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PANCREAS

110 Patients with adenosquamous carcinomas of the pancreas (PASC): imaging differentiation of small (≤ 3 cm) versus large (> 3 cm) tumors

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Abstract

Objective This study examined radiological imaging features of small (≤ 3 cm) and large (> 3 cm) adenosquamous carcinomas of the pancreas (PASC) lesions to better understand the morphology of these lesions.

Methods Images from 110 patients with pathologically proven PASC (80 males and 30 females, mean age: 62.6 years) were retrospectively reviewed. Two radiologists analyzed images and reached a consensus regarding the following features: location, shape, margins, presence of solid and necrotic components, rim enhancement, density/intensity during the portal venous phase, invasion of surrounding organs, vascular invasion, venous tumor thrombus formation, and enlarged lymph nodes. Differences in the imaging features between the two groups were evaluated with the Chi-square test or Fisher's exact test.

Results There were 41 small PASC lesions (mean age: 60.59 years) and 69 large PASC lesions (63.74 years). Statistical analysis demonstrated significant differences in the location, shape, adjacent organ and vessel invasion, and venous tumor thrombus formation ($P < 0.05$). Small PASC lesions were more frequently detected in the pancreatic head and had an ovoid shape. There was no significant difference in the presence of solid and necrotic components ($P = 0.090$), including approximately 3/4 of the lesions with necrosis and 1/4 purely solid lesions, enlarged lymph nodes ($P = 0.068$) and other features.

Conclusion Regardless of the tumor size, 75% of PASC lesions present with central necrosis while 25% are purely solid. Small PASC lesions can be associated with lymph node metastasis at a relatively early stage. Large PASC lesions are likely to invade adjacent tissues and be associated with venous tumor thrombus formation.

Keywords Adenosquamous carcinoma · Pancreas · Diagnostic imaging · Retrospective study

Introduction

Pancreatic cancer is the seventh most common fatal malignancy among both men and women worldwide, accounting for an estimated one hundred and seventy-four and one hundred and fifty-seven thousand deaths, respectively [1]. The 5-year survival rate of pancreatic cancer is 7%, which is the lowest of all tumors [2]. Pancreatic adenocarcinoma accounts for 85% of pancreatic cancer [3], whereas adenosquamous carcinomas of the pancreas (PASC), an extremely rare and unique subtype, accounts for approximately 0.38–4% of pancreatic malignancies [4–9]. Histologically, PASC has a significant proportion of cells with at least 30% malignant squamous differentiation in addition to neoplastic cells with ductal differentiation [10]. PASC is also referred to as "adenoacanthoma" and "mucoepidermoid carcinoma" and is regarded to be more clinically aggressive and have a

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worse prognosis than conventional adenocarcinoma of the pancreas [9, 11–13].

A retrospective study revealed that inclusion of a platinum agent in the adjuvant regimen was associated with significantly longer median survival, highlighting the need for prospective investigation of platinum-containing adjuvant therapy regimens and perhaps neoadjuvant regimens [14]. Therefore, accurate diagnosis and recognition of PASC is necessary for clinical diagnosis and treatment but difficult to accomplish before surgery. PASC has nonspecific clinical symptoms and presents with abdominal pain, abdominal distension, jaundice, low back pain, and emaciation. The imaging features of PASC have not been comprehensively discussed in scattered case reports and small studies due to the rarity of this disease [13, 15]. Several small studies have revealed the presence of central necrosis as the only accepted feature for the diagnosis of an adenosquamous variant of pancreatic carcinoma [16–18]. However, compared with other studies [16, 17], we have found a relatively large number of solid lesions in our practice and want to investigate further if this finding is associated with the lesion size or if there are any other differentiating features of small or large PASC lesions. The purpose of this study was to evaluate the radiological imaging features of pathologically proven PASC and to compare these imaging features in small (< 3 cm) and large PASC lesions (> 3 cm).

Materials and methods

Study population

This study was approved by institutional review board of two hospitals, and informed patient consent was waived for this study. We retrospectively reviewed the pathology records from September 1998 to January 2018 from the two hospitals to identify 132 cases. Patients who met the following criteria were included in our study: (1) confirmed PASC by histopathologic examination and (2) enhancement computed tomography (CT) or magnetic resonance imaging (MRI) performed before any treatment. We excluded nine patients with primary adenosquamous carcinoma of other organs, including two of the extrahepatic bile duct and gallbladder invading the head of the pancreas, three of the ampulla of Vater, two of the duodenum, and one of the stomach. In addition, three patients with PASC whose preoperative images were unavailable were excluded. Thus, data from 110 patients were included in our study. Of them, 102 patients underwent surgical resection, and the remaining 8 were diagnosed based on biopsy, including 2 by endoscopic ultrasound-guided fine-needle aspiration, 2 by needle biopsy of hepatic metastasis and 4 by biopsy of the primary lesion during open surgery. These patients included 80 men and 30 women (mean age: 62.6 years, range 41–80 years) with chief complaints of abdominal pain (most common), low back pain, abdominal distension, jaundice, weight loss, anorexia, vomiting, hyperglycemia, elevated carbohydrate antigen 19-9 levels, incidental findings, and melena. The mean lesion size was 3.9 ± 1.37 cm (range 1.1–8.7 cm). Seventy PASC lesions were located in the pancreatic head, sixteen in the body, and twenty-four in the tail.

CT technique

Multiphasic contrast-enhanced CT images including nonenhanced, arterial phase, portal venous phase, and equilibrium phase images were available for 89 patients. Multidetector CT was performed with one of the following CT scanners: 16-channel CT scanner [(Brilliance 16, Philips Healthcare, Cleveland, Ohio, USA) ($n = 6$), or (Sensation 16, Siemens Medical Solutions, Forchheim, Germany) ($n = 3$)]; 64-channel CT scanner [(Somatom Sensation 64 Cardiac, Siemens Medical Solutions, Forchheim, Germany) ($n = 52$), or (Somatom Definition AS, Siemens Medical systems, Erlangen, Germany) ($n = 18$)]; and 640-channel CT scanner (Aquilion One, Toshiba Medical, Tochigi, Japan) ($n = 10$).

First, unenhanced images were acquired. For dynamic contrast-enhanced scanning, a total of 80–100 mL of nonionic contrast medium (Omnipaque 300 mg/mL; GE Healthcare, Milwaukee, WI, USA) was administered at a rate of 3–4 mL/s via the antecubital vein with a power injector. The scanning delay time after the contrast injection was 25 s for the arterial phase, 60 s for the portal venous phase, and 100 s for the equilibrium phase; or 20–25 s for the arterial phase, 40–50 s for the portal venous phase, and 85–100 s for the equilibrium phase. The following scanning parameters were used: section thickness of 3 mm, maximum allowable tube current of 160 mAs or tube current–time product of 300–432 mAs, peak voltage of 120 kV, and field of view of 320 mm × 320 mm.

MRI technique

MR images were available for 62 patients. MR images were obtained using one of the following MR scanners: 1.5-Tesla scanner (Magnetom® Avanto, Siemens AG, Erlangen, Germany) ($n = 19$) or 3.0-Tesla scanner [(MAGNETOM Skyra, Siemens Healthcare, Erlangen, Germany) ($n = 7$), (Signa HDxt 3.0 T, GE Healthcare, Milwaukee, WI) ($n = 25$), or (DISCOVERY MR750, GE Healthcare, Milwaukee, WI) ($n = 11$)].

The MR examination consisted of axial unenhanced fat-saturated T1-weighted images (T1WI) (TR, 160–250 ms; TE 2.1–4.5 ms), axial fat-saturated T2-weighted images (T2WI) (TR, 2800–6000 ms; TE, 68–91 ms), and additional contrast-enhanced T1WI. The other imaging parameters for

T1WI and T2WI were as follows: standard field of view of 280 mm, 360 mm or 380 mm, slice thickness of 5 mm, slice spacing of 1.0–1.5 mm, and matrix of 256 × 256. Transverse contrast-enhanced T1WI with breath-hold were attained after administration of 0.1 mmol/kg of Omniscan (GE Healthcare, UJ, USA) at a rate of 2–3 mL/s. The arterial phase, portal venous phase, equilibrium phase, and delayed phase were 18–19 s, 40–50 s, 90 s, and 180–300 s, respectively, or 15–20 s, 60 s, 180 s, and 300–480 s, respectively, after the injection.

Image analysis

All images were reviewed simultaneously by two experienced abdominal radiologists (15 and 8 years of experience) by consensus. The following features were evaluated in all lesions: location (head including the pancreatic uncinate process or body/tail), maximal lesion diameter on axial images, shape (ovoid or irregular), margins (sharp or indistinct), presence of solid and necrotic components, calcification, rim enhancement (presence or absence), density/intensity during the portal venous phase (hypo-, iso-, or hyperintense compared with the surrounding normal pancreatic parenchyma), pancreatic duct dilatation, common bile duct dilation, invasion of surrounding organs, vascular invasion, venous tumor thrombus formation, enlargement of lymph nodes, and ascites.

The presence of solid and necrotic components was evaluated visually and classified into three levels: purely solid, mixed necrotic (necrotic component less than 50%), and mainly necrotic (more than 50%). The rim enhancement pattern was defined as an area of decreased density/intensity surrounded by a relatively bright thin rim [15]. The enhancement of the solid portion of the lesion compared with that of the surrounding pancreatic parenchyma was evaluated in the portal venous phase and defined as hypo-, iso-, or hyperintense. Dilatation of the pancreatic duct and common bile duct was defined as greater than 3 mm and 10 mm, respectively. Invasion of adjacent tissues manifested as infiltration and loss of adjacent fat planes with ill-defined margins. Venous tumor thrombus formation was recognized by direct signs of enhanced emboli [19]. Nodes with a short axis > 10 mm were considered enlarged lymph nodes.

Statistical analysis

Quantitative variables are expressed as the mean ± standard deviation, and categorical variables are expressed as counts and proportions. To compare the differences in imaging features between small and large PASC lesions, univariate analysis was performed with the Chi-square test or Fisher's exact test for categorical variables. The Mann–Whitney test for continuous variables was used to compare patient age. Values of $P < 0.05$ were considered to indicate a statistically significant difference, and all P values were two sided. Statistical analysis was performed with SPSS statistical software package (version 23.0, SPSS Inc, Chicago, IL).

Results

The 110 patients were divided into two groups according to tumor size. There were 41 small PASC lesions and 69 large PASC lesions. The patients' demographic and clinical characteristics are summarized in Table 1. The mean age of patients with small (60.59 years) and large PASC lesions (63.74 years) was not significantly different ($P = 0.083$). There was no significant difference in sex between the two groups ($P = 0.091$). However, there was a slight male (80, 72.7% males vs. 30, 27.3% females) predominance among all patients. Small PASC lesions were located in the pancreatic head in 38 cases, and the pancreatic body/tail in 3 cases, while large PASC lesions were located in the pancreatic head in 32 cases and the pancreatic body/tail in 37 cases. Small PASC lesions were more frequently detected in the head of the pancreas ($P < 0.05$).

The differences in imaging features between the two groups are shown in Table 2. In terms of the appearance of the primary lesion, there was a significant difference only in shape between small and large PASC lesions. Although lesions in the two groups tended to be ill-defined ($P = 0.708$), the most frequent morphology of small PASC lesions was ovoid, whereas large PASC lesions were usually irregular in shape ($P < 0.05$). No significant difference in solid and necrotic components ($P = 0.090$) (Fig. 1) or rim enhancement ($P = 0.601$) (Figs. 1a and 2) was

Table 1 Clinical characteristics of the patients

Feature	Small (≤ 3 cm) ASC	Large (> 3 cm) ASC	*P* value
No. of patients	41	69	
Age (years)	60.59 ± 9.12	63.74 ± 9.13	0.083[†]
Sex (%)			0.091[‡]
Male	26 (63.4%)	54 (78.3%)	
Female	15 (36.6%)	15 (21.7%)	
Female: male	1:1.73	1:3.60	
Tumor size (cm)*	2.56 ± 0.46	4.70 ± 1.08	
Tumor location			< 0.05[‡]
Head	38 (92.7%)	32 (46.4%)	
Body/tail	3 (7.3%)	37 (53.6%)	

*Mean tumor size ± standard deviation

[†]Mann–Whitney test

[‡]Chi-square test

Table 2 Imaging differences between small and large PASCs

Feature	Small (≤ 3 cm) PASC	Large (> 3 cm) PASC	*P* value
Shape (%)			< 0.05*
Ovoid	24 (58.5%)	21 (30.4%)	
Irregular	17 (41.5%)	48 (69.6%)	
Margin (%)			0.708†
Sharp	2 (4.9%)	6 (8.7%)	
Indistinct	39 (95.1%)	63 (91.3%)	
Components (%)			0.090†
Pure solid lesion	14 (34.1%)	12 (17.4%)	
Mixed necrotic lesion	25 (61.0%)	48 (69.6%)	
Mainly necrotic lesion	2 (4.9%)	9 (13.0%)	
Calcification (%)			1.000†
Present	3 (7.3%)	5 (7.2%)	
Absent	38 (92.7%)	64 (92.8%)	
Ring enhancement (%)			0.601*
Present	31 (75.6%)	49 (71.0%)	
Absent	10 (24.4%)	20 (29.0%)	
Density/intensity during portal venous phase (%)			0.679*
Hypo-	9 (21.9%)	15 (21.7%)	
Iso-	10 (24.4%)	22 (31.9%)	
Hyper-	22 (53.7%)	32 (46.4%)	
Pancreatic duct dilation (%)			0.334*
Present	27 (65.9%)	39 (56.5%)	
Absent	14 (34.1%)	30 (43.5%)	
Choledochus dilation (%)			0.054*
Present	20 (48.8%)	21 (30.4%)	
Absent	21 (51.2%)	48 (69.6%)	
Invasion of surrounding organs (%)			< 0.05*
Present	18 (43.9%)	51 (73.9%)	
Absent	23 (56.1%)	18 (26.1%)	
Vascular invasion (%)			< 0.05*
Present	19 (46.3%)	58 (84.1%)	
Absent	22 (53.7%)	11 (15.9%)	
Enlargement of lymph nodes (%)			0.068*
Present	17 (41.5%)	41 (59.4%)	
Absent	24 (58.5%)	28 (40.6%)	
Venus tumor thrombus (%)			< 0.05*
Present	0 (0)	23 (33.3%)	
Absent	41 (100%)	46 (66.7%)	
Ascites (%)			0.155†
Present	0 (0)	5 (7.2%)	
Absent	41 (100%)	64 (92.8%)	

*Chi-square test

†Fisher's exact test

observed between small and large PASC lesions. Purely solid lesions were found in twenty-six (23.6%) PASC lesions. The pattern and degree of enhancement were not significantly different between small and large PASC lesions.

Furthermore, with regard to growth pattern and indirect signs of PASC, the occurrences of adjacent organ and vessel invasion and venous tumor thrombus formation were statistically significantly different between small and large PASC lesions ($P < 0.05$). However, the two groups

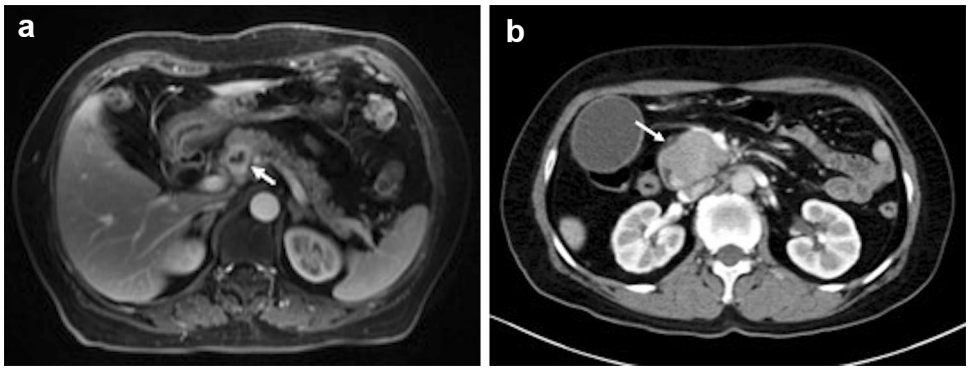

Fig. 1 Axial MR scans in a 69-year-old woman with a small (1.9 cm) PASC lesion in the pancreatic head and axial CT scans in a 55-year-old woman with a large (4.0 cm) PASC lesion. **a** Axial enhanced T1-weighted image obtained the during portal venous phase showing a small lesion with central necrosis (arrow). **b** CT scan obtained during the portal venous phase showing a purely solid mass with an irregular shape (arrow)

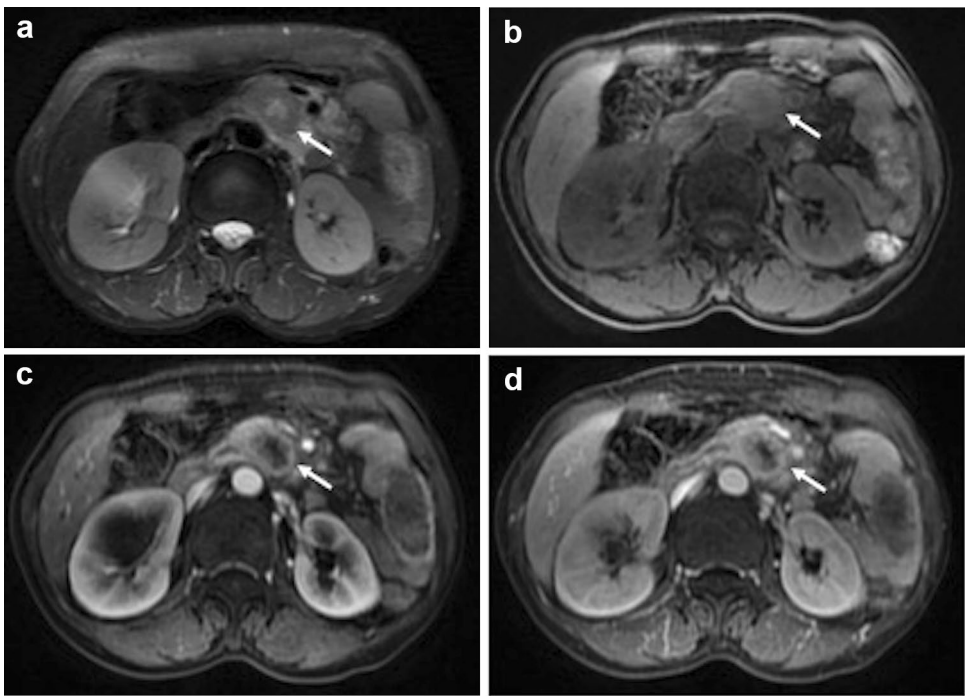

Fig. 2 Axial MR scans in a 65-year-old woman with a 3-cm PASC lesion in the pancreatic body. **a** Axial T2-weighted image showing a slightly hyperintense lesion with central necrosis (arrow). **b** Axial T1-weighted image showing a homogeneously hypointense lesion (arrow). **c**, **d** Rim enhancement with a central area of decreased intensity (arrow) of a lesion on an enhanced MR scan obtained during the arterial phase and portal venous phase

showed no significant difference in pancreatic duct dilation ($P=0.334$), common bile duct dilation ($P=0.054$), enlarged lymph nodes ($P=0.068$), or ascites ($P=0.155$). Eighteen (43.9%) small PASC lesions with invasion of the surrounding organs invaded only three upper abdominal organs, including the common bile duct, duodenum, and stomach. The duodenum (23 cases), left adrenal gland (18 cases), and spleen (12 cases) were the three organs most frequently invaded by large PASC lesions (51, 73.9%) (Fig. 3). Other organs infiltrated by large PASC lesions were as follows: common bile duct (11 cases), stomach (10 cases), transverse colon (8 cases), jejunoileum (1 case), and left kidney (1 case). Venous tumor thrombus formation was detected in twenty-three lesions, all of which were large PASC lesion (Fig. 4). Portal vein, splenic vein, and superior mesenteric vein tumor thrombus formation was identified in 2, 23 (100%), 1 lesion(s), respectively.

Discussion

PASC, a rare subtype of pancreatic malignant neoplasm with a dismal prognosis, has attracted attention in recent years. PASC has more aggressive behavior with invasion of surrounding tissues and simultaneous metastases and is associated with significantly worse overall survival following

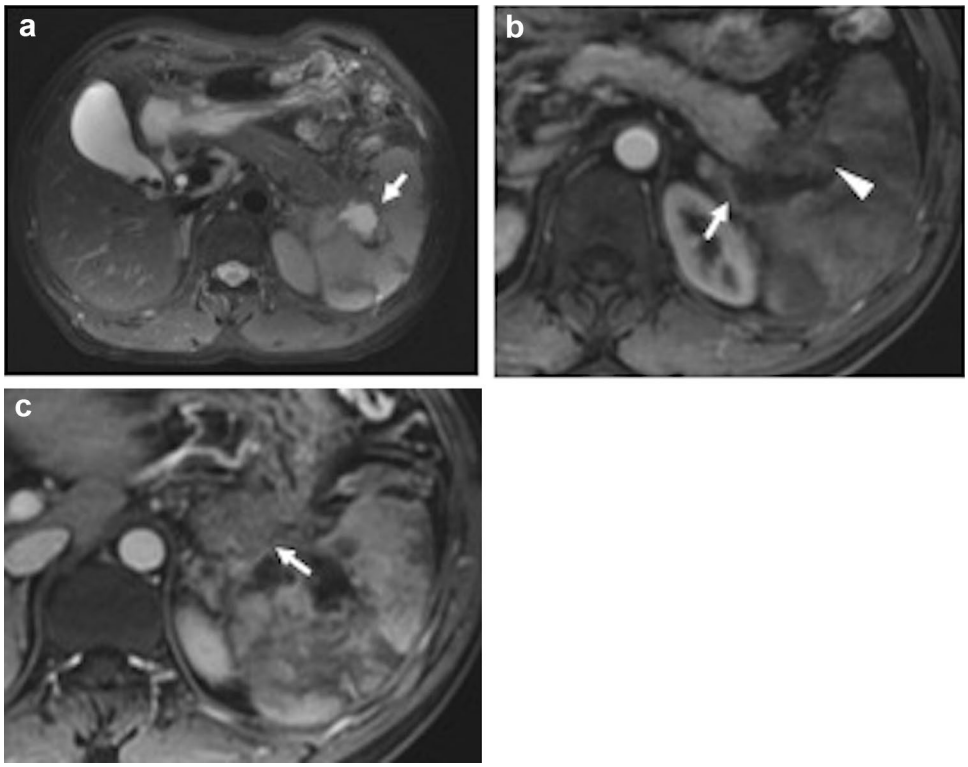

Fig. 3 Axial MR scans in a 55-year-old man with a 5.0-cm PASC lesion in the pancreatic tail. **a** Axial T2-weighted image showing an irregular mass (arrow) with central necrosis and an ill-defined border outside the pancreatic parenchyma. **b** Slight rim enhancement and invasion of the left adrenal gland (arrow) and spleen (arrowhead) by the lesion during the arterial phase. **c** Loss of the fat plane between the mass and the posterior gastric wall indicative of invasion (arrow)

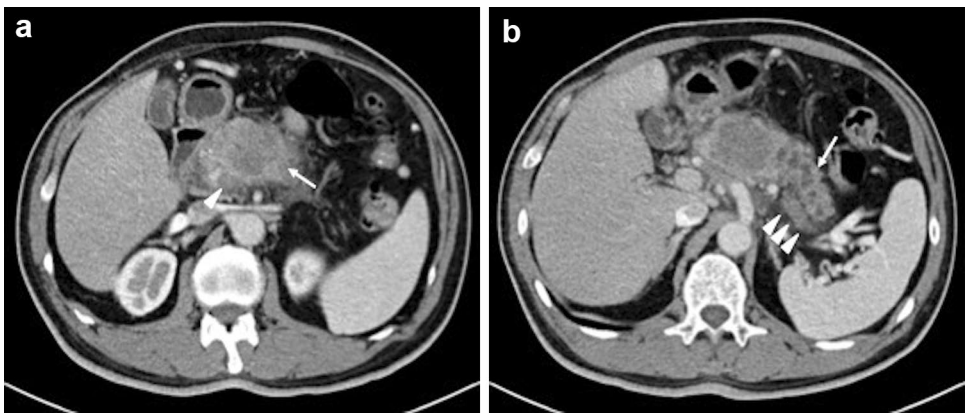

Fig. 4 Axial CT scans in a 64-year-old man with a 4.8-cm PASC lesion in the pancreatic body. **a** Axial CT image during the portal venous phase showing a solid mass with rim enhancement (arrow) and a tumor thrombus in the splenic vein (arrowhead). **b** Axial CT image during the equilibrium phase showing a filling defect in the splenic vein (arrowhead), behind the upstream ductal dilation (arrow)

resection than conventional adenocarcinoma of the pancreas (median survival of all patients and surgical patients, 8.4 vs 15.8 months and 12.0–14.8 vs 20.5 months, respectively) [4, 5, 7, 13], as suggested by many previous studies that mainly focused on the clinical characteristics and outcomes of PASC. A retrospective study revealed that a lack of adjuvant therapy [hazard ratio (HR) 3.6], lymph node involvement (HR 3.5), and age (HR 1.0) in a multivariable model and a lack of inclusion of a platinum agent in the adjuvant regimen (HR 2.4) and larger tumor diameter (HR 1.3) in a second multivariable model were independently predictive of poor survival [14]. Therefore, accurate diagnosis and preoperative evaluation for PASC are important for clinical decisions. However, the imaging features of PASC suggested by very limited studies with small sample sizes are still incompletely described; furthermore, even pancreatic fine-needle aspiration failed to diagnose PASC with a specificity of less than 10% [8]. Our study, which to our knowledge is the largest imaging study of PASC reported to date, is the first study to focus on the diversity of imaging appearances in different-sized PASC lesions and their growth trends to describe differentiation of small and large PASC lesions to better understand the morphology of these lesions.

In our study, PASC lesions occurred most frequently in males (male:female, 2.67:1) in their 60s, which differed from a review that implied an almost 1:1 ratio (males vs females, 63 vs 57) [20]. There are no obviously specific clinical manifestations of PASC, and abdominal pain, low back pain,

abdominal distension, jaundice, and weight loss are possible symptoms. Twenty-seven (39.1%) patients with large PASC lesions and seven (17.0%) with small PASC lesions had two or more symptoms. These tumors are more commonly involved in the pancreatic head (63.6%), whereas a large population-based study reported that tumors located in body and/or tail were slightly more common [11], which was also supported by the findings of Simone et al. [9]. PASC lesions in the body and/or the tail tended to grow larger, and small PASC lesions were almost located in the pancreatic head. We speculate that pancreatic head cancer may be detectable at an early stage because of symptoms of biliary obstruction. On the other hand, large PASC lesions were located in the pancreatic body and/or tail which grew and became huge infiltrative lesions outside the pancreas in the left superior retroperitoneal space, which is relatively larger than space around the head of the pancreas. Surrounding organs, such as the gastrointestinal tract, spleen, left adrenal grand, and left kidney, could be infiltrated in the early stages. However, symptoms including abdominal pain, backaches, and fecal occult blood can go unnoticed or are so slight that they might be ignored.

In terms of imaging manifestations, almost all PASC lesions were ill-defined and the shape of large PASC lesions was mainly irregular because of their more obvious infiltrative growth, while small PASC lesions were usually visually determined to be ovoid. Approximately, 75% of PASC lesions had different degrees of necrosis and cystic portions with rim enhancement, regardless of the tumor size, similar to the results reported in many previous studies. One possible explanation for this finding is that angiogenesis for blood supply cannot catch up with the growth of the tumor [21]. In other words, approximately one-fourth of PASC lesions were purely solid regardless of the tumor size, including 14 small and 12 large PASC lesions. Pancreatic adenocarcinomas are usually solid, and approximately 1% undergo cystic degeneration [22] and area larger in size (mean size, 7.3 cm) [23]. We cannot explain this phenomenon, but we hypothesize that a small pancreatic tumor with necrosis and signs of malignancy is a powerful clue in the differential diagnosis of PASC. The tumors were hyper- to hypointense compared with the surrounding normal pancreatic parenchyma during the portal venous phase, with no visual rule. Therefore, we hypothesize that it is not easy to conclude whether PASC lesions are tumors with hypervascularity or hypovascularity.

The presence of a venous tumor thrombus was only observed in large PASC lesions, and the splenic vein was involved in 100% of cases. Tumor thrombi frequently involve the portal vein and mostly occur in advanced hepatocellular carcinoma. In addition, there has been much more research regarding malignant thromboses in hepatoma than in pancreatic carcinoma, regarding which there are only a few case reports. Therefore, we referenced these researches and drew on the diagnostic criteria for tumor thrombus formation: the presence of enhancement. There was so substantial overlap in vessel expansion by a thrombus and the apparent diffusion coefficient values of a thrombus between benign and malignant thrombi that we did not use them as criteria [19, 24]. As a result, 20.9% of PASC lesions were associated with a tumor thrombus. To date, the detailed mechanism of tumor thrombus development has not been elucidated [25], however, two reasonable hypotheses have been generated. First, tumor thrombus formation in the portal systems may occur by direct venous tumor invasion, which may be the reason why the tumor thrombi in our study all occurred in large PASC lesions. Second, Li et al. revealed that three vascular-specific growth factors (vascular endothelial growth factor, angiopoietin-2, and endocrine gland-derived vascular endothelial growth factor) are related to carcinogenesis and portal vein tumor thrombus formation in hepatocellular carcinoma [26]. Additionally, another study demonstrated that higher vascular endothelial growth factor A, hypoxia-inducible factor 1-alpha, and angiopoietin-2 levels were observed in PASC [27]. In terms of prognosis, aggressive surgical resection of pancreatic carcinoma with tumor thrombus may result in better outcomes [25]. Conversely, tumor thrombus formation in conventional adenocarcinomas of the pancreas is rarely seen in routine clinical practice [17]. Thus, we believe that evaluating tumor thrombus formation in PASC is of great significance both for differential diagnosis and clinical guidance.

Due to their malignant nature, PASC lesions were found to frequently infiltrate adjacent tissues. Large PASC lesions were more likely to invade surrounding organs and vessels than small PASC lesions. Katz et al. and Yin et al. reported that PASC has a considerable propensity for lumen invasion [4, 28]. In our study, invasion of duodenum was the most common, occurring in 33 cases, followed by the common bile duct in 24 cases and the left adrenal gland in 18 cases. However, there was no significant difference in enlarged lymph nodes between the two groups, which indicated that lymph node metastasis can occur at a relatively early stage. Therefore, venous tumor thrombus formation and enlarged lymph nodes at a relatively early stage may be helpful features to identify PASC and offer some guidance for surgery. There are several limitations in our study. First, it was limited by its retrospective nature. Second, using different types of CT and MR scanners and enhancement protocols may have caused deviation in enhancement patterns.

In conclusion, regardless of the tumor size, 75% of PASC lesions presented with central necrosis, while 25% were purely solid. Small PASC lesions can be associated with lymph node metastasis at a relatively early stage. Large PASC lesions are likely to invade adjacent tissues and be associated with venous tumor thrombus formation. These

imaging differences can help to deepen our understanding of PASC.

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