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PANCREAS

Differentiation of aggressive from non-aggressive pancreatic solid pseudopapillary neoplasms using computed tomography

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Abstract

Purposes Microscopic aggressive behaviors may be related with the prognosis of solid pseudopapillary neoplasms (SPNs). In this study, we investigate computed tomography (CT) features and differential diagnosis of aggressive and non-aggressive SPNs in pancreas.

Materials and methods 122 patients with pathologically proven SPNs in pancreas were included. Patients' age, tumor site, texture, shape, margins, exophytic growth, capsule, calcification, hemorrhage, pancreatic duct dilatation or pancreatic parenchyma atrophy, peripancreatic infiltration or metastases, vascular encasement, and enhancement pattern were assessed. The diagnostic accuracy was analyzed by using the receiver operating characteristic curve (ROC).

Results There were 30 aggressive SPNs and 92 non-aggressive SPNs. Aggressive SPNs showed significantly higher frequencies of an ill-defined margin, patient age > 40.5 years, and tumor size < 42.1 mm, but lower frequencies of complete capsule, hemorrhage compared with non-aggressive SPNs ($p < 0.05$). Lack of complete capsule and age > 40.5 years were independent risk factors of aggressive SPNs (odd ratio 7.08 and 3.1, respectively). When we applied the two predictors in the logistic regression model, the area under the curve (AUC) was 0.77 with sensitivity of 86.7% and specificity of 55.4%.

Conclusion Size less than 42.1 mm, lack of complete capsule, ill-defined, and absent bleeding are useful CT imaging features for predicating aggressive SPNs. Patient age > 40.5 years and lack of complete capsule showed acceptable diagnostic performance for discriminating aggressive from non-aggressive SPNs.

Keywords Solid pseudopapillary neoplasm · Pancreas · Aggressive · Computed tomography

Introduction

Solid pseudopapillary neoplasms (SPNs) of the pancreas are usually considered a rare tumor with low-grade malignant potential, which account for approximately 0.9% to 2.7% of all exocrine pancreatic tumors [1]. However, SPNs are increasingly detected due to the increased use of advanced imaging modalities. The number of reported cases has increased sevenfold since 2000 [2]. A nationwide survey from Yoon et al. [3] revealed that SPNs were the third most common (18.3%, 195/1064) cystic neoplasm of the exocrine pancreas. SPNs are recently reported to be most common pancreatic neoplasm among female patients under the age of 40 [4]. Moreover, a multicenter retrospective study [5] in 2018 showed that SPNs were the most common tumor in all resected pancreatic cystic neoplasms in China (31.7%, 713/2251).

According to the 2010 World Health Organization (WHO) classification criteria, SPNs were defined as epithelial low-grade malignant neoplasm [1]. Surgery is the only curative treatment for SPNs, and 85–95% of patients are cured [6, 7]. But recurrences and metastases may occur after incomplete resections. Gao et al. [8] reported that positive margin might increase the risk of postoperative relapses of SPNs. Therefore, radical resections such as pancreaticoduodenectomy and distal pancreatectomy with/without splenectomy are usually preferred during the past decade [9, 10].

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However, those surgical strategies may result in a high rate of morbidity and long-term endocrine/exocrine dysfunction due to wide resection of the pancreatic parenchyma. Given the indolent biological behavior of SPNs and the young age of onset, tumor enucleation (EU) is increasingly used for an alternative approach [11–13], while the oncologic safety of EU remains a real important concern [14, 15]. SPNs are heterogeneous tumor with a small percentage of patients harboring aggressive behaviors, such as positive margins, perineural invasion, vascular invasion, regional lymph node, and distant metastases [1, 13, 16]. Microscopic aggressive behaviors are one of the significant prognostic factors for recurrence [17, 18]. Once the SPNs with microscopic aggressive behaviors were not completely removed, it is prone to recur or metastasize.

Most of the patients with SPNs show few or no symptoms, and the tumor markers were within the range such as CEA, AFP, and CA19-9 [19]. Thus, the vast majority of tumors are diagnosed by computed tomography (CT) or magnetic resonance imaging (MRI). Meanwhile, CT is the most commonly used imaging modality when pancreatic disease is suspected [20, 21]. Hence, it would be of great clinical value to show the association between imaging features and microscopic aggressive behaviors for the correct preoperative differentiation aggressive from non-aggressive SPNs. However, only short case series, single-center report, or case report from either surgical or pathologic point of view with limited emphasis on their imaging features have been reported [4, 22, 23]. Recently, Rastogi et al. [24]. showed that CT attenuation and progressive enhancement at delayed phase may be valuable predicators of aggressive SPNs ($n=40$). However, only 15 aggressive SPNs were included in their study. To our best knowledge, few studies have shown the differences in CT imaging findings between aggressive and non-aggressive SPNs based on larger population. Therefore, the purpose of our study was to retrospectively evaluate the utility of CT in the differentiation between aggressive SPNs and non-aggressive SPNs.

Materials and methods

Patients

Between January 2012 and May 2017, 136 consecutive patients with pathologically proven pancreatic SPNs at our institution and three related institutions were identified through a review of pathological and radiological database. The inclusion criteria were shown as follows: (a) patients with surgically proven SPN; (b) patients who underwent CT examination performed within the 30 days preceding surgery. Fourteen patients were excluded for the following reasons: (a) tumor not identified on preoperative CT ($n=2$); (b) suboptimal image quality of CT examination ($n=2$); (c) inadequacy of histopathological data ($n=9$); (d) undergoing local treatment prior to CT scan ($n=1$). Finally, a total of 122 patients (33.5 ± 13.8 years) were included in our study (Fig. 1). Our institutional review board approved this study, and patient informed consent was waived due to its retrospective nature.

CT imaging technique

Among these 122 patients, 51 patients underwent triple-phase CT examination (unenhanced, arterial, and portal venous phase), and other 71 patients underwent quadruple-phase CT examination (unenhanced, arterial, portal venous, and delayed phase). The following CT scanner was used in this study: 16-channel CT scanner [Sensation 16, Siemens Healthcare, Erlangen, Germany, ($n=9$); Brilliance 16, Philips Healthcare, Cleveland, OH ($n=19$)], 64-channel CT scanner [Brilliance 64, Philips Healthcare, DA Best, the Netherlands, ($n=35$); Optima CT660, GE Healthcare, Milwaukee, WI, USA, ($n=13$); Optima CT680, GE Healthcare, Milwaukee, WI, USA, ($n=20$)], and 128-channel CT scanner [Brilliance ICT, Philips Healthcare, Cleveland, OH, USA, ($n=26$)]. Detector collimation of 0.75, 0.625, and 0.625 mm were used for 16-, 64- and 128-detector CT examination, respectively. Other imaging parameters were shown as follows: Pitch of 0.9–1.5, 2.5–3 mm thick sections, matrix of 512×512, gantry rotation time of 0.5–0.75 s, tube voltage of 120 kV, and automated tube current modulation with a noise index (200–400 mA).

For contrast-enhanced examination, a total of 1.5 mL/kg of non-ionic contrast material with different iodine concentrations (300–350 mg/mL) was injected using a power injector at a rate of 3–4 ml/s via an intravenous catheter. A 20-ml flush of sterile saline followed. Then arterial phase, portal venous phase, delayed-phase images were acquired at approximately 30–35 s, 55–60 s, 120–180 s from the start of contrast material injection, respectively. Images were reconstructed at 2 mm intervals with a 2-mm section thickness. Detailed CT imaging parameters are summarized in Table 1.

Qualitative and quantitative CT image analysis

The CT images were independently analyzed on a workstation by two radiologists (xx. and xxx, with 12 and 10 years of experience in abdominal imaging, respectively) who were aware of pancreatic lesion but blinded to the clinical information, CT diagnosis, and histopathologic findings.

Qualitative analysis included the following parameters: (a) tumor site (head-neck, or body-tail); (b) tumor texture; (c) tumor shape (oval/round, or irregular); (d) tumor margins (well defined or ill-defined); (e) presence of exophytic growth; (f) presence of complete capsule; (g) presence of

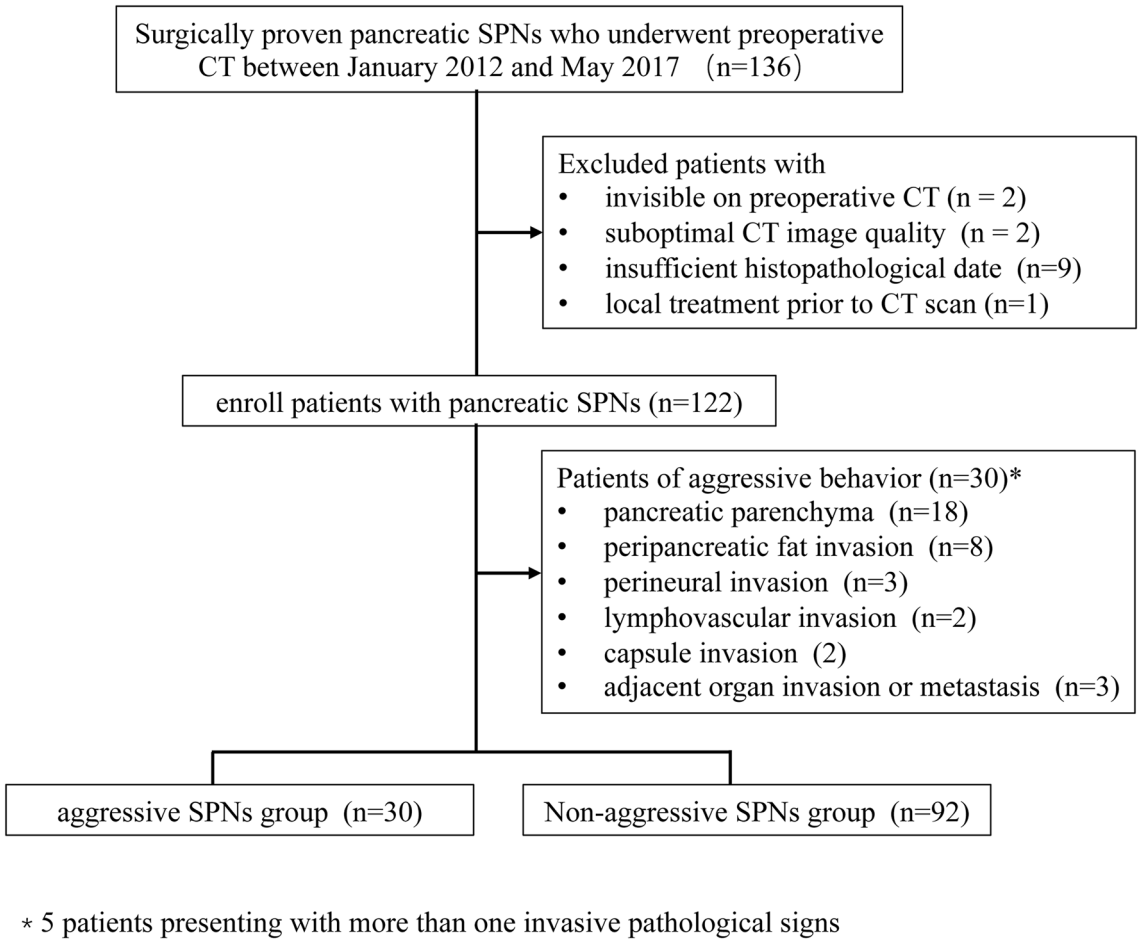

Fig. 1 Flow diagram of study group inclusion process

Table 1 CT scanner parameter

Parameter	Sensation (n = 9)	Brilliance 16 (*n* = 19)	Brilliance 64 (*n* = 35)	Optima CT660 (*n* = 13)	Optima CT680 (*n* = 20)	Brilliance ICT (*n* = 26)
No. of channels	16	16	64	64	64	128
Section collimation (mm)	0.75	0.75	0.625	0.625	0.625	0.625
Section thickness (mm)	3	3	2.5–3	2.5–3	2.5–3	2.5
Reconstruction interval (mm)	2	2	2	2	2	2
Pitch	1–1.5	1.1	0.9–1.2	0.9–1.2	0.9–1.2	0.9
Rotation time (s)	0.5	0.5	0.75	0.75	0.75	0.75
Tube voltage (kVp)	120	120	120	120	120	120
Matrix	512×512	512×512	512×512	512×512	512×512	512×512

calcification; (h) presence of hemorrhage; (i) presence of pancreatic duct dilatation or pancreatic parenchyma atrophy; (j) presence of vascular encasement; and (k) dynamic enhancement pattern. Any discrepancy was resolved by consensus.

The definition of tumor texture was obtained from a previous study [25], they and were classified into four types according to the proportion of cystic and solid components: purely cystic, mixed solid and cystic, solid with minor cystic component (10% of tumor with cystic component), and

purely solid. The cystic or necrotic components were defined as CT attenuation < 20 Hounsfield units (HU) and without enhancement. And fluid-debris level within the tumor, or hyperattenuation present at greater than 45 HU [24], and absence of enhancement were interpreted as hemorrhage. The lesions were described as whether it had a sharp margin on either unenhanced CT or dynamic enhancement. If the center of lesions is outside the pancreatic contour based on the axial images with the largest cross-sectional area of the tumor and the reconstructed coronal images, the term of exophytic growth was considered. The complete capsule refers to the continuous circular fibrous tissue surrounding the tumor, which shows delayed enhancement. The dilatation of main pancreatic duct defined has diameter > 3 mm. Dynamic enhancement pattern was classified into progressive enhancement during all dynamic imaging or washout on either portal venous phase or delayed phase using CT attenuation values of the tumor and normal pancreatic parenchyma around the tumor.

Quantitative image analysis, including tumor size (largest diameter of the tumors) and CT attention on each phase, was performed by another radiologist (xx, with 13 years of experience in abdominal radiology). The maximal diameter (mm) was measured on the axial or coronal images with the largest cross-sectional area of the tumor. Consider that this study includes images from multiple CT scanners and iodinated contrast material which will affect the accuracy of measured CT attenuation value, CT attenuation radio was used. It was defined as the CT attenuation value of tumor divided by that of the normal pancreatic parenchyma at the same phase, and CT attenuation values of tumor were determined by drawing a round or oval region of interest (ROI) as large as possible showing the most remarkable enhancement in the largest cross-sectional area of solid components, or the wall of cystic tumor. CT attenuation values of normal pancreatic parenchyma were measured around the tumor. Calcification, cystic or necrotic components, macroscopically enhanced blood vessels, pancreatic duct, peripancreatic fat, and artifacts were excluded from the ROI. Each ROI measured 3 times, then the average CT attenuation value and CT radio were calculated.

Histopathologic analysis

All resected SPNs were reviewed in conjunction with the original surgical pathology reports according to the 2010 WHO criteria by a pathologist (xx, with 12 years of experience in abdominal disease) blinded to CT imaging data. The histological features of aggressive biological behavior included cellular atypia, capsule invasion, lymph node metastasis, lymphovascular invasion, perineural invasion, and peripancreatic fat tissue invasion were documented. Finally, SPNs were considered aggressive if it showed any of the above signs, otherwise it was considered non-aggressive SPN. The interval between CT examination and surgical resection of the neoplasm was 1–29 days (11.7 ± 4.8 days).

Statistical analysis

Qualitative data were expressed as counts and proportions, and were analyzed using the Chi-square test or Fisher's exact test. Quantitative data were analyzed for normality using the Kolmogorov–Smirnov test. Those parameters showing a normal distribution are expressed as mean ± SD and analyzed using Student *t* test, and the other data showing non-normal distribution are expressed as the median with the interquartile range (IQR) and analyzed using Mann–Whitney *U* test. Continuous variables were converted into binary categorical variables using optimal cut-off values and logistic regression analyses were performed to determine independent risk factors. In addition, receiver operating characteristic curve (ROC) was used to identify the cut-off values of size and age, and evaluate the diagnostic performance for the regression model. Interobserver agreement was evaluated by means κ statistics. The strength of agreement was assessed as poor if $\kappa < 0.20$, fair if $\kappa = 0.21$–0.40, moderate if $\kappa = 0.41$–0.60, good if $\kappa = 0.61$–0.80, and excellent if

Table 2 Demographic and clinical information of 122 SPNs

Variables	Aggressive SPNs ($n = 30$)	Non-aggressive SPNs ($n = 92$)	*P* value
Sex*			0.064
Female	20 (67)	76 (83)	
Male	10 (33)	16 (17)	
Age (years)[a]	38.5 ± 15.5	31.9 ± 12.9	0.022
≤ 40.5	15 (50)	73 (79)	0.002*
> 40.5	15 (50)	19 (21)	
Clinical manifestation*			0.172
Epigastric plain	15(50)	35 (38)	
Abdominal discomfort	7 (23)	22 (24)	
Palpable mass	4 (13)	6 (7)	
Back pain	2 (7)	7 (8)	
Asymptomatic	8 (27)	38 (41)	
Type of operation*			0.12
Whipple surgery	9 (30)	23 (25)	
Distal pancreatectomy	12 (40)	30 (33)	
DP + splenectomy	1 (3)	21 (23)	
Middle pancreatectomy	4 (13)	7 (8)	
Enucleation	4 (13)	11 (12)	
The interval time (days)[a]	11.8 ± 3.9	11.7 ± 5.1	0.927

*Data are number of patients, with the percentage in parentheses. *P* value was calculated with the x^2 or Fisher exact test

[a]Data are mean ± standard deviation, *P* value was calculated with Student *t* test

$\kappa = 0.81–1.00$. A p value < 0.05 was considered to indicate a significant statistical difference. All statistical analyses were performed with commercially available software (SPSS 24.0 for Windows; Chicago, USA).

Results

Pathological and clinical characteristics

In our series, 37.7% (46/122) patients were asymptomatic. The common symptoms were epigastric pain (50/122), abdominal discomfort (29/122), palpable mass (10/122), and back pain (9/122). 21 (17.2%) patients presented with more than one symptom.

All tumors were successfully resected [Whipple surgery ($n = 32$), distal pancreatectomy ($n = 42$), distal pancreatectomy with splenectomy ($n = 22$), middle pancreatectomy ($n = 11$), enucleation ($n = 15$)], and all surgical margins were negative. 122 patients had unifocal tumor and were diagnosed as SPNs by pathology. A total of 30 patients (20 females and 10 males, mean age, 38.5 ± 15.5 years) were diagnosed as aggressive SPNs [pancreatic parenchyma invasion (n = 18), peripancreatic fat invasion ($n = 8$), perineural invasion ($n = 3$), capsule invasion ($n = 2$), lymphovascular invasion ($n = 2$), duodenum infiltration ($n = 1$), synchronous liver and spleen metastases ($n = 1$), and lymph node metastasis ($n = 1$), and 5 patients presenting with more than one invasive pathological sign]. No tumors presented severe nuclear atypia or a high mitotic rate. The other 92 patients

Table 3 CT imaging findings of aggressive and non-aggressive SPNs

CT feature	Aggressive SPNs ($n = 30$)	Non-aggressive SPNs ($n = 92$)	P value	κ
Site*			0.248	0.86
Head–neck	15 (50)	35 (38)		
Body–tail	15 (50)	57 (62)		
Size(mm)[a]	39.8 (27.5-55.6)	52.4 (35.9-85.4)	0.01	
≤ 42.1	20 (67)	31 (34)	0.001*	
> 42.1	10 (33)	61 (66)		
Tumor texture*			0.085	0.75
Purely solid	10 (33)	17 (18)		
Solid with minor cystic component	9 (30)	18 (20)		
Mixed solid and cystic	9 (30)	50 (54)		
Purely cystic	2 (7)	7 (8)		
Shape*			0.142	0.74
Oval or round	12 (40)	51 (55)		
Lobulated	18 (60)	41 (45)		
Margins*			0.027	0.78
Well defined	12 (40)	58 (63)		
Ill-defined	18 (60)	34 (37)		
Exophytic growth*	14 (47)	58 (63)	0.113	0.81
Capsule*	4 (13)	51 (55)	< 0.001	0.70
Calcification*	10 (33)	36 (39)	0.569	0.93
Hemorrhage*	3 (10)	33 (36)	0.007	0.80
Pancreatic duct dilatation or pancreatic parenchyma atrophy*	1 (3)	5 (5)	1	0.92
Vascular encasement*	6 (20)	18 (20)	0.959	0.90
progressive enhancement*	17 (63)	53 (65)	0.875	0.88
CT attention value ratio[a]				
Pre-contrast	0.74 (0.67–0.86)	0.79 (0.69–0.96)	0.258	
Arterial phase	0.57 (0.51–0.68)	0.59 (0.50–0.67)	0.735	
Portal phase	0.77 (0.72-0.91)	0.74 (0.68–0.82)	0.580	
Delayed phase	0.84 (0.78–0.95)	0.89 (0.78–0.95)	0.382	

*Data are number of patients, with the percentage in parentheses. P value was calculated with the x^2 or Fisher exact test

[a]Data are median (i. q. r), P value was calculated with Mann–Whitney U test

(76 females and 16 males, mean age, 31.9 ± 12.9 years) were non-aggressive SPNs.

Demographic and clinical data are shown in Table 2. The age of patient with aggressive SPNs was significantly older than non-aggressive SPNs ($p = 0.022$). The ratio of male to female patient was higher in aggressive SPNs [33.3% (10/20) vs. 17.4% (16/76)], but no significant difference was observed ($p = 0.064$). In addition, no significant differences in clinical manifestations and surgical procedures were observed between the two groups ($p = 0.479$, $p = 0.12$, respectively).

Image analysis

Firstly, we evaluated the interobserver agreement for qualitative imaging parameters. Good to excellent strength of agreements were achieved. The κ values were ranged from 0.70 to 0.93. Qualitative and quantitative analyses of CT findings of aggressive and non-aggressive SPNs are summarized in Table 3. Ill-defined tumor margin (Figs. 2, 3) was more common in aggressive SPNs than non-aggressive SPNs [60% (18/30) vs. 37% (34/92), $p = 0.027$]. Hemorrhage [10% (3/30) vs. 36% (33/92), $p = 0.007$] and complete capsule [13% (4/30) vs. 55% (51/92), $p < 0.001$] were more common in non-aggressive SPNs (Figs. 4, 5) than aggressive SPNs (Figs. 2, 5). No significant differences were found in the following CT features between non-aggressive and aggressive SPNs: site, texture, shape, exophytic growth, calcification, vascular encasement, pancreatic ductal dilatation, and enhancement pattern. The size of aggressive SPNs was significantly smaller than that of non-aggressive SPNs [39.8 mm, (27.5–55.6) vs. 52.4 mm, (35.9–85.4), $p = 0.01$] (Figs. 1, 2, 3, 4). But the ratio of CT attention value was not significantly different between the two groups on each phase.

Diagnostic performance analysis

We determined the optimal cut-off values for the age of patients to be 40.5 years and for the largest diameter of the tumors to be 42.1 mm on ROC analysis (Fig. 6).

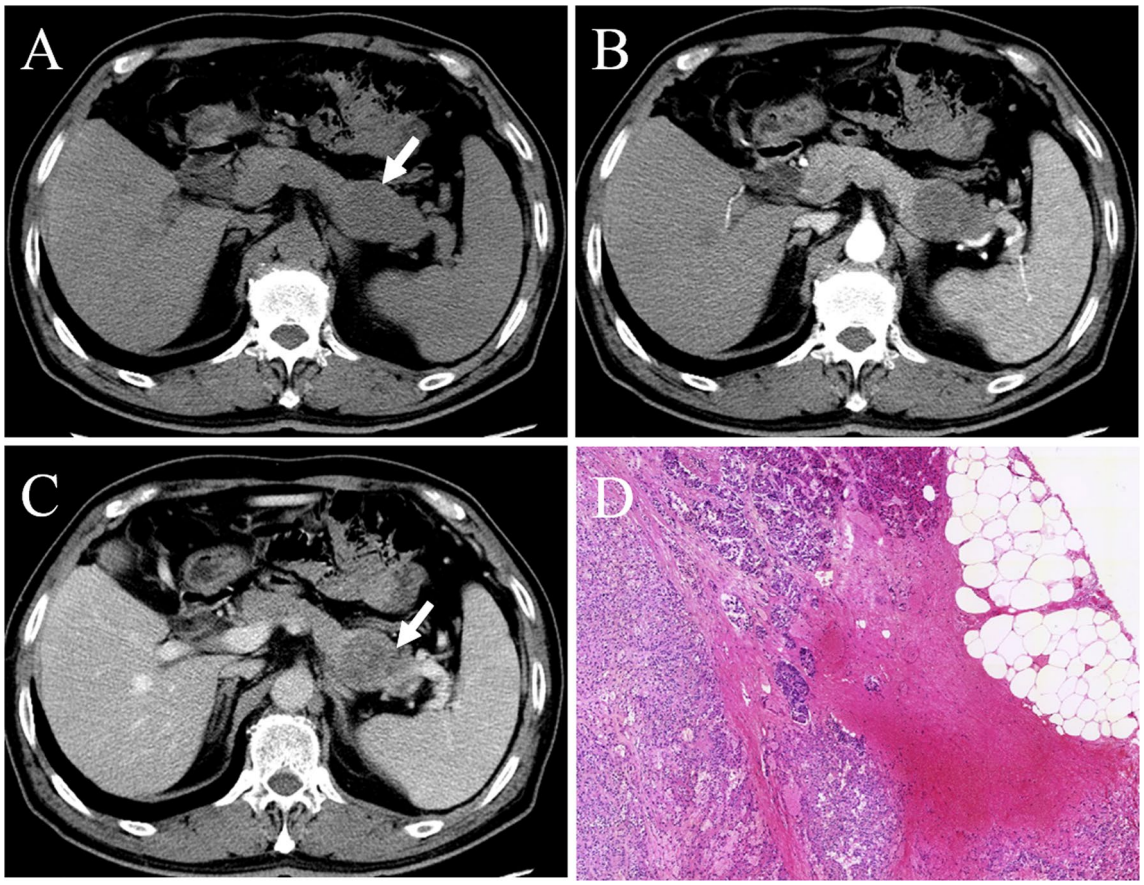

Fig. 2 A 59-year-old man with a 3.5-cm purely solid, aggressive SPN of pancreas. Axial unenhanced scan (**a**) shows a homogeneous, slightly hypoattenuating lesion (arrow) in tail of pancreas. The mass shows lobulated, poor enhancement on the arterial phase (**b**) and progressed enhancement on portal venous (**c**). The tumor has no capsule and shows ill-defined margin and manifests heterogeneous, slight hypodense to pancreatic parenchyma on portal venous phase image. Histological examination (**d**) shows the tumor invades into the adjacent peripancreatic fat tissue. (Original magnification, × 10; H–E stain.)

Then, sensitivity, specificity, accuracy, odds ratio (OR), and 95% confidence intervals (CI) are shown in Table 4. Lack of complete capsule (odds ratio 7.08; 95% CI 2.2–23.3) and age > 40.5 years (odds ratio 3.1; 95% CI 1.2–7.9) were found to be independent risk factors of aggressive SPNs. The area under the curve (AUC) was 0.71 for lack of complete capsule and 0.647 for age > 40.5 years. When we applied the two predictors in the logistic regression model, the area under the curve (AUC) was 0.77 with sensitivity of 86.7% and specificity of 55.4% (Fig. 7). If size was added into the model, the AUC was 0.80 with sensitivity of 77.0% and specificity of 72.0%.

Discussion

All SPNs are currently classified as low-grade malignant neoplasms in WHO 2010 report. However, most researchers prefer to classify SPTs using the WHO 2000 histological criteria or divide SPNs into aggressive and non-aggressive as vast majority of SPNs have a good prognosis [26]. However, the value of imaging findings in differentiating those lesions was unknown. In this study, we showed that CT imaging findings may be useful for the differentiation between aggressive and non-aggressive SPNs with acceptable diagnostic performance (AUC = 0.77).

It is usually difficult to preoperative differential diagnosis aggressive SPNs from non-aggressive SPNs except in patients with obvious invasion to adjacent organs or with distant metastasis [23, 27]. And many previous reports showed that there were no significant differences in age, sex, symptomatology, laboratory data, tumor marker, tumor size and location, tumor composition, and growth pattern between benign and malignant SPNs [22, 28]. However, our results demonstrate that the patient age, size, and morphologic features of the tumor, such as margin, capsular, and hemorrhage are valuable predictors in differentiating the aggressive and non-aggressive SPNs in CT imaging. The classification of SPNs may be associated with the results.

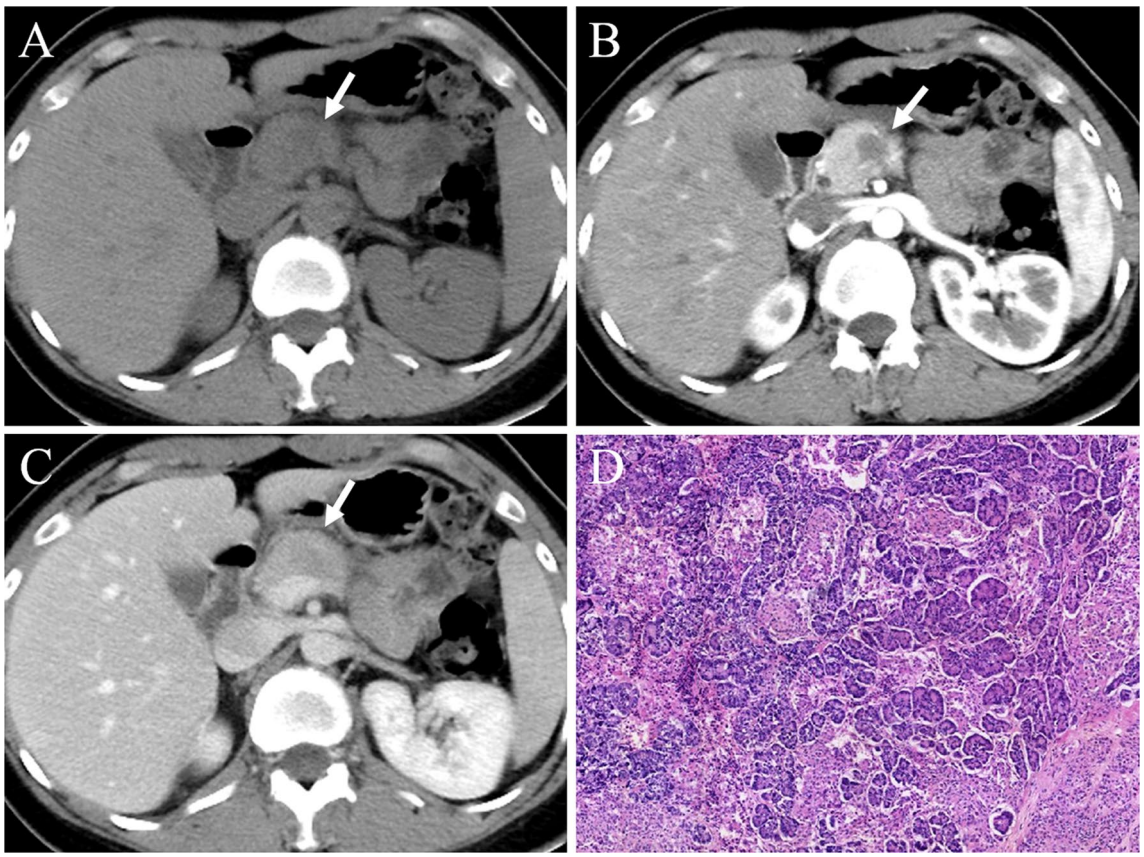

Fig. 3 A 47-year-old man with a 1.2-cm purely solid, aggressive SPN of pancreas. Axial unenhanced scan (**a**) shows a slightly hypoattenuating lesion (arrow) in body of pancreas. Arterial phase (**b**) CT image shows ill-defined hypoattenuating lesion compared with the adjacent parenchyma (arrows). The lesion shows slightly hypoattenuation on portal venous phase (**c**). Histological examination (**d**) demonstrates that there were no fibrous capsules and the cancer cells infiltrate the adjacent tissues. (Original magnification, × 10; H–E stain.)

The most common imaging features of aggressive SPNs were ill defined, lack of complete capsular, absence of hemorrhage, the size < 42.1 mm, and the age > 40.5 years. Many previously reports revealed that incomplete capsule or non-enveloped was more common in the malignant group [21, 24, 29]. Our study was consistent with these findings. But so far, little consensus about tumor size in predicting aggressive SPNs has been reached [17]. Patients with aggressive SPNs were usually presented with larger tumor size [28, 30]. Many studies also showed that there were limited potential for the tumor size in predicting tumor behavior, including some large sample studies [18]. However, in this study, we found that aggressive SPNs were usually small than non-aggressive SPNs. Small SPNs usually appeared as solid tumor with no capsule and ill-defined margins. Besides, a smaller percentage of patients with aggressive SPNs reported no symptoms (27%) compared to non-aggressive SPNs (41%) in our study. Thus, we speculated that aggressive SPNs may be more likely to cause symptoms and be detected at a smaller size. Many studies showed that the tumor size in men was significantly smaller, and SPNs in males have a significantly greater propensity to aggressive and metastasize, which suggests that progesterone and/or other sex hormones may have a role in oncoregulation [31, 32]. Consequently, further study should be done with more detailed information. Previous studies also showed that small SPNs tended to show less prominent cystic degeneration, hemorrhage, necrotic debris, and encapsulation [33–35], while the large SPNs are well-encapsulated mass with varying solid and cystic components caused by hemorrhagic degeneration [19, 25].

Ercelep et al. [13] reported that the mean age of malignant patients was significantly higher than benign patients. Similar results were observed in our study. Moreover, our

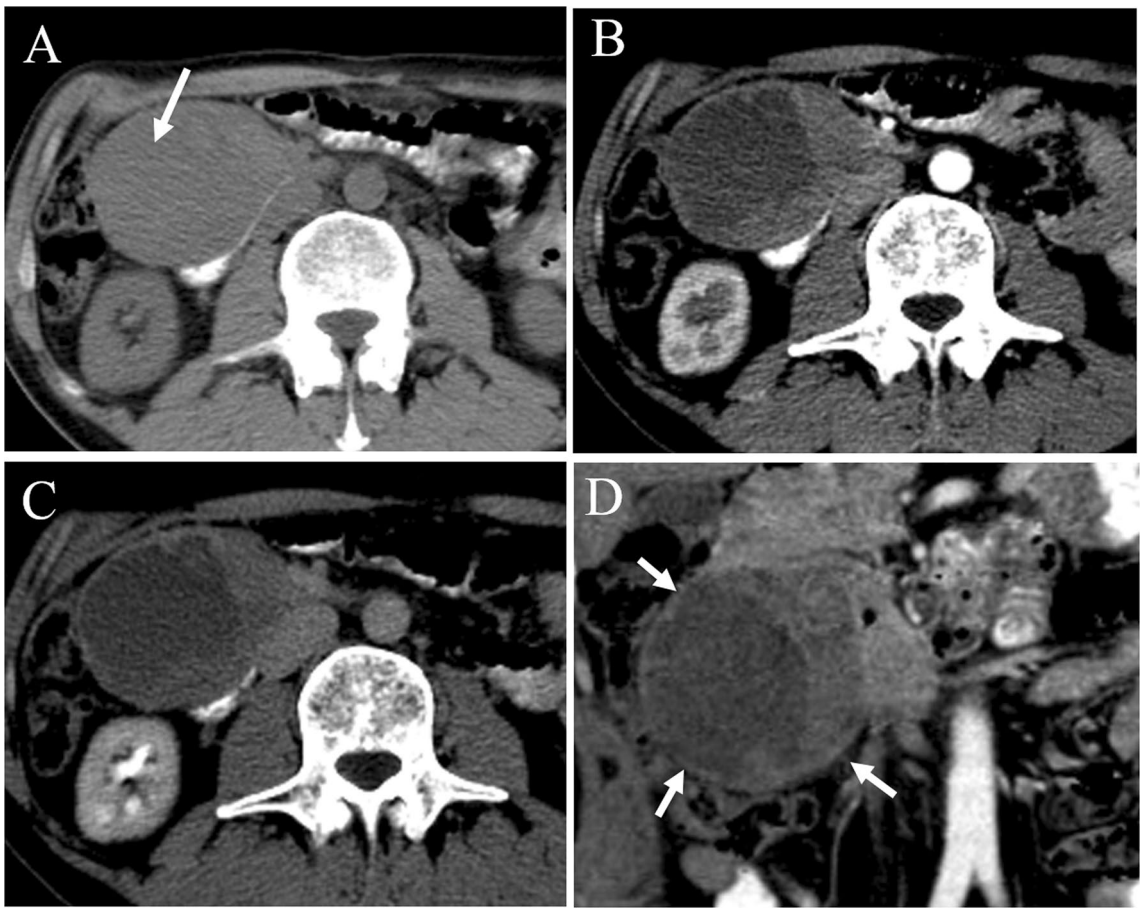

Fig. 4 A 36-year-old woman with a 7.5-cm non-aggressive SPN of pancreas. Unenhanced and enhanced CT images show a large thick-walled, mixed solid, and cystic mass arising from the head of the pancreas. Unenhanced scan (**a**) shows a homogeneous isoattenuation or slight hyperattenuation mass (arrows) with CT value of 47 HU representing hemorrhage within the tumor (arrow). Solid parts and the wall of tumor was progressively enhanced on arterial phase (**b**) and portal venous phase (**c**). Coronal CT image (**d**) demonstrates a complete capsule (arrow) surrounding the tumor

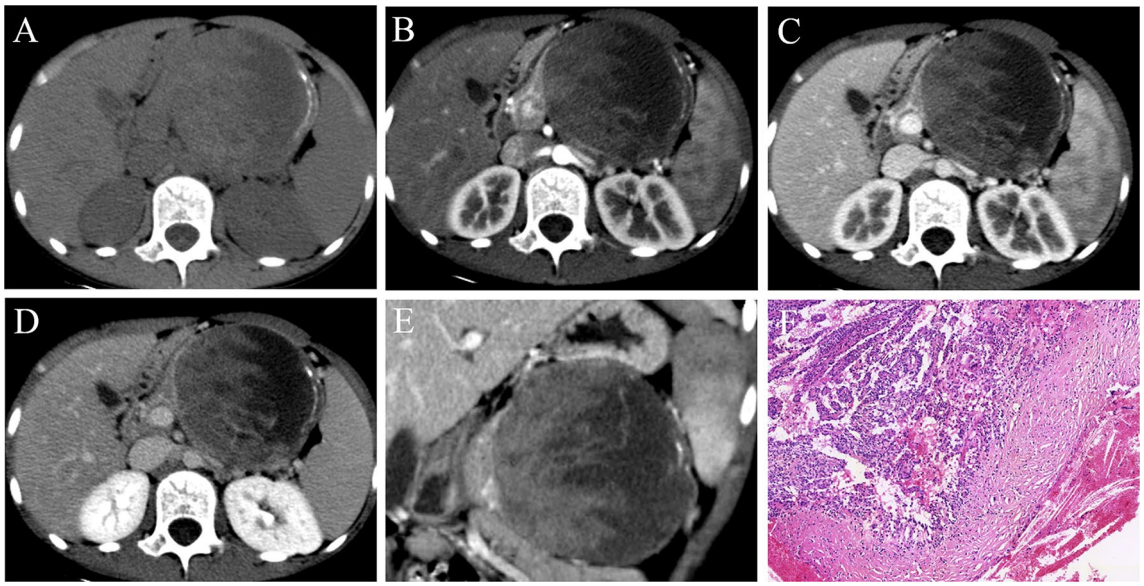

Fig. 5 A 13-year-old adolescent girl with a 8.7-cm non-aggressive SPN of pancreas. Axial unenhanced scan (**a**) shows a mixed solid and cystic mass with peripheral calcifications (arrow) in body–tail of pancreas. Solid parts and the wall of tumor show progressive enhancement on arterial phase (**b**), portal venous phase (**c**), and delayed-phase CT images (**d**). Coronal CT image (**e**) demonstrates a well-defined peripheral capsule (arrow). Histological examination (**f**) demonstrates the thick capsule (arrow) surrounding the tumor. (Original magnification, × 10; H–E stain)

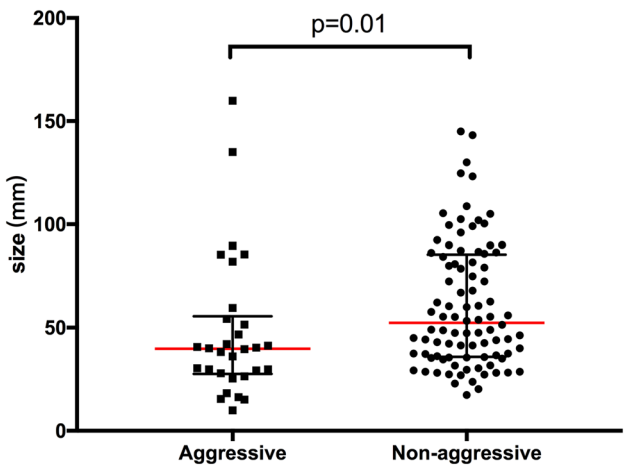

Fig. 6 The size (the maximal diameter) of aggressive and non-aggressive SPNs

data also showed that the combination of age and imaging findings could reach a better diagnostic performance in differentiating aggressive and non-aggressive SPNs. In addition, Machado and colleagues [36] showed that age at the time of diagnosis was higher in male than female patients. Also, they observed that SPNs were more aggressive in male patients. Our data also showed similar tendency. And some studies reported that old age at presentation of tumor or male patients can be regarded as a predictor of malignant potential.

There were several limitations in our study. First, because of its retrospective nature, they may exhibit selection and verification bias. Second, the CT scanners, protocols, and contrast material were inconsistent for multi-institutional nature. However, the reconstruction section thickness was consistent, and we believe that 2 mm is an acceptable reconstruction section thickness for a pancreatic tumor. Third, although our study has the large number of SPNs reported on CT imaging, the number of aggressive SPNs patients was relatively small, which might have an impact on statistical power. Further studies with larger sample size are required to validate our data and to precisely define the most valuable predictive CT imaging findings for aggressive SPNs. Finally, some subjects did not undergo delayed-phase imaging which may affect the imaging evaluation, in particular to capsule sign.

In conclusion, our data indicate that age > 40.5 years, size < 42.1 mm, lack of complete capsular, ill-defined, and absent bleeding were useful findings in discriminating aggressive SPNs from non-aggressive SPNs. The combined model including lack of complete capsule and

Table 4 Sensitivity and specificity of significant Variables in differentiating aggressive SPNs from non-aggressive SPNs on univariate analysis

Variables	AUC*	Sensitivity(%)	Specificity(%)	Accuracy(%)	Odds ratio*
Lack of capsule	0.71 (0.61–0.81)	86.7	55.4	63.1	8.81 (2.61–25.03)
Age > 40.5 years	0.65 (0.53–0.77)	50	79.3	72.1	3.84 (1.6–9.22)
Size < 42.1 mm	0.67 (0.55–0.78)	66.3	66.7	66.4	3.94 (1.64–9.43)
Ill defined	0.62 (0.5–0.73)	60	63	62.3	2.56 (1.1–5.95)
Absent bleeding	0.63 (0.52–0.74)	90	35.9	50.8	5.03 (1.42–17.86)

*Data in parentheses are the 95% CI

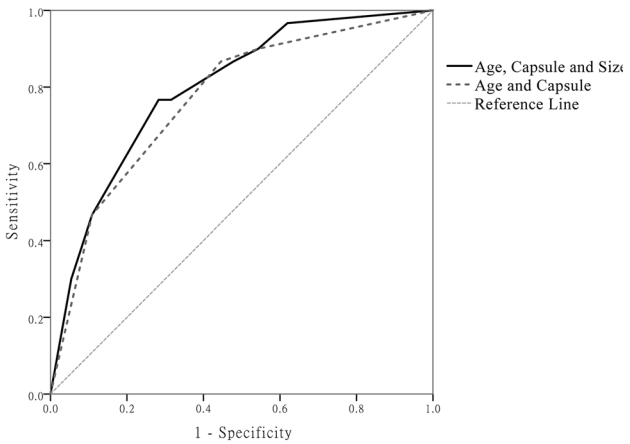

Fig. 7 Receiver operating characteristic (ROC) curve for diagnostic performance of CT regarding the differentiation of aggressive SPNs from non-aggressive SPNs. The area under the curve is 0.77

age > 40.5 years showed acceptable diagnostic performance in the differentiation of two groups.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed content Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to CECT examinations by written consent.

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