Temporal progression of pancreatic cancer computed tomography findings until diagnosis: A large-scale multicenter study

Gonda, Masanori ; Masuda, Atsuhiro ; Kobayashi, Takashi ; Iemoto, Takao ; Kakuyama, Saori ; Ezaki, Takeshi ; Ikegawa, Takuya ; Hirata, Yuichi ⋯

(Citation)
United European Gastroenterology Journal,12(6):761-771

(Issue Date)
2024-07

(Resource Type)
journal article

(Version)
Version of Record

(URL)
https://hdl.handle.net/20.500.14094/0100489428

Received: 16 November 2023 | Accepted: 13 February 2024

DOI: 10.1002/ueg2.12557

ORIGINAL ARTICLE

UNITED EUROPEAN GASTROENTEROLOGY ueg journal WILEY

Temporal progression of pancreatic cancer computed tomography findings until diagnosis: A large-scale multicenter study

Masanori Gonda[1] | Atsuhiro Masuda[1] | Takashi Kobayashi[1] | Takao Iemoto[2] | Saori Kakuyama[3] | Takeshi Ezaki[4] | Takuya Ikegawa[5] | Yuichi Hirata[6] | Hidetaka Tsumura[7] | Kyohei Ogisu[8] | Ryota Nakano[1,9] | Seiji Fujigaki[10] | Takashi Nakagawa[11] | Megumi Takagi[12] | Kodai Yamanaka[13] | Yu Sato[14] | Koichi Fujita[15] | Keisuke Furumatsu[16] | Takao Kato[17] | Arata Sakai[1] | Hideyuki Shiomi[1,9] | Tsuyoshi Sanuki[10] | Yoshifumi Arisaka[8] | Yoshihiro Okabe[6] | Hirochika Toyama[18] | Keitaro Sofue[19] | Yuzo Kodama[1]

[1]Division of Gastroenterology, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Hyogo, Japan

[2]Department of Gastroenterology, Kitaharima Medical Center, Ono, Hyogo, Japan

[3]Department of Gastroenterology, Takatsuki General Hospital, Takatsuki, Osaka, Japan

[4]Department of Gastroenterology, National Hospital Organization Kobe Medical Center, Kobe, Hyogo, Japan

[5]Department of Gastroenterology, Japanese Red Cross Kobe Hospital, Kobe, Hyogo, Japan

[6]Department of Gastroenterology, Kakogawa Central City Hospital, Kakogawa, Hyogo, Japan

[7]Department of Gastroenterology, Hyogo Cancer Center, Akashi, Hyogo, Japan

[8]Department of Gastroenterology, Nippon Life Hospital, Osaka, Osaka, Japan

[9]Division of Gastroenterology and Hepatobiliary and Pancreatic Diseases, Department of Internal Medicine, Hyogo Medical University, Nishinomiya, Hyogo, Japan

[10]Department of Gastroenterology, Hyogo Prefectural Harima-Himeji General Medical Center, Himeji, Hyogo, Japan

[11]Department of Gastroenterology, Chibune General Hospital, Osaka, Osaka, Japan

[12]Department of Gastroenterology, Osaka Saiseikai Nakatsu Hospital, Osaka, Osaka, Japan

[13]Department of Gastroenterology, Konan Medical Center, Kobe, Hyogo, Japan

[14]Department of Internal Medicine, Hyogo Prefectural Tamba Medical Center, Tamba, Hyogo, Japan

[15]Department of Gastroenterology, Yodogawa Christian Hospital, Osaka, Osaka, Japan

[16]Department of Gastroenterology, Akashi Medical Association Akashi Medical Center, Akashi, Hyogo, Japan

[17]Department of Gastroenterology, Hyogo Prefectural Awaji Medical Center, Sumoto, Hyogo, Japan

[18]Department of Hepato-Biliary-Pancreatic Surgery, Kobe University Graduate School of Medicine, Kobe, Hyogo, Japan

[19]Department of Radiology, Kobe University Graduate School of Medicine and Kobe University Hospital, Kobe, Hyogo, Japan

Correspondence

Atsuhiro Masuda, Division of Gastroenterology, Department of Internal Medicine, Kobe University Graduate School of

Abstract

Background: Focal parenchymal atrophy and main pancreatic duct (MPD) dilatation have been identified as early signs of pancreatic ductal adenocarcinoma. However,

Masanori Gonda, Atsuhiro Masuda and Takashi Kobayashi contributed equaly to this work.

Medicine, 7-5-2 Kusunoki-cho, Chuo-ku, Kobe, Hyogo 650-0017, Japan.
Email: atmasuda@med.kobe-u.ac.jp

Funding information
Pancreas Research Foundation of Japan; Japan Society for the Promotion of Science, Grant/Award Numbers: 19H03698, 19K08444, 22H03058

limited evidence exists regarding their temporal progression due to previous study limitations with restricted case numbers.

Objective: To ascertain a more precise frequency assessment of suspicious pancreatic ductal adenocarcinoma findings as well as delineate the temporal progression of them.

Methods: A multicenter retrospective study was conducted on patients diagnosed with pancreatic ductal adenocarcinoma between 2015 and 2021. We included patients who had undergone at least one computed tomography (CT) scan ≥6 months before diagnosing pancreatic ductal adenocarcinoma. The temporal progression of suspicious pancreatic ductal adenocarcinoma findings on CT was investigated.

Results: Out of 1832 patients diagnosed with pancreatic ductal adenocarcinoma, 320 had a previous CT before their diagnosis. Suspicious pancreatic ductal adenocarcinoma findings were detected in 153 cases (47.8%), with focal parenchymal atrophy (26.6%) being the most common followed by MPD dilatation (11.3%). Focal parenchymal atrophy was the earliest detectable sign among all suspicious findings and became visible on average 2.7 years before diagnosis, and the next most common, MPD dilatation, 1.1 years before diagnosis. Other findings, such as retention cysts, were less frequent and appeared around 1 year before diagnosis. Focal parenchymal atrophy followed by MPD dilatation was observed in 10 patients but not in reverse order. Focal parenchymal atrophy was more frequently detected in the pancreatic body/tail. No significant relationship was found between the pathological pancreatic ductal adenocarcinoma differentiation or tumor stage and the time course of the CT findings. All cases of focal parenchymal atrophy progressed just prior to diagnosis, and the atrophic area was occupied by tumor at diagnosis. Main pancreatic duct dilatation continued to progress until diagnosis.

Conclusion: This large-scale study revealed that the temporal progression of focal parenchymal atrophy is the earliest detectable sign indicating pancreatic ductal adenocarcinoma. These results provide crucial insights for early pancreatic ductal adenocarcinoma detection.

KEYWORDS
computed tomography, early diagnosis, focal parenchymal atrophy, main pancreatic duct dilatation, pancreatic cancer, pancreatic ductal adenocarcinoma, pre-diagnostic imaging, retention cysts, temporal progression

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal cancers with over 80% of PDAC diagnosed at an advanced stage and characterized by massive invasion or distant metastasis. Therefore, early PDAC detection is essential to improve prognosis. However, PDAC screening for the general population has yet to be established. Despite improvements in diagnostic imaging accuracy, including CT, magnetic resonance cholangiopancreatography (MRCP), and endoscopy, the 5-year PDAC survival rate remains less than 10%.[1,2] The primary reason is the lack of a clear understanding of early PDAC imaging features and their progression over time.

Recently, focal pancreatic parenchymal atrophy and MPD dilatation on CT have been reported as early PDAC signs, including high-grade pancreatic intraepithelial neoplasm (PanIN).[3] Some reports mention that focal pancreatic parenchymal atrophy is more frequently observed in pre-diagnostic CT images of PDAC patients than in controls.[4–7] However, due to study limitations, including small sample sizes and lack of methodological objectivity, PDAC CT findings found at all stages have not been fully elucidated. Notably, the temporal progression of various suspicious PDAC CT findings has not been sufficiently investigated yet.

Therefore, we conducted a comprehensive multicenter retrospective study involving a substantial cohort of over 300 patients

diagnosed with various PDAC stages, including pre-diagnostic CT scans. The primary outcome of this study was to ascertain a more precise frequency assessment of relevant findings as well as delineate the temporal progression and extent of PDAC radiological signs.

Key summary

Summarize the established knowledge on this subject

- Pancreatic ductal adenocarcinoma (PDAC) has one of the poorest prognoses of all cancers, but diagnosis at an early stage can improve the prognosis.
- On imaging, focal parenchymal atrophy and main pancreatic duct (MPD) dilatation without mass are signs of early PDAC.
- The frequency and temporal progression of Computed Tomography (CT) findings prior to PDAC diagnosis in all stages have not yet been fully investigated.

What are the significant and/or new findings of this study?

- This study is the largest-scale study on the pre-diagnostic images of PDAC and revealed that 47.8% had findings suspicious for PDAC on previous CT scans prior to diagnosis.
- Focal parenchymal atrophy and MPD dilatation were visible on CT 2.7 years and 1.1 years before diagnosis on average, and Focal parenchymal atrophy was more frequently detected in the pancreatic body/tail.
- There was no significant relationship between pathologic PDAC differentiation or tumor stage and the time course of CT findings suspicious for PDAC.
- Focal parenchymal atrophy typically precedes MPD dilatation, but not in reverse order, and the two findings progressed until the diagnosis of PDAC.

MATERIALS AND METHODS

Study design and patients

This retrospective, multicenter, observational study enrolled patients with a confirmed histopathological PDAC diagnosis between April 2015 and March 2022 at 17 facilities in the KPEC study group. This study was approved by the Institutional Review Board (IRB) of each facility (IRB number B200075). Patients with pancreatic cancer other than ductal adenocarcinoma and those with recurrent PDAC were excluded from the study. Patients who had undergone plain or contrast-enhanced abdominal CT ≥ 6 months before diagnosing PDAC were selected for further evaluation. We reviewed the data from the clinical records at the time of PDAC diagnosis, including age, sex, family history of PDAC, tumor size and location, histopathological type, as well as the *Union* for International Cancer Control (UICC) TNM classification (eighth edition).

Assessment of CT findings

The number of previous abdominal CT examinations, the timing, and their indications were reviewed. We investigated whether suspicious PDAC findings were present in the pre-diagnostic CT images. Suspicious PDAC findings were classified into six categories: focal parenchymal atrophy, MPD dilatation, pancreatic mass or swelling, retention cyst, pancreatic inflammation, and MPD stricture. On the CT images, a pancreatic mass or swelling was defined as pancreatic parenchyma enlargement beyond the line connecting the head and tail side margins of the lesion. Focal parenchymal atrophy on the CT image was characterized by pancreatic parenchymal narrowing of at least half below the line connecting the head and tail side margins of the lesion. Focal parenchymal atrophy severity was documented as the radial diameter ratio of the pancreas at the atrophic site to the adjacent normal site. MPD dilatation was defined as an MPD with $a > 3$ mm maximal diameter.[5] The diameter of the dilated pancreatic duct was also measured to evaluate the degree and change in MPD dilatation over time. MPD stricture was defined as the localized invisibility of the pancreatic duct without MPD dilatation. In this study, retention cysts were defined as cystic lesions besides the MPD stricture or mass lesion. Pancreatic inflammation was characterized by focal or diffuse parenchymal enlargement with surrounding fat stranding. Based on tumor location, assessments were performed separately for head and body/tail lesions. All CT images were independently evaluated by one radiologist with 21 years of experience who specialized in pancreatic imaging and two gastroenterologists with 23 as well as 11 years of experience. Assessors were aware of patients diagnosed with PDAC. When their judgment differed, a final decision was made through discussion until a consensus was found.

Statistical analysis

The chi-square test (or Fisher's exact test, if appropriate) was performed to assess the associations between categorical data. Numerical data were compared using Student's *t*-test or analysis of variance assuming equal variance. Agreement among the evaluators was measured using Fleiss' kappa values. In all analyses, two-sided *p* values were calculated and values less than 0.05 were considered statistically significant. All statistical analyses were conducted using the SPSS software v29.0.1.0 (SPSS Inc.).

RESULTS

Patient characteristics according to suspicious PDAC findings

Of the 1832 registered patients diagnosed with PDAC at 17 facilities, 320 (17.5%) patients with CT imaging ≥6 months prior to PDAC

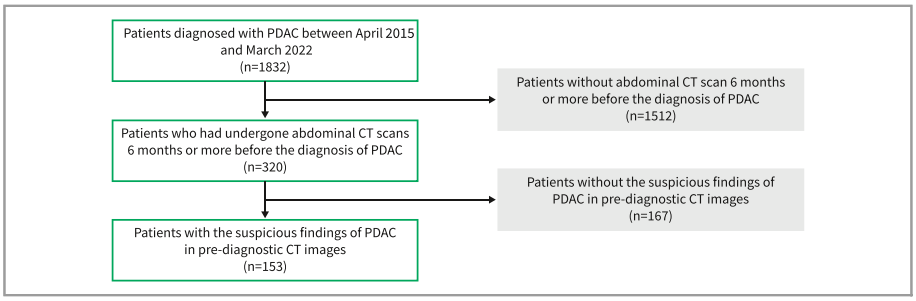

FIGURE 1 Subject flow diagram. CT, computed tomography; PDAC, pancreatic ductal adenocarcinoma.

diagnosis were selected for further assessment (Figure 1). The indications for past CT were postoperative surveillance for other organ cancers in 86 cases, scrutiny of diseases outside the pancreas in 86 cases, abdominal symptom scrutiny in 41 cases, screening in 38 cases, pancreatic disease scrutiny in 28 cases, diabetes scrutiny in 17 cases, high tumor marker-level scrutiny in five cases, and unknown in 19 cases. Postoperative surveillance of other organ diseases included 21 cases of colorectal cancer, 13 of gastric cancer, nine involving the cardiovascular system, eight of esophageal cancer, six of lung cancer, five of breast cancer, five of renal cancer, four of prostate cancer, three of uterine cancer, two of bile duct cancer, one each of duodenal cancer, liver cancer, oral cancer, larynx cancer, skin cancer, ovarian cancer and thyroid cancer, and three unknown cases. The clinical characteristics of the 320 patients included in this study are demonstrated in Table 1.

The median age of the selected 320 patients was 73.7 (range 29–96) years, and 189 (59.1%) were male. The median tumor size was 26.2 mm (range 0–75 mm). There were 7, 83, 71, 6, 24, 59, and 70 patients with clinical stage 0, Ia, Ib, IIa, IIb, III, and IV, respectively. The tumors were distributed as follows: 164 (51.3%) in the pancreatic head and 156 (48.7%) in the body/tail. Regarding histopathology, 143 (44.7%) cases were identified as well or moderately differentiated adenocarcinoma, 43 (13.4%) were poorly differentiated adenocarcinoma, and 134 (41.9%) were unclassified cases. In the unclassified cases, determining differentiation was impossible with endoscopic ultrasound (EUS)-guided fine needle aspiration/biopsy or surgical information.

Suspicious PDAC findings on previous CT scans were observed in 153 (47.8%) of the 320 patients. Group characteristics with and without suspicious CT findings were compared. Between the two groups, there were no significant differences in age, sex, family history of PDAC, tumor size, clinical stage, *T* factor, or differentiation. However, PDAC in the pancreatic body/tail was significantly more common in the group with suspicious CT findings. Additionally, we investigated whether there were any CT imaging condition biases between the two groups. The total number of pre-diagnostic CT scans for the 320 patients was 844, with 2.6 median scans per patient. Of these, 451 CT scans were obtained using contrast enhancement. Thin-slice CT scans were performed 64 times. There were no significant differences between the two groups in the number, contrast enhancement, and slice thickness of CT scans.

Among the 153 patients presenting with pancreatic abnormalities on previous CT scans, 114 patients went unnoticed by radiologists during the initial examinations. Conversely, 39 patients were initially flagged by radiologists for abnormal pancreatic findings on the prior CT scans. This subset included 18 patients with MPD dilatation, seven patients with focal parenchymal atrophy in the pancreas, five patients with swelling in the pancreatic region, five patients with pancreatic cysts, and four patients with pancreatic inflammation. Despite subsequent evaluations, including EUS and MRCP in 9 patients and close follow-up for 30 patients, none of these individuals received a PDAC diagnosis during those assessments.

Time course of suspicious PDAC CT findings on pre-diagnostic CT

We examined the frequency of suspicious CT findings over different periods based on the diagnosis time (Table 2).

Patients were grouped into seven categories based on the time between the CT scan and diagnosis: ≥0.5 to <1 year, ≥1 to <2 years, ≥2 to <3 years, ≥3 to <5 years, ≥5 to <7 years, ≥7 to <10 years, and >10 years. For each category, the scan was counted once, and the most recent scan within that specific period was used for assessment. Overall, 585 CT imaging sessions were included in this assessment: 302 for pancreatic head tumors and 283 for body/tail tumors. Suspicious PDAC findings were observed in 66/107 CT images performed ≥0.5 to <1 year before diagnosis (61.7%). There were no suspicious pancreatic findings in CT images for more than 10 years before diagnosis. Focal parenchymal atrophy was the most common finding observed in CTs from any period, especially for those more than 3 years before diagnosis. Other findings were observed in scans from the category that had scans 2 years prior to their diagnosis. Subsequently, these results were compared with PDAC location (Supplemental Table S1). Computed tomography findings suspicious of PDAC in pancreatic head cases were 29/58 (50.0%) and 19/71 (26.8%) for scans performed ≥0.5 to <1 year, and ≥1 to <2 years prior, respectively. Suspicious scan findings for patients with PDAC in the body/tail were found in 37/49 (75.5%) and 52/84 (61.9%) scans taken ≥0.5 to <1 year and ≥1 to <2 years prior, respectively. In all groups, suspicious CT findings of every category were observed more

TABLE 1 Clinical characteristics according to CT findings suspicious of PDAC.

Characteristics	All patients (*N* = 320)		Patients with suspicious findings (*N* = 153)		Patients without suspicious findings (*N* = 167)		*p* value
Age (years), median (range)	73.7	(29–96)	72.8	(29–96)	74.6	(30–93)	0.10
Sex							0.20
Male	189	(59.1%)	96	(62.7%)	93	(55.7%)	
Female	131	(40.9%)	57	(37.3%)	74	(44.3%)	
Tumor size (mm), median (range)	26.2	(0–75)	27.5	(0–75)	24.9	(0–75)	0.07
Clinical stage[a]							0.08
0	7	(2.2%)	4	(2.6%)	3	(1.8%)	
IA	83	(25.9%)	31	(20.3%)	52	(31.0%)	
IB	71	(22.2%)	41	(26.7%)	30	(18.0%)	
IIA	6	(1.9%)	3	(2.0%)	3	(1.8%)	
IIB	24	(7.5%)	7	(4.6%)	17	(10.2%)	
III	59	(18.4%)	29	(19.0%)	30	(18.0%)	
IV	70	(21.9%)	38	(24.8%)	32	(19.2%)	
T factor							0.32
Tis	7	(2.2%)	4	(2.6%)	3	(1.8%)	
T1a	0	(0%)	0	(0%)	0	(0%)	
T1b	15	(4.7%)	8	(5.2%)	7	(4.2%)	
T1c	84	(26.3%)	31	(20.3%)	53	(31.7%)	
T2	124	(38.7%)	65	(42.5%)	59	(35.3%)	
T3	24	(7.5%)	13	(8.5%)	11	(6.6%)	
T4	66	(20.6%)	32	(20.9%)	34	(20.4%)	
Tumor location							<0.001
Head	164	(51.3%)	51	(33.3%)	113	(67.7%)	
Body/tail	156	(48.7%)	102	(66.7%)	54	(32.3%)	
Tumor differentiation							0.54
Well	68	(21.3%)	31	(20.3%)	37	(22.2%)	
Moderate	75	(23.4%)	32	(20.9%)	43	(25.7%)	
Poorly	43	(13.4%)	24	(15.7%)	19	(11.4%)	
Unclassified[b]	134	(41.9%)	66	(43.1%)	68	(40.7%)	
Number of pre-diagnostic CT scans	844		434		410		0.20
Median number of total individual CT scans	2.64	(1–16)	2.84	(1–14)	2.46	(1–16)	0.20
CT enhancement							0.99
Plain	393	(46.6%)	202	(46.5%)	191	(46.6%)	
Contrast-enhanced	451	(53.4%)	232	(53.5%)	219	(53.4%)	
CT slice							0.98
Thin slice (<3 mm)	64	(7.6%)	33	(7.6%)	31	(7.6%)	
Thick slice (≥3 mm)	780	(92.4%)	401	(92.4%)	379	(92.4%)	

Note: (%) indicates the case percentage with specific clinical features according to the suspicious PDAC findings on the pre-diagnostic CT scan.

Abbreviations: N/A, not applicable; PDAC, Pancreatic ductal adenocarcinoma.

[a]Clinical stage is diagnosed based on the TNM Classification of Malignant Tumors, eighth edition.

[b]Unclassified cases are those for which differentiation diagnosis was not possible with EUS-FNA or insufficient information in surgical cases.

frequently in PDAC affecting the body/tail than in the head, especially focal parenchymal atrophy.

The frequency and time of suspicious CT finding appearance were analyzed based on the patients (Table 3). Of these, 153 (47.8%) exhibited suspicious PDAC findings on previous CT scans, including focal parenchymal atrophy in 85 cases (26.6%), MPD dilatation in 36 cases (11.3%), mass or swelling in 22 cases (6.9%), retention cysts in 16 cases (5.0%), pancreatic inflammation in 12 cases (3.8%), and MPD stricture in six cases (1.9%); furthermore, the mean appearance time of each finding was 2.7 years (0.5–8.9), 1.1 years (0.5–2.2), 0.8 years (0.5–2.1), 0.9 years (0.5–2.4), 0.9 years (0.5–1.9), and 1.0 years (0.6–2.3) prior to diagnosis, respectively. The inter-evaluator reliability was moderate to almost perfect by Fleiss' kappa. The respective Fleiss' kappa values for focal parenchymal atrophy, MPD dilatation, mass or swelling, retention cysts, pancreatic inflammation, and MPD stricture were 0.886 (95%. CI 0.726–1.046), 0.837 (95%. CI 0.677–0.997), 0.850 (95%. CI 0.690–1.010), 0.702 (95%. CI 0.542–0.862), 0.630 (95%. CI 0.470–0.790) and 0.793 (95%. CI 0.633–0.953).

Focal parenchymal atrophy was the most frequent and earliest finding of suspected PDAC on pre-diagnostic CT. In cases where focal parenchymal atrophy and MPD dilatation appeared, MPD dilatation always overlapped with focal parenchymal atrophy (Figure 2); focal parenchymal atrophy appeared first, followed by MPD dilatation or both simultaneously. However, MPD dilatation did not appear before focal parenchymal atrophy. Patients with PDAC of the head had a significantly lower focal parenchymal atrophy frequency than those with PDAC of the body/tail (10.4% vs. 43.6%, $p < 0.001$). Furthermore, the appearance time for each suspicious finding before diagnosis tended to be shorter in patients with PDAC affecting the head than the body/tail.

Additionally, we examined the relationship between PDAC differentiation and the time course of the CT findings (Supplemental Table S2). Suspicious PDAC findings obtained from CT images were

TABLE 2 Incidence of pre-diagnostic CT findings suspicious of PDAC.

	Time before PDAC diagnosis (year)													
	≥10		<10 to ≥7		<7 to ≥5		<5 to ≥3		<3 to ≥2		<2 to ≥1		<1 to ≥0.5	
No. of CT scans[a] of all cases ($N = 585$)	6		19		44		132		122		155		107	
Any suspicious findings of PDAC	0	(0%)	2	(10.5%)	3	(6.8%)	27	(20.5%)	37	(30.3%)	71	(45.8%)	66	(61.7%)
Focal parenchymal atrophy	0	(0%)	2	(10.5%)	3	(6.8%)	27	(20.5%)	32	(26.2%)	46	(29.7%)	20	(18.7%)
Main pancreatic duct dilatation	0	(0%)	0	(0%)	0	(0%)	0	(0%)	2	(1.6%)	20	(12.9%)	18	(16.8%)
Mass or swelling	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(0.8%)	5	(3.2%)	18	(16.8%)
Retention cyst	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(0.8%)	4	(2.6%)	13	(12.1%)
Pancreatic inflammation	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	4	(2.6%)	8	(7.5%)
Main pancreatic duct stricture	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(0.8%)	0	(0%)	5	(4.7%)

Abbreviation: PDAC, Pancreatic ductal adenocarcinoma.

[a]Where the patient underwent CT more than once during each period, the most recent CT was used for assessment.

TABLE 3 Frequency and timing of CT findings suspicious of PDAC according to the tumor location.

	No. of patients (frequency of CT findings)							Average time of appearance of suspicious findings before diagnosis; years (range)						
	All patients ($N = 320$)		PDAC in pancreatic head ($N = 164$)		PDAC in pancreatic body/tail ($N = 156$)		p value	All patients ($N = 320$)		PDAC in pancreatic head ($N = 164$)		PDAC in pancreatic body/tail ($N = 156$)		p value
Any suspicious findings of PDAC	153	(47.8%)	51	(31.1%)	102	(65.4%)	<0.001	1.9	(0.5–8.9)	1.4	(0.5–4.6)	2.2	(0.5–8.9)	<0.001
Focal parenchymal atrophy	85	(26.6%)	17	(10.4%)	68	(43.6%)	<0.001	2.7	(0.5–8.9)	2.3	(0.5–4.6)	2.7	(0.5–8.9)	0.27
Main pancreatic duct dilatation	36	(11.3%)	17	(10.4%)	19	(12.2%)	0.61	1.1	(0.5–2.2)	1.0	(0.5–2.2)	1.2	(0.5–2.2)	0.38
Mass or swelling	22	(6.9%)	7	(4.3%)	15	(9.6%)	0.06	0.8	(0.5–2.1)	0.7	(0.5–1.2)	0.9	(0.5–2.1)	0.48
Retention cyst	16	(5.0%)	5	(3.0%)	11	(7.1%)	0.10	0.9	(0.5–2.4)	0.8	(0.5–1.0)	1.0	(0.5–2.4)	0.37
Pancreatic inflammation	12	(3.8%)	4	(2.4%)	8	(5.1%)	0.21	0.9	(0.5–1.9)	0.9	(0.5–1.9)	0.9	(0.5–1.5)	0.91
Main pancreatic duct stricture	6	(1.9%)	4	(2.4%)	2	(1.3%)	0.45	1.0	(0.6–2.3)	1.1	(0.6–2.3)	0.8	(0.8)	0.61

Abbreviation: PDAC, Pancreatic ductal adenocarcinoma.

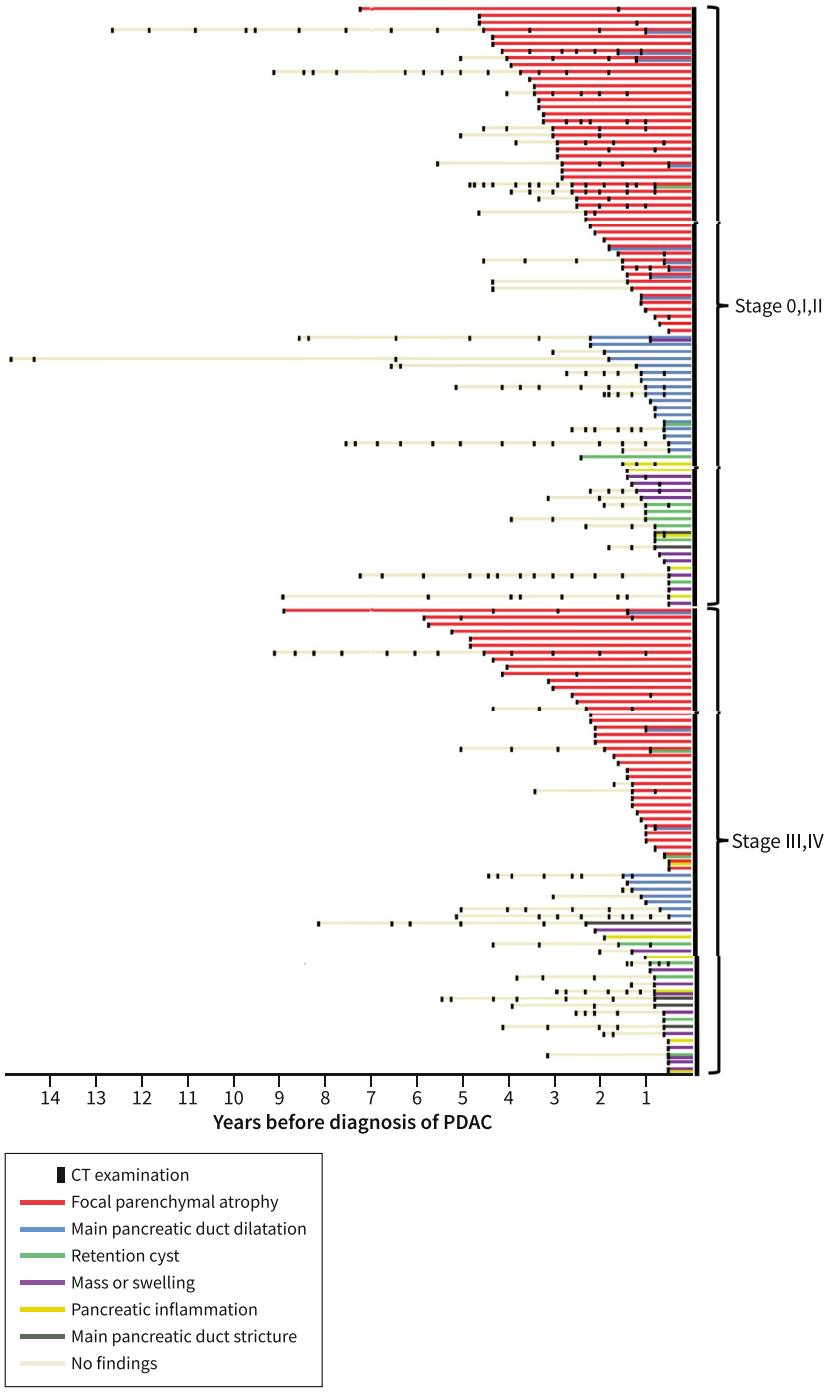

FIGURE 2 Time course of suspicious computed tomography (CT) PDAC findings in patients. Black points indicate the timing of the CT examination. Each bar indicates the presence of CT findings. Bars in contact indicate comorbid findings in the same patient. PDAC, pancreatic ductal adenocarcinoma.

observed in 44.1% well-to moderately differentiated PDAC cases and 55.8% poorly differentiated cases. No significant relationship was observed between the pathological PDAC differentiation and the frequency or time of appearance of suspicious CT findings. Additionally, we examined the relationship between the PDAC stage at diagnosis and suspicious CT findings (Supplemental Table S3). There were no significant differences in the frequency of suspicious CT findings between patients with PDAC diagnosed at stage 0/I and those diagnosed at stage II/III/IV. The time course of suspicious CT findings in each patient is demonstrated in Figure 2. No significant difference in the appearance time of the findings was observed between patients diagnosed with PDAC stage 0/I or stage II/III/IV.

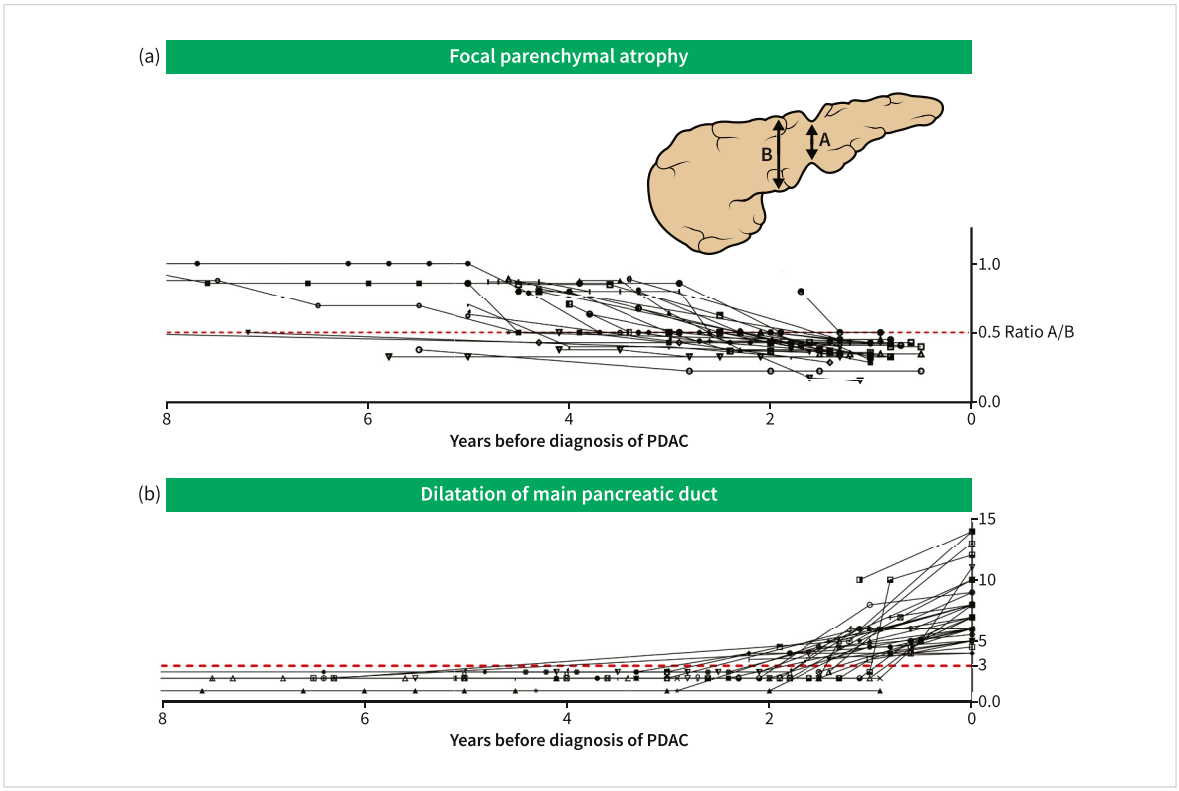

FIGURE 3 The progression of suspicious computed tomography (CT) PDAC findings. (a) Focal parenchymal atrophy (b) dilatation of main pancreatic duct. Each line indicates a patient. Each point indicates the timing of the CT examination. The red dashed lines indicate the cut-off values defined in this study. The degree of focal parenchymal atrophy was evaluated as the ratio of the radial pancreas diameter at the atrophic site to the adjacent downstream normal site. PDAC, pancreatic ductal adenocarcinoma.

Progression of focal parenchymal atrophy and MPD dilatation

We assessed focal parenchymal atrophy changes during the observation period for each patient. The proportion of pancreatic parenchymal narrowing under the line connecting the head and tail side margins of the lesion decreased over time in almost all patients with focal parenchymal atrophy for whom two or more CTs were available (Figure 3a). Similarly, MPD dilatation progressed over time in all patients (Figure 3b). However, at the time of diagnosis, focal parenchymal atrophy was no longer present in all cases; the developing PDAC mass occupied the atrophic area (Figure 3a).

Subgroup study for patients with symptom, pancreatic diseases and family history

In addition to our primary analysis, we conducted a subgroup study focusing on patients with symptoms, those undergoing scrutiny or follow-up for pancreatic disease, and those with a family history of PDAC.

Among patients presenting with abdominal symptoms (n = 41), abnormal imaging findings suggestive of PDAC revealed a significant association with pancreatitis when compared to cases without symptoms [9.8% (4/41) versus 2.9% (8/279), p = 0.03].

In the cohort subjected to close examination or follow-up for pancreatic disease (n = 28), 16 patients had pancreatic cysts, eight were diagnosed with chronic pancreatitis, and four with post-acute pancreatitis. However, no significant difference was observed in the occurrence of these findings between patients with or without pancreatic disease [57.1% (16/28) versus 46.9% (137/292), p = 0.30]. Within the subset of eight patients with chronic pancreatitis, focal parenchymal atrophy was observed in 25.0% (2/8) of cases, while MPD dilatation was noted in another 25.0% (2/8) of patients. Moreover, there were no significant differences in the prevalence of these abnormal findings between patients with and without chronic pancreatitis [focal parenchymal atrophy, 25.0% (2/8) versus 26.6% (83/312), p = 0.92; MPD dilatation, 25.0% (2/8) versus 10.9% (34/312), p = 0.21].

Based on family history of PDAC, excluding 102 patients without the data, those with a family history (n = 9) tended to exhibit a higher prevalence of imaging findings suspicious for pancreatic cancer on previous images compared to patients without a family history [77.8% (7/9) versus 49.3% (103/209), p = 0.09]. Specific findings in cases with a family history included four patients with focal parenchymal atrophy and one patient each with MPD dilatation, MPD stenosis, and pancreatic inflammation. However, no significant differences were identified in the prevalence of each of these abnormal findings between patients with and without a family history.

Typical case presentation

An 81-year-old man was diagnosed with PDAC (cStage III) (Figure 4). He had undergone resection for colon cancer 10 years earlier and contrast-enhanced CT imaging every year since then. Computed tomography scans obtained 8 and 5 years before his PDAC diagnosis demonstrated no specific findings. A CT scan taken 3 years prior demonstrated focal parenchymal atrophy in the pancreatic body, while a scan done 2 years ago revealed its progression. Furthermore, a scan taken a year before exhibited further progression and the caudal MPD. Computed tomography imaging at PDAC diagnosis revealed a pancreatic body mass and progressive dilatation (7 mm) of the caudal MPD.

DISCUSSION

In this multicenter study of pre-diagnostic CT images from over 300 PDAC cases, focal parenchymal atrophy and MPD dilatation were observed in 26.6% and 14.4% patients, respectively. The focal parenchymal atrophy incidence was reportedly 10.9%–37.9%, appearing 1–5 years before PDAC diagnosis.[5,6,8–10] Our study revealed similar supporting results to those of previous studies. Several studies have consistently highlighted a higher incidence of focal parenchymal atrophy in carcinoma in situ or small/early PDAC (41.8%–70%) compared to benign lesions (3.9%–15.8%).[3,4,6,11] These observed prevalence rates strongly suggest an intimate association between focal parenchymal atrophy and the very early stages of PDAC.

In contrast, the characteristics and clinical significance of focal pancreatic atrophy in benign disease are unclear. As an additional relatively small control group analysis, we reviewed the CT findings of 30 consecutive patients with chronic pancreatitis and autoimmune pancreatitis at our hospital between April 2022 and March 2023. Among the patients with chronic pancreatitis, 96.7% (29/30) exhibited diffuse pancreatic atrophy, while 3.3% (1/30) exhibited focal pancreatic atrophy in the body of the pancreas. Notably, there was no significant progression of focal pancreatic atrophy observed in chronic pancreatitis patients. The atrophy ratio and the proportion of pancreatic parenchymal narrowing under the line connecting the head and tail side margins of the lesion changed slightly from 0.44 to 0.42 for 3 years in this patient. Among the patients with autoimmune pancreatitis, pancreatic atrophy was identified in 90% (27/30), and all instances of atrophy were observed in diffuse pancreatic parenchyma. Thus, the morphology of the atrophy and whether it is progressive or not are important factors in distinguishing pancreatic atrophy with malignancy from that with a benign lesion.

The causal relationship between focal pancreatic atrophy and PDAC remains elusive. Histopathologically, some studies have indicated that focal atrophy may reflect fat replacement, inflammatory cell infiltration, and fibrosis around high-grade PanINs.[12–15] However, the relationship between fat replacement, inflammation, fibrosis, and focal parenchymal atrophy with early carcinogenesis of PDAC has not been thoroughly investigated. Interestingly, focal pancreatic atrophy often occurs in the body or tail rather than the head of the pancreas. Possible explanations for this phenomenon are that the pancreatic head is anatomically thicker than the body and tail, making focal parenchymal atrophy difficult to detect even if present, and that

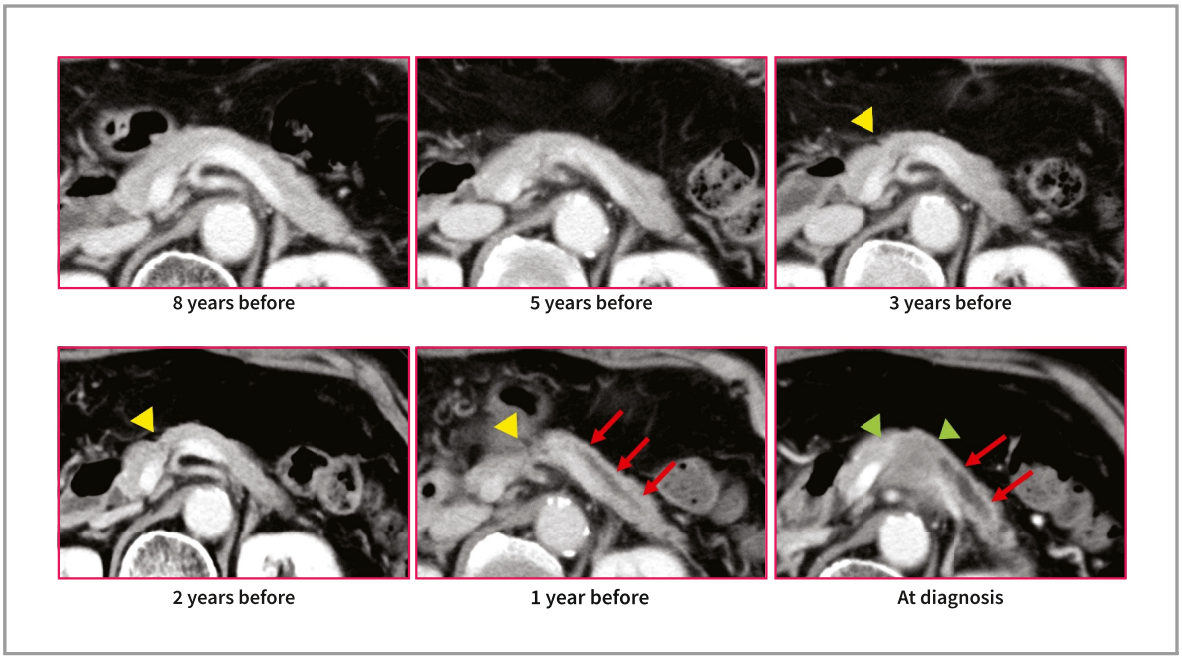

FIGURE 4 Case presentation. The yellow arrowhead indicates focal parenchymal atrophy. The red arrow indicates main pancreatic duct dilatation. The green arrowhead indicates the mass.

the appearance of the findings may differ because the genetic and molecular characteristics of the head and body/tail are different in different parts of the pancreas.[6]

Similar to previous studies, focal parenchymal atrophy in our study often appeared 3 years before diagnosing PDAC and MPD dilatation commonly appeared 1 year before diagnosis. Focal parenchymal atrophy, followed by upstream MPD dilatation, was confirmed in 10 patients. Notably, there were no cases in the reverse order. These results indicate that focal parenchymal atrophy is the earliest PDAC CT finding and MPD dilatation is a secondary change due to the unclear microscopic stenosis of the pancreatic duct at the focal atrophic site. Additionally, all focal parenchymal atrophy and MPD dilatation cases progressed during the observation period. This phenomenon suggests an irreversible and progressive nature of the disease, which is consistent with malignancies, including PDAC. Furthermore, the fact that focal parenchymal atrophy appears significantly earlier than MPD dilatation suggests that its cause may not be pancreatic duct obstruction. Detecting the emergence or progression of focal parenchymal atrophy could enable the early diagnosis of high-grade PanIN or PDAC when curative treatment options are more viable.

Consequently, conducting a subgroup study focused on patients with symptoms and risk factors is important for elucidating key imaging findings that clinicians should prioritize in surveillance of high-risk individuals. However, this retrospective analysis, utilizing historical images, did not unveil specific imaging findings in pancreatic cancer surveillance for individuals with risk factors.

In this study, almost half of the patients seemed to have a chance for an earlier diagnosis. However, endoscopic retrograde cholangiopancreatography (ERCP) is considered to be highly invasive for patients only with focal pancreatic atrophy. Therefore, based on our results, we suggest consultation with a gastroenterologist and follow-up with imaging examination every 3–6 months. If additional findings such as the progression of atrophy or expansion of the MPD are observed, PDAC should be suspected and a specific examination must be suggested. Strictly, the capability of focal parenchymal atrophy to predict future PDAC diagnoses remains an open question. To address these critical questions, large-scale and long-term prospective studies are required.

This retrospective study had several limitations. First, all the selected 320 patients underwent a CT scan for clinical indications unrelated to PDAC; their clinical backgrounds might have affected the results. Second, the interval and number of previous CT examinations were not constant. In some cases, we could not accurately define the point of appearance of suspicious findings. Third, there was no regulation of choice for contrast-enhanced CT scans. Recently, hypoattenuation findings on contrast-enhanced CT have been reported as early findings of pancreatic cancer.[16] However, because contrast-enhanced or not was clinically selected, it is impossible to examine the usefulness of hypoattenuation findings in this study. Fourth, radiographic image interpretation may have been more careful and thorough than in normal clinical situations, making a positive judgment more likely.

CONCLUSION

In a large-scale study, suspicious PDAC findings on pre-diagnostic CT scans were confirmed in 47.8% of patients with PDAC. The most characteristic PDAC findings were progressive focal parenchymal atrophy approximately 2.7 years before the diagnosis, followed by progressive MPD dilatation approximately 1.1 years prior to diagnosis. Focal parenchymal atrophy is more likely to occur in the PDAC of the pancreatic body/tail than in the head. Although further studies are needed, these results might provide a deeper understanding of the oncogenesis and progressive mechanism of PDAC and indicate the possible use of CT scans in early PDAC detection.

AUTHOR CONTRIBUTIONS

Atsuhiro Masuda designed and supervised the study. Masanori Gonda, Atsuhiro Masuda, and Takashi Kobayashi wrote the manuscript. Masanori Gonda, Atsuhiro Masuda and Keitaro Sofue reviewed all CT findings in the study. Takao Iemoto, Saori Kakuyama, Takeshi Ezaki, Takuya Ikegawa, Yuichi Hirata, Hidetaka Tsumura, Kyohei Ogisu, Ryota Nakano, Seiji Fujigaki, Takashi Nakagawa, Megumi Takagi, Kodai Yamanaka, Tsuyoshi Sanuki, Koichi Fujita, Keisuke Furumatsu, and Takao Kato collected the data. Masanori Gonda, Atsuhiro Masuda, Takashi Kobayashi and Keitaro Sofue analyzed and interpreted the data. All authors critically revised this manuscript for important intellectual content and gave final approval of the version to be published.

ACKNOWLEDGMENTS

The authors would like to thank the following KPEC study group members for their support in this study: Shiei Yoshida, Department of Gastroenterology, National Hospital Organization Kobe Medical Center; Ikuya Miki, Department of Gastroenterology, Hyogo Cancer Center; Eiji Funatsu, Department of Gastroenterology, Chibune General Hospital; Arata Sakai, Takeshi Tanaka, Masahiro Tsujimae, Kohei Yamakawa, Shigeto Ashina, Shohei Abe, Shigeto Masuda, Hisahiro Uemura, Shinya Kohashi, Noriko Inomata, Kae Nagao, Noriyuki Harada, Mika Miki, Noriko Juri, and Yosuke Irie, Division of Gastroenterology, Department of Internal Medicine, Kobe University Graduate School of Medicine. KPEC (Kobe University Pancreatobiliary Endoscopic Club) study group included 17 facilities as follows: Kitaharima Medical Center, Takatsuki General Hospital, National Hospital Organization Kobe Medical Center, Japanese Red Cross Kobe Hospital, Kakogawa Central City Hospital, Hyogo Cancer Center, Nippon Life Hospital, Hyogo Medical University Hospital, Hyogo Prefectural Harima-Himeji General Medical Center, Chibune General Hospital, Osaka Saiseikai Nakatsu Hospital, Konan Medical Center, Hyogo Prefectural Tamba Medical Center, Yodogawa Christian Hospital, Akashi Medical Association, Akashi Medical Center, Hyogo Prefectural Awaji Medical Center, Shiso Municipal Hospital, and Kobe University Hospital. This work was supported by JSPS KAKENHI (Grants-in-Aid for Scientific Research), Grant No.19K08444 (Atsuhiro Masuda), Grant Nos.19H03698 and

22H03058 (Yuzo Kodama). This work was supported by the Pancreas Research Foundation of Japan (Atsuhiro Masuda).

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Supporting data for the findings of this study can be obtained upon reasonable request from the corresponding author. However, due to confidentiality reasons, the data cannot be made publicly available.

ETHICS APPROVAL

This study was approved by the Institutional Review Board (IRB) of each facility (IRB number B200075) and conducted in accordance with the Helsinki Declaration. The IRB waived the need for informed consent for patients in this retrospective study.

CONSENT FOR PUBLICATION

Not applicable.

ORCID

Atsuhiro Masuda https://orcid.org/0000-0002-2138-1207
Koichi Fujita https://orcid.org/0000-0002-0768-1801

REFERENCES

1. Vincent A, Herman J, Schulick R, Hruban RH, Goggins M. Pancreatic cancer. Lancet. 2011;378(9791):607–20. https://doi.org/10.1016/S0140-6736(10)62307-0
2. Rawla P, Sunkara T, Gaduputi V. Epidemiology of pancreatic cancer: global trends, etiology and risk factors. World J Oncol. 2019;10(1):10–27. https://doi.org/10.14740/wjon1166
3. Nakahodo J, Kikuyama M, Nojiri S, Chiba K, Yoshimoto K, Kamisawa T, et al. Focal parenchymal atrophy of pancreas: an important sign of underlying high-grade pancreatic intraepithelial neoplasia without invasive carcinoma, i.e., carcinoma in situ. Pancreatology. 2020;20(8):1689–97. https://doi.org/10.1016/j.pan.2020.09.020
4. Yamao K, Takenaka M, Ishikawa R, Okamoto A, Yamazaki T, Nakai A, et al. Partial pancreatic parenchymal atrophy is a new specific finding to diagnose small pancreatic cancer (≤10 mm) including carcinoma in situ: comparison with localized benign main pancreatic duct stenosis patients. Diagnostics. 2020;10(7):445. https://doi.org/10.3390/diagnostics10070445
5. Toshima F, Watanabe R, Inoue D, Yoneda N, Yamamoto T, Sasahira N, et al. CT abnormalities of the pancreas associated with the subsequent diagnosis of clinical stage I pancreatic ductal adenocarcinoma more than 1 year later: a case-control study. AJR Am J Roentgenol. 2021;217(6):1353–64. https://doi.org/10.2214/AJR.21.26014
6. Miura S, Takikawa T, Kikuta K, Hamada S, Kume K, Yoshida N, et al. Focal parenchymal atrophy of the pancreas is frequently observed on pre-diagnostic computed tomography in patients with pancreatic cancer: a case-control study. Diagnostics. 2021;11(9):1693. https://doi.org/10.3390/diagnostics11091693
7. Takaji R, Yamada Y, Shimada R, Matsumoto S, Daa T, Endo Y, et al. Retrospective evaluation of venous phase contrast-enhanced computed tomography images in patients who developed pancreatic adenocarcinomas after treatment for nonpancreatic primary cancer. BJR Open. 2021;3(1):20200069. https://doi.org/10.1259/bjro.20200069
8. Fukushima D, Nishino N, Hamada K, Horikawa Y, Shiwa Y, Nishida S, et al. Characteristic radiological features of retrospectively diagnosed pancreatic cancers. Pancreas. 2020;49(1):76–88. https://doi.org/10.1097/MPA.0000000000001456
9. Gonoi W, Hayashi TY, Okuma H, Akahane M, Nakai Y, Mizuno S, et al. Development of pancreatic cancer is predictable well in advance using contrast-enhanced CT: a case-cohort study. Eur Radiol. 2017;27(12):4941–50. https://doi.org/10.1007/s00330-017-4895-8
10. Nakahodo J, Kikuyama M, Fukumura Y, Horiguchi S.-I, Chiba K, Tabata H, et al. Focal pancreatic parenchyma atrophy is a harbinger of pancreatic cancer and a clue to the intraductal spreading subtype. Pancreatology. 2022;22(8):1148–58. https://doi.org/10.1016/j.pan.2022.10.003
11. Kanno A, Masamune A, Hanada K, Maguchi H, Shimizu Y, Ueki T, et al. Multicenter study of early pancreatic cancer in Japan. Pancreatology. 2018;18(1):61–7. https://doi.org/10.1016/j.pan.2017.11.007
12. Yokode M, Akita M, Fujikura K, Kim M.-J, Morinaga Y, Yoshikawa S, et al. High-grade PanIN presenting with localised stricture of the main pancreatic duct: a clinicopathological and molecular study of 10 cases suggests a clue for the early detection of pancreatic cancer. Histopathology. 2018;73(2):247–58. https://doi.org/10.1111/his.13629
13. Bachem MG, Schünemann M, Ramadani M, Siech M, Beger H, Buck A, et al. Pancreatic carcinoma cells induce fibrosis by stimulating proliferation and matrix synthesis of stellate cells. Gastroenterology. 2005;128(4):907–21. https://doi.org/10.1053/j.gastro.2004.12.036
14. Maehira H, Sugiura T, Kanemoto H, Okamura Y, Itoh T, Kuribara T, et al. A case of carcinoma in situ of the pancreas with a surrounding fibrotic region. Suizo. 2014;29(6):919–25. https://doi.org/10.2958/suizo.29.919
15. Satoh T, Kikuyama M, Kawaguchi S, Kanemoto H, Muro H, Hanada K. Acute pancreatitis-onset carcinoma in situ of the pancreas with focal fat replacement diagnosed using serial pancreatic-juice aspiration cytologic examination (SPACE). Clin J Gastroenterol. 2017;10(6):541–5. https://doi.org/10.1007/s12328-017-0776-6
16. Park BK, Koh HD, Won SY, Cho YS, Seo JH, An C, et al. Suspicious findings observed retrospectively on CT imaging performed before the diagnosis of pancreatic cancer. J Gastrointest Oncol. 2023;14(2):1008–18. https://doi.org/10.21037/jgo-22-863

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Gonda M, Masuda A, Kobayashi T, Iemoto T, Kakuyama S, Ezaki T, et al. Temporal progression of pancreatic cancer computed tomography findings until diagnosis: a large-scale multicenter study. United European Gastroenterol J. 2024;1–11. https://doi.org/10.1002/ueg2.12557