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ORIGINAL ARTICLE

Diffuse pancreatic parenchymal atrophy, an imaging finding predictive of the development of pancreatic ductal adenocarcinoma: A case–control study

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Key words
computed tomography, main pancreatic duct, pancreatic cancer, pancreatic ductal adenocarcinoma, pancreatic parenchymal atrophy.

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Abstract

Background and Aim: Pancreatic ductal adenocarcinoma (PDAC) is a lethal cancer, partly because its early detection is difficult. This study aimed to identify computed tomography (CT) findings associated with PDAC prior to diagnosis.
Methods: Past CT images were retrospectively collected from the PDAC group ($n = 54$) and the control group ($n = 90$). The following imaging findings were compared: pancreatic mass, main pancreatic duct (MPD) dilatation with or without cutoff, cyst, chronic pancreatitis with calcification, partial parenchymal atrophy (PPA), and diffuse parenchymal atrophy (DPA). In the PDAC group, CT findings were examined during the pre-diagnostic period and 6–36 months and 36–60 months before diagnosis. Multivariate analyses were performed using logistic regression.
Results: MPD dilatation with cutoff ($P < 0.0001$) and PPA ($P = 0.023$) were identified as significant imaging findings 6–36 months before diagnosis. DPA was identified as a novel imaging finding at 6–36 months ($P = 0.003$) and 36–60 months ($P = 0.009$) before diagnosis.
Conclusion: DPA, MPD dilatation with cutoff, and PPA were identified as imaging findings associated with pre-diagnostic PDAC.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal cancers. The 5-year survival rate of PDAC remains at 3–15%.[1] On the other hand, the 5-year survival rate of PDAC in stage 0 (carcinoma in situ: CIS) according to the Union for International Cancer Control staging system is 85.8%. If PDAC is detected when less than 10 mm in diameter, the 5-year survival rate is 80.4%.[2] Therefore, early detection is essential for improving prognosis.

Detecting early-stage PDAC, that is, tumors less than 10 mm in diameter or CIS, is challenging. It is difficult to be identified by any imaging modality generally used for PDAC, which includes computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic ultrasonography (EUS), because a visible mass is too small or not formed.[3] However, EUS has the potential to detect small masses that CT and MRI do not detect, but it is highly dependent on the skill of the operator and is not generally available in all hospitals.[3] Most CIS is not detectable even with EUS.

The importance of secondary imaging findings associated with the presence of tumors that can be easily detected by abdominal ultrasonography, CT, or MRI, such as the dilation of the main pancreatic duct (MPD) or the presence of a pancreatic cyst, has been reported.[4] There are also several reports describing secondary imaging findings associated with PDAC that are not detected with imaging, namely those associated with pre-diagnostic PDAC. These findings include MPD dilatation with cutoff, MPD dilatation without cutoff, pancreatic cysts, upstream parenchymal atrophy (UPA), and focal parenchymal atrophy (FPA).[5]

In the present study, we evaluated CT findings associated with pre-diagnostic PDAC by comparing past CT images of patients with PDAC diagnosed at our institute with past CT images of patients without confirmed PDAC recent images.

Methods

Study design and patients. A retrospective, single-center, case–control study was conducted to clarify the characteristic CT findings of pre-diagnostic PDAC using CT images obtained prior to the detection of PDAC. Patients with a pathologic diagnosis of PDAC who underwent CT examinations from January 2015 to March 2022 were enrolled as part of the PDAC group. Pancreatic cancers other than PDAC such as intraductal papillary mucinous carcinoma were excluded. There were 257 patients diagnosed with PDAC during the study period, of which 21 patients were

excluded because of the lack of pathologic diagnosis. Another 182 patients were excluded because they did not undergo CT examinations that included the pancreas during the 6–60 months before diagnosis. Ultimately, 54 patients were included in the PDAC group (Fig. 1). Previous reports had shown some findings of definite and suspected PDAC on CT images obtained from 6 to 36 months before diagnosis but few findings on CT images obtained 36 months or more before diagnosis.[6,7] Therefore, patients in the PDAC group were further divided in two groups: PDAC 6–36 M group ($n = 39$) and PDAC 36–60 M group ($n = 26$). Patients in the 6–36 M group underwent CT between 6 and 36 months before diagnosis; patients in the 36–60 M group underwent CT between 36 and 60 months before diagnosis. Eleven patients belonged to both groups because they underwent CT examinations during both periods. To investigate the changes in imaging findings between 36 and 60 months before diagnosis and the time of PDAC diagnosis, the PDAC 6–36 M group was further divided into the PDAC 6–18 M group ($n = 24$) and the PDAC 18–36 M group ($n = 23$). Eight patients belonged to both groups.

Consecutive patients aged 63 years or older who visited our department for regular check-ups for liver disease between April 2017 and March 2018 and underwent CT examinations including the pancreas were enrolled as part of the control group; 113 patients met the criteria. Among them, 90 patients who underwent recent abdominal CT or MRI in which PDAC was not detected and had previous CT examinations performed ≥36 months (average, 49.5 months) before the recent imaging examination were enrolled in the control group. Among them, 82 patients underwent another CT examination between 6 and 36 months before the recent imaging examinations.

Definitions. In this study, the following CT findings in the prediagnostic CT images were compared between the PDAC group and the control group: pancreatic mass, pancreatic cyst, MPD dilatation without cutoff, MPD dilatation with cutoff, chronic pancreatitis with calcification, PPA, and DPA. MPD diameter of 4 mm or more in the pancreatic head and 3 mm or more in the pancreatic body tail was defined as MPD dilatation. Chronic pancreatitis with calcification was defined as multiple calcifications in the parenchyma or a pancreatic stone in the pancreatic duct; a single calcification in the parenchyma was not included. PPA was defined as FPA and UPA according to the detailed definitions of Yamao et al.[8] FPA was defined based on the following parameters: (i) bilateral or unilateral partial invagination of the pancreatic parenchyma of 4 mm or less in width from the MPD wall measured at a minimal distance; (ii) FPA length ranging from 10 to 25 mm; and (iii) upstream parenchyma width greater than 6 mm. UPA was defined as overall upstream parenchymal atrophy with width of 4 mm or less from the MPD wall.[8] We added width of the pancreas of 10 mm or less as another definition of PPA if MPD was not detected on CT. DPA was defined as diffuse atrophy from the pancreatic head to tail in axial images with a pancreatic body width of 10 mm or less and non-localized atrophy in most or all the pancreas, including head of the pancreas.

CT Evaluation. The protocol of CT examinations performed prior to the diagnosis of PDAC was different for each patient in this study based on the year of the examination, the purpose, and the target organ of the CT examination. The proportion of plain CT examinations in the past was 57% in the PDAC group and 6.7% in the control group. Imaging findings from past CT images of the PDAC and control groups were independently evaluated

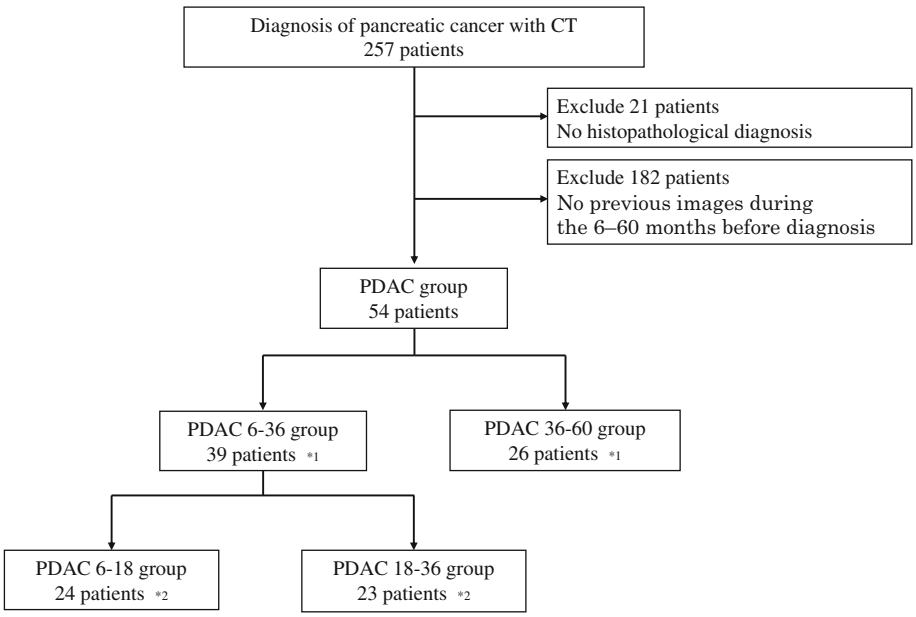

Figure 1 Study flow chart. CT, computed tomography, PDAC, pancreatic ductal adenocarcinoma. *1: Eleven patients belonged to both groups since they underwent CT examinations in both periods. *2: Eight patients belonged to both groups.

by a team of two reviewers. The team consisted of a gastroenterologist with more than 25 years of experience and a radiologist with more than 15 years of experience. Each investigator interpreted the presence or absence of each of the six findings. PPA was further evaluated separately for FPA and UPA. After each investigator completed all the evaluations, interobserver agreement for all findings was calculated using weighted kappa statistics. Reproducibility was interpreted based on the kappa value: no agreement, <0; slight agreement, 0.00–0.20; fair, 0.21–0.40; moderate, 0.41–0.60; substantial, 0.61–0.80; and almost perfect, 0.81–1.00. If the two investigators disagreed on imaging findings, they held discussion until agreement was reached.

Statistical analysis. Continuous variables were presented as medians (range) and compared using the unpaired *t*-test. Fisher's exact test was used to compare categorical variables. Multivariate logistic regression was performed. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of the R *commander* designed to add statistical functions frequently used in biostatistics. $P < 0.05$ was defined as statistically significant.

Results

Patient characteristics and imaging findings by group. In the PDAC group, the median age at diagnosis was 76 (57–89) years; 27 (50%) patients were female. The other patient characteristics are summarized in Table 1. In the control group, the median age was 76.5 (63–90) years at the time of the recent CT or MRI examination; 43 (47.8%) patients were female. There were no significant differences in the gender or age distribution between the PDAC, PDAC 6–36 M, and PDAC 36–60 M groups and the control group. At diagnosis, prevalence of pancreatic mass, MPD dilatation with cutoff, cyst, PPA, and UPA were significantly higher in the PDAC group than in the control group (Table 2).

Table 1 Characteristics of patients with pancreatic ductal adenocarcinoma (PDAC)

	PDAC ($n = 54$)
Female, *n* (%)	27 (50.0)
Age, years, median (range)	76 (57–89)
PDAC location, *n* (%)	
Head	28 (51.9)
Body	14 (25.9)
Tail	12 (22.2)
UICC stage, *n* (%)	
0	2 (3.7)
IA	3 (5.6)
IB	0 (0)
IIA	12 (22.2)
IIB	11 (20.4)
III	10 (18.5)
IV	16 (29.6)
Treatment, *n* (%)	
Pancreatic resection	17 (31.5)
Chemotherapy	19 (35.2)
Best supportive care	18 (33.3)

UICC, Union for International Cancer Control.

Interobserver agreement was analyzed using weighted kappa statistics. The kappa value for pancreatic cyst was 0.84, which indicated almost perfect agreement. The kappa values for MPD dilatation without cutoff, MPD dilatation with cutoff, chronic pancreatitis with calcification, UPA, and DPA were 0.65, 0.64, 0.70, 0.65, and 0.74, respectively, which indicated substantial agreement. The kappa values for FPA and PPA were 0.46 and 0.52, respectively, which indicated moderate agreement.

Comparison of imaging findings in the past CT examinations

PDAC 6–36 M group versus control group. Univariate analyses showed that prevalence of pancreatic mass, MPD dilatation with cutoff, PPA, FPA, UPA, and DPA were significantly higher in the PDAC 6–36 M group than in the control group ($P = 0.032$, $P < 0.0001$, $P = 0.004$, $P = 0.031$, $P = 0.037$, and $P = 0.032$, respectively) (Table 2). Multivariate analysis showed that MPD dilatation with cutoff ($P < 0.0001$), PPA ($P = 0.023$), and DPA ($P = 0.003$) are imaging findings independently and significantly associated with pre-diagnostic PDAC in the period 6–36 months before diagnosis (Table 2).

The incidence by location of PDAC in this group was 53.8% (21/39) in the pancreatic head, 20.5% (8/39) in the pancreatic body, and 25.6% (10/39) in the pancreatic tail. For pancreatic duct dilatation with cutoff and PPA, the location was 100% matched to that of PDAC occurrence, whereas for cyst the match was 23.5% (Table 3). When PPA was classified into FPA and UPA, FPA was detected in the pancreatic head in two cases, in the pancreatic body in two cases, and in the pancreatic tail in two cases; UPA was detected in the pancreatic head in no case, in the pancreatic body-tail in one case, and in the pancreatic tail in two cases. The location and measurement results for each case are summarized in Table S1(a).

PDAC 36–60 M group versus control group. In univariate analysis, DPA was more frequently observed in the PDAC 36–60 M group than in the control group ($P = 0.049$) (Table 2). In multivariate analysis, DPA was an imaging finding that was independently and significantly associated with pre-diagnostic PDAC in the period 36–60 months before diagnosis ($P = 0.009$) (Table 2).

The incidence by location of PDAC in this group was 50% (13/26) in the pancreatic head, 26.9% (7/26) in the pancreatic body, and 23.1% (6/26) in the pancreatic tail. For pancreatic duct dilatation with cutoff and PPA, the location was 100% matched to that of PDAC occurrence, whereas for cyst the match was 42.9% (Table 3). When PPA classified into FPA and UPA, FPA was detected in the pancreatic head in no case, in the pancreatic body in two cases, and the pancreatic tail in one case, whereas UPA was detected in the pancreatic tail in only one case. The location and measurement results for each case are summarized in Table S1(b).

Changes in CT findings by time period. To investigate the changes in CT findings from >36 months before diagnosis to the

Table 2 Comparison of characteristics or computed tomography (CT) findings between patients with pancreatic ductal adenocarcinoma (PDAC) and controls

	Comparison between PDAC and Controls									Multivariate analysis	
				Past examination							
	At diagnosis			6–36 M			36–60 M			6–36 M	36–60 M
Characteristic or CT finding	PDAC, ($n = 54$)	Control, ($n = 90$)	*P* value	PDAC, ($n = 39$)	Control, ($n = 82$)	P value	PDAC, ($n = 26$)	Control, ($n = 90$)	*P*-value	*P*-value	*P*-value
Female, *n* (%)	27 (50)	43 (47.8)	0.864	22 (56.4)	35 (42.7)	0.177	11 (42.3)	43 (47.8)	0.661	0.212	0.547
Age, years median (range)	76 (57–89)	76.5 (63–90)	0.612	75 (56–87)	75.5 (62–89)	0.902	72 (53–85)	72 (56–86)	0.713	0.557	0.329
Mass, *n* (%)	47 (87.0)	0 (0)	<0.0001	3 (7.7)	0 (0)	0.032	0 (0)	0 (0)	NA	0.067	NA
MPD dilatation without cutoff, *n* (%)	4 (4.7)	4 (4.4)	0.473	2 (5.1)	3 (3.7)	0.657	2 (7.7)	4 (4.4)	0.615	0.496	0.669
MPD dilatation with cutoff, *n* (%)	40 (74.1)	0 (0)	<0.0001	11 (28.2)	0 (0)	<0.0001	1 (3.8)	0 (0)	0.224	<0.0001	0.202
Cyst, *n* (%)	36 (66.7)	26 (28.9)	<0.0001	17 (43.6)	24 (29.3)	0.151	7 (26.9)	23 (25.6)	1.000	0.673	0.756
Chronic pancreatitis with calcification, *n* (%)	7 (13.0)	11 (13.9)	1.000	6 (15.4)	13 (15.9)	1.000	4 (15.4)	13 (14.4)	1.000	0.241	0.582
PPA, *n* (%)	27 (50.0)	5 (5.6)	<0.0001	9 (23.1)	4 (4.9)	0.004	4 (15.4)	5 (5.6)	0.112	0.023	0.190
FPA, *n* (%)	4 (7.4)	4 (4.4)	0.473	6 (15.4)	3 (3.7)	0.031	3 (11.5)	4 (4.4)	0.186	-	-
UPA, *n* (%)	24 (44.4)	1 (1.1)	<0.0001	3 (7.7)	1 (1.2)	0.037	1 (3.8)	1 (1.1)	0.400	-	-
DPA, *n* (%)	0 (0)	0 (0)	NA	3 (7.7)	0 (0)	0.032	2 (7.7)	0 (0)	0.049	0.003	0.009

DPA, diffuse parenchymal atrophy; FPA, focal parenchymal atrophy; M, months; MPD, main pancreatic duct; NA, not available; PPA, partial parenchymal atrophy; UPA, upstream parenchymal atrophy.

Table 3 Location of computed tomography findings in the pancreas (head/body/tail)

	PDAC 6-36 M				PDAC 36-60 M			
	Head	Body	Tail	Match of sites with PDAC	Head	Body	Tail	Match of sites with PDAC
Cyst *n*, (%)	11 (64.7)†	6 (35.3)†	12 (70.6)†	4 (23.5)	5 (71.4)†	5 (71.4)†	5 (71.4)†	3 (42.9)
MPD dilatation with cutoff, *n* (%)	6 (54.5)	3 (27.3)	2 (18.2)	11 (100)	0 (0)	0 (0)	1 (100)	1 (100)
PPA	2 (22.2)	3 (33.3)	4 (44.4)	9 (100)	0 (0)	2 (50.0)	2 (50.0)	4 (100)

†Overlapping data.
MPD, main pancreatic duct; PDAC, pancreatic ductal adenocarcinoma; PPA, partial parenchymal atrophy.

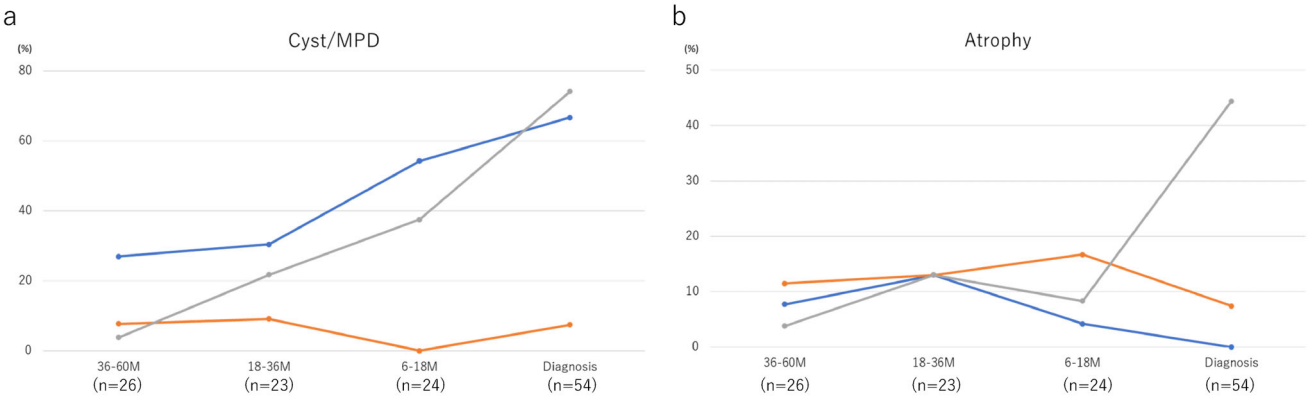

Figure 2 (a) Changes in the prevalence of computed tomography (CT) findings associated with cyst and main pancreatic duct (MPD) dilatation. The prevalence of cyst, MPD dilatation without cutoff, and MPD dilatation with cutoff for each time period (36–60 months, 18–36 months, and 6–18 months before diagnosis and time of diagnosis) is shown. The prevalence of cyst and MPD dilatation with cutoff increased from 36 months before diagnosis to the time of diagnosis. (b) Changes in the prevalence of CT findings associated with parenchymal atrophy. The prevalence of parenchymal atrophy (diffuse parenchymal atrophy [DPA], focal parenchymal atrophy [FPA], or upper parenchymal atrophy [UPA]) for each time period (36–60 months, 18–36 months, and 6–18 months before diagnosis and time of diagnosis) is shown. The prevalence of UPA was highest at the time of diagnosis. The prevalence of FPA and DPA was similar before diagnosis, and the prevalence of both was lower at the time of diagnosis. M, months. (a): —●—, Cyst; —●—, MPD dilatation without cutoff; —●—, MPD dilatation with cutoff. (b): —●—, DPA; —●—, FPA; —●—, UPA.

time of diagnosis, CT findings of the PDAC, PDAC 6–18 M, PDAC 18–36 M, and PDAC 36–60 M groups were compared. Differences in the prevalence of each CT finding are shown in Figure 2. The prevalence of cyst and MPD dilatation with cutoff increased from 36 months before diagnosis and was highest at diagnosis (Fig. 2a). In terms of atrophy, the prevalence of UPA was highest at the time of diagnosis, whereas the prevalence of FPA and DPA were almost constant until diagnosis. At the time of diagnosis, the prevalence of FPA and DPA were lower because of the appearance of PDAC (Fig. 2b).

Typical Images of DPA. Past CT images and CT images at the time of diagnosis of three typical patients with DPA in the PDAC group are shown in Figure 3. In all three patients, the pancreas, including head of the pancreas, was almost entirely atrophic on past CT images and subsequently developed PDAC as identified in the CT images at diagnosis. PDACs originated from the head, body, or tail of the pancreas. DPA was fully visible in plain CT.

The patient represented in Figure 3c was the only patient with DPA who underwent pancreatic resection. We reviewed histopathologic images of the noncancerous pancreatic tissue from the head side of the PDAC obtained with distal pancreatectomy. Hematoxylin and eosin (H&E)-stained specimens showed severe atrophy of the pancreatic parenchyma, fatty replacement, and mild fibrosis (Fig. 4). There was no inflammatory cell infiltration or extensive fibrosis suggestive of chronic pancreatitis.

Discussion

By comparing the past CT images of 54 patients with PDAC before diagnosis and images of 90 controls, MPD dilatation with cutoff, PPA, and DPA were identified as imaging findings that are independently and significantly related to pre-diagnostic PDAC in the period 6–36 months before diagnosis. DPA was identified as the only significant imaging finding related to pre-diagnostic PDAC in the period 36–60 months before diagnosis. Moreover, histopathologic examination of resected pancreatic tissue with DPA showed that atrophy of the pancreatic parenchyma

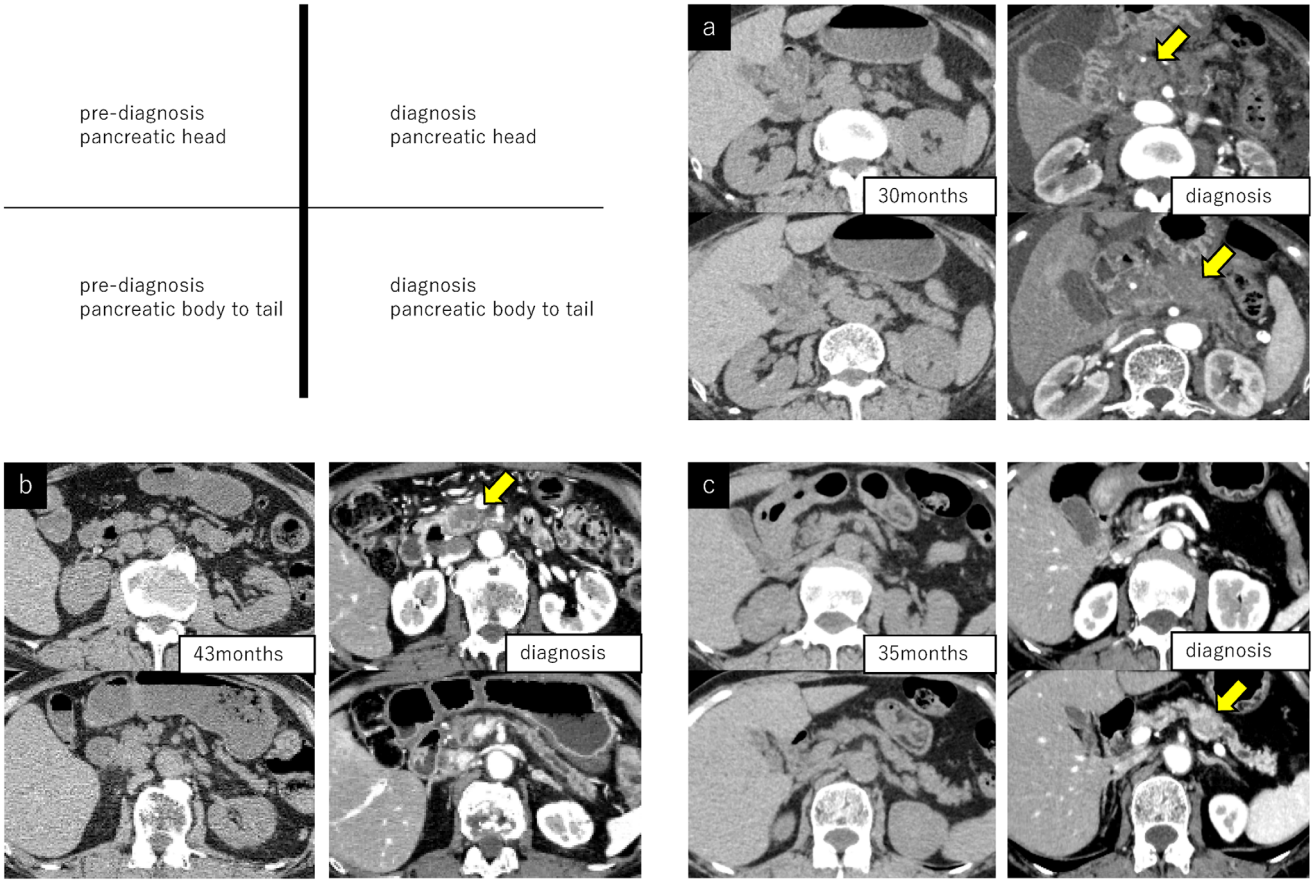

Figure 3 Typical cases with diffuse parenchymal atrophy in the pancreatic ductal adenocarcinoma (PDAC) group on past computed tomography (CT) images and CT images at diagnosis. (a) CT images of a 75-year-old female at 30 months prior to the diagnosis (left panels) and at the time of diagnosis (right panels). PDAC developed in the body of the pancreas. (b) CT images of a 73-year-old male at 43 months prior to the diagnosis (left panels) and at the time of diagnosis (right panels). PDAC developed in the head of the pancreas. (c) CT images of a 71-year-old female at 35 months prior to the diagnosis (left panels) and at the time of diagnosis (right panels). PDAC developed in the tail of the pancreas. The yellow arrows indicate PDAC.

and fatty infiltration into the pancreas were notable findings but inflammation and fibrosis were scarce.

Recently, several reports have found a relationship between FPA and early pancreatic cancer.[8–11] FPA is thought to arise from low-grade pancreatic intraepithelial neoplasm (PanIN) the pre-cancerous stage of PDAC.[12] Fibrosis or fat replacement occurred in the pancreatic parenchyma at the site of FPA. Nakahodo *et al*. proposed three mechanisms through which pancreatic parenchymal atrophy with fibrosis and fat replacement was induced.[10] One of them, indirect change might result from a pancreatic juice drainage disorder. It is possible that obstructive pancreatitis around branch duct fibrosis results in atrophy of the parenchyma in the drainage area of each branch duct.[13,14] CIS has a low papillary or flat structure, but it can obstruct the flow of pancreatic juice. FPA may occur in pancreatic tissue surrounding malignant tumors and spread to upstream parenchyma as a result of disruption of pancreatic ductal flow.[8] FPA is caused by impaired pancreatic drainage from branch ducts, whereas UPA occurs when the MPD is obstructed by tumor progression. Therefore, FPA and UPA seem to be serial phenomena depending on the degree of tumor progression. The mechanism proposed by Nakahodo *et al*. supports this idea. In this study, we also found cases of transition from FPA to UPA. There are issues regarding FPA. The imaging finding of FPA has not been universally defined yet. We adopted the definition described by Yamao *et al*. because their definition was the most detailed and clear.[8] However, interobserver agreement for FPA was lowest (0.463) among the imaging findings evaluated. We propose that PPA, a combination of FPA and UPA, is an appropriate imaging finding of pre-diagnostic PDAC.[8] PPA was identified as an imaging finding that is independently and significantly associated with pre-diagnostic PDAC in the period 6–36 months before diagnosis.

Previous reports describing the relationship between pancreatic atrophy and PDAC have focused on localized pancreatic parenchymal atrophy. However, we found a new classification of pancreatic atrophy, DPA extending from the head to tail in the pancreas is to be associated with pre-diagnostic PDAC. DPA was more frequently observed in the PDAC 6–36 M group ($P = 0.032$) and the PDAC 36–60 M group ($P = 0.049$) than in the control group. Multivariate analysis also identified DPA as

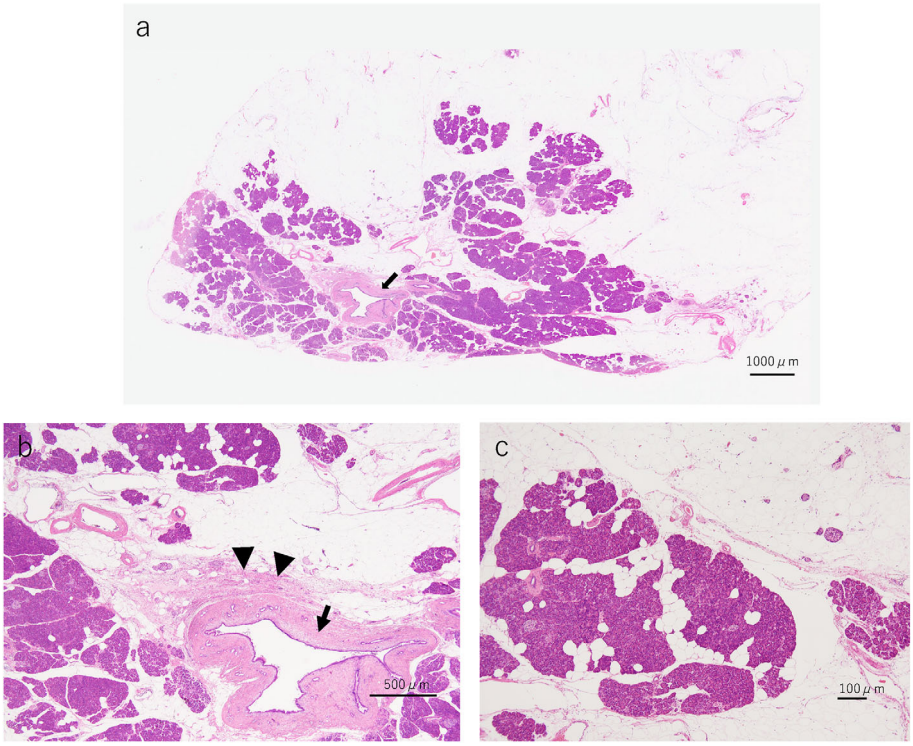

Figure 4 Histopathology of diffuse parenchymal atroph (DPA). A 71-year-old woman with DPA developed pancreatic ductal adenocarcinoma (PDAC) in the pancreatic tail. (a) A loupe image of hematoxylin and eosin-stained sections of a resected specimen in the noncancerous portion of the pancreatic body, which was taken from about 2.5 cm away from the lesion. An arrow indicates the main pancreatic duct. (b) Interlobular fatty deposit and mild fibrosis (arrow heads) are shown in a low magnified view. An arrow indicates the main pancreatic duct. (c) Interlobular fatty infiltrations are seen under high magnification. However, these findings were not specific findings shown in the noncancerous portion of PDA but sometimes shown in the noncancerous portion of PDAC developed in elderly people.

an imaging finding that is independently and significantly associated with pre-diagnostic PDAC in the periods 6–36 months ($P = 0.003$) and 36–60 months ($P = 0.009$) before diagnosis. There are two ways to conceptualize the relationship between DPA and pancreatic carcinogenesis: Either the development of PDAC causes DPA, or pre-existing DPA facilitates pancreatic carcinogenesis. First, it seems that DPA does not belong to the FPA–UPA axis. Considering that FPA and UPA, namely PPA, are caused by impaired pancreatic juice outflow from branch ducts and the MPD due to the existence of PDAC, if cancer causes DPA, PDAC should be located in the head of the pancreas. However, in this study, patients with DPA developed PDAC not only in the pancreatic head but also in the pancreatic body and tail. Yachida *et al*. reported the duration between the appearance of cancer cells and metastasis could be estimated as an average of 6.8 ± 3.4 years.[15] It is possible that cancer cells were already present during the study period. Therefore, it cannot be denied that cancer cells or some secondary factor related to carcinogenesis might have caused DPA. Second, a different hypothesis is possible: DPA might provide a favorable environment for the proliferation of a PDAC parental clone. As shown in Figure 4, the histopathologic specimen of noncancerous pancreatic tissue not affected by PDAC had severe atrophy of the pancreatic parenchyma, fatty change, mild fibrosis, and no inflammatory cell infiltration, which indicated that DPA was not caused by chronic pancreatitis. Extensive replacement of pancreatic acinar cells by fat cells was found. Fatty change in the pancreatic parenchyma is considered a risk factor for PDAC.[16–18] However, pancreatic steatosis is not always accompanied by pancreatic atrophy.[4] DPA might involve a mechanism that is different from the effect of fatty cells on pancreatic carcinogenesis. Further investigations are required to address this issue.

Our study has the following strengths. In this study, we were able to identify appropriate controls. The controls ($n = 90$) underwent CT examinations more than 36 months before the recent CT or MRI examination, which confirmed the absence of PDAC. And most of them ($n = 82$) underwent another CT examination between 6 and 36 months before the recent examination. Comparing the past CT findings of patients with PDAC with those from the past CT examinations of controls facilitated multivariate analysis, which was rarely performed in previous studies. Moreover, the results allowed us to identify DPA as a novel finding associated with pre-diagnostic PDAC.

Our study also has several limitations. This study is a retrospective analysis at a single center with a relatively small sample size. As this is a retrospective study, the methods of CT imaging were not standardized. In addition, since the definition of pancreatic atrophy as an imaging finding is inconsistent across

studies and some reports do not include a definition of atrophy, it can be difficult to reproduce our results. No article defining pancreatic atrophy separately defines the pancreatic head and the pancreatic body tail. Since there are differences in the volume of the pancreas and the location of the main pancreatic duct between the pancreatic head and the pancreatic body-tail, a different definition will be an issue for the future. Although about half of PDAC developed in the pancreatic head, PPA that could be detected by the definition of pancreatic atrophy used in this study was found mostly in the body to tail, suggesting the limitation of this definition. And, the high proportion of plain CT images for diagnosis in the PDAC group compared to controls may be a limitation of this study. Although it might have little effect on the diagnosis of pancreatic atrophy and calcification, small masses within the pancreas might not be detected by plain CT. Moreover, the diagnosis of small pancreatic cysts (diameter <10 mm) within the pancreas and MPD dilatation might be affected by using plain CT images, but small cysts were often difficult to distinguish from fat replacement even with enhanced CT. Nonetheless, the diagnosis of pancreatic cysts and MPD dilatation was supported by high interobserver agreements. We defined DPA as present when there was diffuse atrophy from the pancreatic head to tail in axial images, the width of the pancreatic body was 10 mm or less, and most or all of the pancreas (including the head of the pancreas) had non-localized atrophy. In addition, because we could examine the tissue specimens from only one patient, the discussion of histologic findings in DPA was based on insufficient evidence. The pancreas also generally tends to atrophy with age. Since the relationship between DPA and aging was not clear in this study, it should also be investigated in the future. Another limitation is that the stage of PDAC was not constant at the time of diagnosis, so there is variation in the predicted timing of pancreatic cancer development.

Conclusion

In this study, MPD dilatation with cutoff and PPA were identified as imaging findings associated with pre-diagnostic PDAC in the period 6–36 months before diagnosis. DPA was identified as another imaging finding associated with pre-diagnostic PDAC in the period 6–60 months before diagnosis. Our findings should be verified in future prospective cohort studies.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Table S1. (a) Location and measurement results for each case with FPA/UPA in the PDAC 6–36 M group. (b) Location and measurement results for each case with FPA/UPA in the PDAC 36–60 M group.