motion. CT perfusion examinations were then performed in a continuous volume scan pattern using the following parameters: tube voltage 100 kV, tube current 80 mA, and a matrix of 512 × 512 pixels. The reconstructed slice thickness was 7.2 mm; the acquisition collimation was 7.2 mm, with 280 slices in each dataset. An average radiation dose of 9.3 mGy was applied. A volume of 50 mL of Omnipaque® 300 (GE Healthcare, Shanghai, China) was administered at a high flow rate (5 mL/s) using a high-pressure syringe. The contrast medium bolus was followed immediately by 15 mL of normal saline flush to increase the peak arterial enhancement. Stationary CT scans were then acquired every 1 s over a period of 70 s, with a delay of 4 s.

The obtained images were independently evaluated by two radiologists with more than 10 years' experience. Dynamic CT perfusion data were analyzed by the pancreatic perfusion CT software package (Syngo, Siemens, Erlangen, Germany). Based on the maximum-slope method, color maps of CT perfusion parameters, including blood flow (BF), blood volume (BV), permeability, time to peak and mean transit time, maximum-density-projection and contrast-enhanced CT images were extracted. Furthermore, regions of interest (ROIs) were positioned on the highest intensity projection of tumor parenchyma to avoid selecting the vascular or the necrotic areas, and normal pancreas tissue in patients with pancreatic adenocarcinoma. For large heterogeneous tumors, the average value of three ROIs in the tumor parenchyma was used. In the control group, ROIs were located on the pancreatic head and cauda. Each CT perfusion parameter was measured three times, and the mean values were used. Relative CT perfusion parameters, including relative BF (rBF), relative BV (rBV), relative permeability (rPermeability), relative peak enhancement (rPE), and relative time to peak (rTTP) were calculated as follows: Relative CT perfusion parameters = parameters of pancreatic adenocarcinoma tumor parenchyma/parameters of adjacent relatively normal pancreatic tissue. The relative CT perfusion parameters in the controls were calculated as parameters of the pancreatic head/parameters of the pancreatic cauda.

Tumor specimens were resected and the expression of vascular endothelial growth factor (VEGF), CD105, CD34, and alpha-smooth muscle actin (α-SMA) was detected by immunohistochemical staining. Yellow and brown yellow were used to indicate positive cells on the premise of excluding non-specific staining. Five random visual fields were selected at high magnification, and 100 cells in each visual field of each section were observed. Microvascular density (MVD) was determined by counting the total number of positive vessel walls in each tumor section. MVD was then graded using a scale of 0-5: 0 point, the proportion of chromogenic cells was less than 5%; 1 point, chromogenic cells ranged from 5% to 25%; 2 points, chromogenic cells ranged from 25% to 50%; 3 points, chromogenic cells ranged from 50% to 75%; 4 points, the proportion of chromogenic cells was more than 75%; 5 points, all cells were positive. Angiogenesis rate (AR) and vascular maturity index (VMI) are important indicators of tumor angiogenesis. AR was calculated using the following formula: AR = (CD105-MVD/CD34-MVD) × 100%. VMI was calculated according to the formula: VMI = (α-SMA-MVD/CD34-MVD) × 100%.

Demographic characteristics including age, gender, and tumor grade were collected at enrollment.

Statistical analysis

Continuous data conforming to a normal distribution are expressed as mean ± standard deviation (SD). Continuous data with non-normal distribution are presented as median (interquartile range, IQR); these data were analyzed using the independent *t*-test or Mann-Whitney U-test where appropriate. Categorical data are presented as count (percentage) and compared using the χ^2 test. Pearson correlation coefficients were employed to assess the correlations between relative CT perfusion parameters and immunohistochemical indices. Statistical analysis was performed using the SPSS 17.0 package (SPSS Inc., Chicago, IL, United States), and two-tailed $P < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics

A total of 68 subjects were enrolled in our analysis: 35 cases (17 males, age range 46-79 years, 25 cases with grade I-II, 10 cases with grade III-IV) in the pancreatic adenocarcinoma group and 33 cases (20 males, age range 28-68 years) in the control group. The rBV, rBF, and rPE values of the tumor parenchyma in patients with pancreatic adenocarcinoma were significantly lower than those in the control group ($P < 0.01$), and the rTTP and rPermeability values of the tumor parenchyma were significantly higher than those of the controls ($P < 0.01$) (Table 1).

In addition, the relative CT perfusion parameters of patients with grade I-II pancreatic adenocarcinoma ($n = 25$) and those with grade III-IV pancreatic adenocarcinoma ($n = 10$) ($P < 0.01$) were significantly different. RBF and rBV values were significantly lower in grade III-IV pancreatic adenocarcinoma than in grade I-II pancreatic adenocarcinoma ($P < 0.01$) (Table 2). Patients with pancreatic adenocarcinoma had a lower density on the maximum-density projection images, as well as lower

Table 1 Demographic features

	Pancreatic adenocarcinoma (*n* = 35)	Controls (*n* = 33)	*P* value
Age (yr)	61.5 (46-79)	48 (28-68)	< 0.001
Gender			
Male	17 (48.6%)	20 (60.6%)	0.342
Female	18 (51.4%)	13 (39.4%)	
rBF	0.222 ± 0.089	1.000 ± 0.023	< 0.001
rBV	0.453 ± 0.193	0.993 ± 0.076	< 0.001
rPE	0.576 ± 0.278	1.003 ± 0.008	< 0.001
rPermeability	6.000 ± 1.395	0.949 ± 0.165	< 0.001
rTTP	1.917 ± 0.208	1.014 ± 0.039	< 0.001

rBF: Relative blood flow; rBV: Relative blood volume; rPermeability: Relative permeability; rPE: Relative peak enhancement; rTTP: Relative time to peak.

Table 2 Relative computed tomography perfusion parameters of grade I-II pancreatic adenocarcinoma *vs* grade III-IV pancreatic adenocarcinoma

	Grade I-II pancreatic adenocarcinoma (*n* = 25)	Grade III-IV pancreatic adenocarcinoma (*n* = 10)	*P* value
rBF	0.266 ± 0.057	0.111 ± 0.042	< 0.001
rBV	0.546 ± 0.127	0.223 ± 0.123	< 0.001
rPE	0.586 ± 0.265	0.552 ± 0.321	0.750
rPermeability	5.841 ± 1.413	6.393 ± 1.336	0.297
rTTP	1.919 ± 0.208	1.911 ± 0.218	0.915

rBF: Relative blood flow; rBV: Relative blood volume; rPermeability: Relative permeability; rPE: Relative peak enhancement; rTTP: Relative time to peak.

values of blood flow, blood volume, and permeability than those of the adjacent relatively normal pancreatic tissue and those in the control group (Figures 1 and 2).

Correlations between relative CT perfusion parameters and immunohistochemical indicators in patients with pancreatic adenocarcinoma

Additionally, VMI values were significantly lower in grade III-IV pancreatic adenocarcinoma than in grade I-II pancreatic adenocarcinoma ($P < 0.05$). VEGF, CD105-MVD, CD34-MVD, and AR showed significantly higher values in grade III-IV pancreatic adenocarcinoma than in grade I-II pancreatic adenocarcinoma ($P < 0.05$). However, no significant difference was observed in (α-SMA)-MVD between grade I-II pancreatic adenocarcinoma and grade III-IV pancreatic adenocarcinoma ($P > 0.05$) (Figure 3). Furthermore, the levels of VEGF, CD105-MVD, and CD34-MVD were significantly higher in grade III-IV pancreatic adenocarcinoma than in grade I-II pancreatic adenocarcinoma. No significant difference was found in (α-SMA)-MVD between grade I-II pancreatic adenocarcinoma and grade III-IV pancreatic adenocarcinoma. A significant correlation was detected between rBF and VEGF, CD105-MVD, AR, and VMI ($P < 0.01$) and between rBV and VEGF, CD105-MVD, CD34-MVD, and VMI ($P < 0.01$). There was a moderate correlation between rBV and AR (r = -0.412, $P < 0.05$), and CD34-MVD (r = -0.407, $P < 0.05$), as depicted in Table 3 and Figure 4A and 4B. No significant correlations were observed between rPermeability, rPE, and rTTP and the immunohistochemical indices ($P > 0.05$) (Table 3).

DISCUSSION

In the present study, we found a correlation between the relative CT perfusion parameters and the immunohistochemical indicators. These findings indicate that CT perfusion parameters may be a useful noninvasive tool for pancreatic adenocarcinoma diagnosis.

CT perfusion imaging is performed on the basis of the central volume principle by monitoring the first pass of a bolus of iodinated contrast agent through the cerebral vasculature[16-19]. The quantitative

Table 3 Correlation between relative computed tomography perfusion parameters and immunohistochemical indicators in pancreatic adenocarcinoma patients

Pearson correlation	rBF	rBV	rPE	rPermeability	rTTP
VEGF	-0.670[b]	-0.557[b]	-0.182	0.107	0.071
CD105-MVD	-0.489[b]	-0.549[b]	-0.002	0.016	0.030
CD34-MVD	-0.241	-0.407[a]	-0.074	0.072	-0.028
AR	-0.497[b]	-0.412[a]	0.049	-0.046	0.020
VMI	0.603[b]	0.499[b]	-0.119	-0.043	0.150

[a]$P < 0.05$.
[b]$P < 0.01$. AR: Angiogenesis rate; VMI: Vascular maturity index.

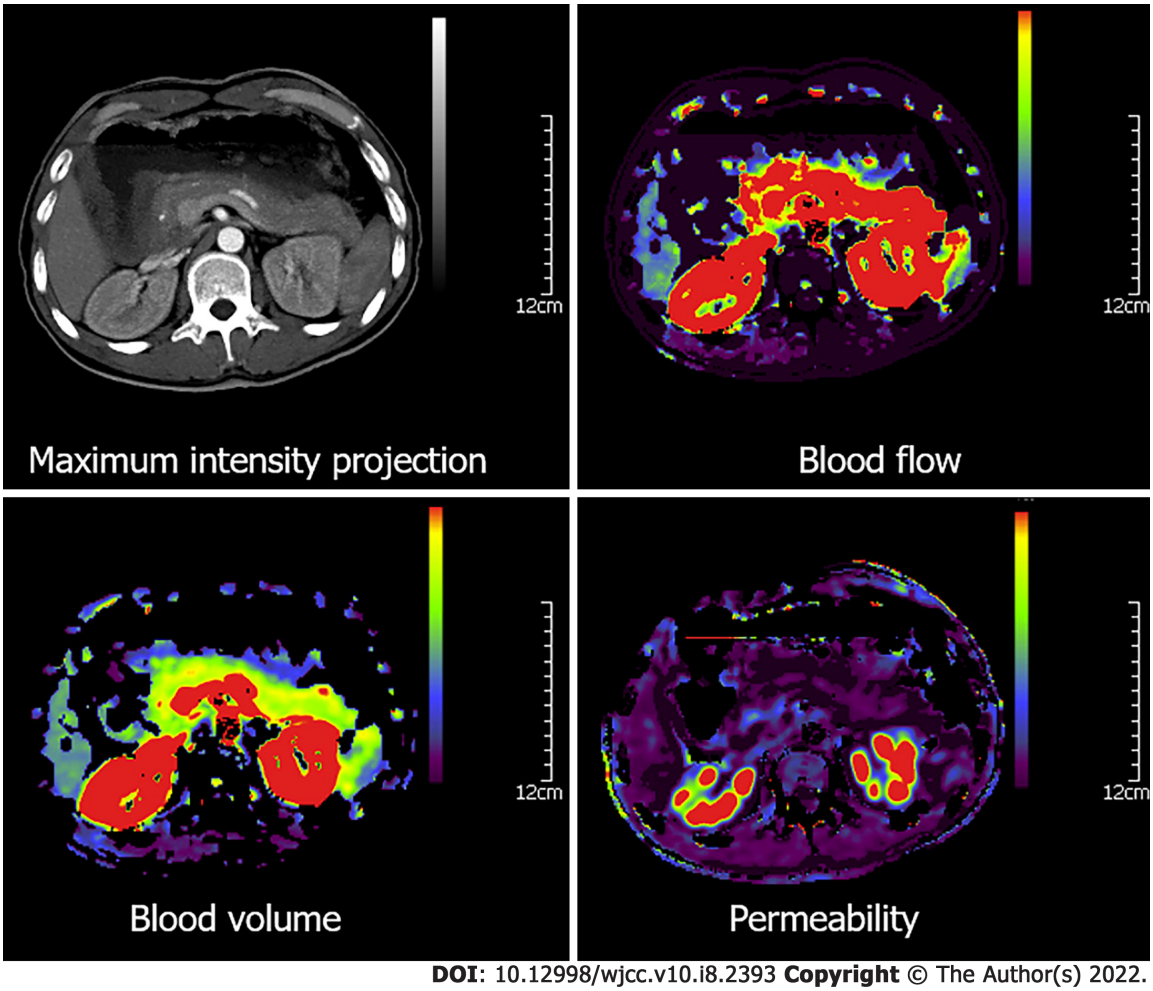

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Figure 1 Representative computed tomography perfusion parameters in the pancreas of a healthy volunteer.

parameters from perfusion CT can reflect the pancreatic tissue vascularity directly and can thus be utilized as a tool for detecting disturbance of the pancreatic microcirculation[20]. The relative CT perfusion parameters are beneficial for the reduction of the individual differences in pancreatic perfusion. The results of this investigation indicated that relative CT perfusion quantitative parameters may be valuable for detecting disturbances in the pancreatic microcirculation in pancreatic adenocarcinoma.

Here, we found that the rBF and rBV values in patients with pancreatic adenocarcinoma were lower than those in the controls. The rBF and rBV values in grade III-IV pancreatic adenocarcinoma were significantly lower than those in grade I-II pancreatic adenocarcinoma. Considering that the rBF and rBV values could reveal blood perfusion in pancreatic adenocarcinoma to some extent, we suggest that low rBF and rBV values may be associated with fibrosis and arteriolosclerosis in pancreatic adenocar-

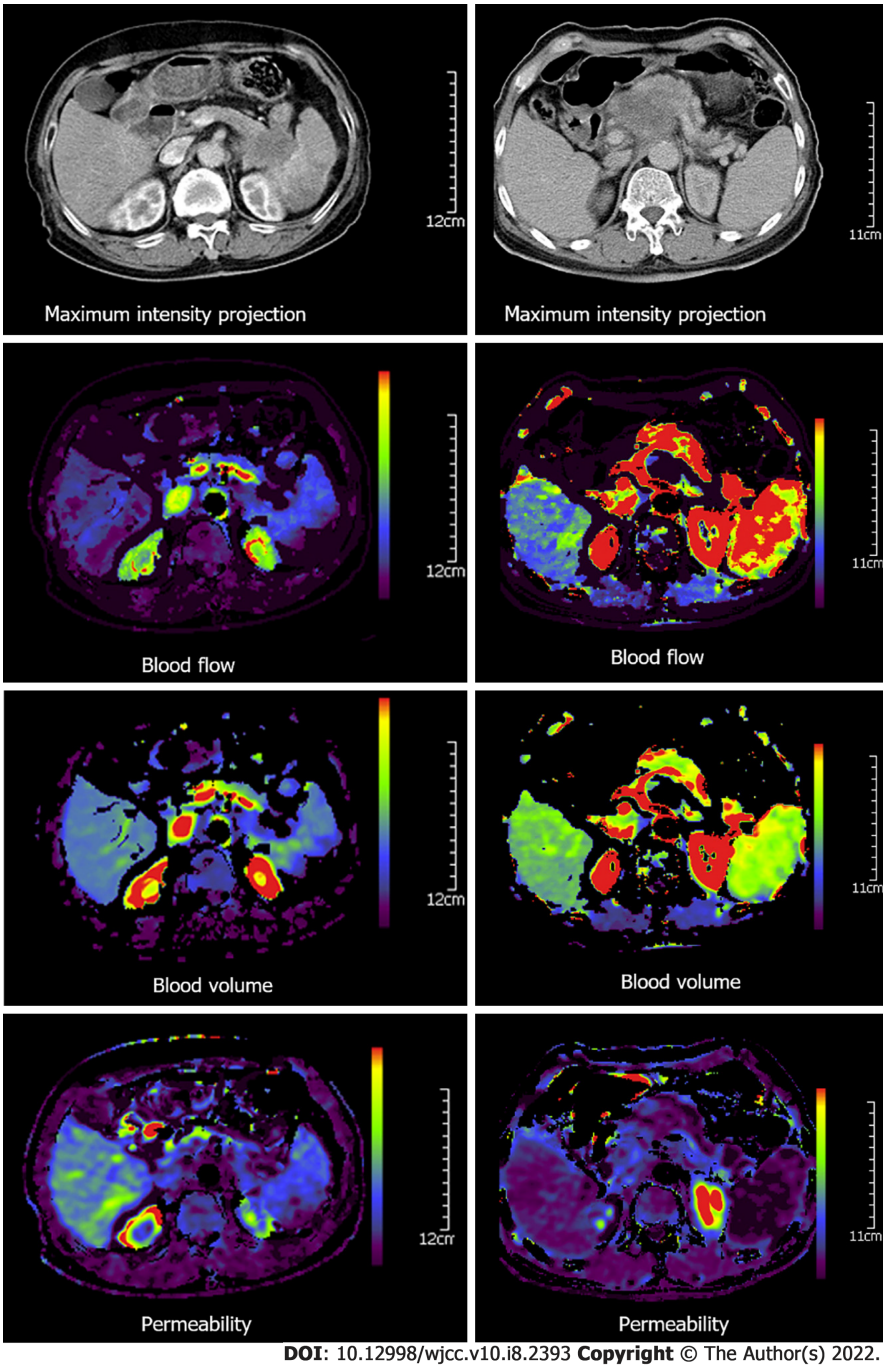

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Figure 2 Representative computed tomography perfusion parameters of grade II (left) *vs* grade III (right) pancreatic adenocarcinoma patients. The pancreatic adenocarcinoma patients had a lower density on the maximum-density projection images, as well as lower values of blood flow, blood volume, and permeability, as compared with the adjacent relatively normal pancreatic tissue.

cinoma. Therefore, rBF and rBV values could provide useful information for the evaluation of angiogenesis in patients with pancreatic adenocarcinoma.

VEGF, CD34, CD105, and AR are frequently used indicators to evaluate tumor angiogenesis. VEGF is critically involved in angiogenesis induction[7,21,22]. CD34 is a total vascular endothelial cell marker, which is present in the vast majority of the blood vessels in the tumor[23]. CD105 is a member of the transforming growth factor-β superfamily that participates in angiogenesis and maintaining vascularity, which is highly expressed in the endothelial cells of nascent tumor blood vessels and the vascular endothelial cells of the tumor margin. CD105 was considered an ideal target in tumor therapy for suppression of tumor angiogenesis[24]. CD105-MVD was found to be an independent prognostic marker for most solid tumors[25]. AR represents the percentage of CD105-MVD/CD34-MVD, reflecting the proportion of neovascularization. In the present study, we found that VEGF, CD105-MVD, CD34-MVD, and AR in grade III-IV pancreatic adenocarcinoma were significantly higher than those in grade I-II pancreatic adenocarcinoma, which is in accordance with the general characteristics of malignant

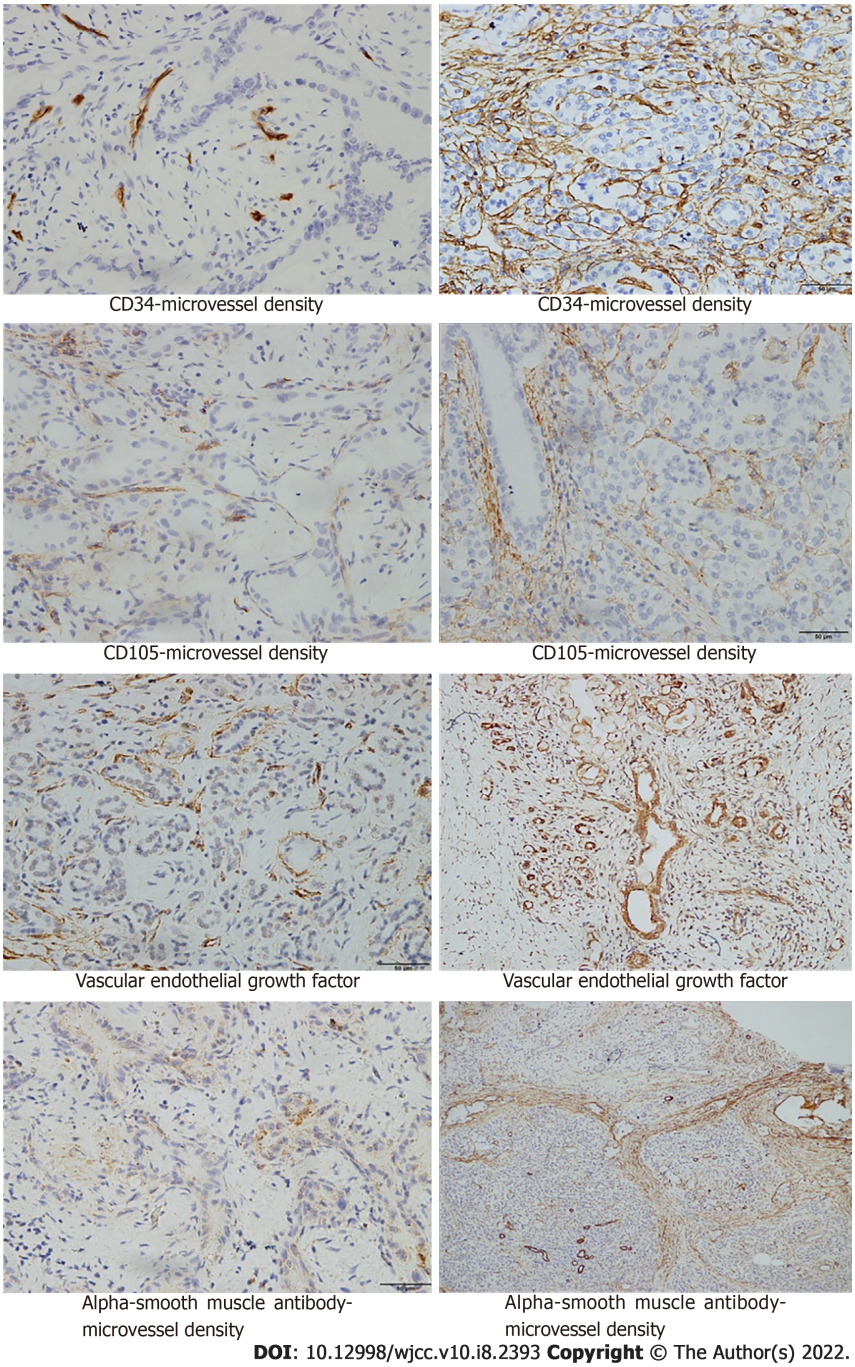

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Figure 3 Immunohistochemical indicators in patients with pancreatic adenocarcinoma. CD34-MVD, CD105-MVD, VEGF, and (α-SMA)-MVD in patients with grade III pancreatic adenocarcinoma (right) were compared with CD34-MVD, CD105-MVD, VEGF, and (α-SMA)-MVD in patients with grade I pancreatic adenocarcinoma (left). Magnification × 400.

tumors, that is, tumor angiogenesis is more pronounced in pancreatic adenocarcinoma with higher malignancy. Negative correlations were found between VEGF, CD105-MVD, AR, and rBF, as well as between VEGF, CD105-MVD, CD34-MVD, and rBV. These results might have been due to the decreased amount of residual pancreatic tissue.

Previous results demonstrated that VMI played a major role in tumor blood supply[26]. Our results showed that VMI was significantly lower in grade III-IV pancreatic adenocarcinoma than in grade I-II pancreatic adenocarcinoma ($P < 0.05$). A positive correlation was observed between rBV, rBF, and VMI. These results could be attributed to larger quantities of mature vessels in grade I-II pancreatic adenocarcinoma than in grade III-IV pancreatic adenocarcinoma[27]. It was reported that the percentage of tumor vessels with function was less than 5% and absence of smooth muscle actin-positive pericyte coverage of tumor vessels correlated with hematogenous metastasis and prognosis of the neoplasm[28]. Accumulating evidence has shown that rBF and rBV correlate with angiogenesis markers to some extent; however, further research is required to confirm these findings.

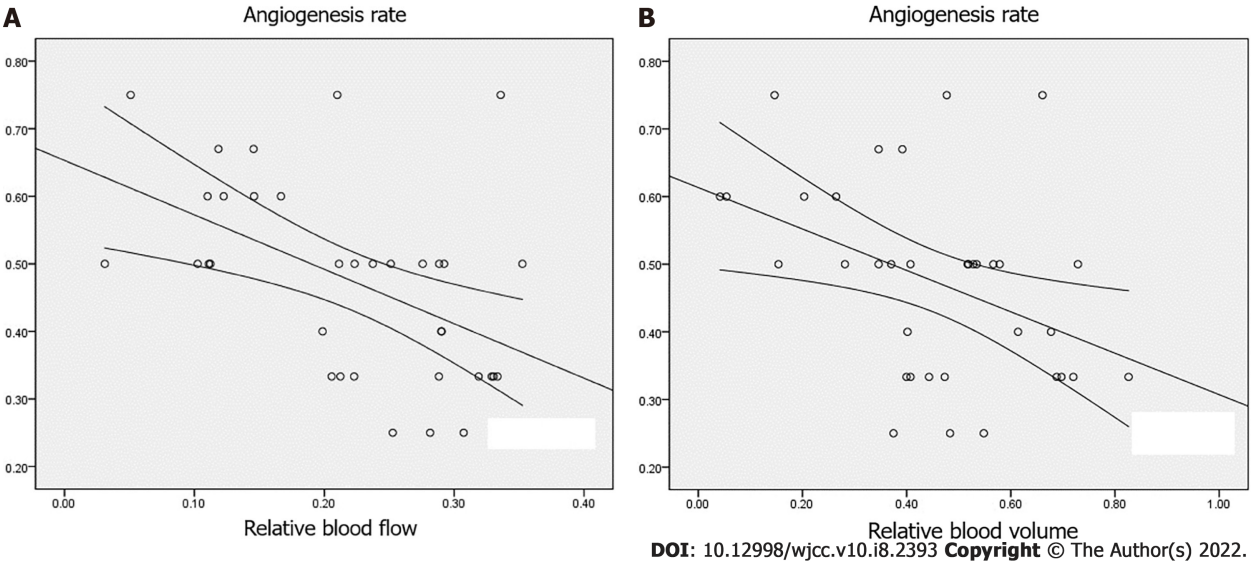

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Figure 4 Correlation between relative blood flow and relative blood volume and angiogenesis rate. A: Correlation between relative blood flow and angiogenesis rate (AR); B: Correlation between relative blood volume and AR.

The relative permeability of the tumor tissue in patients with pancreatic adenocarcinoma was higher than that in normal controls, which is similar to previously reported findings[16,29]. Furthermore, this outcome is consistent with the influence of the increased immature neovascularization in pancreatic adenocarcinoma. The incomplete endothelium of immature tumor vessels augmented the permeability of the blood vessel walls. However, certain controversies have been reported. For example, Ho *et al*[20] found no significant difference between the permeability of pancreatic adenocarcinoma and that of normal tissues. Additionally, Matsusaki *et al*[30] reported that the permeability of tumor tissue in patients with pancreatic adenocarcinoma was lower than that in normal controls. Perhaps these results were associated with the existence of fibrosis and sclerosis in pancreatic adenocarcinoma.

This study is not without limitations. The sample size was relatively small, and thus a future larger study is warranted to confirm the present results. In addition, there may be selection bias due to the single center design of our investigation despite our attempts to consecutively include potential subjects for analysis.

CONCLUSION

In conclusion, the rBF and rBV values of pancreatic adenocarcinoma are correlated with the immunohistochemistry indices of angiogenesis to a certain extent. These findings suggest that perfusion CT imaging may be an appropriate technique for quantitative assessments of pancreatic adenocarcinoma microvasculature.

ARTICLE HIGHLIGHTS

Research background

Pancreatic adenocarcinoma is one of the most common malignant tumors of the digestive system. More than 80% of patients with pancreatic adenocarcinoma are not diagnosed until late stage and have distant or local metastases.

Research motivation

To investigate the value of computed tomography (CT) perfusion imaging in the evaluation of angiogenesis in pancreatic adenocarcinoma patients.

Research objectives

To investigate the value of computed tomography (CT) perfusion imaging in the evaluation of angiogenesis in pancreatic adenocarcinoma patients.

Research methods

This is a retrospective cohort study. Patients with pancreatic adenocarcinoma and volunteers without pancreatic diseases underwent CT perfusion imaging from December 2014 to August 2017 in Huashan Hospital, Fudan University Shanghai, China.

Research results

A total of 35 pancreatic adenocarcinoma patients and 33 volunteers were enrolled. The relative blood flow (rBF), and relative blood volume (rBV) were significantly lower in patients with pancreatic adenocarcinoma than in the control group ($P < 0.05$). Conversely, the relative permeability in patients with pancreatic adenocarcinoma was significantly higher than that in controls ($P < 0.05$). In addition, rBF, rBV, and the vascular maturity index (VMI) were significantly lower in grade III-IV pancreatic adenocarcinoma than in grade I-II pancreatic adenocarcinoma ($P < 0.05$). Vascular endothelial growth factor (VEGF), CD105-MVD, CD34-MVD, and angiogenesis rate (AR) were significantly higher in grade III-IV pancreatic adenocarcinoma than in grade I-II pancreatic adenocarcinoma ($P < 0.05$). Significant correlations between rBF and VEGF, CD105-MVD, AR, and VMI ($P < 0.01$) were observed. Moreover, the levels of rBV were statistically significantly correlated with those of VEGF, CD105-MVD, CD34-MVD, and VMI ($P < 0.01$).

Research conclusions

Perfusion CT imaging may be an appropriate approach for the quantitative assessment of tumor angiogenesis in pancreatic adenocarcinoma.

Research perspectives

Further research on perfusion CT imaging for quantitative assessment of tumor angiogenesis in pancreatic adenocarcinoma is warranted.

FOOTNOTES

Author contributions: Liu W drafted the manuscript and assisted with data analysis; Yin B and Yu Y participated in the design and oversight of the study, and were involved in data collection; Lu N participated in the design of the study and assisted with data analysis; Liang ZH was involved in data collection and assisted with data analysis; all authors have read and approved the final manuscript.

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