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Original Article

Study of the correlation between MRI quantitative analysis and pathological features of pancreatic tumors

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Abstract: Objective: To investigate the application value of functional magnetic resonance imaging (fMRI) in the pancreatic cancer diagnosis, the correlation between its quantitative parameters and the fibrosis content as well as the expression of fibroblast activation protein (FAP). Methods: 50 pancreatic cancer patients that underwent routine MRI and DCE-MRI (dynamic contrast enhancement magnetic resonance imaging) scans from December 2013 to December 2015 in our hospital were selected in this study. ROI was used to detect the values of ADC (apparent diffusion coefficient), K^{trans} (transfer constant), Ve (extracellular extravascular volume fraction), Vp (vascular volume fraction) and k_{ep} (rate constant). The values of DCE-MRI quantitative parameters of pancreatic cancerous regions and non-cancerous regions were compared and analyzed. Pancreatic cancer patients, confirmed by pathology, were performed Masson staining and FAP immunohistochemical staining. In addition, the Pearson correlation analysis was used to respectively test the ADC, K^{trans}, Ve, and Vp values of pancreatic cancer fibrosis contents, and FAP staining scores. Results: The ADC values of pancreatic cancer regions and non-cancerous regions were respectively $(1.162\pm0.193)*10^{-3}$ mm^2/s and $(1.578\pm0.287)*10^{-3}$ mm^2/s; the values of K^{trans}, Ve, Vp, K_{ep} in pancreatic cancerous regions were (0.185±0.13)/min, (26.48±11.19)%, (3.517±3.18)%, (0.946±1.15), and the values in non-cancerous regions were (0.975±0.57)/min, (14.98±9.11)%, (8.492±9.79)%, (7.905±6.91). The difference between the groups was statistically significant; the ADC values of pancreatic cancer was negatively correlated with the fibrosis content and FAP staining expression (r=-0.546, P=0.038; r=-0.489, P=0.035); and the K^{trans} value of cancerous regions was negatively correlated with the fibrosis content and the expression of FAP staining (r=-0.612, P=0.015; r=-0.499, P=0.032); in the cancerous regions, the Ve value was positively related to fibrosis content (r=0.461, P=0.047). Conclusion: The differences of ADC, K^{trans}, Ve, Vp and k_{ep} value of pancreatic cancerous regions and non-cancerous regions had statistical significance, and these quantitative parameters were correlated with the fibrosis contents and FAP staining scores. Thus the DCE-MRI could provide important quantitative information for the diagnosis and pathological characteristics of pancreatic cancer.

Keywords: Magnetic resonance imaging, dynamic contrast enhanced, pancreatic cancer, fibroblast activation protein, fibrosis

Introduction

Pancreatic cancer, which threatens human health very much, is one of the common malignant tumor diseases. It was reported that the high mortality rate of pancreatic cancer was equal to its incidence rate, and the 5-year survival rate was lower than 5% [1, 2]. At present, CT and MRI examination are the common imaging examination methods of pancreatic lesions. Although the roles of CT enhanced scan in the diagnosis, differential diagnosis and preoperative evaluation of pancreatic diseases have been confirmed by clinical research, the exposure to radiation damage of patients is the biggest drawback. In recent years, with continuous development in magnetic resonance scanning technology and the emergence of fast sweep sequence, especially the application of three-dimensional volumetric interpolated breath-hold sequences (VIBE) technology, it has made the application value of fMRI in the pancreatic lesions increasingly concerned by scholars.

Recently, dynamic contrast enhanced magnetic resonance imaging (DCE-MRI), as an inspection

method of early diagnosis and treatment of tumors, can compare the changes of contrast medium concentration in the different pharmacokinetic model quantification tissues and organs to reflect the microvascular generation and distribution of tissues and organs, as well as the function of tumor blood vessels [3].

The parameter values that DCE-MRI can calculate include K^{trans}, Ve, Vp and K_{ep}. K^{trans} is transport constant and K^{trans} can reflect the rate of contrast agent penetrate from blood vessels to extracellular space. Ve is for the percentage of extravascular extracellular volume and Vp is the percentage of vascular capacitance. The value of K_{ep} means rate constant which can reflect the rate of extravascular extracellular space reflux to blood vessel. Some studies indicated that DCE-MRI related quantitative parameters had a close connection with tumor micro vessel density and fibrosis [4]. Fibroblast activation protein (FAP) is one of the specific markers of tumor associated fibroblasts and it can express in tumor stroma specifically. FAP is of great value in improving the accuracy of tumor diagnosis, preventing the recurrence of the disease and determining the prognosis of the disease more accurately. At present, the application and research of DCE-MRI in pancreatic cancer are mainly based on semi quantitative analysis.

There is still a lack of quantitative analysis research of pancreatic cancer, besides, the relationship between the quantitative parameters and the pathology of pancreatic tumors still remain unclear. Therefore, the purpose of this research was to explore the application value of quantitative analysis of magnetic resonance imaging in the diagnosis of pancreatic cancer, and further study the correlation between pancreatic cancer fMRI quantitative parameters and pathological characteristics, to search for the relationship between MRI imaging representation and pathology as well.

Materials and methods

Subjects investigated

50 patients with pancreatic cancer that underwent routine MIR and DCE-MRI in our hospital from December 2013 to December 2015 were selected. All patients were diagnosed as pancreatic cancer by pathologic biopsy and clinical examination. The ages of patients ranged from 44 to 72 years old including 30 males and 20 females. The main clinical manifestations told that there were 29 patients occurring dyspepsia, weight loss, abdominal and back pain, and 25 cases occurring jaundice as well.

MRI inspection method

All patients were performed MRI routine examination and DCE-MRI scans with Siemens Magetom Troi A Tim System 3.0 T MR. MRI routine scan: T1 weighted images (T1WI) adopted VIBE sequence, which indicated TR/TE was 6.45/2.82 ms, layer thickness 2.0 mm, interval parameter 0.0 mm and 60 layers.

T2 weighted imaging (T2WI) used spin echo sequence, which indicated TR/TE was 2000/81 ms, layer thickness 5.0 mm, interval parameter 0.0 mm, 30 layers. DCE-MRI scan: Before the MRI routine scans began, the venous indwelling needles were placed into intravenous. VIBE sequence was used to carry out DCE-MIR examination. With reference to the transverse position of T2WI images, select the maximum level of the lesion as the central scan. Scanning parameters: TR/TE was 3.31/1.07 ms, layer thickness 3.0 mm, interval parameter 0.0 mm, 36 layers. The scan range included the entire pancreas, the time resolution was 7 s, with a total of 60 times, and 7 min of the total imaging time. After the first dynamic, use high pressure injector to antecubital vein bolus Gd-DTPA (total amount: 0.1 mmol/Kg, rate of 0.2 ml/s). Take equal volume of physiological saline to irrigation catheter after bolus injection. Finally, carry out the routine enhancement T1WI scan of transverse, sagittal, coronal and use fat suppression T1WI to enhance scan.

The processing of DCE-MRI data, calculation of K^{trans}, Ve, Vp, k_{ep} and ADC values

Input the data into workstation and use the Functool2 software to measure the values of K^{trans}, Ve, Vp, k_{ep} and ADC (apparent diffusion coefficient). Two experienced radiologists selected regions they were interested (ROI) in obvious enhancement area of tumor parenchyma of pancreatic cancer. After image calibration, obtained pcolor from Tofts with Vp drug metabolism kinetics model and performed quantitative analysis.

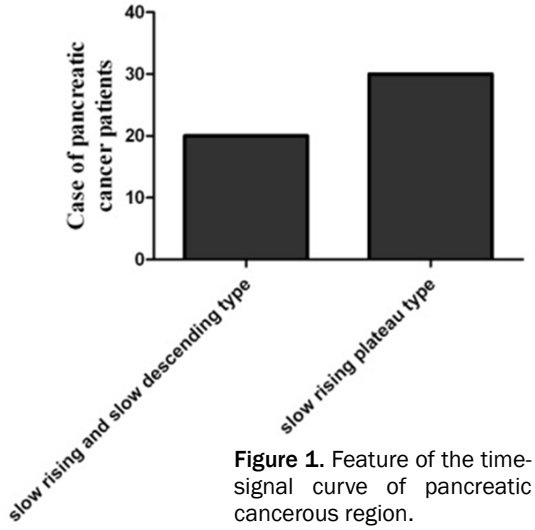

Figure 1. Feature of the time-signal curve of pancreatic cancerous region.

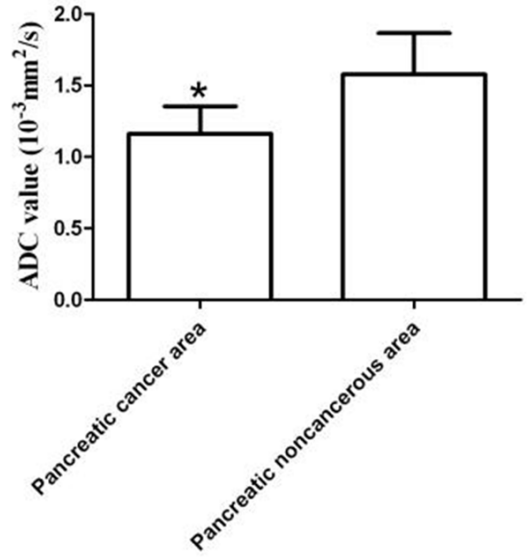

Figure 2. Comparison of ADC values between pancreatic cancerous region and non-cancerous region, *P<0.05.

Masson staining

Pancreatic cancer tissue samples were fixed in 10% formalin. The paraffin section was dewaxed to water and stained by masson compound for 5 min, washed by 0.2% acetic acid and 5% phosphotungstic acid for 5 min. Then the sections were bathed thoroughly in aqueous solution of 0.2% phosphotungstic acid with brilliant green stain for 5 min, and washed again by 0.2% acetic acid. At last, it was dehydrated through absolute ethyl alcohol and mounted in Xylene transparent agent and neutral balsam. Select five 10× magnifiers, use IPP6.0 software for the analysis of the percentage of fibrosis area, and calculate the average.

FAP immunohistochemical staining

Collect paraffin-embedded pancreatic cancer tissue samples, cut them into 4-5 μm slice thickness. Antigen retrieval was carried outwith 10 mmol/L citrate buffer solution (pH 6.0) by hyperbaric heating in order to eliminate the activity of endogenous peroxidase. After blocked in 10% goat serum for 1 h, the primary antibody was dropped (Rabbit anti human FAP monoclonal antibody) into the sample in an incubator at 4°C overnight. Then it reacted with the secondary antibody (Beijing Zhongshanqiao Biological Co.), which was marked with horseradish enzyme. Coloration was developed with DAB and followed the counter staining of the cell nuclear with hematoxylin. The sections were then dehydrated, mounted, viewed and photographed by inverted microscope. As the negative controls, PBS was adopted instead of the primary antibody.

Criteria for staining

The fiber contents of pancreatic neoplasms were observed under 10× magnifier, those ≤10% were regarded as negative. We graded the expressive degree of FAP according to the staining proportion and intensity. 10 visions of each section were chosen randomly under 40× magnifier, among them the criteria of visible staining proportion was as follows: 0 point for ≤10%, 1 point for 11%-25%, 2 points for 26%-50%, 3 points for 51%-75%, 4 points for >75%. Staining intensity criteria was as follows: 1 point for light brown, 2 points for brown, 3 points for dark brown. Marks of staining cell's proportion plus marks of staining intensity were the final scores.

Statistical treatment

All the data were statistically analyzed by SPSS19.0. MRI quantitative parameters of pancreatic cancerous regions and non-cancerous regions were compared by T-test. Pearson correlation test was adopted to test the correlation between the MRI quantitative parameters of functional pancreatic cancer and expressive degree of FAP.

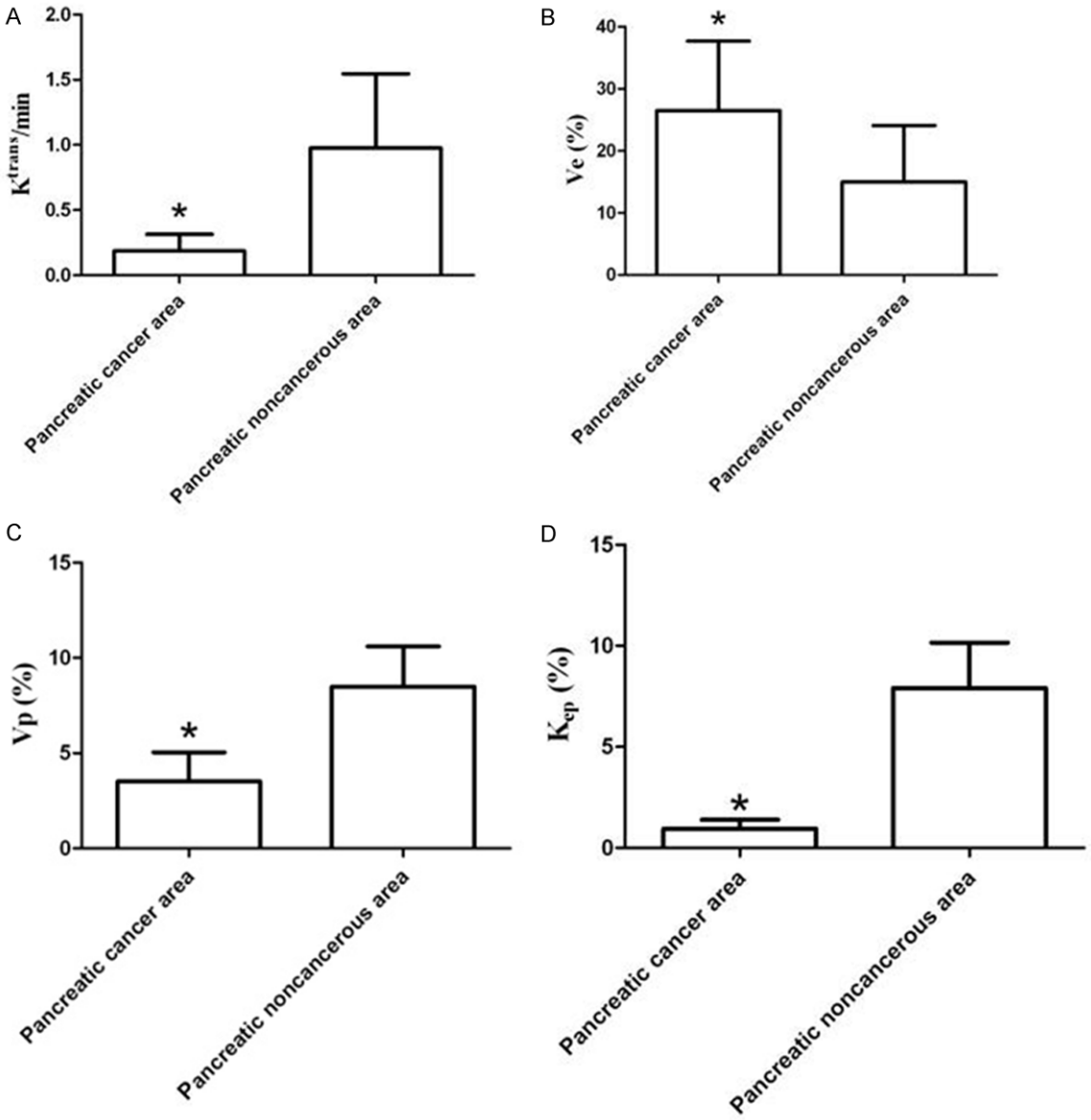

Figure 3. Comparison of quantitative parameter between pancreatic cancerous region and non-cancerous region *P<0.05. A: K^{trans}; B: Ve; C: Vp; D: K_{ep}.

Table 1. FAP expression scores of pancreatic cancer and non-cancerous areas

Group	FAP scores				
	5	4	3	2	1
Pancreatic cancer	25	11	4	10	0
Non-cancerous area	0	50	0	0	0

Results

Image representation of DCE-MRI

The image of pancreatic cancerous regions showed hypo vascularization and feature of delay enhancement. The non-cancerous region presented early-intensive and fast in and out. As the time-signal curve showed, there were 50 cases of fast rising and fast descending type in non-cancerous regions, 30 cases of slow rising plateau type in pancreatic cancerous regions and 20 cases of slow rising and slow descending type in cancerous regions (see **Figure 1**).

Comparison of DCE-MRI quantitative parameters

The ADC values of in pancreatic cancerous regions in 50 cases were (1.162±0.193)*10^{-3} mm^2/s. As for the non-cancerous region, the ADC values were (1.578±0.287)*10^{-3} mm^2/s.

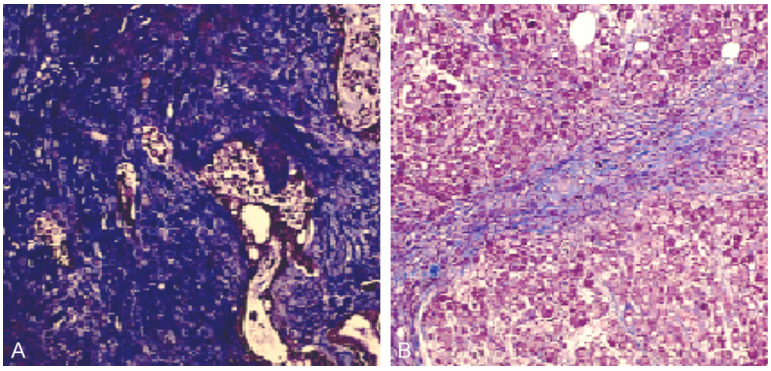

Figure 4. Masson staining of pancreatic carcinoma. A: A large amount of fibrous components in the cancerous area (darker-staining); B: A small amount of visible fibrous components in the non-cancerous area (oxford blue).

Table 2. The correlation between pancreatic cancer area fibrosis and ADC values, K^{trans} and Ve

Quantitative parameters	Fibrosis		FAP expression	
	Correlation coefficient	*P* values	Correlation coefficient	*P* values
ADC	-0.546	0.038	-0.489	0.035
K^{trans}	-0.612	0.015	-0.499	0.032
Ve	0.461	0.047	0.359	0.137

The distinction and statistical significance ($P<0.05$) exist in the comparison of ADC values between non-cancerous region and pancreatic cancerous region (see **Figure 2**). Besides, there also exists statistical significance ($P<0.05$) in the differences between DCE-MRI quantitative parameters of non-cancerous regions and pancreatic cancerous regions (see **Figure 3**).

Pathological findings of pancreatic neoplasms

The pathological findings of 50 cases of pancreatic tumors were all pancreatic ductal adenocarcinoma, in which the number of high differentiation, high-moderate differentiation, moderate differentiation, moderate-poor differentiation and poor differentiation cases were 12, 2, 22, 6 and 8. The FAP expression scores of pancreatic cancer after immunohistochemical staining were shown in **Table 1**. The results of pancreatic cancer of Masson staining suggested that there were a large amount of fibrous components in pancreatic cancer tissues, compared to a small amount of visible fibrous tissue components in non-cancerous area, which were about 2.3%, see **Figure 4**.

The correlation between ADC of pancreatic cancer, K^{trans}, Ve and FAP staining and fibrosis

There was a negative correlation between the ADC values and the fibrosis ($r=-0.546$, $P=0.038$) and FAP expression ($r=-0.489$, $P=0.035$) respectively; the K^{trans} was also negatively correlated with the fibrosis ($r=0.612$, $P=0.015$), and the expression of FAP staining ($r=-0.499$, $P=0.032$) respectively; while there was a positive correlation between Ve and fibrotic content ($r=0.461$, $P=0.047$), and so was FAP staining ($r=0.359$, $P=0.137$), but no significant difference, as shown in **Table 2**.

Discussion

Pancreatic cancer is a highly malignant gastrointestinal tumor, with insensitiveness to conventional radiotherapy and chemotherapy, and easy to relapse as well as metastasis after surgery. In recent years, with the development of biological technology, there is some progress made in view of the molecular biological characteristics of pancreatic cancer.

Studies have shown that parenchyma of pancreatic tumor tissue is rich in fibrotic components, which can not only resist chemotherapy and radiotherapy, but also provide a micro-environment for infiltration and metastasis of tumor [5]. Further studies have shown that the expression of fibroblast activation protein (FAP) is closely related to the large number of fibrotic hyperplasia in the tumor. The expression of FAP is also related to the process of tumor growth and tissue healing [6]. FAP protein is a cell surface glycoprotein, which is synthesized and secreted by fibroblasts activated in the tumor stroma. It can provide a good microenvironment for the growth, metastasis and invasion of tumor by activating the growth factors binding to the matrix protein, hydrolyzing the substrate in the matrix and degrading the extracellular matrix, so as to play its role in tumor development and progression [7, 8]. It was reported that the inhibition of FAP expression

can reverse the changes in the extracellular matrix, reduce fibrosis, so as to enhance the efficacy of patients and prolong survival time [9]. In this study, in view of the high expression of FAP in pancreatic tumors and the prognosis of patients with cancer, FAP is regarded as the pathological parameters of pancreatic cancer. In addition, we also consider the more fibrosis in the tumor tissues increases, the more obvious resistance to radiotherapy and chemotherapy, the stronger tumor cell transfer and infiltration as well as the slower apoptosis will be. Therefore, interstitial fibrosis of the tumor is also considered as an important parameter.

DCE-MRI is a new magnetic resonance imaging technique in recent years, which can effectively evaluate microvascular changes compared with conventional MRI enhancement. There were some research applying DCE-MRI semi-quantitative parameters such as maximum signal intensity, peak time, area under the curve, maximum slope to reflect the microvascular growth and distribution of pancreatic tumors. However, it turned out that the DCE-MRI semi-quantitative parameters cannot fully reflected physiological and pathological changes of pancreatic tumors.

In this study, the hemodynamics parameter K^{trans} value, Ve value, Vp value and k_{ep} values were calculated by using the quantitative analysis of DCE-MRI, and applying to the two compartment pharmacokinetic model as well as intravascular contrast medium transferring between the two compartment by the concentration gradient. K_{ep} is equal to the K^{trans}/Ve, described as the proportional constant of the contrast medium reflowing from extravascular volume to intravascular after tissue perfusion reaching a balance. Some studies have reported that the correlation between k_{ep} and microvessel density is better than the correlation between K^{trans} and microvessel density [11]. The study results showed that, compared with the non-cancerous regions tissue, the K^{trans} and k_{ep} values of pancreatic cancer regions reduced significantly, indicating that the blood vessels of pancreatic cancer were immature, new vessels were incomplete and vascular permeability increased which caused the leakage of contrast medium. K^{trans} represents the rate of contrast medium transferring from intravascular to extravascular and reflects the blood perfusion, which can provide the important information for neoplasm angiogenesis. The K^{trans} value changes with the tumour cells permeability areas, extracellular volume capacity, injection rates of contrast media, tumor vessels and some other factors. The fibrous tissue hyperplasia in pancreatic neoplasms stroma makes extracellular space reduced and structure more compact, which leads to the barrier of contrast media permeability and the reduction of K^{trans} value [12].

An increasing attention is paid to the study of Ve value, which can evaluate the curative effects of tumor. Ve value represents the extracellular extravascular volume in the unit volume of tissues. Compared with the normal tissue, Ve value of malignant tumor increases significantly [13]. In this study, it was also found that Ve of pancreatic cancerous regions increased more obviously than that of the non-cancerous regions and there was statistical difference ($P<0.05$), which might be related to the increased extracellular matrix and the hyperplasia of collagenous fiber [14]. Vp value represents the functional vascular volume and the bigger the Vp value is, the richer the tumor blood vessels are. This study showed that the Vp value of pancreatic cancerous regions decreased more obviously than that of the non-cancerous regions and there was statistical difference ($P<0.05$). This conclusion was inconsistent with the previous study reports [15, 16]. It might be related to the factors like the injection speed of contrast media, integral dose of contrast media and different choices of pharmacokinetic model. ADC values can evaluate the early diagnosis, detection and prognosis of tumors; and it can make quantitative analysis of different pathophysiological status. This study showed that the ADC values of pancreatic cancerous regions decreased more obviously than that of the non-cancerous regions and there was statistical difference ($P<0.05$), which might be related to the blood perfusion and the diffusion level of extracellular volume water molecules [18, 19].

The study showed that, compared with the normal tissue, the content in the pancreatic cancer tissue increased significantly and the range increased obviously. It was reported that the changes of the fibrosis in tumor stroma influenced the diffusion and osmosis of contrast

media or intracellular water molecules directly, and thus changed the quantitative parameter of ADC, K^{trans} and Ve values [20]. The results also showed that high expression of FAP protein was closely related to the fibrosis in the pancreatic tumor and the change of ADC values showed a negative correlation with change of the content of fibrosis. We speculated the ADC values had a connection with the FAP expression and it had been verified. This was consistent with previous study [21]. Furthermore, the results showed that the content of fibrosis had a positive correlation with Ve value, and had a negative correlation with the K^{trans}. It may be due to the increase of fibrosis growth leading to the reduction of blood vessel density. In addition, the pressure and content of extracellular volume increased, which made the contrast medium had obstacle to infiltrate the extravascular, so that the K^{trans} value of the DCE-MRI quantitative parameters became smaller and the Ve value became greater.

In conclusion, the differences of ADC, K^{trans}, Ve and k_{ep} values between pancreatic cancerous regions and the non-cancerous regions all have statistical significance, and these quantitative parameters have definite correlation with the contents of fibrosis and FAP stain scores. Consequently, DCE-MRI provides important quantitative information for the diagnosis and the pathology characteristics of pancreatic cancer.

Disclosure of conflict of interest

None.

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