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The application of high-field magnetic resonance perfusion imaging in the diagnosis of pancreatic cancer

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Abstract

Pancreatic cancer is the fourth leading cause of cancer death in the world. It is a disease of insidious progression and high lethality. The present study was to investigate the diagnostic value of high-filed magnetic resonance (MR) perfusion imaging in pancreatic cancer. Thirty-three patients with suspected pancreatic cancer were recruited in our study and underwent routine MR imaging. When compared with para-tumoral and normal tissue, the pancreatic lesions showed significant lower slope, peak enhancement (PE), and signal enhancement ratio (SER) as well as higher time to peak (TTP). Para-tumoral tissue was found to have significantly lower slope and PE, slightly higher TTP than normal tissue. MR perfusion imaging displays hemodynamic alterations in both pancreatic cancer and surrounding pancreatic tissue, and provides indirect assessment of tumor vascularity. In conclusion, high field MR perfusion imaging has important clinical significance in early diagnosis of pancreatic cancer.

Abbreviations: MRI = magnetic resonance imaging, PC = pancreatic cancer, PE = peak enhancement, ROI = regions of interest, SER = signal enhancement ratio, TIC = time–intensity curves, TNM = tumor-node-metastasis, TTP = time to peak.

Keywords: MR perfusion imaging, pancreatic cancer, perfusion imaging technique

1. Introduction

Pancreatic cancer (PC) is the fourth leading cause of cancer death in the world. It is a disease of insidious progression and high lethality, with a 5 years survival rate of only 6%.[1] PC has remained challenging to treat with few patients eligible for resection and median survivals of 6 to 12 months for those with metastatic diseases, despite use of multiagent chemotherapy.[2,3] It typically spreads rapidly and is seldom detected in early stage because of its insidious onset. As a result, most patients, when diagnosed, are at advanced stages, and complete surgical resection is usually precluded.[4,5] The poor prognosis of patients with PC is attribute to the lack of effective means of early diagnosis. Only 5% to 10% of patients are candidates for potentially curative resection at the time of diagnosis.[6] From this perspective, a throughout understanding of this lethal disease targeting early detection is required. Intra-tumor hemodynamics, or tumor perfusion, provides useful information in understanding pathological background of cancers.[7] In particular, high field magnetic resonance perfusion imaging, or perfusion weighted imaging (PWI), is such a noninvasive method introduced as to assess intra-tumor hemodynamic changes recently. Thus, in this study, we used high field magnetic resonance perfusion to evaluate the hemodynamic alterations in pancreatic cancer. We aimed to evaluate the microscopic pathology changes of pancreatic cancer and investigated the diagnostic value of perfusion imaging in patients with pancreatic cancer.

2. Materials and methods

2.1. Patient demographics

Between February 2011 and September 2012, 33 patients with suspected pancreatic cancer (19 males and 14 females; age range: 41–76 years; median age: 56.2 years) in our hospital were retrospectively studied. All these patients underwent 3.0 Tesla MR perfusion imaging as part of their MR scan protocol. These patients presented with upper abdominal pain or abdominal discomfort. Among them, 17 patients experienced jaundice, 8 patients had left lower back pain, and all patients had certain degree of weight loss. Twenty-four lesions were located in the head of pancreas, and 9 lesions were in the body or tail of pancreas. The diagnosis of pancreatic cancer was confirmed by surgery and postoperative pathology in 19 patients. Clinical manifestations, elevated tumor biomarkers and imaging findings were considered to make the diagnosis in the remaining 14 patients. Twelve patients had liver metastasis at the time of presentation. The sixth edition of the tumor-node-metastasis (TNM) classification of the International Union against Cancer for pancreatic cancer (2009 version) was used to classify these patients: stage I (2 patients), stage II (11 patients), stage III (15 patients), and stage IV (5 patients).[8] The study was approved by the Research Ethics Committee of Henan University. Informed consent was obtained from all patients.

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2.2. MR scanner and pulse sequences

Magnetic resonance imaging (MRI) was performed using a 3.0 Tesla superconducting MRI scanner (MAGNETOM Verio, Siemens Healthcare, Erlangen, Germany) with a phased-array body coil. No patients had MRI contraindications such as cardiac pacemakers or ferromagnetic surgical implants. Fasting for 6 to 8 hours was required in all patients, and all ferromagnetic items were removed before examination. Patients were also instructed how to breathe and hold breath in order to cooperate during examination. The scan included ranges from upper border of diaphragm to lower border of kidney when patient was in supine position. Conventional transverse and coronal scans of upper abdomen were firstly performed. Imaging included precontrast transversal 3D T1-weighted fat-suppressed volume interpolated body examination (VIBE) (TR/TE 3.92/1.39 ms), transversal T2-weighted fat-suppressed blade (TR/TE 3900/110 ms), diffusion-weighted imaging ($b = 50$, $b = 800$), and coronal T2-weighted half fourier acquisition, single shot, fast spin echo sequence (TR/TE 1100/90 ms). Slice thickness 5 mm with a gap of 1 mm was used. The MR perfusion imaging was then performed, aiming at pancreatic lesions predetermined by conventional scans in each patient. A 0.2 mmol/kg bolus of gadodiamide-DTPA was rapidly administered manually (at a rate of approximately 3.0 mL/s) by 1 investigator via dorsal hand vein or median cubital vein. Immediately afterward, a 20-mL saline flush was administered at the same injection rate. Dynamic scanning started after the initiation of contrast bolus injection with 2D turbo fast low angle shot sequences (TR 347 ms, TE 2.08 s; TI 178 ms; slice thickness 5 mm; interslice gap 1.5 mm; field of view 400 mm; flip angle, 8°; matrix, 192×192; band width 900 HZ/PX). Fifty continuous 2.08 seconds acquisitions were acquired with 6 slices in each scan and a total of 300 images were obtained. During perfusion imaging, bellyband was used and thoracic breathing was recommended to reduce breath-induced artifacts. Subsequent contrast-enhanced scan was performed with transverse T1WI fat-suppressed VIBE sequence (TR/TE 3.92/1.39 ms) and breath hold acquisitions were acquired to cover the pancreas.

2.3. MR imaging acquisition and data postprocession

Fifty images displaying the largest tumor part were selected and sent to mean curve software (Siemens) for postprocession. Regions of interest (ROI) were manually delineated in pancreatic lesions, peritumoral tissue, normal tissue, as well as aortic region. Peritumoral tissue was defined as pancreatic tissue within 5 mm from the lesions. Pancreatic tissue beyond 5 mm from the lesions was defined as normal tissue. Aortic region was delineated in reference to signals from the lumen of abdominal aorta. Care was taken in covering the largest possible region excluding adjacent organs and large vessels. For pancreatic lesions, ROIs were placed to cover solid components of lesions. After ROIs placement, time–intensity curves (TIC) and related intensity data were automatically created at the click of function key "curve." Semi-quantitative analysis of TICs was also performed using perfusion parameters including slope, peak enhancement (PE), time to peak (TTP), and signal enhancement ratio (SER), which were calculated from given signal intensity data.

2.4. Statistical analysis

Continuous variables were expressed as mean ± SD (standard deviation) and compared using a 2-tailed unpaired Student *t* test; categorical variables were compared using χ^2 or Fisher analysis. All statistical evaluations were carried out using SPSS software (Statistical Package for the Social Science, version 12.0, SPSS Inc, Chicago, IL). *F* test was used to compare means of slope, PE, TTP, and SER among different tissues. If a significant difference was observed, student - newman - keuls (SNK)-q test was further applied for pairwise comparisons. Besides, mean slope, PE, TTP, and SER of pancreatic lesions were also compared in respect to clinical stages (Stage I, II vs Stage III, IV) with 2 independent sample *t* test. *P* value $<.05$ was considered statistically different.

3. Results

Routine MR imaging revealed lesions with evident abnormal intensity in 28 patients. These lesions, without distinct borders, were located either in the head or in the body/tail of pancreas. The solid component demonstrated a slightly low signal intensity on T1-weighted images, a slightly high intensity on T2-weighted images, a high intensity on T2-weighted fat-suppressed images, and a high intensity on diffusion-weighted imaging. In the remaining 5 patients, MR images showed diffuse enlargement of pancreas body and tail with low intensity. Necrosis was noted in 19 lesions, which showed patchy high-intensity signal on T2-weighted images. For metastases, 12 patients had multiple liver metastases, 15 patients had lymph node metastases, and 11 patients had superior mesenteric venous or portal venous invasion.

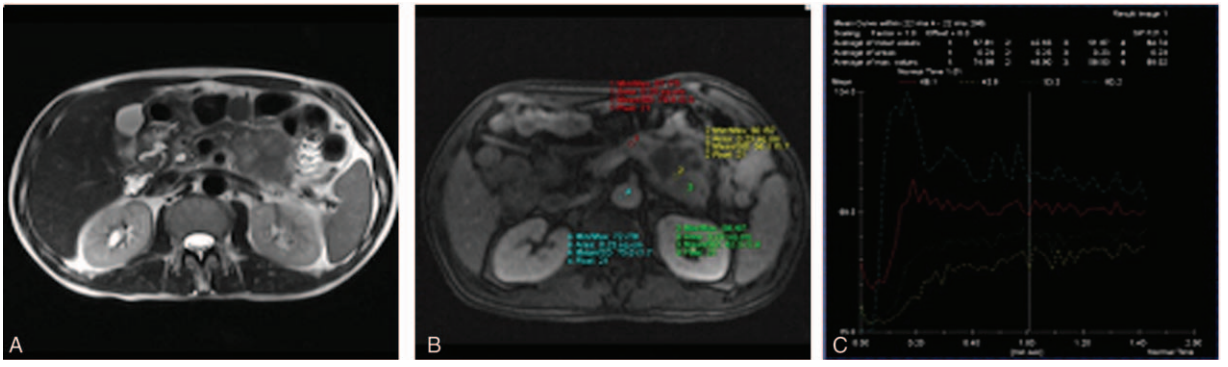

Figure 1. 61-year-old male with pancreatic cancer in the body and tail of pancreas. Transversal T2-weighted images showed moderate high and high intensity in pancreatic body and tail (A). Schematic showed placement of ROIs. Pancreatic lesions (yellow), peritumoral tissue (green), normal tissue at pancreatic neck (red), and aortic region (green). (B) TIC of pancreatic lesions demonstrated slow enhancement pattern without obvious peak. Lower perfusion compared with peri-tumoral region and normal region was identified (C). ROIs = regions of interest, TIC = time–intensity curves.

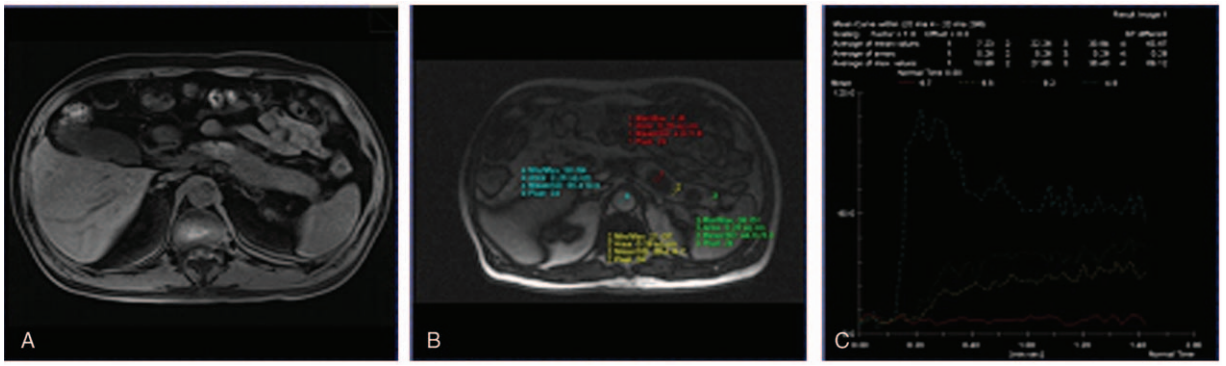

Figure 2. 81-year-old male with pancreatic cancer in the body of pancreas. Transverse fat-suppressed T1-weighted images showed widen pancreatic body with slightly low intensity (A). ROIs placement (B). TICs (C). ROIs = regions of interest, TIC = time–intensity curves.

The TIC of pancreatic lesions demonstrated gradual slow enhancement without obvious peak. For normal tissue, the TICs showed early rapid enhancement and washout pattern; for paratumoral tissue, post-peak plateau or slow rise was observed after early rapid enhancement (Figs. 1–3). In regard to perfusion parameters, lesions had significantly lower slope, PE, and SER as well as higher TTP than other tissue ($P < .05$); paratumoral tissue showed lower PR and TTP than normal tissue. The detailed information of perfusion parameters was shown in Table 1. In addition, similar patterns (gradual slow enhancement) of pancreatic lesions were found in patients across clinical stages. It was notable that the necrotic regions demonstrated approximately a flat curve on TIC. Between stage 1/2 and stage 3/4, no significant differences in slope, TTP, and SER were found (Tables 2 and 3).

4. Discussion

First-pass contrast-enhanced MR perfusion imaging, one of the most common modalities, is used in our study. This technique takes advantage of local intensity changes induced by first-pass contrast and acquires a series of dynamic images with fast-imaging sequences by monitoring intensity changes at fixed slices. More specifically, when paramagnetic contrast flows through tissue capillary bed, increased intravascular magnetic susceptibility induces alterations of local magnetic environment.

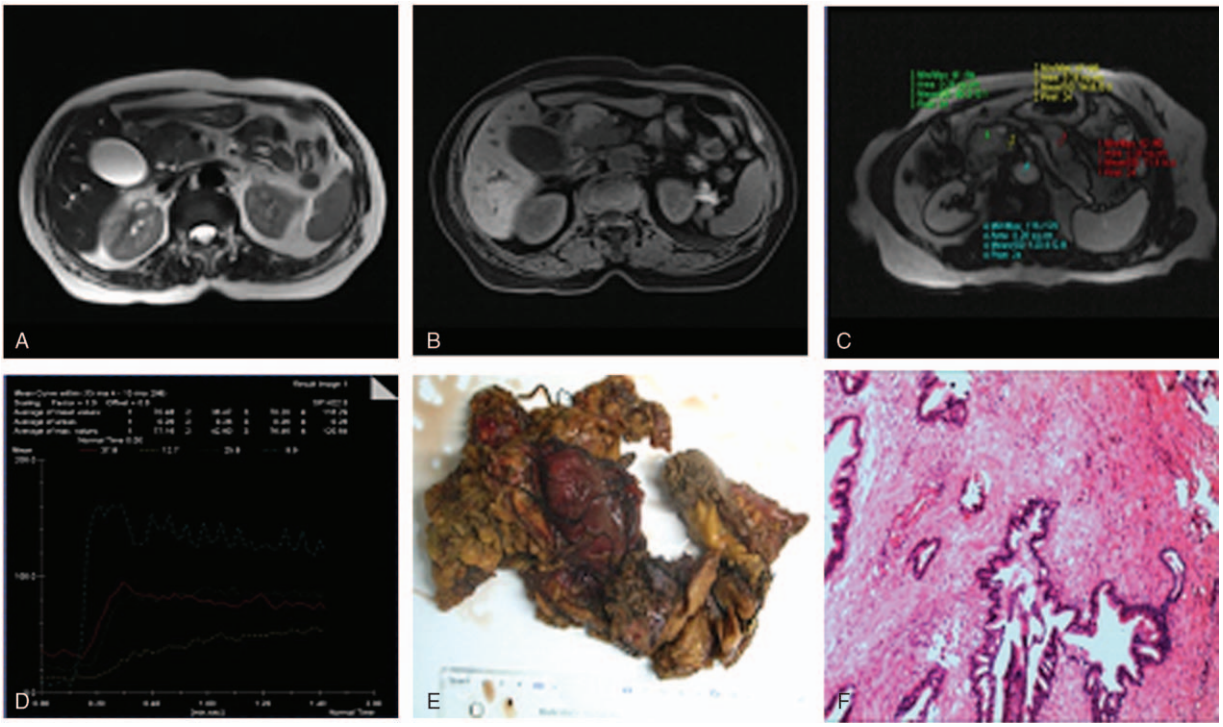

Figure 3. 69-year-old female with pancreatic cancer in the head of pancreas. Transversal T2-weighted images showed mass in the head of pancreas with slightly high intensity (A). Transversal fat-suppressed T1-weighted images showed slightly low intensity (B). ROIs placement (C). TICs (D). Resected tissue, including partial stomach, duodenum, partial pancreas, and omentummajus, were sent for postoperative pathology (E). Results showed highly-differentiated adenocarcinoma in the pancreatic head. Invasive growth into surrounding pancreatic tissue and basal lamina of duodenum was identified. Histological evaluation of resected common bile duct, stomach, and duodenum revealed negative resection margins. No lymph metastases, however, were found at greater/lesser curvature of stomach, small intestine and pancreas (HE x400) (F). ROIs = regions of interest, TIC = time–intensity curves.

Table 1

Comparison of perfusion parameters among pancreatic lesion, peritumoral tissue, normal tissue, and aortic region.

Regions	N	PE	Slope	TTP (s)	SER
Pancreatic lesions (Group A)	33	35.20	3.01 ± 6.42	78.63 ± 6.22	2.81 ± 8.94
Paratumoral tissue (Group B)	33	65.40	4.34 ± 3.55	23.47 ± 4.20	5.70 ± 6.71
Normal tissue (Group C)	33	97.20	6.27 ± 5.26	15.60 ± 2.04	8.63 ± 3.51
Aortic region (Group D)	33	162.50	8.87 ± 2.11	11.84 ± 3.23	10.52 ± 5.21

For statistical analysis, *F* test was used to compare the means of relevant perfusion parameters among groups. Results showed $F_{(PE)} = 4.38$, $F_{(SLOP)} = 3.71$, $F_{(TTP)} = 8.44$, $F_{(SR)} = 4.02$, $P < .05$, which indicated differences among groups. SNK-q test was further used for pairwise comparisons. Results were shown in Table 2.
PE = peak enhancement, SER = signal enhancement ratio, TTP = time to peak.

A significant T1/T2 shortening then occurs due to induced resonance frequency changes and proton spin dephasing of hydrogen protons in close proximity.[9] Thus, amplified signal intensity on T1-weighted images or reduced intensity on T2-weighted images is expected. In addition, the intensity changes of certain slice over time can be evaluated using the so-called TICs, which are based on intensity changes obtained from a series of dynamic images. A variety of mathematical models are available to calculate relevant perfusion parameters from TICs. In perfusion imaging, it is notable that first-pass data are used. During that phase, the intensity changes are least influenced by diffusion, as contrast remains exclusively in the vessels and greatest gradient across capillary walls is achieved. Therefore, the TICs and relevant parameters, based on acquired first-pass data, are a good reflection of real tissue perfusion and micro-vessel distribution.[10]

In 1991, Ichikawa et al[11] first performed perfusion weighted MR imaging of the upper abdomen in 61 patients. Afterwards Coenegrachts et al[12–14] applied this technique in patients with pancreatitis and found a significant difference in perfusion parameters in the multiple comparison among patients with acute pancreatitis, chronic pancreatitis, and healthy volunteers. They also used perfusion imaging in patients with pancreatic cancer, and demonstrated lower perfusion in pancreatic lesions compared with normal pancreas tissue. In respect to normal pancreatic tissue, Bali et al's study[15] showed that different regions of pancreas, namely head, body, and tail of pancreas, may have different perfusion parameters. However, similar regional perfusion difference was not observed in studies from Chinese authors.[16] One group of these Chinese authors also investigated perfusion parameters of pancreatic lesions, nonlesion regions, and normal pancreatic tissue. Paired comparison showed that there was a significant difference between any 2. The authors then concluded that the perfusion difference between lesions and nonlesion regions may suggest the extent of invasion, while the difference in TTP between nonlesion regions and normal pancreatic tissue indicated the existence of potential malignancy.[17] Furthermore, Tajima et al[14] found out that TIC and TTP from dynamic contrast-enhanced MRI (DCE-MRI) provided reliable information to differentiate pancreatic cancer from tumor-forming pancreatitis. The TTP of the former was often beyond 2 minutes and the latter between 1 and 2 minutes. The TTP of normal pancreatic tissue was less than 1 minute.

In perfusion imaging, the perfusion changes in tumor are used to evaluate intra-tumor vascularity alterations in vivo.[18] Several perfusion parameters are now available for semi-quantitative analysis. The slope of TIC, correlated with vessel number and vascular permeability, reflects degree of tissue vascularity. TTP, the time required to achieve peak, provides comprehensive overview of both blood flow and blood volume. Another commonly used parameter, SER, has highly positive correlation with tissue perfusion and acts as a good reflection of blood flow.[19] In normal pancreatic tissue, a homogenous enhancement is usually expected for its evenly-arranged glandular tissue, intact endothelium, and rich blood supply. However, for pancreatic cancer, the degree and pattern of enhancement is far more complicated. Pancreatic cancer often has poor vascularization and distinct micro-capillary patterns from other tumors. Histologically, pancreatic cancer cells are interspersed among fibrous mesenchyme (the predominant component of pancreatic cancer) and remaining pancreatic tissue, and their relative percentage vary depending on the aggressiveness of the cancer. As a result, the unique distribution of these components in pancreatic lesions contributes to the overall enhancement pattern.[20]

In our study with 33 patients, MR images showed lowest perfusion in pancreatic lesions, which was further confirmed by lowest SER, slope, PE, and highest TTP. This decreased blood flow and volume could be partially explained by local changes involving focal fibrosis and peripheral vessel sclerosis. Increased vascular permeability, increased blood flow resistance, and decreased blood flow rate were also responsible for the perfusion changes.[21]

Our study also found that paratumoral tissue had lower SER, slope, PE, and higher TTP than normal tissue, which suggested possible cancer cell invasions in paratumoral region. The result was not surprising, as pancreatic cancer is highly invasive and paratumoral tissue is often found involved at initial diagnosis. Our results were consistent with that of Villringer and Belliveau.[22] In addition, the hemodynamic difference between pancreatic lesions and paratumoral tissue, as shown by perfusion parameters, implied the extent of local tumor invasion. By the same token, the difference between paratumoral and normal tissue suggested that potential pathology changes might already

Table 2

Pairwise comparisons of perfusion parameters (*P* value).

P	Group A and B	Group A and C	Group B and C
$P_{(PE)}$	.012	.000	.013
$P_{(slop)}$	.022	.000	.021
$P_{(TTP)}$	.014	.000	.001
$P_{(SR)}$	.010	.000	.017

Table 3

Comparisons of perfusion parameters across clinical stages.

Clinical stages	N	Slope	TTP (s)	SER
Stage 1/2	13	2.76 ± 5.19	74.1 ± 4.84	2.63 ± 5.34
Stage 3/4	20	3.05 ± 4.81	74.1 ± 5.28	2.71 ± 4.65
t value		−0.684	−0.861	−0.901
P vaule		>0.05	>0.05	>0.05

SER = signal enhancement ratio, TTP = time to peak.

occur in paratumoral region. As we all know, clear delineation of lesion boundary was of vital importance in making surgical plans.

Our study further investigated the effect of clinical stages on relevant perfusion parameters. No difference, however, was found between lesions in stage 1/2 and stage 3/4. This finding implied that intra-tumor blood volume, blood flow, and transit time were not directly related to clinical stages.

The high field MR perfusion imaging has its advantages over conventional DCE-MRI. Although DCE-MRI is widely used in evaluating overall blood supply to the pancreatic cancer, it cannot provide accurate information about intra-tumor micro-circulations or hemodynamic changes. Perfusion imaging, on the contrary, directly shows perfusion alterations in tumor tissue and serves as a noninvasive tool to assess micro-capillary distribution in vivo.

Currently, CT scans and DCE-MRI are both reliable methods in the diagnosis of pancreatic cancer. But MRI is preferred imaging modality for primary pancreatic cancer.[23] In general, MRI has several advantages, such as multifunction, multiplane imaging, high soft tissue resolution, radiation-free, and trauma-free.[24] Besides, simultaneous anatomical and functional display is available in MR perfusion imaging, and repeated examinations can be performed to monitor therapy efficacy. Apart from clearer delineation of pancreatic lesions attributable to high soft tissue resolution and sharp contrast, high field MR perfusion imaging also provides useful information about intra-tumor perfusion and hemodynamic changes. In that perspective, perfusion imaging is expected to increase tumor detection rate and improve qualitative diagnostic accuracy.[13] In addition to aiding diagnosis, the use of PWI as a noninvasive method to evaluate tumor angiogenesis in vivo might also aid in therapy selection, response prediction, and efficacy monitoring.[25,26]

There are several limitations of this study: the sample size is too small in this study, and further studies with larger sample size are needed to confirm the present results. Since the high field MR perfusion imaging has its advantages over DCE-MRI and CT scans, further comparsion studies should be performed to confirm which modality is superior in early diagnosis of pancreatic cancer.

In conclusion, high field MR perfusion imaging has important clinical significance in early diagnosis of pancreatic cancer.

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