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Article

Introducing the "K-Shaped Sign", A New Finding on CT to Detect Early-Stage Pancreatic Cancer

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Running head: A new finding on CT to detect early-stage pancreatic cancer.

Abstract: Background: Pancreatic invasive ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer mortality in Japan. The early diagnosis of pancreatic cancer, which will increase the number of patients with resectable tumors, is urgently needed. The purpose of the present study was to examine the earliest signs of pancreatic abnormalities on CT in order to facilitate the diagnosis and treatment of PDAC. **Methods:** Forty-one patients with pancreatic cancer and their 154 CTs were selected for the present study. We used the images that were acquired prior to the diagnosis and examined the pancreas in these images to observe serial changes in the morphology of the pancreas after selecting CT images in which PDAC was suspected. We also confirmed whether the main pancreatic duct was observed around that area of the pancreas. Four thousand two hundred seventy-seven patients without pancreato-biliary disease with 4630 CTs were selected for the control group. **Results:** Two pancreas shapes were detected: localized constriction of the pancreatic parenchyma referred to as the K-shaped sign, and localized fatty changes. Twenty-four (58.5%) of 41 patients showed the K-shaped sign. The main pancreatic duct without dilatation was noted around the K-shaped sign in 9 of the 24 patients. Eight of 41 patients (19.5%) showed localized fatty changes. Nine of 41 patients (21.9%) showed no abnormality. In the control group, only seven of 4277 patients (0.16%) showed the K-shaped sign. **Conclusions:** The K-shaped sign including localized fatty changes is the earliest CT sign that presents with pancreatic abnormalities. The K-shaped sign does not indicate PDAC itself but may predict its future development.

Keywords: fatty infiltration; main pancreatic duct dilatation; pancreatic invasive ductal adenocarcinoma.

1. Introduction

Pancreatic invasive ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer mortality in Japan. Since it is generally diagnosed at an advanced stage, the majority of tumors are not resectable[1,2]. Therefore, patients with PDAC have an extremely poor prognosis. The early diagnosis of PDAC, which will increase the number of patients with resectable tumors, is urgently needed. Signs that will contribute to the early detection of PDAC need to be identified. The purpose of the present study was to examine the earliest signs of pancreatic abnormalities on CT in order to facilitate the diagnosis and treatment of PDAC.

2. Methods and Materials

2.1. Study population and data: patients and CT

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This was a retrospective study. All cases included in the present study were initially identified using a picture archiving and communication system (PACS) of patients diagnosed with PDAC on CT between 2011 and 2017 at Tokyo Dental College Ichikawa General Hospital. Search keywords were pancreatic cancer and pancreatic head, body, and tail cancer. The search modality was abdominal CT.

The initial study population included 308 patients with 1595 CTs. In all cases, clinical data (presenting systems, age at diagnosis, previous medical and surgical histories, and blood glucose and HbA1c levels) were obtained from electronic medical records.

Sixty-seven of 308 patients with 665 CTs were excluded from the present study due to other pancreatic diseases.

Two hundred and forty-one of 308 patients with 930 CTs were diagnosed with PDAC based on PACS and medical records. For the purpose of study, we selected the CT images in which PDAC was suspected and used the images that were acquired prior to the diagnosis. We added CTs that initially showed PDAC to the present study. A total of 200 of 241 patients were excluded from the present study because they had never undergone abdominal CT at our hospital prior to their diagnosis of PDAC. A total of 776 of 930 abdominal CTs were excluded because they were obtained in follow-up examinations for PDAC.

Therefore, forty-one patients with 154 CTs were selected for the present study.

All 41 patients underwent CTs for other diseases: 25 for abdominal pain including enterocolitis, ureteral stones, and gallstones, 9 for post-operative follow-ups, such as breast cancer, colon cancer, gastric cancer, and arteriosclerosis obliterans, and 7 for medical check-ups. None of the 41 patients had any symptoms related to PDAC at the time of abdominal CT.

The search modality for the control group was abdominal CT of patients more than 60 years old, taken between April 2016 and March 2017 at Tokyo Dental College Ichikawa General Hospital. The initial control group population included 4522 patients with 4522 CTs. We excluded 245 patients with 245 CTs because of overlap of patients. Four thousand two hundred seventy-seven patients with 4277 CTs were selected for the control group. Informed consent was obtained from all patients who performed abdominal CTs.

In all cases, clinical data (presenting systems, age at diagnosis, previous medical and surgical histories, and blood glucose and HbA1c levels) were obtained from electronic medical records.

CTs were performed between 2004 and 2017 with 3 different CT machines (Philips IDT 16 (2004-2008), Phillips Brilliance 64 (2008-2017), and TOSHIBA Aquilion ONE 320 (2015-2017)). The slice thicknesses of CTs ranged between 1 and 5 mm and axial CT images were obtained. One hundred and seventeen out of 154 CTs (76%) were non-contrast abdominal CTs, while the remaining 37 (24%) were non-contrast and contrast CTs.

2.2. Shape of the pancreas

After selecting CT images in which PDAC was suspected, we used the images that were acquired prior to the diagnosis and examined the pancreas in these images to observe serial changes in the morphology of the pancreas. We also confirmed whether the main pancreatic duct was observed around that area of the pancreas. In the control group, we also reviewed previous CTs when we found changes in the morphology of pancreas in the period of observation.

2.3. Time period for the development of pancreatic cancer

We investigated the duration needed for pancreatic abnormalities to progress to pancreatic cancer.

3. Results

3.1. Patients and CTs

In the most recent abdominal CTs of all patients, 18 of 41 patients (20 males and 21 females, mean age 74.8 years old (age range 48-87 years)) had cancer of the pancreatic head, 15 pancreatic body, 5

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pancreatic uncinate, and 3 pancreatic tail. Nine of 41 patients underwent pancreatectomy, and all 9 were pathologically diagnosed with PDAC. All 41 patients received chemotherapy. Thirty-four of 41 patients died of PDAC, while seven currently remain alive with follow-up ranging from 24-60 months (mean 48 months).

Abdominal CT was performed four times on average (range 1-11 times) for each patient before PDAC was detected. Abdominal CT was performed once for 19 patients, 3 times for 9, 5 times for 5, 7 times for 2, and 4, 9, and 11 times for one each.

3.2. Shape of the pancreas

Three pancreas shapes were detected: A) localized constriction of the pancreatic parenchyma referred to as the K-shaped sign (Fig. 1), B) localized fatty changes and C) no abnormality. Patients were classified into the following three groups (Groups A, B, and C) based on these pancreatic changes.

We defined these groups as follows:

Group A, the K-shaped sign:

1. Presence of a caliber change in the pancreas in more than 2 slices on abdominal CT.
2. The caliber change has the K or X shape on CT axial images (Fig. 1).
3. The main pancreatic duct is maintained without dilatation even though a caliber change is observed.

Group B, localized fatty changes:

1. Less than 0 Hounsfield Units on CT.
2. No diffuse fatty changes in the pancreas.
3. No evidence of localized fatty changes in the oldest abdominal CT.
4. No-K-shaped sign.

Group C, no abnormality: No evidence of abnormal pancreatic lesions throughout the CT series.

Thirty-two of 41 patients (78.0%) exhibited some pancreatic changes suggestive of Group A or B.

Twenty-four (58.5%) of 41 patients belonged to Group A. The K-shaped sign was detected in the pancreatic body in 12 (Fig. 2), the head in 9 (Fig. 3), the tail in 2, and the uncinate process in 1. The main pancreatic duct without dilatation was noted around the K-shaped sign in 9 of 24 patients (Fig. 4).

Eight of 41 patients (19.5%) belonged to Group B. Localized fatty changes were detected in the pancreatic head and uncinate process (Fig. 5) in 4 patients each. The main pancreatic duct without dilatation was not observed around localized fatty changes; however, some branch pancreatic ducts were detected in 1 of the 8 patients. These results are shown in Table 1.

Older CTs were available for 19 of 32 patients when the Group A or B finding was detected. In the oldest CT, there was no evidence of the K-shaped sign or localized fatty change in the pancreas of any of the 19 patients (Fig. 2a, 3a, 4a, and 5a). These CTs appeared to be like those of Group C. The Group A or B finding persisted in 13 of 32 patients until pancreatic cancer was identified on the most recent abdominal CT.

Nine of 41 patients (21.9%) belonged to Group C. PDAC was observed in the pancreatic head in 4, the body in 3, the tail in 1, and the uncinated process in 1 in the most recent CT. The main pancreatic duct was not observed in any of the 9 patients.

3.3. Time period for the development of pancreatic cancer

PDAC was detected within 21.8 months on average (range 2-62 months) in Group A, and within 19 months on average (range 8-38 months) in Group B. In Group C, pancreatic cancer was observed within 70.4 months on average (range 34-128 months).

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In the control group, CTs of 2136 males and 2141 females, mean age 72.6 years old (age range 60-92 years old) were reviewed. The K-shaped sign (Group A) was identified in 7 of the 4277 control patients (0.16%). Five of the 7 control patients showed the K-shaped sign in the pancreatic body and 2 of them showed it in pancreatic tail. Two of the 7 control patients had the K-shaped sign in older abdominal CTs. Six of the 7 control patients with the K-shaped sign have received follow-up CTs for 23 months. The K-shaped sign progressed in one of the 7 control patients in 6 months. Dilatation of the main pancreatic duct also progressed. Thus, Endoscopic retrograde pancreatography (ERP) and serial pancreatic juice aspiration cytological examination (SPACE) were performed. Focal interruption of the main pancreatic duct suggestive of a malignant lesion was visualized on ERP but no malignant cells were detected on SPACE. Distal pancreatomy was performed, and pancreatic tail carcinoma *in situ* was diagnosed pathologically (Fig. 6). Fat tissue was visualized around the K-shaped sign. We could not categorize into Group B in the control group because we were not able to observe enough older CTs in each patient. Thus 4270 of 4277 patients belonged to Group C.

Table 1. CT findings of Group A, B and C.

	CT findings	n=41 (%)	Pancreatic cancer			
			head	body	uncinate process	tail
Group A	K-shaped sign	15 (36.6%)	5	7	1	2
	K-shaped sign with main pancreatic duct visualization	9 (21.9%)	4	5	0	0
Group B	Localized fatty changes	7 (17.0%)	4	0	3	0
	Localized fatty changes with main pancreatic duct visualization	1 (2.4%)	0	0	1	0
Group C	No abnormality	9 (21.9%)	4	3	1	1

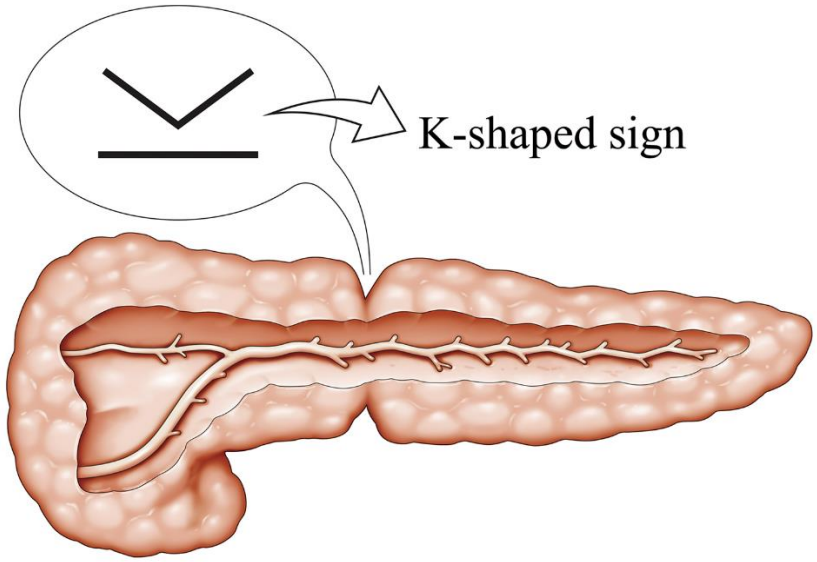

Figure 1. Illustration of the K-shaped sign. The K-shaped sign indicates the localized constriction of the pancreatic parenchyma. It resembles a "K" on CT axial images. The main pancreatic duct is maintained without dilatation even though localized constriction of the pancreatic parenchyma is visualized. Therefore, this pancreatic change is not related to the main pancreatic duct in the early stages.

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Figure 2. Group A (the K-shaped sign in the pancreatic body). **(a)** April 2005: The pancreatic body shows no evidence of pancreatic abnormalities (circle). **(b)** January 2013: The K-shaped sign is visualized in the pancreatic body (circle). **(c)** December 2016: A poorly enhanced lesion suggestive of pancreatic body cancer with main pancreatic duct dilatation is observed in the area of the K-shaped sign (circle).

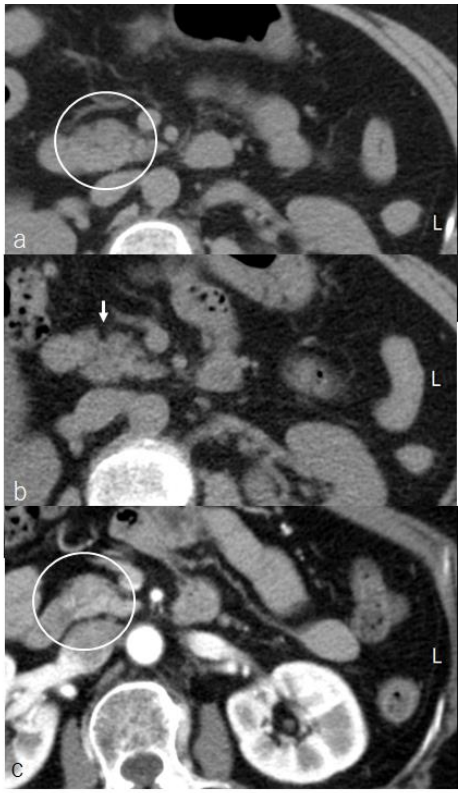

Figure 3. Group A (the K-shaped sign in the pancreatic head). **(a)** May 2004: The pancreatic head has a normal appearance (circle). **(b)** September 2012: A slit-like low density area suggestive of the K-shaped sign is observed (arrow). **(c)** Pancreatic head cancer is present instead of the K-shaped sign (circle).

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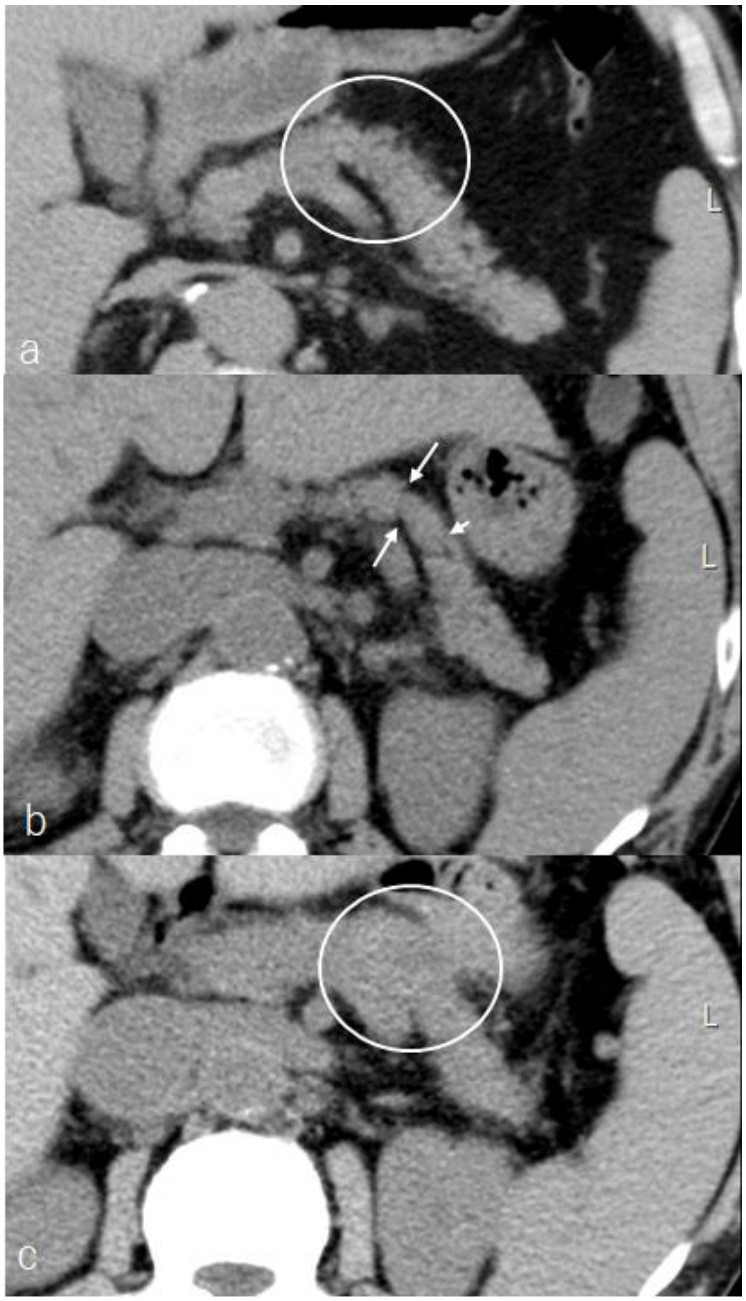

Figure 4. Group A K-shaped sign with the main pancreatic duct in the pancreatic body. **(a)** March 2003: The pancreatic body has a normal appearance (circle). **(b)** August 2011: The K-shaped sign (arrow) and main pancreatic duct (arrowhead) are observed. The main pancreatic duct is intermittent in front of the K-shaped sign. **(c)** August 2013: Pancreatic body cancer is present in the K-shaped sign area (circle).

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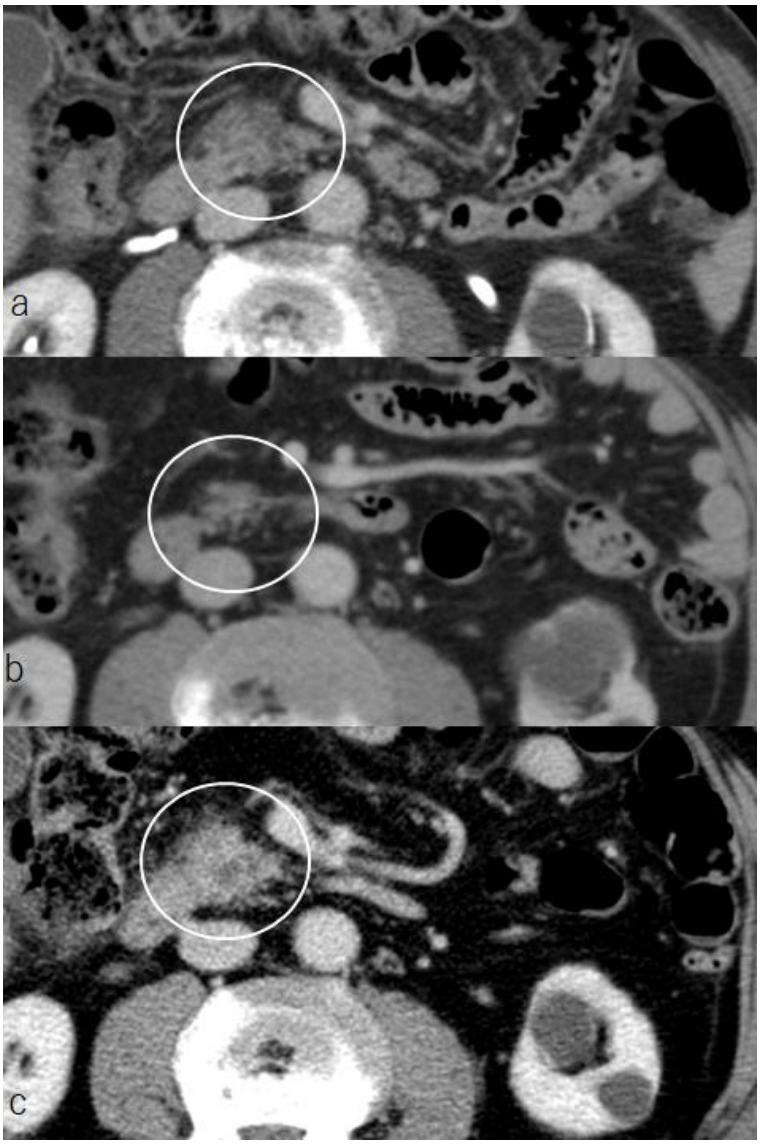

Figure 5. Group B (Localized fatty changes in the pancreatic uncinate process). **(a)** August 2014: The pancreatic uncinate process (circle) and other pancreatic areas (not shown) already exhibit diffuse fatty changes. **(b)** July 2016: Localized fatty changes in the pancreatic uncinate process have progressed (circle). **(c)** January 2017: An irregularly shaped, poorly enhanced lesion, known as pancreatic uncinate cancer, is present (circle). Localized fatty changes have disappeared (circle).

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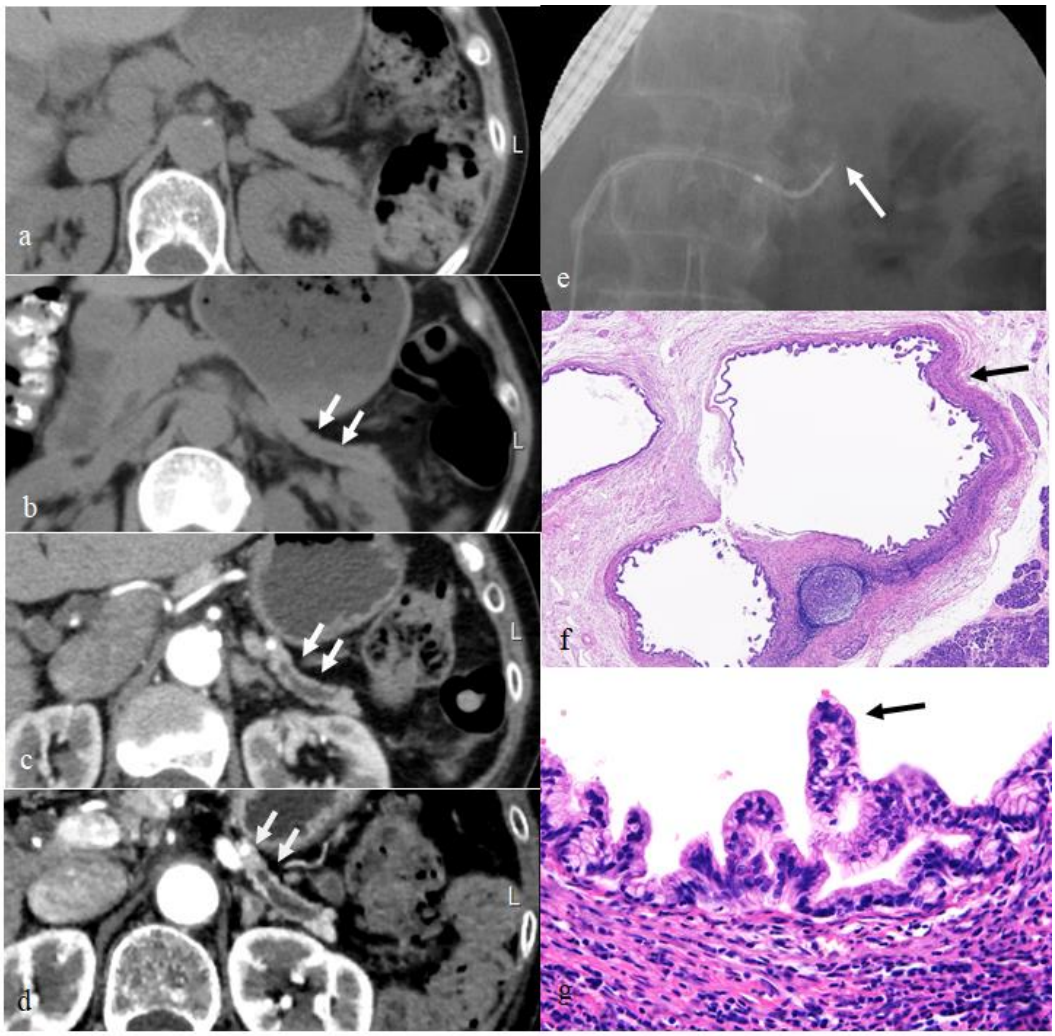

Figure 6. Pancreatic tail cancer in situ. **(a)** June 2009: A slit-like low density area which does not meet criteria of the K-shaped sign is visualized in the pancreatic tail. Main pancreatic duct without dilatation is seen. (arrows). **(b).** June 2010: Pancreatic tail shows the K-shaped sign and main pancreatic duct (arrows) with slightly atrophic change. **(c)** June 2017: Main pancreatic duct dilatation is progressing (arrows). Interruption of the main pancreatic duct is visualized at the area of the K-shaped sign but pancreatic cancer is not detected. **(d)** October 2017: Main pancreatic duct dilatation is getting worse. Then, we suspected pancreatic cancer and performed ERP. **(e)** ERP: The main pancreatic duct is interrupted at the pancreatic tail (arrow). **(f)** H-E stain (low power view): The pancreatic ducts are cystically dilated (arrow). **(g)** H-E stain (high power view): the ductal cells have mildly enlarged nuclei with condensed chromatin, and they form complex papillary structures. No invasion is recognized. These findings are consistent with carcinoma *in situ*.

4. Discussion

Our results suggest that the K-shaped sign and localized fatty changes are the earliest CT findings indicating pancreatic abnormalities. On CT, the K-shaped sign appeared to be composed of dense fat tissue and consequently narrowing the pancreatic parenchyma. This appearance was similar to localized fatty changes. Localized fatty changes were clearly observed in the pancreatic head and uncinate process, and gradually decreased the sizes of both areas. Based on these results, the K-shaped sign and localized fatty changes are the same finding but occur in different areas.

The K-shaped sign was also visualized in the very rare cases of the control group. The specificity was 99.9% and predictive value of a positive test is 14.3%. In addition, one patient who belonged to the control group was diagnosed as pancreatic cancer *in situ*. Those results suggest that the K-shaped sign is a special finding for early detection of pancreatic cancer, and when identified, follow-up CT evaluations are needed.

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Gangi et al. [3] reported that the earliest finding consistently detected in pancreatic cancer was pancreatic duct dilatation, followed by pancreatic duct cut off and a pancreatic mass. Their CT findings indicated an obstruction of the main pancreatic duct due to PDAC. In the present study, a pancreatic duct abnormality was not identified as the only CT finding, the K-shaped sign or localized fatty changes were also observed. Although our CT findings did not show PDAC itself, they are novel findings that predict early pancreatic abnormalities.

The fatty tissue responsible for creating the K-shaped sign has yet to be identified. Hori et al.[4] examined pancreatic fatty infiltration histopathologically and reported a positive relationship between the extent of fatty infiltration in the pancreas and pancreatic ductal adenocarcinoma. Kikuyama et al. [5] identified 3 cases of pancreatic carcinoma *in situ* and reported that pancreatic carcinoma *in situ* had a high fatty change of the parenchyma adjacent to the lesion on CT. Toyama et al. [6] reported a case of pancreas head carcinoma associated with fat replacement of the body and tail and considered that obstruction of the main pancreatic duct by a cystic lesion or carcinoma in the pancreas head is a possible cause of fatty degeneration of the pancreatic parenchyma. Those reports suggest that fatty changes of pancreas are related to occurrence of pancreatic cancer and support our present CT results.

We used 3 different CT machines in the present study because pancreatic abnormalities were monitored over a long period of time. Since 1998, multi-detector row CT (MDCT) has offered a faster volume coverage speed with no loss of image quality, which facilitates optimal pancreatic parenchymal and peripancreatic vascular enhancements [7-9]. We agree that MDCT is the gold standard machine currently used worldwide to diagnose pancreatic cancer, and facilitates the generation of multiplanar reconstructions, such as curved planar reformations, thereby providing the potential to enhance the detection and staging of pancreatic cancer.

However, MDCT is not sufficiently sensitive to detect small tumors; the sensitivity of MDCT to tumors that are less than 10 mm in diameter is only 33-44% [10]. The K-shaped sign that we identified on CT could be observed in all areas of the pancreas without using thin slices and could be identified using any abdominal CT, including non-contrast CT, single helical CT, and MDCT. Therefore, the K-shaped sign is ideal for the screening of early pancreatic cancer. Only the shape of the pancreas needs to be examined to identify pancreatic abnormalities, such as early pancreatic cancer, pancreatic cancer *in situ*, and the pre-status of pancreatic cancer.

The period during which pancreatic cancer develops after the K-shaped sign is detected remains unclear. In the present study, we used abdominal CT, which was performed incidentally. Groups A and B showed pancreatic cancer on CT within 19-21.8 months. This result may be used as a rough standard for the progression of pancreatic cancer from the K-shaped sign and localized fatty changes. Therefore, when the K-shaped sign or localized fatty changes are observed, *in situ* or PDAC might be anticipated within 21.8 months. Six patients in the control group seemed to have "false positive" findings, but they have not yet been followed-up long enough to exclude subsequent pancreatic cancer.

Pancreatic cancer developed after a longer period of time in Group C than in the other groups. The K-shaped sign may have been visualized in these patients if they underwent abdominal CT for several times before pancreatic cancer was diagnosed.

5. Limitations

The present study had some limitations. Since it was a retrospective study, a prospective study needs to be performed to establish when and how patients with the K-shaped sign will develop pancreatic cancer. Furthermore, we were unable to perform abdominal CT under the same conditions because different machines were used throughout the duration of the present study. In addition, the examined abdominal CTs were performed incidentally and not to examine the pancreas; Thus, we were unable to align the period of abdominal CT for the detection of pancreatic cancer. Moreover, it is difficult to quantify the constriction of the pancreas on this present CT study. CT volumetry may be a good tool for measuring the rate of reductions in the volume of the pancreas.

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6. Conclusion

The K-shaped sign including localized fatty changes appears to be the earliest CT sign for patients with pancreatic abnormalities. The K-shaped sign does not indicate pancreatic cancer itself but may predict its future development. If the K-shaped sign is observed on CT, patients need to be carefully followed up and subsequent examinations, such as EUS and ERCP, considered for the early detection of pancreatic cancer.

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Statement of Ethics: This study was approved by the Institutional Review Board of Tokyo Dental College Ichikawa General Hospital. All procedures performed in present study involving human participants were in accordance with the ethical standards of institutional and/or national research committees and the 1964 Declaration of Helsinki and its later amendments or similar ethical standards. Written informed consent for inclusion in this study was obtained from patients prior to performing CTs

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Author Contributions: MJ was responsible for conception, design, and quality control of this study. KY and MJ performed the study selection, data extraction, statistical analyses and were major contributors in writing the manuscript. MJ performed pancreatectomy and reviewed and edited the manuscript. All authors have read and approved the final version of the manuscript.

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