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A comparison of enhancement patterns on dynamic enhanced CT and survival between patients with pancreatic neuroendocrine tumors with and without intratumoral fibrosis

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Abstract

Purpose: To compare CT findings and survival between patients with pancreatic neuroendocrine tumors (pNETs) with and without fibrosis.
Methods: Forty-five pNET patients with intratumoral fibrosis (group A) were matched for age, gender, and tumor size and grade with 45 pNET patients without (group B), and CT images were retrospectively reviewed. Hounsfield units (HUs) of tumors in unenhanced, arterial and portal phases, HU ratio (tumor to normal parenchyma) in each phase, enhancement patterns, visible enhancement pattern changes, and survival were compared.
Results: Group A showed progressive enhancement patterns, while group B showed early enhancement and wash-out patterns ($p < 0.05$). HUs of tumors and HU ratio in the unenhanced phase were significantly higher in group A than group B ($p \leq 0.024$), whereas those in the arterial phase were significantly lower in group A than group B ($p \leq 0.003$). Peripheral to full or peripheral to peripheral enhancement change was more frequent in group A, while full to full enhancement change was more frequent in group B ($p < 0.05$). Group A showed significantly lower overall survival than group B ($p = 0.029$).
Conclusions: pNETs with fibrosis showed a progressive enhancement pattern and worse overall survival than pNETs without, which showed an early enhancement and wash-out pattern.

Key words: Pancreas—Neuroendocrine tumor—Dynamic enhanced CT—Enhancement pattern—Fibrosis

Abbreviations and acronyms

pNET	Pancreatic neuroendocrine tumor
CT	Computed tomography
HU	Hounsfield unit
ROI	Region of interest

According to the 2010 WHO classification [1], pancreatic neuroendocrine tumors (pNETs) are a group of heterogeneous tumors, including grade 1 and 2 NETs and grade 3 neuroendocrine carcinomas, and range from less aggressive to malignant/highly aggressive [grade 1, Ki-67 index ≤ 2%, mitotic count < 2/10 high power field (HPF); grade 2, Ki-67 index = 3–20%, mitotic count = 2–20/10 HPF; grade 3, Ki-67 index > 20%, mitotic count > 20/10 HPF]. Early detection and sur-

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gical removal are the treatment of choice in these tumors and have a proven survival benefit [2–4].

Computed tomography (CT) is the primary modality for the diagnosis and staging of pNETs [5]. Because treatment protocols differ according to tumor grade, predicting the tumor grade on CT before treatment is important when planning the management of pNETs. Several studies evaluated the correlation between dynamic enhancement degree or pattern on CT and tumor grade [6–11]. Kim et al. recently reported that a portal enhancement ratio of pNETs on preoperative CT may indicate the grade of pNETs, thus assisting treatment decision making, and is a prognostic CT biomarker in pNET patients [8, 12]. Cappelli et al. reported that all malignant pNETs showed "early enhancement and plateau" or "progressive enhancement" and none of the malignant pNETs showed an early enhancement and rapid wash-out pattern on dynamic CT [6]. From these results, the authors concluded that the enhancement pattern of pNETs has a strong correlation with histological prognostic factors. Additionally, they suggested that fibrosis and microvascular density may be important factors in determining the degree and timing of enhancement. Progressive enhancement patterns have also been observed in pNETs [13, 14], the possible cause of which may be fibrous stroma within the tumors.

These results led us to hypothesize that, apart from tumor grade, the presence of fibrosis within pNETs may be an important factor in determining enhancement patterns on CT. Therefore, this case–control study aimed to compare enhancement patterns, other CT findings, and patient survival between pNETs with and without fibrosis.

Methods

Our institutional review board approved this study and waived the need for informed consent because the data were retrospectively analyzed.

Study population

A computerized search of our institution's database from January 2001 to July 2014 identified 322 patients with surgically confirmed pNETs. Forty-seven of these patients had pNETs with fibrosis, two of whom were excluded from the study due to a lack of preoperative dynamic enhanced CT or poor image quality. Therefore, 45 patients [17 males (37.8%) and 28 females (62.2%)] made up group A. They were matched for age, gender, and tumor size and grade at a ratio of 1:1 with 45 patients who were pathologically diagnosed as having pNETs without fibrosis at a similar time to the patients in group A and had preoperative dynamic enhanced CT (group B). Therefore, the study included 90 patients.

CT imaging protocol

Various CT units were used over a 10-year period; these included a Sensation 16, SOMATOM Definition, SOMATOM Definition flash, or SOMATOM Definition AS + scanner (Siemens Medical Solutions, Erlangen, Germany), and a LightSpeed 16, LightSpeed Plus, or LightSpeed VCT scanner (GE Healthcare, Milwaukee, WI, USA). Unenhanced-, arterial-, and portal venous-phase dynamic CT images were obtained for all patients. For contrast enhancement, 100–120 mL of 300–370 mgI/mL iopromide (Ultravist 300 or 370; Bayer Schering Pharma, Berlin, Germany) was administered intravenously at a rate of 3–4 mL/sec using an automatic power injector through an 18-gauge intravenous cubital line, followed by a 20 mL saline flush at the same flow rate. Arterial-phase images were obtained using a 10–15 s delay after the attenuation of the aorta at the thoracolumbar junction had reached 100 Hounsfield units (HUs). Portal venous-phase images were obtained using a fixed 75 s delay after contrast injection. Coronal reformations of portal venous-phase images have routinely been performed at a slice thickness of 5 mm for all CT scans at our institution since 2008. The scan parameters were as follows: beam collimation, 16×0.75, 32×0.6, or 64×0.6 mm; beam pitch, 1; gantry rotation time, 0.5 s; field of view to fit; 120 kVp; and an automated dose reduction system (CARE Dose 4D, Siemens Medical Solutions; Auto mA/Smart mA, GE Healthcare) with the maximum allowable tube current set at 200 or 400 mAs.

Image analysis

All CT images were analyzed by two board-certified abdominal radiologists (J.H.B. and C.K., with experience of 17 and 8 years, respectively), who were blinded to intratumoral fibrosis status or tumor grade, by consensus. The size and location of pNETs were analyzed on CT. Attenuation was measured by placing a square shape of the region-of-interest (ROI) over the tumor and downstream normal pancreatic parenchyma during the unenhanced, arterial, and portal venous phases. The size of the ROI was adjusted to be as large as possible while avoiding the artifact and adjacent vascular structure. After measuring attenuation, the HU ratio (the ratio of HUs in the tumor to normal parenchyma) in each phase was calculated. The enhancement pattern, i.e., progressive enhancement or early enhancement and wash-out, was determined by both attenuation and the HU ratio. A progressive enhancement pattern was defined as when tumor attenuation or the HU ratio gradually increased from the unenhanced to the portal venous phase, while an early enhancement and wash-out pattern was defined as when tumor attenuation or the HU ratio increased

from the unenhanced to the arterial phase, and then decreased from the arterial to the portal venous phase. Enhancement pattern changes from the arterial to the portal venous phase (peripheral to full enhancement of the tumor; peripheral to peripheral enhancement; full to peripheral enhancement; or full to full enhancement) were visually evaluated. Other CT findings were also analyzed, including heterogeneity of the enhancement (homogeneous enhancement, or cystic change <50 or $\geq 50\%$ of the whole tumor), calcification, margin characteristics (well-defined [no spiculation or infiltration in $>80\%$ of the perimeter of the tumor] or ill-defined [spiculation or infiltration in $\geq 20\%$ of the perimeter of the tumor]) [8, 12], the number of cases with a dilated main pancreatic duct (diameter of main pancreatic duct ≥ 4 mm) [8], the diameter of the main pancreatic duct, the presence of direct invasion of other adjacent organs and lymph node and distant metastasis. These features were evaluated on portal venous-phase images.

Pathologic evaluation

Two pathologists with 13 years and 6 years of clinical experience in biliary and pancreatic pathology (S.H. and S.A.) reviewed all included patients' pathology slides to re-evaluate tumor grade and the presence of intratumoral fibrosis in consensus. For evaluation of intratumoral fibrosis, Masson's trichrome stain was performed in all representative formalin-fixed, paraffin-embedded tissue blocks from each case. When the pNETs had stromal fibrosis occupying more than 30% of the total tumor area, these cases were classified as group A, whereas when the pNETs had stromal fibrosis less than 30% of the total tumor area, these were classified as group B [15]. The presence of lymphovascular/perineural invasion and serotonin production was also evaluated pathologically using immunohistochemistry.

Statistical analysis

To assess differences in demographic data between groups A and B, Student's t test and Mann–Whitney U test were used for continuous variables and the Chi-square test for categorical variables. To compare the enhancement pattern and degree, other CT findings and lymphovascular/perineural invasion between the two groups, Student's t test and Mann–Whitney U test were used for continuous variables and the Chi-square test and Fischer's exact test for categorical variables. Sensitivity and specificity of significantly different enhancement patterns and CT findings between both groups for tumor fibrosis were calculated. Kaplan–Meier survival analysis with a log-rank test was performed to investigate and compare mean survival time in both groups, and the number of patients at risk was also evaluated. All statistical analyses were performed using statistical software (SPSS package, version 21.0; SPSS, Chicago, IL, USA). A p-value < 0.05 was considered significantly different.

Results

Baseline characteristics

Baseline demographic characteristics of both groups are shown in Table 1. There were no significant differences between the two groups in terms of patient gender or age ($p > 0.999$ and $p = 0.945$, respectively). Tumor size and location were also comparable between the two groups ($p = 0.771$ and $p = 0.35$, respectively). The proportion of tumor grade in both groups was the same ($p > 0.999$). Four patients (8.9%) in group A and none in group B ($p = 0.117$) had serotonin-producing pNETs.

Analysis of enhancement degree and pattern

Table 2 shows the enhancement degree and pattern of pNETs in both groups. Attenuation and the HU ratio

Table 1. Demographic characteristics of the pNET patients with and without intratumoral fibrosis

	Group A[a] (n = 45)	Group B[b] (n = 45)	*P*-value
Gender, *n* (%)			>0.999
Male	17 (37.8)	17 (37.8)	
Female	28 (62.2)	28 (62.2)	
Age, y (mean ± SD)	51.7 ± 11.5	51.5 ± 9.7	0.945
Tumor size, *cm* (mean ± SD)	2.7 ± 2.0	2.4 ± 1.4	0.771
Tumor location, *n* (%)			0.350
Head	17 (37.8)	23 (51.1)	
Body	10 (22.2)	10 (22.2)	
Tail	18 (40.0)	12 (26.7)	
Histologic grade of tumor, *n* (%)			>0.999
Grade 1	34 (75.6)	34 (75.6)	
Grade 2	7 (15.6)	7 (15.6)	
Grade 3	4 (8.9)	4 (8.9)	
Serotonin-producing tumor, *n* (%)	4 (8.9)	0 (0.0)	0.117

[a] pNET patients with an intratumoral fibrotic component
[b] pNET patients without an intratumoral fibrotic component
pNET pancreatic neuroendocrine tumor; *SD* standard deviation

were significantly higher in group A than in group B in the unenhanced phase ($p = 0.024$ and $p = 0.005$, respectively), whereas they were lower in group A than in group B in the arterial phase ($p = 0.001$ and $p = 0.003$, respectively).

The pNETs in group A showed more frequently a progressive enhancement pattern than those in group B (Fig. 1); most of the pNETs in group B showed an early enhancement and wash-out pattern (Fig. 2) ($p \leq 0.004$). The sensitivity and specificity of progressive enhancement pattern using HU and HU ratio for tumor fibrosis are shown in Table 3. Peripheral to full or peripheral to peripheral enhancement from the arterial phase to the portal venous phase was more frequent in group A, while full to full enhancement was more frequent in group B ($p = 0.011$).

Comparison of other CT findings

Table 4 shows the other CT findings in both groups. These were not significantly different between the two groups (all $p > 0.05$), except tumor margin and frequency of dilation of the main pancreatic duct. A well-defined margin was more frequently noted in group B than in group A ($p = 0.002$). The presence of dilation of the main pancreatic duct was significantly more common in group A than in group B ($p = 0.035$). The sensitivity and specificity of ill-defined tumor margin and dilated main pancreatic duct for tumor fibrosis are shown in Table 3.

Lymphovascular/perineural invasion and survival outcomes

Lymphovascular/perineural invasion in the pathologic examination was significantly more common in group A than in group B [80% (34/45) vs. 57.8% (26/45); $p = 0.039$]. Figure 3 shows the Kaplan–Meier curve for patient survival in both groups. After a mean follow-up of 84.5 months for the entire cohort, group A showed significantly worse overall survival than group B (5-year survival, 80% for group A vs. 98% for group B; $p = 0.029$).

Discussion

Our study demonstrated that pNETs with fibrosis showed a progressive enhancement pattern on dynamic enhanced CT, while pNETs without fibrosis showed an early enhancement and wash-out pattern. Moreover, the survival rate of pNET patients with intratumoral fibrosis was worse than that of pNET patients without intratumoral fibrosis.

Microvascular density and tumor blood flow have been suggested as possible factors contributing to such enhancement patterns in pNETs [10, 11, 16–18]. The present study suggests that fibrosis may be another important contributing factor, in addition to microvascular density and tumor blood flow suggested in the previous studies. Several studies reported [6, 7, 13, 14] that pNETs with a significant amount of fibrosis tend to show a progressive enhancement pattern rather than an early enhancement and wash-out pattern on CT. Cappelli et al. found that no pNETs showing an early enhancement and wash-out pattern on dynamic CT including those during the delayed phase had fibrosis, while 83% of pNETs showing a progressive enhancement pattern had fibrosis [6]. Therefore, the authors concluded that fibrosis may affect enhancement patterns. However, grade 1 pNETs with a fibrotic component were not included in their study, even though fibrotic components

Table 2. Enhancement degree and pattern in pNETs with and without fibrosis

	Group A[a] ($n = 45$)	Group B[b] ($n = 45$)	p-value
Attenuation in each phase (mean ± SD)			
Unenhanced phase, HU	42.5 ± 7.5	38.6 ± 8.2	0.024
Arterial phase, HU	146.2 ± 48.2	183.1 ± 49.7	0.001
Portal venous phase, HU	173.4 ± 43.1	166.7 ± 32.5	0.406
HU ratio in each phase (mean ± SD)			
Unenhanced phase	1.02 ± 0.28	0.88 ± 0.23	0.005
Arterial phase	1.40 ± 0.52	1.61 ± 0.38	0.003
Portal venous phase	1.62 ± 1.53	1.39 ± 0.28	0.513
Enhancement pattern using HU, *n* (%)			<0.001
Progressive enhancement	33 (73.3)	8 (17.8)	
Early enhancement & wash-out	12 (26.7)	37 (82.2)	
Enhancement pattern using HU ratio, *n* (%)			0.004
Progressive enhancement	23 (51.1)	9 (20)	
Early enhancement & wash-out	22 (48.9)	36 (80)	
Visible enhancement pattern change, *n* (%)			0.011
Peripheral to full	10 (22.2)	6 (13.3)	
Peripheral to peripheral	7 (15.6)	0 (0.0)	
Full to peripheral	1 (2.2)	0 (0.0)	
Full to full	27 (60.0)	39 (86.7)	

[a] pNETs with a fibrotic component
[b] pNETs without a fibrotic component
pNETs pancreatic neuroendocrine tumors; *HU* Hounsfield unit; *SD* standard deviation

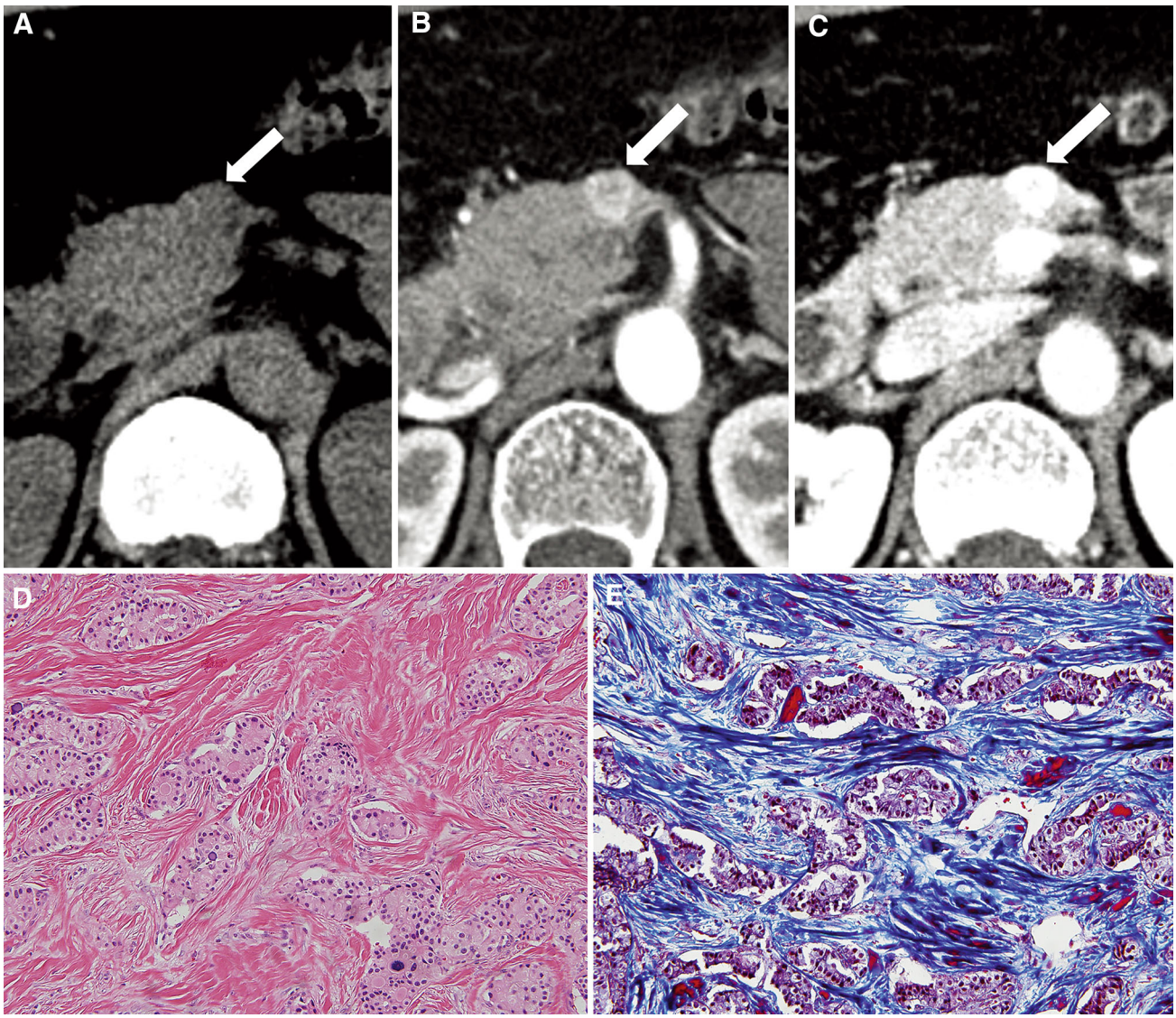

Fig. 1. Pancreatic neuroendocrine tumor (grade 1) with an intratumoral fibrotic component in a 67-year-old female. (**A–C**) A 1.7-cm well-enhancing mass (arrows) is noted in the pancreas neck on dynamic CT images. The attenuation of this tumor was 41 HUs **(A)** on the unenhanced-phase image, 171 HU **(B)** on the arterial-phase image, and 222 HUs **(C)** on the portal venous-phase image, which shows a progressive enhancement pattern. A visible enhancement pattern is peripheral enhancement in the arterial phase to full enhancement in the portal venous phase. **(D)** Microscopically, the tumor shows organoid nests with prominent stromal fibrosis more than 30% of the total tumor area (hematoxylin and eosin, original magnification, × 200) and **(E)** large amount of fibrosis is highlighted with blue color on Masson's trichrome stain (original magnification, × 200).

can be found in grade 1 and 2, as well as grade 3 tumors, and may be another important factor affecting enhancement patterns. In the present study, we adjusted all factors such as age, gender, and tumor size and grade between pNETs with and without a fibrotic component for a precise comparison; 75.6% of pNETs (34 of 45) in both groups were grade 1. Therefore, we suggest that an intratumoral fibrotic component may be an important cause of the various enhancement patterns, despite it being present in less aggressive pNETs. Further studies will be required to investigate the correlation between the presence of fibrosis and tumor grade because most pNETs included in this study were grade 1 or 2.

This study showed that the pNET patients with intratumoral fibrosis had significantly worse overall survival than those without intratumoral fibrosis. This result may be due to the more frequent lymphovascular/perineural invasion in pNETs with fibrosis because there were no significant differences between the two groups in terms of the other results, including direct adjacent organ invasion, lymph node metastasis, distant metastasis, and tumor size and grade. The more fre-

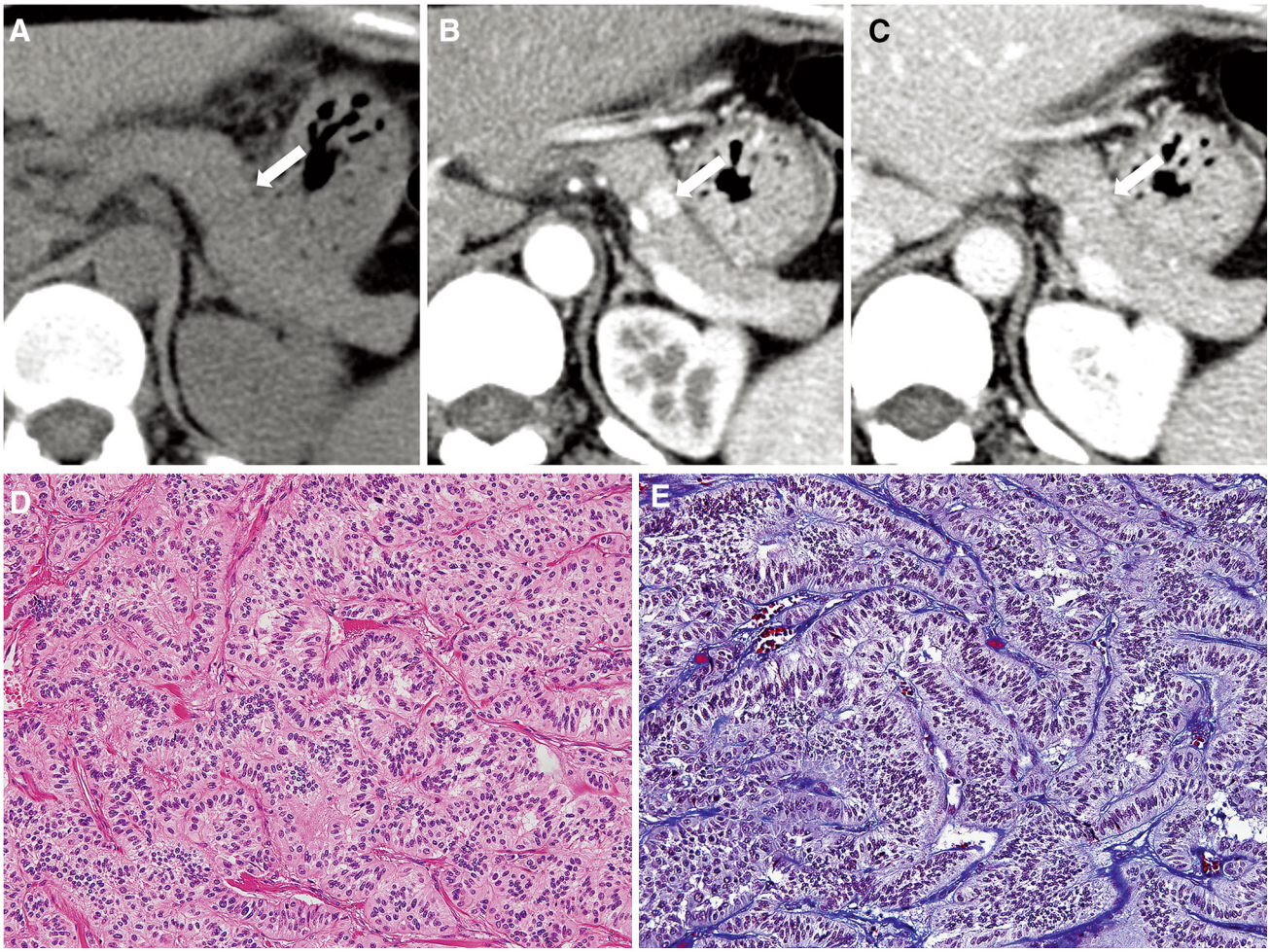

Fig. 2. Pancreatic neuroendocrine tumor (grade 2) without an intratumoral fibrotic component in a 39-year-old female. (**A**–**C**) A 0.8-cm mass (arrows) is noted in the pancreas tail on dynamic CT images. The attenuation of this tumor was 42 HUs **(A)** on the unenhanced-phase image, 179 HUs **(B)** on the arterial-phase image, and 141 HUs **(C)** on the portal venous-phase image, which shows an early enhancement and wash-out pattern. The tumor shows iso-attenuation compared to normal pancreatic parenchyma **(A)** on the unenhanced-phase image and **(C)** portal venous-phase image. Visible attenuation is full enhancement in both the arterial phase and the portal venous phase. Microscopically, the tumor shows hypercellular nests with scanty fibrosis in both **(D)** hematoxylin and eosin stain and **(E)** Masson's trichrome stain (original magnification, × 200).

Table 3. Sensitivities and specificities of significant enhancement patterns and CT findings for tumor fibrosis

	Sensitivity (95% CI)	Specificity (95% CI)
Progressive enhancement pattern using HU	73.3 (58.1–85.4)	82.2 (68–92)
Progressive enhancement pattern using HU ratio	51.1 (35.8–66.3)	80 (65.4–90.4)
Ill-defined tumor margin	33.3 (20–49)	93.3 (81.7–98.6)
Main pancreatic duct dilatation	28.9 (16.4–44.3)	88.9 (76–96.3)

CI confidence interval
Data are %

quent occurrence of peritumoral infiltration on CT in pNETs with fibrosis than in pNETs without was consistent with this result, despite it not being statistically significant ($p = 0.059$). Therefore, we suggest that the presence or absence of fibrosis in pNETs may be an important independent prognostic factor, particularly lower grade pNETs. A further study including a larger patient cohort is needed to investigate the correlation between the presence of fibrosis in pNETs and overall survival.

As the proportion of pNET grade was the same in both groups in this study, the lack of a significant difference between the groups in terms of the attenuation and HU ratio of pNETs during the portal venous phase is consistent with the previous findings that the enhancement degree of pNETs in the portal venous phase correlates well with pNET grade [8]. However, previous studies on the relationship between the enhancement degree and grade of pNETs did not investigate the significance of fibrosis [8]. Cappelli et al. only investigated the presence and amount of intratumoral fibrosis in pNETs, and their relationship with enhancement patterns on dynamic CT [6]. Our results showed that the presence or absence of fibrosis in pNETs is an important factor for the enhancement degree of pNETs as well as the enhancement patterns on dynamic CT.

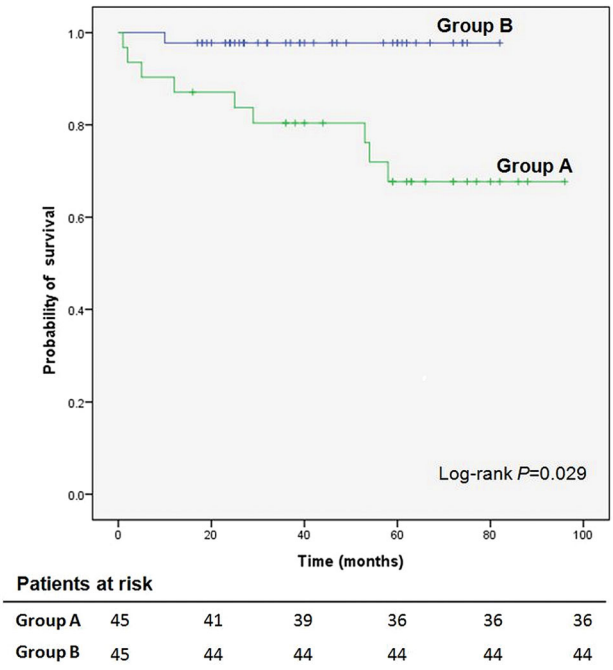

Fig. 3. Kaplan–Meier analysis of the survival of pNET patients with and without intratumoral fibrosis. The number of surviving patients at the given time periods is shown in the table below the graph. Group A indicates pNET patients with intratumoral fibrosis and group B indicates those without intratumoral fibrosis.

There are several limitations to this study. First, the CT parameters used were diverse because the study period covered more than 10 years. Second, as this was a retrospective, case–control study, selection bias may have occurred during case-matching. Third, the pNET with fibrosis group was not subdivided according to the amount of fibrosis. A further study on the correlation between the amount of fibrosis within pNETs and enhancement patterns on CT or survival outcomes will provide valuable information. Fourth, we did not investigate the microvascular density of pNETs, which may be associated with the degree and timing of enhancement. Fifth, the size of pNET >2 cm is generally considered to be a sign of increased aggressive behavior. In this study, we did not consider the tumor size in the evaluation of tumor fibrosis, because we matched tumor size between the two groups. Therefore, future study should also consider the tumor size and microvascular density of pNETs.

In conclusion, pNETs with fibrosis showed a progressive enhancement pattern on dynamic enhanced CT and worse overall survival than pNETs without fibrosis, which showed an early enhancement and wash-out pat-

Table 4. Comparison of other CT findings between pNETs with and without fibrosis

	Group A[a] ($n = 45$)	Group B[b] ($n = 45$)	p-value
Heterogeneity			0.563
Homogeneous	29 (64.4)	32 (71.1)	
Heterogeneous			
Cystic change $< 50\%$	10 (22.2)	10 (22.2)	
Cystic change $\geq 50\%$	6 (13.3)	3 (6.7)	
Calcification	3 (6.7)	7 (15.6)	0.180
Margin			0.002
Well-defined	30 (66.7)	42 (93.3)	
Ill-defined	15 (33.3)	3 (6.7)	
Presence of capsule	1 (2.2)	2 (4.4)	>0.999
Peritumoral infiltration	12 (26.7)	5 (11.1)	0.059
Main pancreatic duct dilatation	13 (28.9)	5 (11.1)	0.035
Mean diameter of main pancreatic duct, *mm* (mean $\pm$ SD)	2.7 ± 2.0	2.3 ± 1.4	0.657
Direct invasion to other organs	8 (17.8)	8 (17.8)	>0.999
Lymph node metastasis	5 (11.1)	1 (2.2)	0.2
Distant metastasis	1 (2.2)	0 (0.0)	>0.999

The data shown are the number of pNETs (percentages) except for mean diameter of the main pancreatic duct
[a] pNETs with a fibrotic component
[b] pNETs without a fibrotic component
pNETs pancreatic neuroendocrine tumors; *SD* standard deviation

tern. Intratumoral fibrotic components may be an important cause of these various enhancement patterns.

Compliance with ethical standards

Funding No funding was received for this study.

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

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

Informed consent Informed consent was waived because of the retrospective nature of this study with pre-existing data. This study was approved by our institutional research board.

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