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Characteristic Radiological Features of Retrospectively Diagnosed Pancreatic Cancers

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Objectives: The aim of this study was to assess the characteristic radiological features of early-stage pancreatic cancer (PC).

Methods: Between 2009 and 2016, 510 PC patients were selected from our hospital cancer registry database based on *International Classification of Diseases for Oncology-3* (C25). Among them, 64 patients (42 males and 22 females; median age, 74 [range, 59–91]) had received repeated abdominal radiological examinations before their diagnosis of PC and were retrospectively investigated for specific radiological findings. The subjects underwent the following imaging examinations: computed tomography, magnetic resonance imaging, and fluoroglucose–positron emission tomography.

Results: Characteristic radiological features before diagnosis of PC were classified into the following 9 features: pancreatic duct ectasia (n = 16), focal low-density area (n = 15), change of cyst size (n = 8), localized tissue atrophy (n = 7), distal atrophy (n = 4), mass in pancreatic lipomatosis tissue (n = 2), mass concomitant with the already known cyst (n = 2), protrusion (n = 1), and parenchymal disproportion (n = 1). Fifty-three cases (84%) had more than one characteristic radiological feature before diagnosis of PC, and their median observation period until diagnosis was 24 (range, 1–120) months.

Conclusions: The 9 characteristic radiological features provide an opportunity to diagnose PC at an early stage.

Key Words: characteristic radiological features, diagnosis, pancreatic cancer, non–contrast-enhanced CT scan

Abbreviations: PC - pancreatic cancer, IPMN - intraductal papillary mucinous neoplasia, MDCT - multidetector row computed tomography scan, EUS - endoscopic ultrasonography), CT - computed tomography, MRI - magnetic resonance imaging, FDG-PET - fluoroglucose–positron emission tomography, ESD - endoscopic submucosal dissection, IPMC - intraductal papillary mucinous carcinoma, Ph - pancreas head, Pb - pancreas body, Pt - pancreas tail, CRT - chemoradiation, NAC - neoadjuvant chemotherapy, BSC - best supportive care, RT - radiation therapy, NCECT - non–contrast-enhanced CT scan, CECT - contrast-enhanced CT scan, LDA - focal low-density area, ERCP - endoscopic retrograde cholangiopancreatography, SMS - superior mesenteric artery, US - extracorporeal ultrasonography

(*Pancreas* 2020;49: 76–88)

Japan has experienced a recent rise in the prevalence of pancreatic cancer (PC) as a result of its aging population. In 2014, the PC prevalence per 100,000 population was 30 in males and 27 in females, and these rates further increased by 1.43 and 1.56 times, respectively, within the following 10 years.[1]

There have been developments in surgical procedures, chemotherapy, and radiotherapy against PC; however, the prognosis of PC patients has remained poor in comparison to all malignant tumors.[2] The overall survival rates of PC are 6% in the United States and 7.7% in Japan.[1,3] Because most patients who make an initial hospital or clinic visit have advanced-stage PC, no more than 20% of patients are indicated for initial resection, and the recurrence rate is significantly high even after curative resection.[2,3] Moreover, the 5-year survival following radical resection is only 25%.[3,4]

Identification of risk factors and early PC diagnosis are the most important in improving overall survival. Pancreatic duct dilatation, chronic pancreatitis, pancreatic cyst, intraductal papillary mucinous neoplasia (IPMN), and deterioration of diabetes mellitus have been reported to be risk factors of PC.[5] Precise examinations using multidetector row computed tomography (MDCT) scan and endoscopic ultrasonography (EUS) have higher sensitivity values (up to 85% and 94%, respectively) than other modalities.[6,7] However, both examinations are usually performed in high-volume centers because they are too time-consuming and technically complicated to be performed as a screening examination. Because symptoms and blood tests are not useful for early diagnosis of PC, a versatile diagnosis modality and imaging evaluation are necessary.

In our study, early or advanced PCs treated at our institution were retrospectively investigated regarding examinations that had been performed before diagnosis to confirm the high-risk characteristic radiological features of PC.

MATERIALS AND METHODS

Between 2009 and 2016, 510 PC patients treated at our institution were selected from our hospital cancer registry database based on *International Classification of Diseases for Oncology-3* (C25). Among them, the first 446 visiting patients had not undergone any abdominal radiological examinations before diagnosis and were therefore excluded. The remaining 64 patients (42 males and 22 females; median age, 74 [range, 59–91]), who had undergone repeated abdominal radiological examinations before PC

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Received for publication May 30, 2019; accepted November 1, 2019.

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The authors declare no conflicts of interest associated with this manuscript.

DOI: 10.1097/MPA.0000000000001456

diagnosis, were investigated for radiological findings or changes relating to PC development. The subjects underwent the following imaging examinations: computed tomography (CT), magnetic resonance imaging (MRI), and fluoroglucose–positron emission tomography (FDG-PET). Extracorporeal ultrasonographic examination was not performed because it cannot always evaluate the entire pancreas in all patients. The interval and frequency of the examinations prediagnosis were dependent on the purpose of each examination.

The observation period until PC diagnosis in patients who had more than 2 abdominal radiological examinations was defined from when the radiological findings were confirmed or from when the most recent examination in patients without radiological findings were performed to the time of PC diagnosis. The image evaluation was independently performed by one gastroenterologist and one radiologist. Our institutional review board approved this retrospective study (approval number, 353; date, February 5, 2019).

There was no study sponsor or financial arrangement for this study. We have no funding sources, or institutional or corporate affiliations.

RESULTS

Patient Background

The 64 patients underwent radiological examinations before PC diagnosis during 16 medical checkups, 13 follow-up consultations for antineoplastic treatment other than PC, 7 cardiovascular disease screenings, 6 pancreatic cystic disease screenings (3 cyst formation, 1 major pancreatic duct dilatation, 2 IPMNs), 4 pancreatic mass follow-ups, 4 gallbladder stone screenings, 5 abdominal pain screenings, 4 urological screenings, 3 pneumonia follow-ups, 1 back pain screening, and 1 screening for deterioration of diabetes mellitus.

The details of the 13 patients who were followed up for antineoplastic treatment other than PC were as follows: 5 patients with gastric cancer were treated via surgery (n = 3) and endoscopic submucosal dissection (ESD) (n = 2); 1 patient underwent total gastrectomy more than 10 years before PC diagnosis; 1 patient with pathological stage IA underwent total gastrectomy 2 years before diagnosis; 1 patient with pathological stage IB underwent distal gastrectomy 3 years before diagnosis; 2 patients with pathological stage IA were treated with ESD with horizontal and vertical margin negativity and with no vascular invasion, 3 and 2 years before diagnosis, respectively; and 2 patients with lung cancer received surgery. The pathological diagnoses of 2 patients were bronchioalveolar cell carcinoma stage IA and acinar adenocarcinoma stage IB, respectively. They were treated 2 years and 4 years before diagnosis, respectively. No lymph node metastasis or vascular invasion was confirmed, and the surgical margin was negative in both patients. Two patients received surgery for colorectal cancer. One patient with pathological stage IIIA was treated via rectal resection more than 5 years before diagnosis. One patient with pathological stage II was treated via transverse colon resection 8 years before diagnosis. One patient with renal pelvic cancer was treated with chemotherapy 5 years before diagnosis. Evident signs of recurrence were not confirmed. Two patients with prostatic cancer were treated with endocrine therapy for 7 years until diagnosis and with radiotherapy 4 years before diagnosis, respectively. To date, no recurrence has yet been observed in either patient. One patient with intraductal papillary mucinous carcinoma (IPMC) was treated via distal pancreatectomy 3 years before diagnosis.

Tumor Characteristics and Clinical Results

Pancreatic cancers at diagnosis were radiologically classified into a mass forming type (n = 62) and cystic type (n = 2). Twenty mass-forming type tumors were pathologically confirmed by examination of resected or biopsied specimens: acinar cell carcinoma (n = 1), mucinous adenocarcinoma (n = 1), neuroendocrine carcinoma (n = 1), and invasive ductal carcinoma (n = 17), including tubular adenocarcinoma (n = 14) and poorly differentiated adenocarcinoma (n = 3). A cystic type tumor (n = 2) was pathologically diagnosed as mucinous cystadenocarcinoma including anaplastic cancer (n = 1) and IPMC (n = 1).

The tumor locations were the pancreas head (Ph: n = 32), pancreas body (Pb: n = 21), and pancreas tail (Pt: n = 11). The Union for International Cancer Control (UICC) seventh edition of tumor staging at diagnosis were stage I (n = 5), stage II (n = 17), stage III (n = 11), and stage IV (n = 31). The tumor locations of each stage were as follows: stage I, Ph:Pb:Pt = 2:2:1; stage II, Ph:Pb:Pt = 13:1:3; stage III, Ph:Pb:Pt = 6:3:2; and stage IV, Ph:Pb:Pt = 11:15:5, respectively. The median tumor size was 32 (range, 6–90) mm. The median tumor sizes of each stage were 25 (range, 6–31) mm for stage I, 30 (range, 18–60) mm for stage II, 36 (range, 24–75) mm for stage III, and 32 (range, 21–90) mm for stage IV.

The initial treatment for stage I was surgery (n = 4) and chemoradiotherapy (CRT) (n = 1), whereas that for stage II was surgery (n = 10), neoadjuvant chemotherapy (NAC) followed by surgery (n = 1), and best supportive care (BSC) (n = 3). The treatments for stage III were CRT (n = 3), BSC (n = 3), radiation therapy (RT) alone (n = 2), surgery (n = 1), chemotherapy alone (n = 1), and RT followed by chemotherapy (n = 1). The treatments for stage IV were CRT (n = 11), chemotherapy alone (n = 8), palliative surgery (n = 3), RT followed by chemotherapy (n = 1), and BSC (n = 8).

The median overall survival days after PC diagnosis for each stage were as follows: 1049 (range, 372–3053) days for stage I; 512 (range, 43–1602) days for stage II; 491 (range, 5–1175) days for stage III; and 212 (range, 9–617) days for stage IV. The 3-year overall survival rates for each stage were 37% for stage I, 15% for stage II, 18% for stage III, and 0% for stage IV.

The median observation period until PC diagnosis was 24 (range, 1–120) months, whereas those for each stage were 7 (range, 6–120) months for stage I, 24 (range, 5–120) months for stage II, 36 (range, 12–60) months for stage III, and 36 (range, 1–120) months for stage IV.

Radiological findings before PC diagnosis were obtained using a non–contrast-enhanced CT (NCECT) scan (n = 33), contrast-enhanced CT (CECT) scan (n = 18), NCECT and CECT (n = 12), and MRI (n = 1). The frequencies of the examinations and median observation periods until PC diagnosis were as follows: once (n = 36, 24 [range, 1–108] months), 2 to 3 times (n = 17, 24 [range, 6–84] months), 4 to 8 times (n = 5, 48 [range, 5–60] months), and 9 to 14 times (n = 6, 60 [range, 36–120] months).

Classification of Characteristic Radiological Features Before PC Diagnosis

Fifty-three patients (84%) had more than one characteristic radiological feature before PC diagnosis. The median observation period until diagnosis in the 53 patients was 24 (range, 1–120) months. The median tumor size was 32 (range, 6–90) mm. The UICC tumor stages at diagnosis were stage I (n = 5, 9%), stage II (n = 13, 25%), stage III (n = 9, 17%), and stage IV (n = 26, 49%). Due to stage III (cases involving the celiac axis or the superior mesenteric artery [SMA]) or stage IV (cases with distant metastasis), 66% (35/53) of the patients with one or more features before PC diagnosis were not indicated for curative resection at

the time of diagnosis. Characteristic radiological features of the 53 cases before diagnosis were classified into the following 9 features: pancreatic duct ectasia (n = 16), focal low-density area (LDA) (n = 14), change in cyst size (n = 8), localized tissue atrophy (n = 7), distal atrophy (n = 4), mass in pancreatic lipomatosis tissue (n = 2), mass concomitant with the already known cyst (n = 2), protrusion (n = 1), and parenchymal disproportion (n = 1) (Fig. 1). The details of each feature are shown in Table 1.

- Pancreatic duct ectasia, focal LDA, and distal atrophy—these are 3 classical features of PC. A lump of cells with or without necrotic tissue was shown as having focal LDA. Pancreatic duct ectasia was caused by ductal obstruction or overflow of pancreatic juice. Distal atrophy was caused by chronic inflammation from ductal obstruction or by fibrosis from PC. Two cases each exhibited 2 of these features; both pancreatic duct ectasia and focal LDA occurred in one patient, and both pancreatic duct ectasia and distal atrophy were found in the other patient.
- Change in cyst size—2 patterns of change in cyst size before PC diagnosis were recognized, including both enlarged and reduced cases.
- Localized tissue atrophy—focal pancreatic tissue atrophy without distal atrophy.
- Mass in pancreatic lipomatosis tissue—a mass in pancreatic tissue with lipomatosis.
- Mass concomitant with the already known cyst—mass that occurred in a part of pancreas other than that where the cyst was previously confirmed.
- Protrusion—an unnaturally protruding lesion.
- Parenchymal disproportion—an unnaturally thick lesion compared with the surrounding tissue or with the previous images of the same area of the pancreas.

Of the feature positive cases, 39% (21/53) were overlooked by general physicians or other department experts. One of the possible reasons for this might be that the purpose of the first examination was not for a gastroenterological matter.

Eleven cases (17%) had no characteristic findings on radiological examinations before diagnosis that would have led to suspected PC. The median observation period until diagnosis in these cases was 36 (range, 5–84) months, and the median tumor size was 30 (range, 18–74) mm. The patient numbers in each of the tumor stages according to the UICC seventh edition were: 0 stage I (0%); 4 stage II (36%); 2 stage III (18%), and 5 stage IV (45%) patients.

Each radiological feature is explained by case series.

Pancreatic Duct Ectasia, Focal Low-Density Area, and Distal Atrophy

Pancreatic duct ectasia (n = 16), focal LDA (n = 14), and distal atrophy (n = 4) are typical characteristic radiological features of suspected PC (Fig. 1A). The percentages of the number NCECT scans performed before PC diagnosis in the current study were 69% (11/16) for pancreatic duct ectasia, 79% (11/14) for focal LDA, and 75% (3/4) for distal atrophy (Table 1). The aims of examination before PC diagnosis in the pancreatic duct ectasia cases were as follows: 4 were followed up for antineoplastic treatment other than PC (3 gastric cancers and one prostatic cancer), 3 medical checkups, 3 pancreatic cystic disease screenings, 2 pancreatic mass follow-up consultations, 1 cardiovascular disease screening, 1 gallstone screening, 1 abdominal pain screening, 1 pneumonia follow-up, and 1 screening for deterioration of diabetes mellitus. The purposes of examination before PC diagnosis in the focal LDA cases were as follows: 6 medical checkups, 3 abdominal pain screening, 1 follow-up for postsurgical state of colonic cancer, 1 pancreatic mass screening, 1 gallstone screening, and 1 urological screening. The aims of examination before PC diagnosis in the distal atrophy cases were as follows: 1 cardiovascular disease screening, 1 pancreatic mass screening, 1 urological screening, and 1 screening for back pain.

The median observation periods until PC diagnosis in the pancreatic duct ectasia cases, focal LDA cases, and distal atrophy cases were 36 (range, 5–120) months, 24 (range, 1–72) months, and 18 (range, 5–72) months, respectively.

The percentages of patients with each feature who were not indicated for curative resection at the time of diagnosis because of stage III or IV disease were as follows: pancreatic duct ectasia cases 50% (n = 8), focal LDA cases 71% (n = 10), and distal atrophy cases 100% (n = 4).

The pathologically confirmed cancer cases were as follows: 5 pancreatic duct ectasia cases (4 well-differentiated tubular adenocarcinomas and 1 IPMC), 4 focal LDA cases (2 well-differentiated tubular adenocarcinomas, 1 acinar cell carcinoma, and 1 neuroendocrine carcinoma); however, no distal atrophy cases were reported.

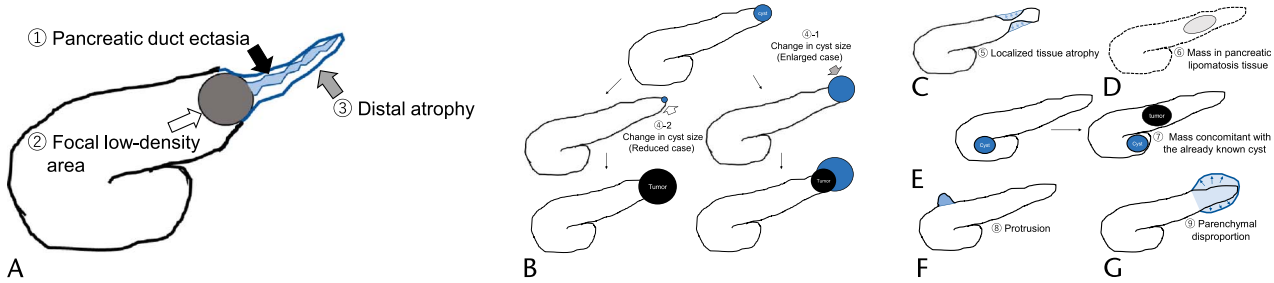

FIGURE 1. Classification of characteristic radiological features before diagnosis. A, ① Pancreatic duct ectasia (black arrow), ② focal LDA (white arrow), ③ distal atrophy (gray arrow)—3 classical features of PC. Mass volume is shown as a focal LDA. Pancreatic duct ectasia was caused by ductal obstruction or overflow of pancreatic juice. Distal atrophy was caused by chronic inflammation from ductal obstruction or by fibrosis from PC. Two cases exhibited 2 of the features. B, ④ Change in cyst size—2 patterns of change before PC diagnosis included enlarged cases (④, 1 gray arrow) and reduced cases (④, 2 white arrow). C, ⑤ Localized tissue atrophy—focal tissue atrophy without distal atrophy. D, ⑥ Mass in pancreatic lipomatosis tissue—mass in the pancreatic tissue with lower imaging density caused by pancreatic lipomatosis. E, ⑦ Mass concomitant with the already known cyst—mass that occurred in a part of pancreas other than that where the cyst was previously confirmed. F, ⑧ Protrusion—unnaturally protruded lesion. G, ⑨ Parenchymal disproportion—unnaturally thick lesion compared with other parts or the same part in a previous imaging.

TABLE 1. Clinical Results of Characteristic Radiological Features Before Diagnosis of PCs

	Pancreatic Duct Ectasia (n = 16)	Focal Low Density Area (n = 14)	Change of Cyst Size (n = 8)	Localized Tissue Atrophy (n = 7)	Distal Atrophy (n = 4)	Mass in the Pancreatic Lipomatosis (n = 2)	Mass Concomitant With Already Known Cyst (n = 2)	Protrusion (n = 1)	Parenchymal Disproportion (n = 1)	No Characteristic Finding Before Diagnosis (n = 11)
Age, median (range), y	72 (60–88)	77 (41–89)	68 (59–83)	79 (56–82)	72 (66–79)	86 (82–90)	68 (68–68)	91	73	69 (60–88)
Sex, male = 1, n (%)	14 (88)	8 (57)	6 (75)	4 (57)	3 (75)	2 (100)	2 (100)	0 (0)	0 (0)	5 (45)
Type of initial examination, n (%)										
NCECT	7 (44)	9 (64)	2 (25)	5 (71)	2 (50)	0 (0)	1 (50)	1 (100)	1 (100)	6 (55)
CECT	5 (31)	3 (21)	4 (50)	2 (29)	1 (25)	0 (0)	1 (50)	0 (0)	0 (0)	2 (18)
NCECT +CECT	4 (25)	2 (14)	2 (25)	0 (0)	1 (25)	1 (50)	0 (0)	0 (0)	0 (0)	3 (27)
MRI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (50)	0 (0)	0 (0)	0 (0)	0 (0)
Tumor location at diagnosis, n (%)										
Ph	14 (88)	6 (43)	3 (38)	1 (14)	1 (25)	1 (50)	1 (50)	1 (100)	0 (0)	5 (45)
Pb	2 (13)	8 (57)	3 (38)	3 (43)	2 (50)	0 (0)	1 (50)	0 (0)	0 (0)	3 (27)
Pt	0 (0)	0 (0)	2 (25)	3 (43)	1 (25)	1 (50)	0 (0)	0 (0)	1 (100)	3 (27)
Tumor size, median (range), mm	30 (25–40)	31 (6–75)	35 (25–62)	30 (21–87)	51 (25–50)	39 (27–50)	28 (21–34)	28	90	30 (18–74)
Histologically proven cases, n (%)	5 (31)	4 (29)	4 (50)	4 (57)	0 (0)	0 (0)	2 (100)	0 (0)	0 (0)	3 (27)
Observation period until diagnosis, median (range), mo	36 (5–120)	24 (1–72)	27 (5–120)	60 (6–72)	18 (5–72)	8 (3–12)	21 (6–36)	48	84	36 (5–84)
UICC seventh stage at diagnosis, n (%)										
I	2 (13)	2 (14)	0 (0)	1 (14)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
II	6 (38)	2 (14)	2 (25)	1 (14)	0 (0)	1 (50)	1 (50)	0 (0)	0 (0)	4 (36)
III	1 (6)	4 (29)	2 (25)	1 (14)	1 (25)	0 (0)	0 (0)	1 (100)	0 (0)	2 (18)
IV	7 (44)	6 (43)	4 (50)	4 (57)	3 (75)	1 (50)	1 (50)	0 (0)	1 (100)	5 (45)
Observation period of each UICC seventh stage until diagnosis, median (range), mo										
I	102 (84–120)	7 (6–7)		6						
II	13 (12–48)	42 (24–60)	12 (5–18)	60		12	36			47 (10–72)
IIII	36	24 (12–72)	36 (36)	60	12			48		24
IV	48 (5–72)	24 (1–72)	60 (6–120)	54 (48–72)	24 (5–72)	3	6		84	36 (5–84)
Examination frequency of each UICC seventh stage until diagnosis, median (range)										
I	10 (9–11)	2 (1–2)		3						
II	2 (1–5)	4 (3–4)	2 (1–2)	9		1	5			1 (1)
III	2	1 (1)	3 (2–3)	14	2			1		1 (1)
IV	1 (1–14)	1 (1)	3 (1–3)	1 (1–12)	1 (1–4)	1	1		2	1 (1)

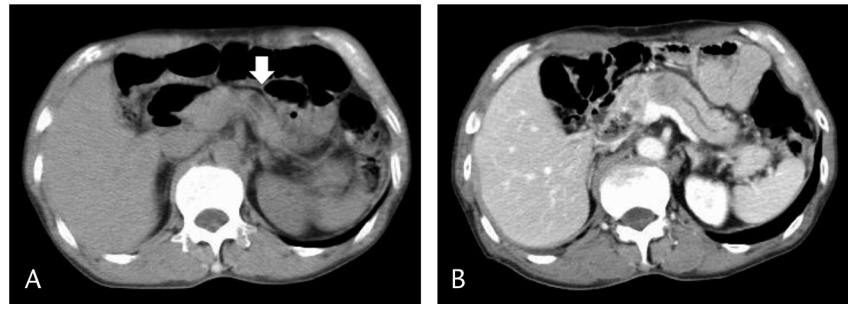

FIGURE 2. A 59-year-old male. Focal LDA on the Pb (white arrow) and distal pancreatic duct ectasia were retrospectively detected by a non–contrast-enhanced chest CT scan during a medical checkup (A). Six years later, a CECT scan revealed a 29-mm pancreatic body cancer with evident major pancreatic duct ectasia (B). Peritonitis carcinomatosa was also confirmed.

Both pancreatic duct ectasia and focal LDA occurred in one patient (case 1), and both pancreatic duct ectasia and distal atrophy were found in another patient (case 2).

In case 1, an NCECT scan was performed for a 59-year-old man to examine lung disease as a medical checkup 6 years before PC diagnosis. Focal LDA on Pb and distal pancreatic duct ectasia were retrospectively pointed out (Fig. 2A). Six years later, the patient visited our hospital complaining of epigastralgia. A CECT scan showed a 29-mm Pb cancer with evident major pancreatic duct ectasia (Fig. 2B). Peritonitis carcinomatosa was also confirmed. He survived for 17 months after finishing CRT.

In case 2, a 66-year-old man complained of epigastralgia on consultation at our hospital. A CECT scan showed pancreatic ductal ectasia and distal atrophy. The major pancreatic duct was obstructed; however, any evident focal LDA at the obstructed region was not definitively confirmed (Figs. 3A, B). Retrospectively, the mass was so small and comparatively well contrast-enhanced to the same level as the pancreatic parenchyma, which may have led to the mass not being recognized. Two pancreatic duct brushing cytologies, each via endoscopic retrograde cholangiopancreatography (ERCP), revealed no malignant cells, which led to observation of the mass. A CECT scan was performed again 4 months after the first CT scan. Focal LDA was evident with a size of 25 mm (Figs. 3C, D). Liver metastasis was also confirmed. The patient survived for 6 months after finishing CRT.

Pancreatic duct ectasia without focal LDA is well known as a possible form of pancreatic intraepithelial neoplasia, which is considered to be an early form of PC. On the other hand, of the 15 focal LDA cases, 14 without pancreatic duct ectasia were also confirmed. A typical focal LDA without pancreatic duct ectasia case is shown in case 3.

In case 3, a 61-year-old man had a medical checkup using a non–contrast-enhanced chest CT scan. Focal LDA without pancreatic duct ectasia was confirmed on the Ph (Figs. 4A, B). Two years after the first CT scan, the patient complained of back pain and visited our hospital. Contrast-enhanced CT scan showed

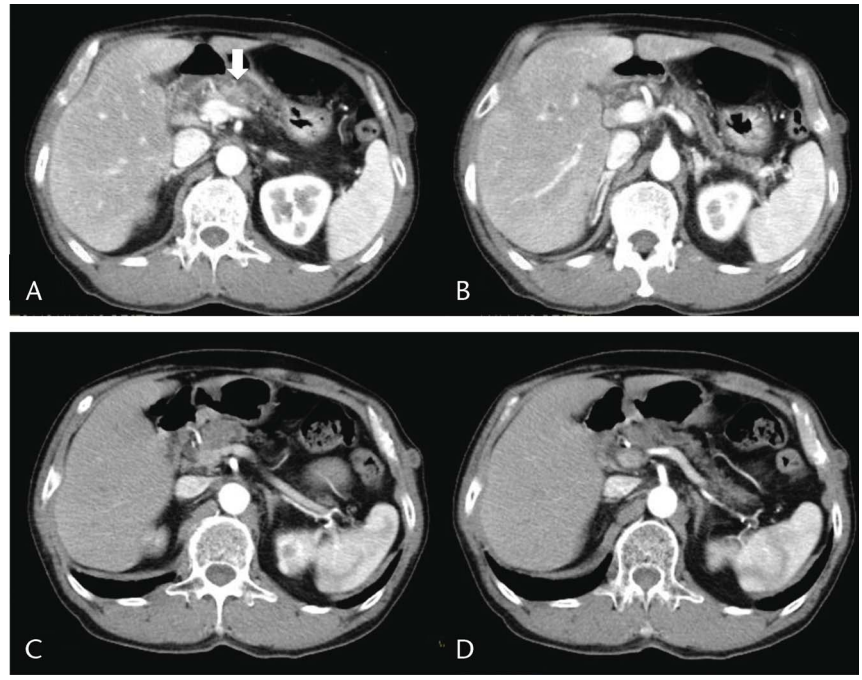

FIGURE 3. A 66-year-old male. A contrast-enhanced CT scan to check epigastralgia showed pancreatic ductal ectasia and distal atrophy. The major pancreatic duct was obstructed, but the mass at the point of obstruction was not clearly recognized (A and B). The mass was very small and well contrast-enhanced to the same level as that of the pancreatic parenchyma (white arrow). Four months later, a CECT detected a 25-mm focal LDA (C and D). Liver metastasis was also confirmed.

enlarged focal LDA 45 mm in size and pancreatic duct ectasia (Figs. 4C, D). Lung metastasis was also confirmed. The patient survived for 4 months after finishing CRT.

Change in Cyst Size

Pancreatic cysts are a well-known risk factor for PC and are classified into congenital cysts or secondary cysts resulting from branch duct obstruction caused by mucus, pancreatic stones, chronic pancreatitis, IPMN, and pancreatic tumors, among others. Eight cases with changes in cyst size before PC diagnosis were confirmed, including enlarged cases (n = 5) and reduced cases (n = 3) (Fig. 1B). The percentage of number of performed NCECT scans before PC diagnosis was 50% (4/8) (Table 1).

The reasons for performing examination before diagnosis were as follows: 3 cardiovascular disease screenings, 2 gastric cancer posttreatment follow-ups (1 surgery and 1 ESD), 2 gallbladder screenings, and 1 pancreatic mass screening.

The median observation period until diagnosis was 27 (range, 5–120) months. Due to having stage III or stage IV disease, 75% (6/8) of the patients were not indicated for curative resection at the time of diagnosis.

Four cases were pathologically confirmed as being cancer (2 well-differentiated tubular adenocarcinomas, 1 moderately differentiated tubular adenocarcinoma, and 1 mucinous cyst adenocarcinoma including anaplastic cancer). Cases with an enlarged cyst and a reduced cyst are shown as cases 4 and 5, respectively.

In case 4, a 77-year-old man had a cyst in the Pt retrospectively confirmed by a contrast-enhanced chest CT scan, which was performed by a cardiologist screening for coronary disease (Fig. 5A). The patient returned to our hospital complaining of chest pain and was admitted to our emergency center 13 months after the first CT scan. A CECT scan was performed to check for coronary disease. The pancreatic cyst had enlarged (Fig. 5B), and 20 months after the first CT scan, he was again admitted to our emergency center complaining of back pain. A CECT scan was performed again to check his back. The pancreatic cyst had further enlarged (Fig. 5C), and focal LDA on the same lesion as previous cyst and liver metastasis were confirmed. He survived for 4 months after finishing CRT.

In case 5, a cyst in the Pt was retrospectively confirmed in a 76-year-old female patient by a contrast-enhanced chest CT scan, which was performed by cardiologist screening for coronary disease (Fig. 6A). The patient complained of back pain and was referred to our surgery department 19 months after the initial CT scan. The pancreatic cyst was not detected in the second CECT scan. Fifteen months later (34 months after the initial CT scan), the patient complained of epigastralgia after a meal and visited our clinic. A CECT scan showed focal LDA on the Pt at the same location as the previous cyst (Fig. 6B). She survived for 16 months after finishing proton beam therapy.

Localized Tissue Atrophy

Inflammation, focal circulation disorder, and fibrosis are speculated to be the causes of localized tissue atrophy.[8] Seven PC cases occurred from localized tissue atrophy (Fig. 1C), and the percentage of the number of NCECT scans performed before PC diagnosis was 71% (5/7) (Table 1).

The purposes of examination before diagnosis were as follows: 4 follow-ups on antineoplastic treatment other than PC (1 colonic cancer, 2 lung cancer, and 1 renal pelvic cancer), 2 medical checkups, and 1 abdominal pain screening.

The median observation period until diagnosis was 60 (range, 6–72) months, and 71% (5/7) of the patients were not indicated for curative resection at the time of diagnosis due to having stage III or IV disease.

Four cases were pathologically confirmed as being cancer (2 well-differentiated tubular adenocarcinomas, 2 moderately differentiated tubular adenocarcinomas, and 1 poorly differentiated tubular adenocarcinoma).

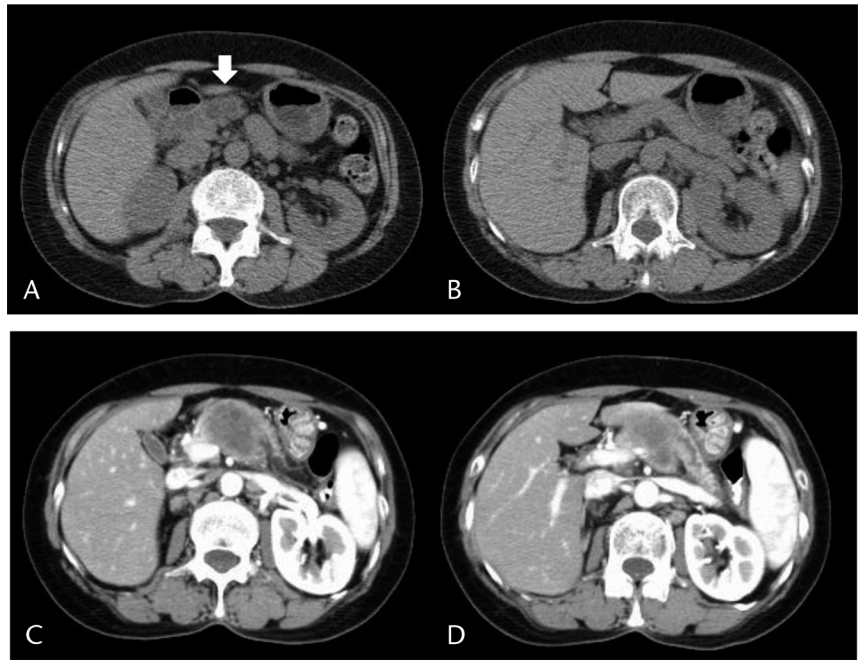

FIGURE 4. A 61-year-old male. Non–contrast-enhanced chest CT during a medical checkup showed focal LDA on the Ph without pancreatic duct ectasia (white arrow, A and B). Two years later, a CECT scan showed enlarged focal LDA and pancreatic duct ectasia (C and D). Lung metastasis was also confirmed.

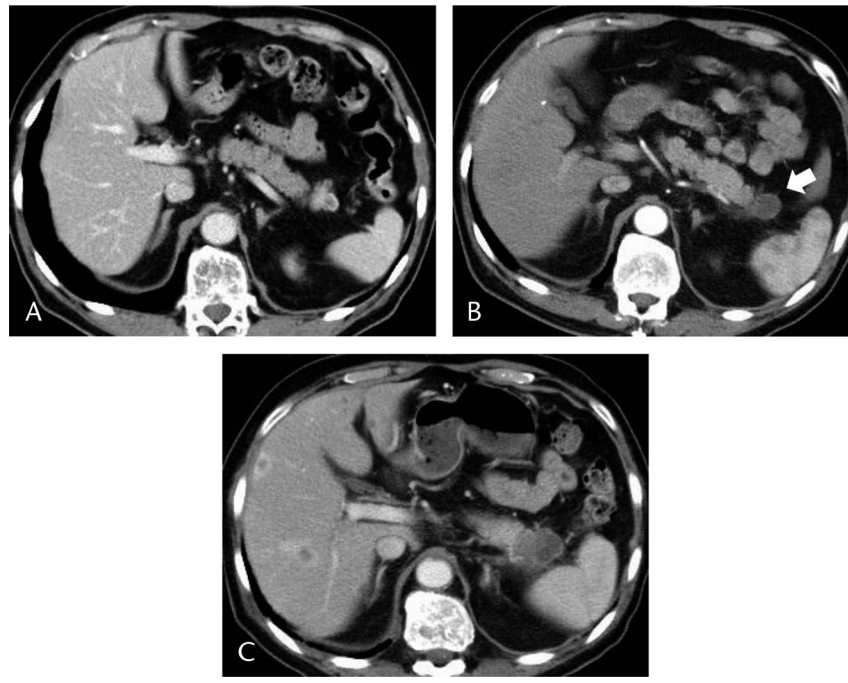

FIGURE 5. A 77-year-old male. A Pt cyst was detected by contrast-enhanced chest CT to screen for coronary disease (A). Thirteen months later, a CECT scan revealed an enlarged pancreatic cyst (white arrow, B). Twenty months after the initial CT scan, a CECT scan showed that the pancreatic cyst had further enlarged. Focal LDA at the same region and liver metastasis were also confirmed (C).

In case 6, an 80-year-old man received repeated CECT scans because he had a radical right colectomy for stage II colonic cancer. Localized tissue atrophy on the Pt without focal LDA was confirmed before the colectomy (Fig. 7A). Twelve months after the colectomy, a CECT scan for investigating carbohydrate antigen 19-9 elevation showed a parenchyma on the proximal side of the localized tissue atrophy, which was developing into focal LDA (Fig. 7B). Fifteen months after colectomy, the localized tissue atrophy completed development into focal LDA (Fig. 7C). The patient survived for 35 months after the distal pancreatectomy. Invasive ductal carcinoma consisting of moderately differentiated-type adenocarcinoma with lymphatic, venous, and perineural invasion was pathologically confirmed in the resected specimen.

In case 7, an 82-year-old man received repeated non–contrast-enhanced chest CT scans as he had partial lung resection for

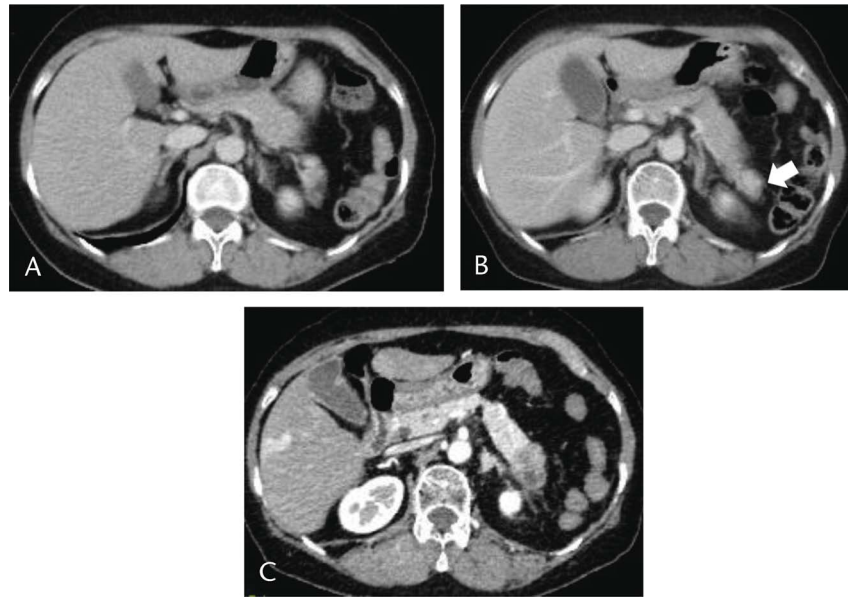

FIGURE 6. A 76-year-old female. A Pt cyst was detected by contrast-enhanced chest CT screening for coronary disease (A). Nineteen months after the first CT scan, the pancreatic cyst was not detected on the second CECT scan (white arrow, B). Thirty-four months after the first CT scan, a CECT scan showed focal LDA on the Pt at the same location of the previous cyst (C).

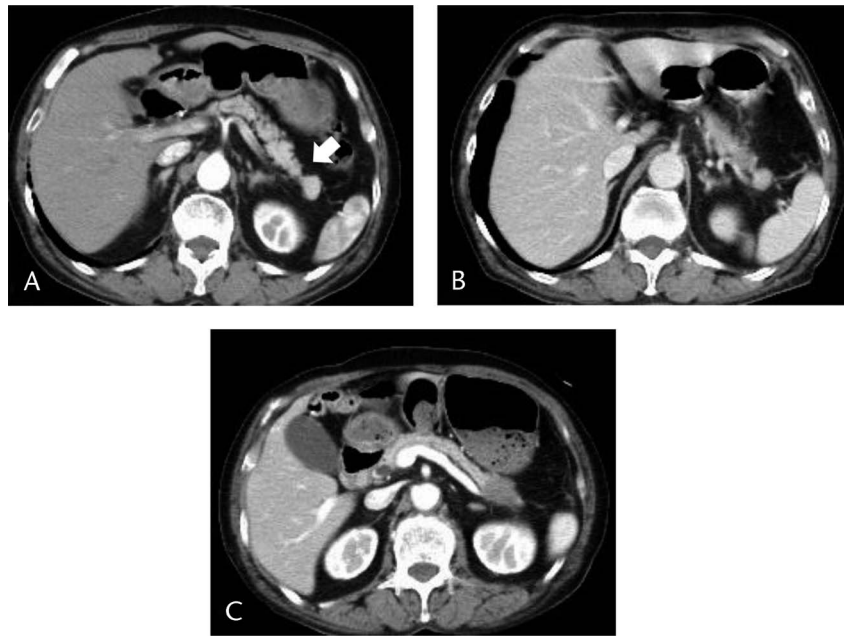

FIGURE 7. A 80-year-old male. The patient had repeated CECT scans as he had radical right colectomy for stage II colon cancer. Localized tissue atrophy on the Pt without focal LDA was confirmed before the colectomy (white arrow, A). Twelve months after the colectomy, the atrophy was developing into focal LDA (B). Fifteen months after the colectomy, the localized tissue atrophy had completely developed into focal LDA (C).

acinar adenocarcinoma stage IB. Localized tissue atrophy on the Pt without focal LDA was confirmed before the lung resection (Fig. 8A). Three years after the lung resection, a distal portion of the localized tissue atrophy had enlarged without focal LDA (Fig. 8B). One year later (4 years after lung resection), the enlarged distal portion developed into hypovascular focal LDA, which had further enlarged, and the localized tissue atrophy was completely undetectable (Fig. 8C). The patient survived for 53 months after the distal pancreatectomy. Invasive ductal carcinoma consisting of moderately and poorly differentiated-type adenocarcinoma with anterior and retroperitoneal tissue and lymphatic invasion pathologically confirmed in the resected specimen.

In case 8, a 79-year-old woman received repeated NCECT scans because she had partial lung resection for bronchioalveolar cell carcinoma stage IA. Localized tissue atrophy on the Pb without focal LDA was confirmed 2 years before the lung resection (Fig. 9A). The atrophied localized tissue atrophy was thickened, and its size was enlarged up to that of a healthy Pb 1 month before the lung resection (Fig. 9B). Eighteen months after the lung resection, the enlarged region developed into focal LDA with its size further enlarged (Fig. 9C). Four years after the initial CT scan, the patient visited our hospital complaining of abdominal distention. A CECT scan showed a further enlarged and invasive focal LDA with hypovascularity and SMA invasion (Fig. 9D). Liver metastasis and peritonitis carcinomatosa were also confirmed. He survived for 3 months after starting chemotherapy.

Mass in the Pancreatic Lipomatosis

Pancreatic tissue is reported to develop fatty metamorphosis as a result of aging, obesity, and diabetes mellitus.[8] The hypodensity of the pancreatic lipomatosis tissue on CT images revealed the contrast density of the focal LDA to be significantly higher, up to remnant pancreatic parenchyma levels. A mass in pancreatic lipomatosis tissue (n = 2) may not be a common finding, but it can increase the risk of even a large PC to be overlooked as remnant pancreatic tissue (Fig. 1D).

The percentage of the number of NCECT scans performed before PC diagnosis was 50% (1/2) (Table 1).

The reasons for examination before diagnosis were as follows: 1 follow-up of prostatic cancer and 1 gallstone screening.

The observation periods until diagnosis of the 2 patients were 3 months and 12 months, respectively. Because the disease was at stage III or IV, 50% (1/2) of the patients were not indicated for curative resection at the time of diagnosis.

In case 9, an 85-year-old man received endocrine therapy for prostatic cancer. Seven years after starting the therapy, a CECT scan was performed as a follow-up on the prostatic cancer. A mass in the pancreatic lipomatosis tissue was detected on the Pb without pancreatic duct ectasia (Figs. 10A, B). Repeated CECT scans revealed focal LDA with SMA invasion at 7.5 years after the endocrine therapy began (Fig. 10C). Peritonitis carcinomatosa was also revealed by the CECT at PC diagnosis. The patient survived for 3 months after starting chemotherapy.

Mass Concomitant With the Already Known Cyst

Mass concomitant with the already known cyst is commonly accepted to be a duct cell carcinoma concomitant with IPMN (-Fig. 1E). Two PC cases were detected during IPMN follow-up.

The percentage of the number of NCECT scans performed before PC diagnosis was 50% (1/2) (Table 1).

The observation periods until diagnosis of the 2 patients were 6 months and 36 months, respectively. Because the disease was at stage III or stage IV, 50% (1/2) of the patients were not indicated for curative resection at the time of diagnosis.

The 2 cases were pathologically confirmed as cancer (1 well-differentiated tubular adenocarcinoma and 1 poorly differentiated tubular adenocarcinoma).

In case 10, a 68-year-old man was referred by a general physician to our surgery department for examination of a Ph pancreatic

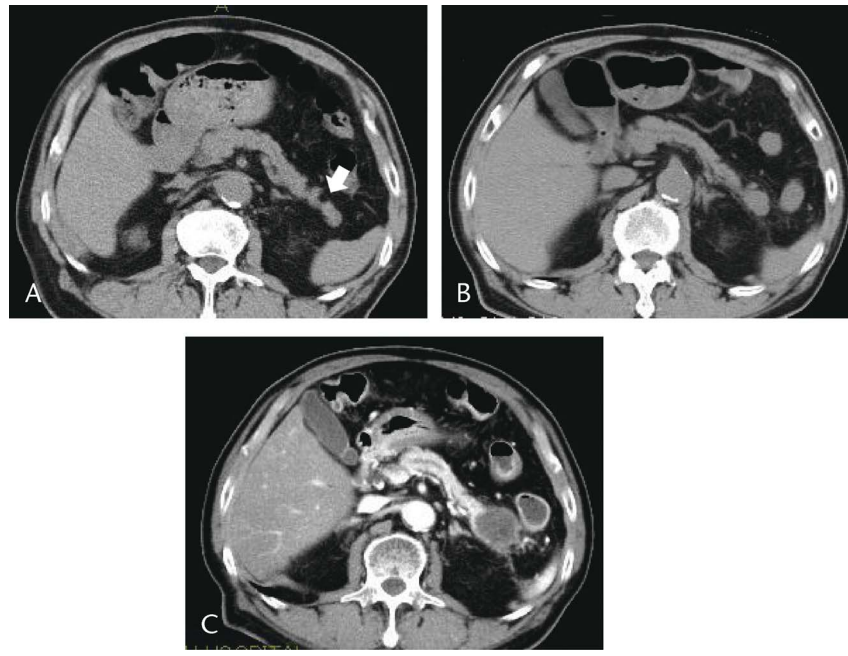

FIGURE 8. A 82-year-old male. The patient had repeated non–contrast-enhanced CT scans due to having had partial lung resection for acinar adenocarcinoma stage IB. Localized tissue atrophy on the Pt without focal LDA was confirmed before the lung resection (white arrow, A). Three years after the lung resection, the parenchyma on the distal side of localized tissue atrophy had enlarged without focal LDA (B). Four years after the lung resection, the enlarged distal portion developed into hypovascular focal LDA with its size further enlarged, and the localized tissue atrophy had completely disappeared (C).

cyst, which was revealed by a CECT scan, as was a slightly dilated pancreatic duct (Figs. 11A–C). Six months after the first CT scan, repeated CECT scans showed a para-aortic lymph node swelling in addition to a Ph pancreatic cyst and a slightly dilated pancreatic duct (Figs. 11D, E). A fluoroglucose–positron emission tomography CT scan was performed to screen for the primary cancer or a

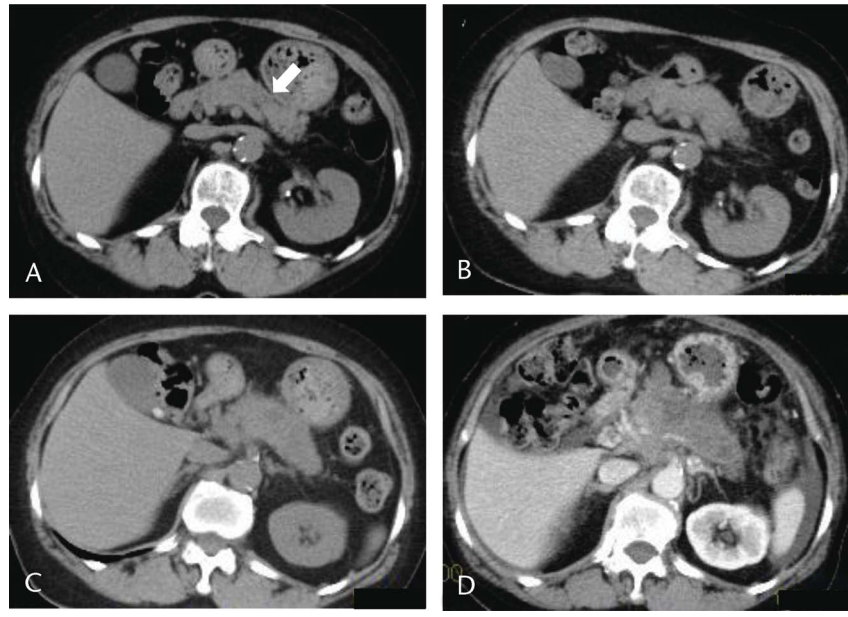

FIGURE 9. A 79-year-old female. The patient had repeated non–contrast-enhanced CT scans as she had partial lung resection for bronchioalveolar cell carcinoma stage IA. Localized tissue atrophy on the Pb without focal LDA was confirmed 2 years before the lung resection (white arrow, A). The same part of the localized tissue atrophy was enlarged to the point where it was the same size as a normal Pb 1 month before the lung resection (B). A year and a half after the lung resection, the enlarged part developed into focal LDA with its size further enlarged (C). Two years after the lung resection, a CECT scan revealed a further enlarged Pb region and invasive focal LDA with hypovascularity, and SMA invasion (D). Liver metastasis and peritonitis carcinomatosa were also confirmed.

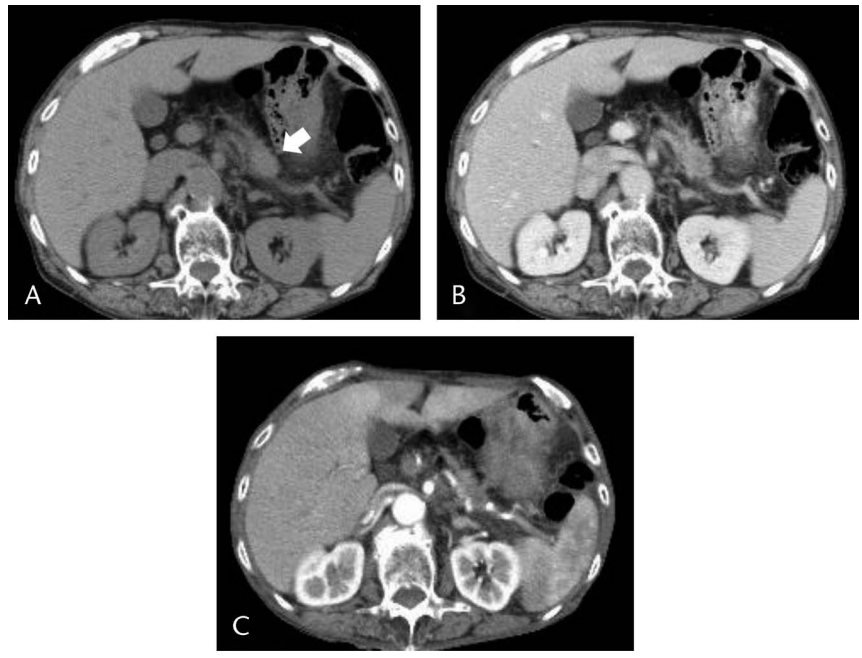

FIGURE 10. A 85-year-old male. The patient had received endocrine therapy for prostatic cancer. Seven years after the endocrine therapy was started, NCECT and CECT scans were performed to follow-up on the prostatic cancer. Mass in pancreatic lipomatosis tissue was observed on the Pb without pancreatic duct ectasia (white arrow, A and B). Three months after the previous CT, repeated CECT scans showed focal LDA with SMA invasion (C). Peritonitis carcinomatosa was also confirmed.

malignant lymphoma. The FDG accumulated in a small part of the Pb and the para-aortic lymph nodes (Fig. 11F). The distal pancreatic duct was dilated from the same lesion as the FDG accumulated lesion in the Pb. Retrospectively, a so-called visually isoattenuating PC[9] with FDG accumulation was confirmed. The patient was treated with NAC followed by distal pancreatectomy. An invasive ductal carcinoma with a poorly differentiated type adenocarcinoma was pathologically confirmed in the resected specimen. He survived for 16 months after surgery.

Protrusion

In case 11, part of the pancreas protruded in an anterior direction (Table 1, Figs. 1F, 12). A non–contrast-enhanced CT scan screening for cardiovascular disease in a 91-year-old woman was performed 4 years before diagnosis by a cardiologist. A small, but subtle, LDA in Ph protruded in an anterior direction (Fig. 12A). Four years after the first CT scan, the patient presented with jaundice on admission at our hospital. A contrast-enhanced CT scan showed focal LDA in the Ph with common bile duct obstruction,

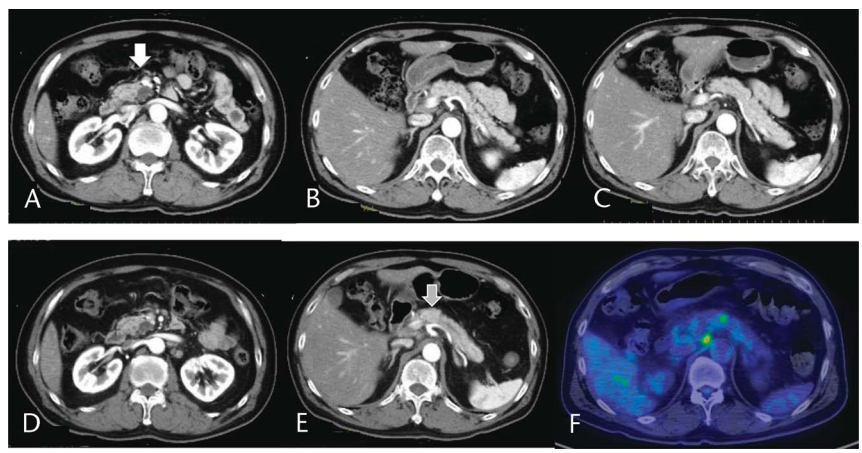

FIGURE 11. A 68-year-old male. The patient was referred to our surgery department by a general physician to examine the pancreatic cyst on the Ph. A CECT scan detected a pancreatic cyst on the Ph and a slightly dilated pancreatic duct (white arrow, A–C). Six months after the first CT scan, repeated contrast-enhanced CT scans showed para-aortic lymph node swelling in addition to the pancreatic cyst on the Ph and a slightly dilated pancreatic duct (D and E). Fluoroglucose–positron emission tomography revealed FDG accumulated in a small lesion on the Pb and para-aortic lymph nodes (F). The distal pancreatic duct was dilated from the same lesion as the FDG accumulated lesion in the Pb. Visually isoattenuating PC of the Pb was retrospectively recognized by FDG accumulation (gray arrow).

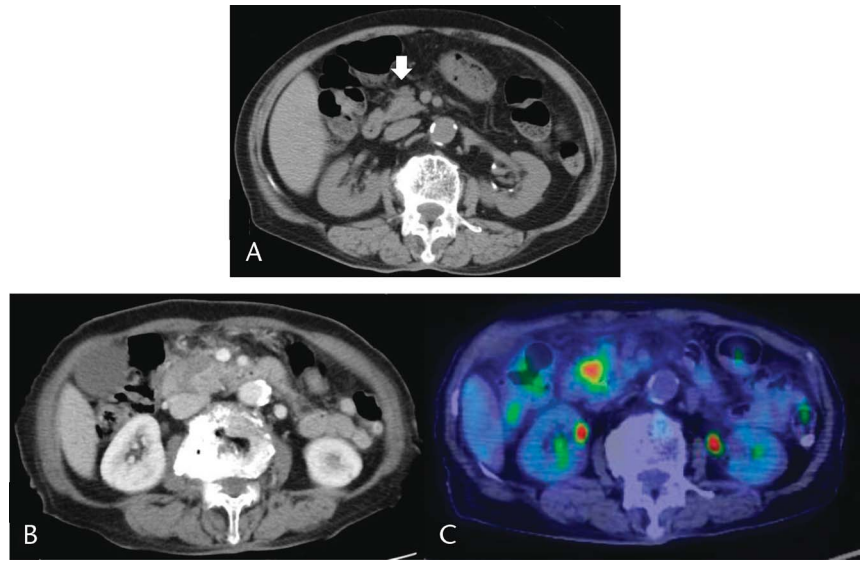

FIGURE 12. A 91-year-old female. Non-CECT screening for cardiovascular disease revealed a small but subtle LDA of the Ph protruded in an anterior direction 4 years before diagnosis (white arrow, A). Four years after the initial CT scan, a CECT scan showed focal LDA in the Ph with common bile duct obstruction, subtle pancreatic duct ectasia, and SMA invasion (B). FDG accumulation of focal LDA was confirmed by a FDG-PET/CT scan (C).

subtle pancreatic duct ectasia, and SMA invasion (Fig. 12B). Fluoroglucose accumulation of focal LDA was confirmed by a FDG-PET/CT scan (Fig. 12C). The patient survived for 8 months after finishing RT.

Pancreatic Disproportion

In case 12, size disproportion of the pancreatic parenchyma was observed (Table 1, Figs. 1G, 13). A 73-year-old woman received a non–contrast-enhanced chest CT scan 7 and 2 years before diagnosis during a medical checkup. The size of the pancreatic tail at 2 years before diagnosis (Fig. 13B) was larger than that at 7 years before diagnosis (Fig. 13A). Seven years after the first CT scan, the patient was admitted to our hospital complaining of abdominal pain. A contrast-enhanced CT scan showed a 90-mm focal LDA on the Pt with peritonitis carcinomatosa (Fig. 13C). The enlarged size of the pancreatic tail was further evident at the time of diagnosis. Following palliative radiotherapy, the patient was referred to the terminal care unit of another hospital.

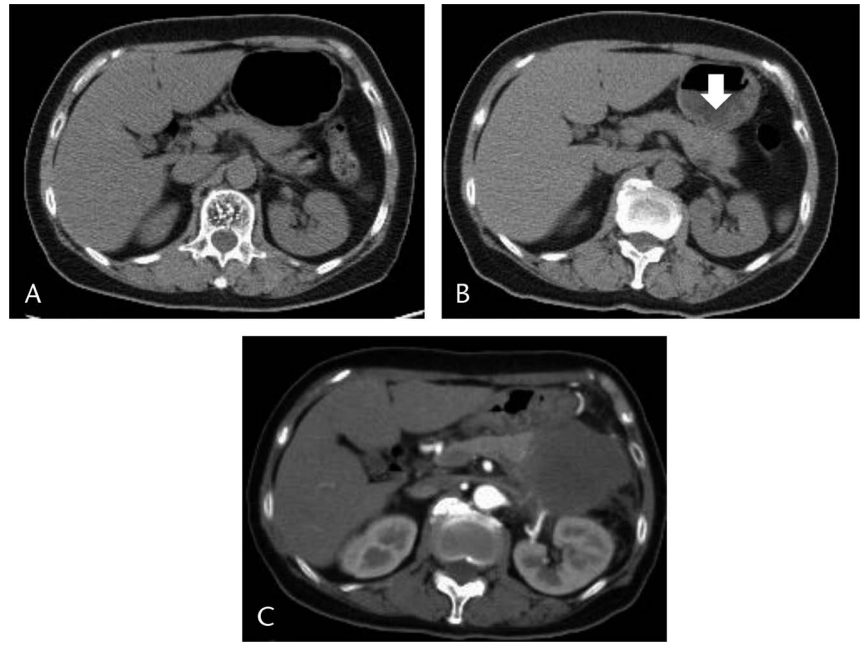

FIGURE 13. A 73-year-old female. The patient underwent non–contrast-enhanced chest CT scans during a medical checkup 7 and 2 years before diagnosis. The size of the Pt at 2 years before diagnosis (white arrow, B) was larger than that of 7 years before diagnosis (A). Seven years after the first CT scan, a CECT scan revealed a 90-mm focal LDA on the Pt (C). Peritonitis carcinomatosa was also confirmed.

DISCUSSION

The 5-year overall survival of PC is 7.7%, despite recent developments in diagnostic imaging; however, that of PC with a tumor size of within 10 mm is reported to be 80.4%. Early diagnosis is therefore expected to be the only breakthrough in improving the overall survival of PC.[10]

On the other hand, according to the genetic progression model of pancreatic carcinogenesis, it takes about 6.8 years for pancreatic intraepithelial neoplasia (PanIN) to develop into an invasive ductal carcinoma. Two to 3 years after PanIN development is regarded as the most important stage for early PC diagnosis.[11] It is therefore clinically necessary to point out the high-risk radiological features 2 to 3 years from PanIN development.

Because all 64 cases in the current study were managed by outpatient clinic doctors at our institution, we were able to evaluate the personal history and changes in radiological findings using an electronic medical chart system. Six CT scans for the purpose of screening for cardiovascular disease and 3 CT scans for follow-up of 2 cases of lung cancer and one pneumonia, accidentally showed characteristic radiological features. This strongly suggests that it is necessary to construct a comprehensive radiologically diagnostic system to consider suspected PC for not only gastroenterologists but also other department doctors.

Current PC screening examinations include extracorporeal ultrasonography (US) and CT scanning. However, US has limitations regarding examination of the pancreatic uncus and tail, and in patients with high body fat and significant intestinal gasses. The sensitivities of US and contrast-enhanced US are reported to be 57% and 87%, respectively.[12] Although CT scanning has issues regarding radiation exposure, it is able to examine the entire pancreas. The sensitivities of NCECT, CECT, and MDCT are reported to be 50%, 77%, and 85% to 100%, respectively.[13–15] However, MDCT is not suitable as a screening examination when taking cost, renal damage, and contrast-enhanced material allergy into consideration. General physicians are asked to perform MDCT while considering the patient's complaint, physical examination, pancreatic enzymes, tumor markers, and risk factors.[16]

The CT scans for 64% (34/53) of the patients with characteristic radiological features were not performed for the purpose of scanning for biliary tract disease, pancreatic disease, back pain, or abdominal symptoms. Occult PC must be taken into consideration even when CT is performed for purposes other than PC-related risk factors.

Among the 9 patterns of characteristic radiological features before PC development, NCECT scan was performed in more than 50% of the cases of each pattern (a total of 39 cases), and all 9 features were confirmed by the NCECT images. With careful observation of NCECT, considering the 9 patterns of the characteristic radiological features, most PCs can be diagnosed before reaching advanced forms.

Because focal LDA, pancreatic duct ectasia, distal atrophy, and mass concomitant with the already known cyst are typical features used to diagnose or suspect already existing PC, they should be recognized as especially important and common findings by not only gastroenterologists but also general physicians for the diagnosis of PC.[10]

Freeny et al[17] reported that pancreatic ducts with normal diameters are less than 3% among all PCs. However, 19% of PCs with a diameter of less than 20 mm have been reported to have normal-sized pancreatic ducts in a recent article using EUS.[18] Recently, developing diagnostic technologies, including EUS, have therefore provided the opportunity to detect small PCs derived from the peripheral branch of the pancreatic ducts before the tumor invades the major pancreatic duct. In our cases, 22% (14/64) of the PCs derived from LDA without pancreatic duct dilation could have been detected using EUS.

Four of the distal atrophy cases in the current study had a shorter median observation period of 18 (range, 5–72) months, and a larger median tumor size of 51 (range, 25–50) mm. Furthermore, 100% (4/4) of the cases were unresectable at the time of PC diagnosis, which means that distal atrophy should never be overlooked when considering the 9 characteristic radiological features.

On the other hand, masses in pancreatic lipomatosis tissue, protrusion, and pancreatic disproportion are relatively uncommon features[8,19] of already formed masses. Therefore, 75% (3/4) of the cases in the current study were regarded unresectable at the time of diagnosis. With the detection of these features on CT even for purposes other than PC screening, early PC diagnosis may be possible.

Change in cyst size and localized tissue atrophy are not frequently reported[18,20]; however, in our study, these features were thought to be important because 75% (6/8) in cyst size change and 71% (5/7) of localized tissue atrophy cases were unresectable at the time of diagnosis. Pancreatic cystic disease is commonly recognized as being a potentially high-risk finding of PC.[21] In the present study, we reported how cystic disease develops to PC by 2 patterns of cyst size change. Enlarging cysts are easily detectable; however, cysts of a lesser size carry a risk of being overlooked because the shape of the pancreas remains relatively normal. Localized tissue atrophy is also of a similar risk of being overlooked because as the disease progresses, the atrophic part thickens and grows to a size of a normal pancreas. With detection of a pancreatic cyst or localized tissue atrophy, it is important to pay the utmost attention to changes.

In addition to the 9 characteristic radiological features, a well-enhanced tumor detected by contrast-enhanced imaging, also known as the "isoattenuating tumor," is an important finding, as seen in cases 2 and 10. Because their amount of necrotic tissue content is less than that of a typical PC, isoattenuating tumors are difficult to detect on CECT images due to the lesser contrast between the tumor and normal pancreatic tissue. Isoattenuating tumors make up 10% of all PCs,[9] and are comparatively small, with a median tumor size of 30 (range, 15–40) mm. If associated findings such as pancreatic duct ectasia are not detected, isoattenuating tumors are easily overlooked on not only conventional venous phase CECT, but also on MDCT.

In the current study, 20.3% (13/64) of the cases developed PC as a second primary cancer during follow-up for antineoplastic treatment, including 5 gastric cancers, 2 lung cancers, 2 colonic cancers, 2 prostatic cancers, 1 renal pelvic cancer, and 1 IPMN. Previous studies have reported that 0.2% to 0.6% of gastric cancer patients, 1.2% of breast cancer patients, and 1.1% of lung cancer patients developed PC as a second primary cancer.[22–24] On follow-up CT after treatment for other organ cancers, attention should be paid regarding de novo PC, as well as recurrence of each cancer.

Almost all of the characteristic radiologic features, except for protrusion and parenchymal disproportion, include cases with a median observation period until diagnosis as being within 6 months. Because the median observation period until diagnosis of stage I disease is 7 months, radiological examinations should be repeated within 6 months, especially for cases with characteristic radiologic features. On the other hand, 10 years as an observation period until PC diagnosis was required in a case of pancreatic duct ectasia and in a case of reduced change of cyst size. More than 10 years as an observation period is desirable in cases with characteristic radiologic features.

Our 9 characteristic radiological features before PC diagnosis could be applied to 84% (53/64) PCs. However, the remaining 11 cases (16%) did not have any characteristic radiological features. A more detailed investigation is required in future.

Hanada et al reported a regional program for early diagnosis of PC. Patients with risk factors such as family history of PC, diabetes mellitus, chronic pancreatitis, familial pancreatitis, IPMN, pancreatic cyst, smoking, and drinking are usually examined using US. If pancreatic duct dilatation or a pancreatic cyst is detected using US, general physicians refer the patients to gastroenterologists who specialize in the pancreas. Precise examinations such as MDCT, magnet resonance pancreatocholangiography, and EUS are performed by a specialist. Endoscopic ultrasonography fine-needle aspiration and ERCP are administered by these specialists if needed.[25]

In addition to this program, if the characteristic radiological features are considered high-risk findings for PC by not only gastroenterologists but also general physicians, diabetes mellitus specialists, and other department specialists, early PC diagnosis is made possible even on a radiological examination for other purposes. We suggest that these 9 characteristic radiological features be used as a new trial for early diagnosis of PC.

CONCLUSIONS

The 9 characteristic radiological features before typically observable PC development provide an opportunity of early PC diagnosis using precise examinations such as EUS, MDCT, and ERCP.

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