

# Purpose

- We treated 241 patients who had an advanced pancreatic cancer from January 2011 to December 2016. All were advanced pancreatic cancer and 42 of the 241 patients (17.4%) could have surgery. We must find a small and early stage of pancreatic cancer as possible as we can.
- However, as the pancreatic cancer has the most malignant potential in all cancers and gets worse quickly, we are not sure when an early pancreatic cancer appears and how it grows.
- So our aim is to find a key finding of pancreatic abnormality on CT, just before the pancreatic cancer appears.

# Material & Methods

- We selected 32 patients (18 males and 14 females, mean age was 75 years old) with pancreatic cancer.
- Before we diagnosed their pancreatic cancer, they all took abdominal CT more than at least one time with various reasons (Table 1).
- Thirteen of the 32 patients had pancreatic head cancer, 12 of them had pancreatic body cancer, 5 of them had uncinate process of the pancreas, and 2 of them had pancreatic tail cancer (Table 2).
- We reviewed all patients' abdominal CT and checked how abnormal findings appeared in the pancreas before finding their pancreatic cancer.
- We also checked how much period the pancreatic cancer occurred in

Table 1. Details of diseases patients had.

Disease	No
Abdominal discomfort	17
Pre-/post operation of cancer	6
Diabetes mellitus	5
Follow up of aortic aneurysm	2
Urinary tract abnormality	2
Total	32

Table 2. Details of pancreatic cancer

Distribution of Pancreatic Cancer	No
Head	13
Body	12
Uncinate process	5
Tail	2
Total	32

# Results

- Twenty-four of the 32 patients (75%) had a localized pancreatic shrinkage before appearing the pancreatic cancer. We called it “K-shaped sign” (Figure 1, Figure 2-4).
- Fifteen of the 24 patients (47%) showed an isolated K-shaped sign (Figure 2, 3).
- Nine of the 32 patients (28%) had both the K-shaped sign and visualization of the main pancreatic duct with/without abnormal dilatation (Figure 4). Four of the 9 patients (44%) had both K-shape sign and a partial main pancreatic duct dilatation which was more than 3mm (Figure 5).
- Eight of the 32 patients (25%) had localized fatty change of pancreas which will become a pancreatic cancer in future (Figure 6, 7).

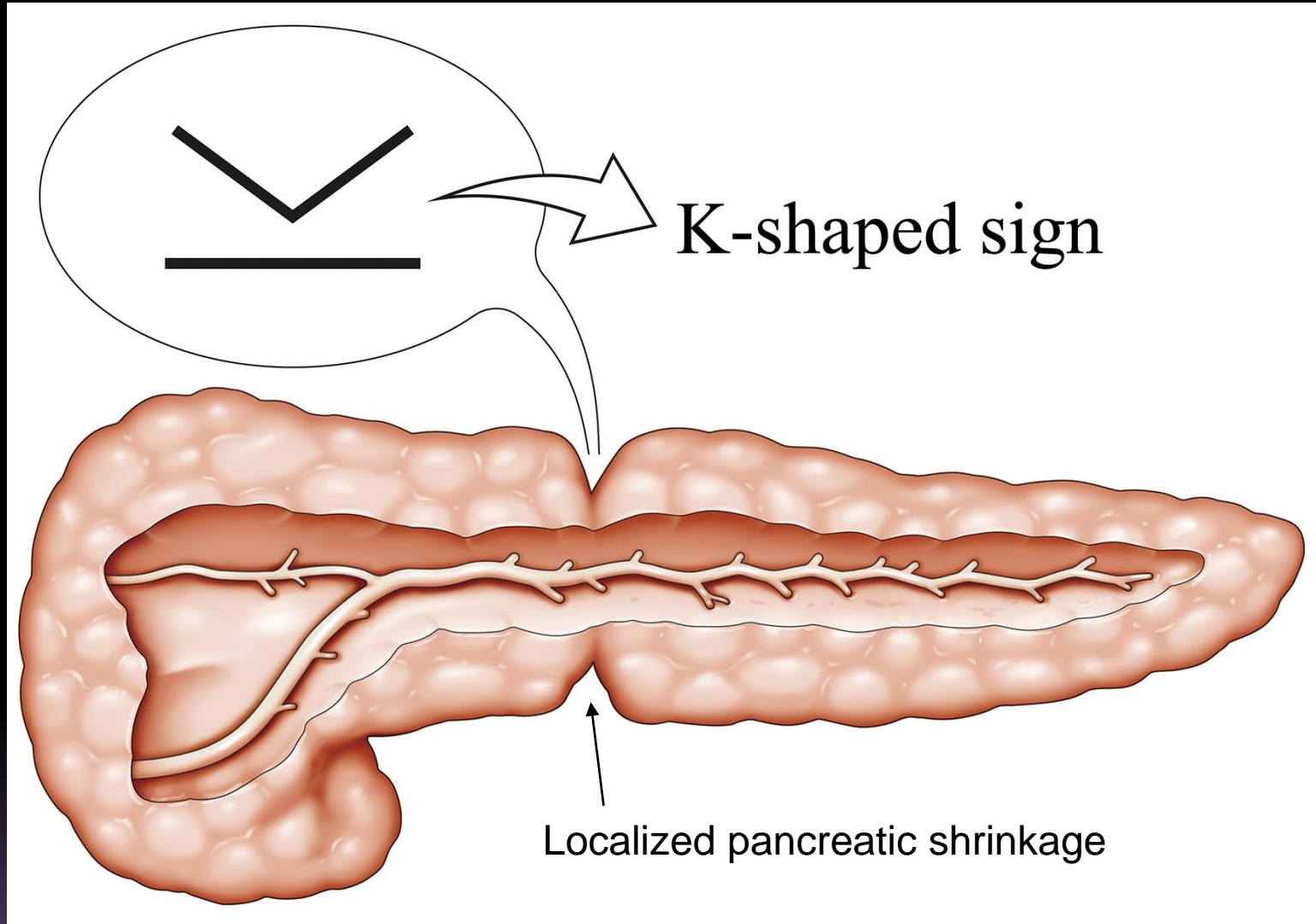
# Results

- Eight of the 32 patients had surgery for their pancreatic cancer: three of the 8 patients had PPPD and 5 of them had DP. All 8 patients had the K-shaped sign on CT. After surgery, six of the 8 patients had a localized shrinkage area which was suggestive of the K-shaped sign (Figure 3, 5). In addition, all 8 patients had fibrotic change along the pancreatic cancer.
- K-shaped sign with/without pancreatic duct dilatation was prominently seen in the pancreatic body and head cancer. On the other hand, focal fatty change of pancreas was not seen in the pancreatic body cancer (Table 3).
- Nineteen of the 32 patients had a normal pancreas on CT before the K-shaped sign occurred.
- Thirteen of the 32 patients had detected the K-shaped sign since the initial abdominal CT. All the 32 patients had the pancreatic cancer in the K-shaped sign's area.
- Pancreatic cancer occurred in 21.1 months in average (range 2-62 months) after detecting of the K-shaped sign.

# Table 3. CT findings before clinical diagnosis of Pancreatic cancer

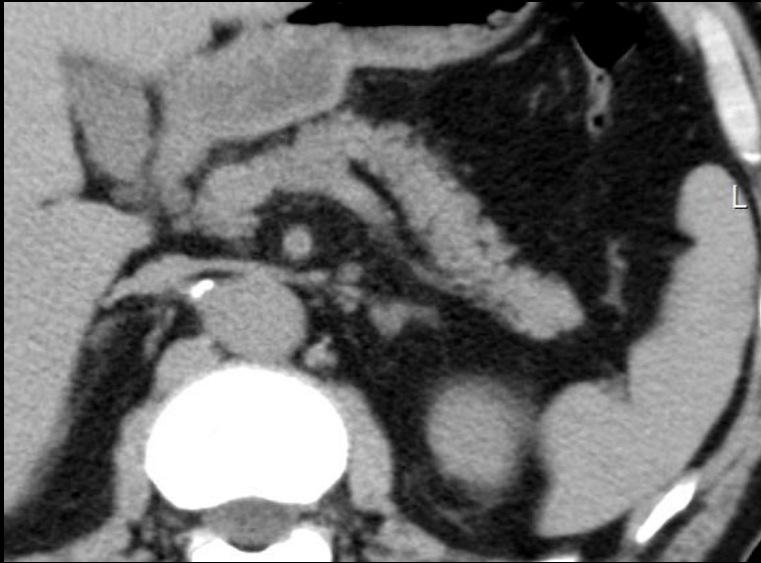
CT findings	Number (n=32)	Pancreatic cancer			
		head	body	uncinate	tail
K-shaped sign	15	5	7	1	2
K-shaped sign and pancreatic duct dilatation	9	4	5	0	0
Localized fatty change of pancreas without K-shaped sign	8	4	0	4	0
Pancreatic duct dilatation	0	0	0	0	0

# Figure 1. K-shaped sign

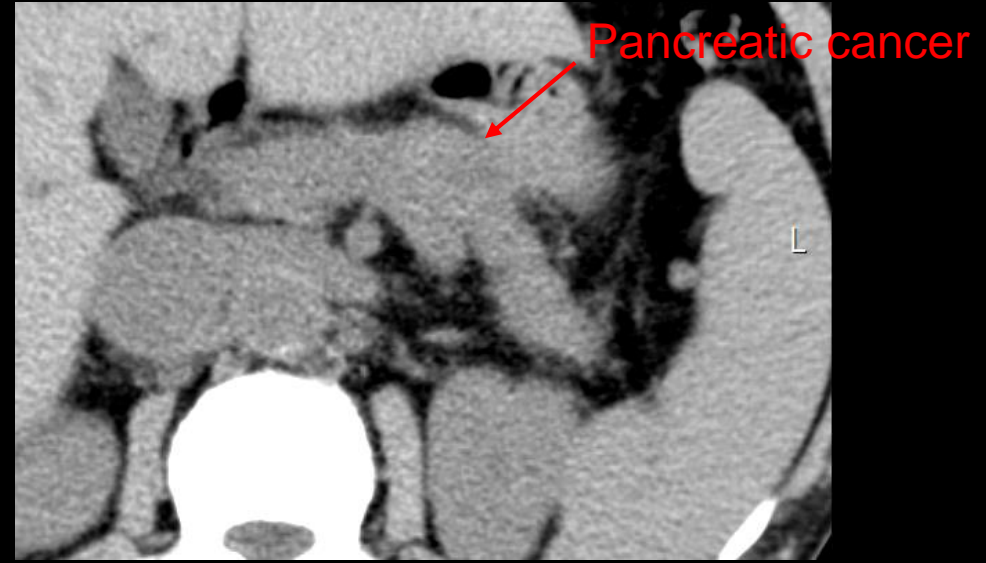


# Figure 2. Change of the pancreas

## Normal pancreas→K-shaped sign→Pancreatic cancer



a. 18 March 2003



c. 8 October 2013



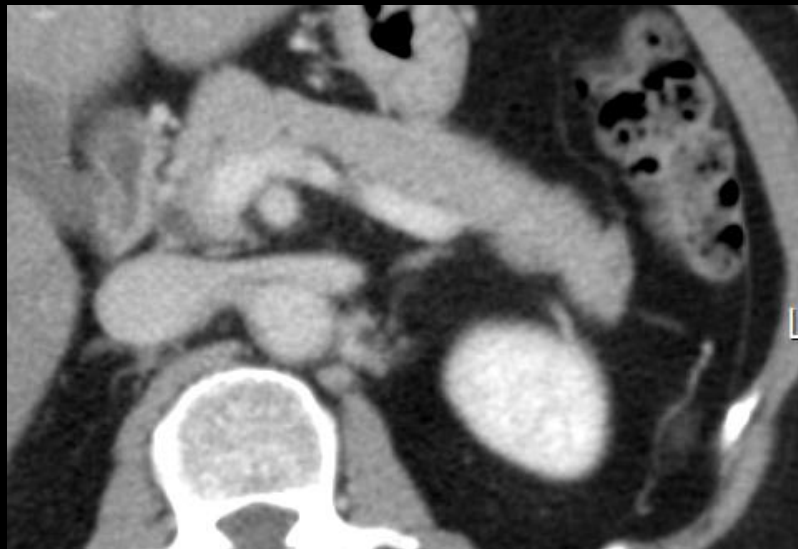
b. 8 August 2011

a. In 2003, the pancreas looks normal without main pancreatic duct dilatation.

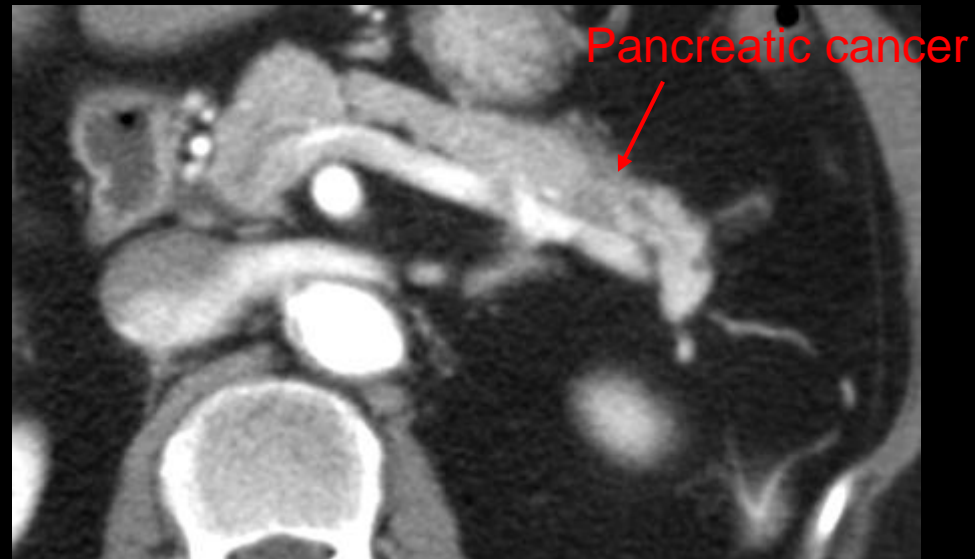
b. In 2011, The pancreatic body shows K-shaped sign (arrows). No main pancreatic duct dilatation is seen.

c. Pancreatic body cancer is visualized in the K-shaped sign's area (arrow).

# Figure 3. Change of the pancreas (Typical K-shaped sign)



a. 22 October 2007



c. 8 August 2012



b. 30 October 2011

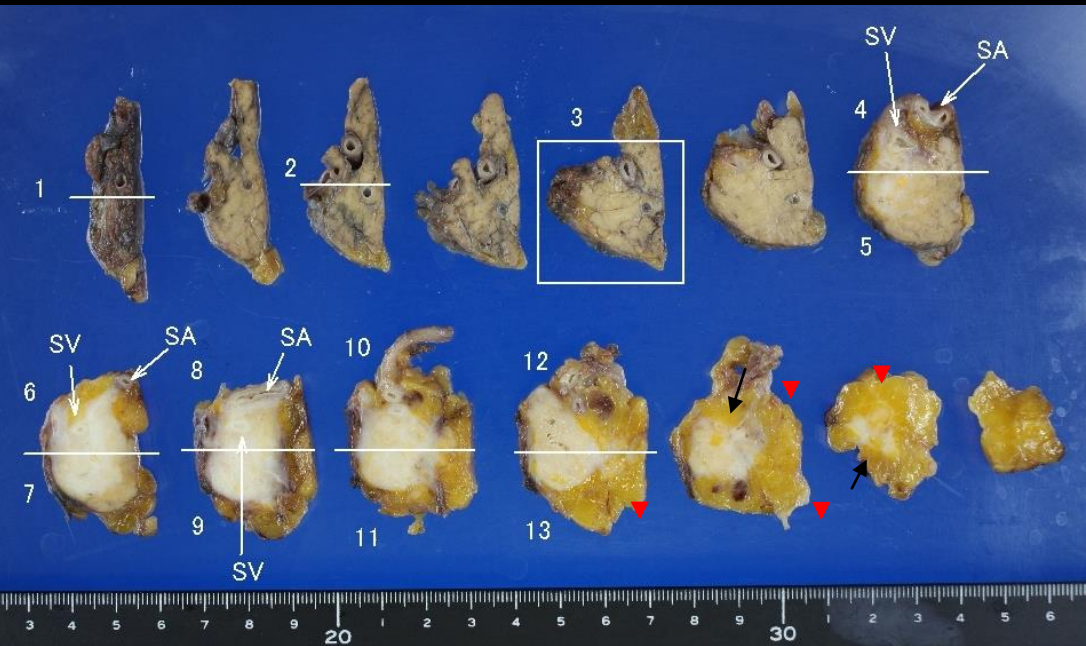
a. In 2007, the pancreas looks normal without main pancreatic duct dilatation or fatty infiltration.

b. In 2011, The pancreatic tail shows typical K-shaped sign (arrows). Localized fatty change of the pancreas occurs. Main pancreatic duct is not visualized on this CT.

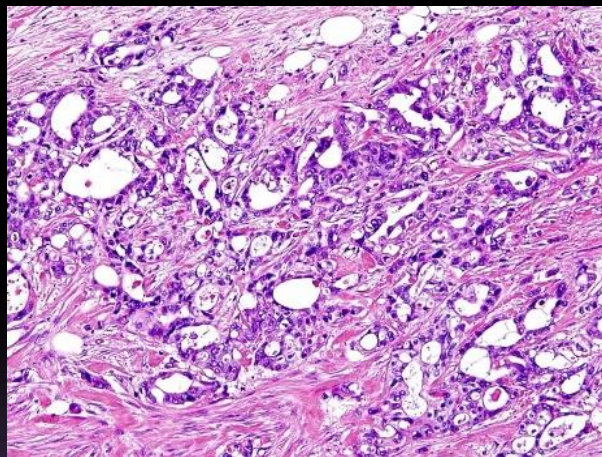
c. Pancreatic tail cancer is visualized in the K-shaped sign's area (arrow).

## Figure 3 (Pathology)

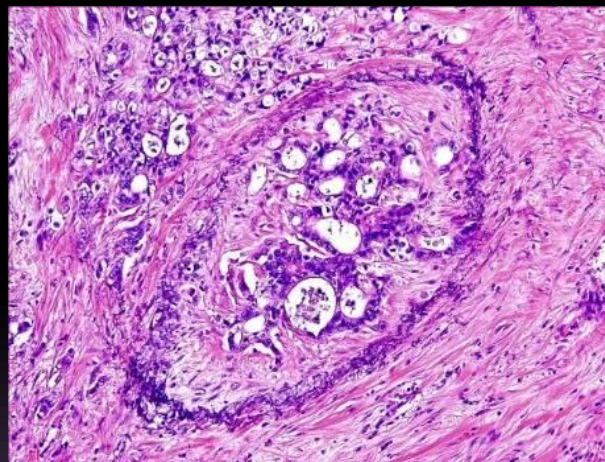
Invasive ductal carcinoma,  
tubular adenocarcinoma, pDPM(-),  
pN1(+), cy(+), R0 moderately-  
differentiated (tub2), TS2 (22mm),  
nodular, IMF $\beta$ , ly1, v3, ne1, mpd(-),  
pS(+), pRP(+), pA(-), pPVsp(+),  
pPLspa(+), pPCM(-)  
T4N1M0 (cy(+), fStage IVa



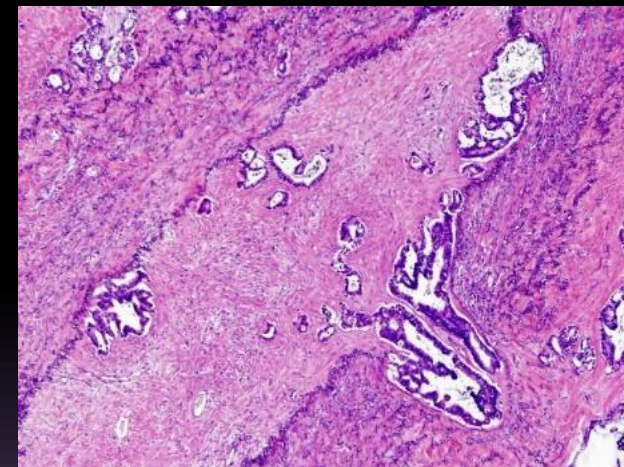
d. Macroscopic specimen: Rudimentary K-shaped sign is visualized (arrows). Fat tissue around the pancreatic cancer and rudimentary K-shaped sign is also seen (arrowheads).



e. Pancreatic cancer  
fibrous change is visualized  
along the cancer.

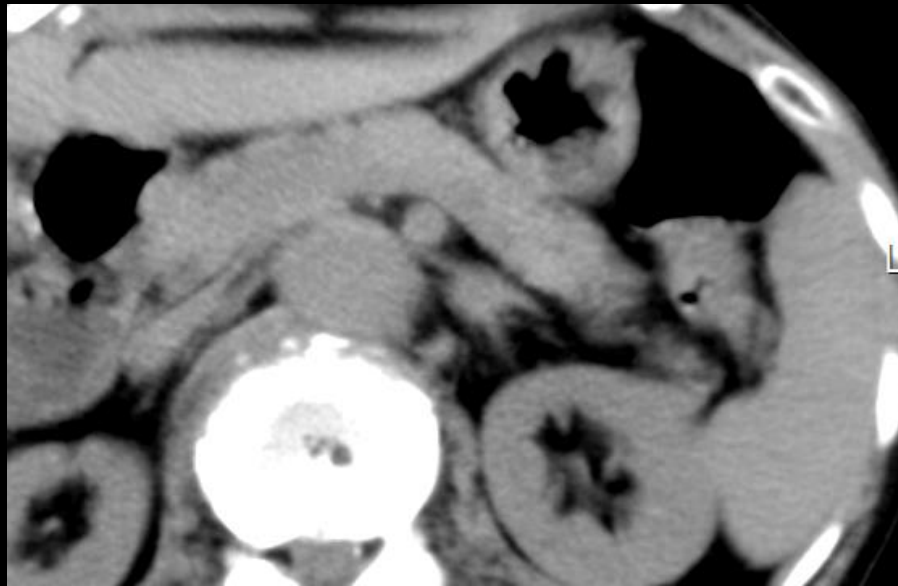


f. Arterial involvement



g. Venous involvement

# Figure 4. K-shaped sign and visualization of pancreatic duct

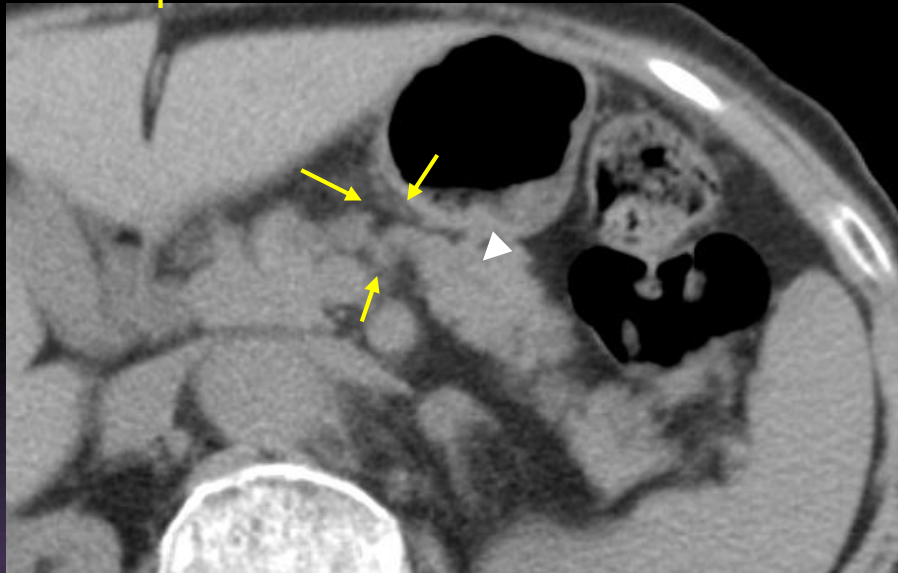


a. 6 April 2005



Pancreatic cancer

c. 1 December 2016



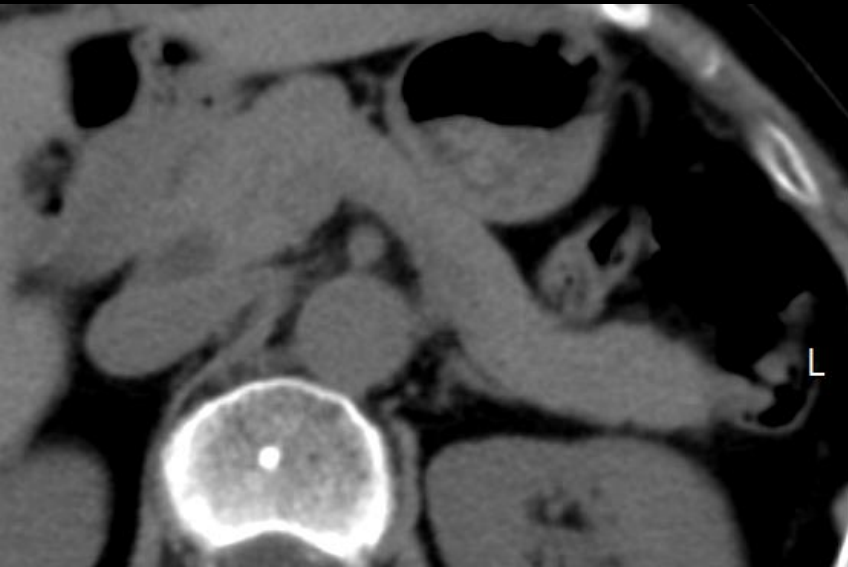
b. 28 January 2013

a. In 2005, the pancreas looks normal.

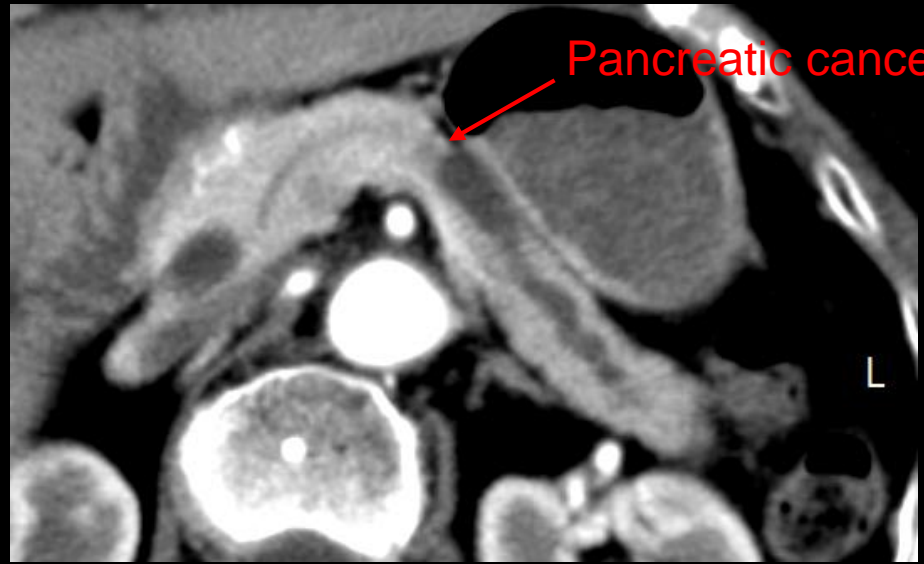
b. In 2013, both K-shaped sign (arrows) and pancreatic duct (arrowhead) are seen. The pancreatic duct is normal size.

c. Pancreatic body cancer is visualized in the K-shaped sign's area (arrow).

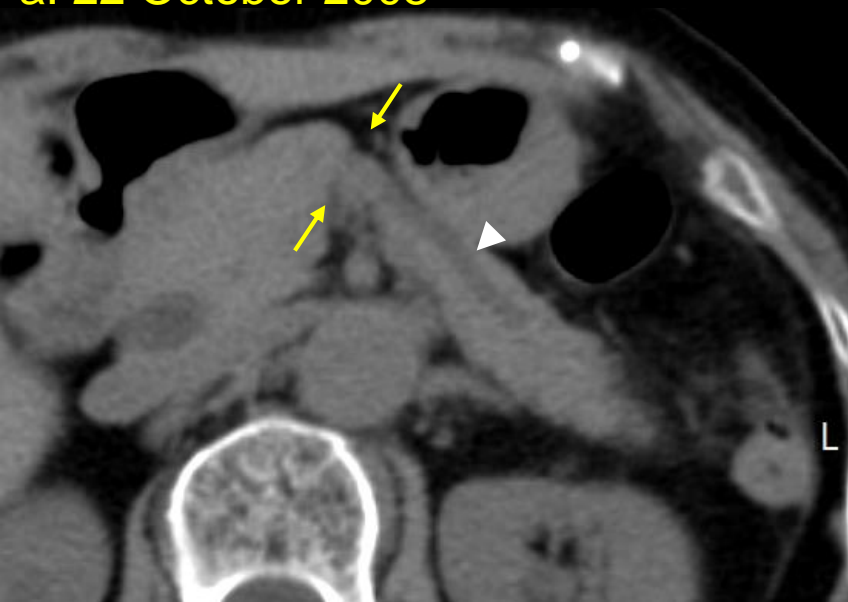
## Figure 5. K-shaped sign with main pancreatic duct dilatation.



a. 22 October 2008



c. 17 August 2016



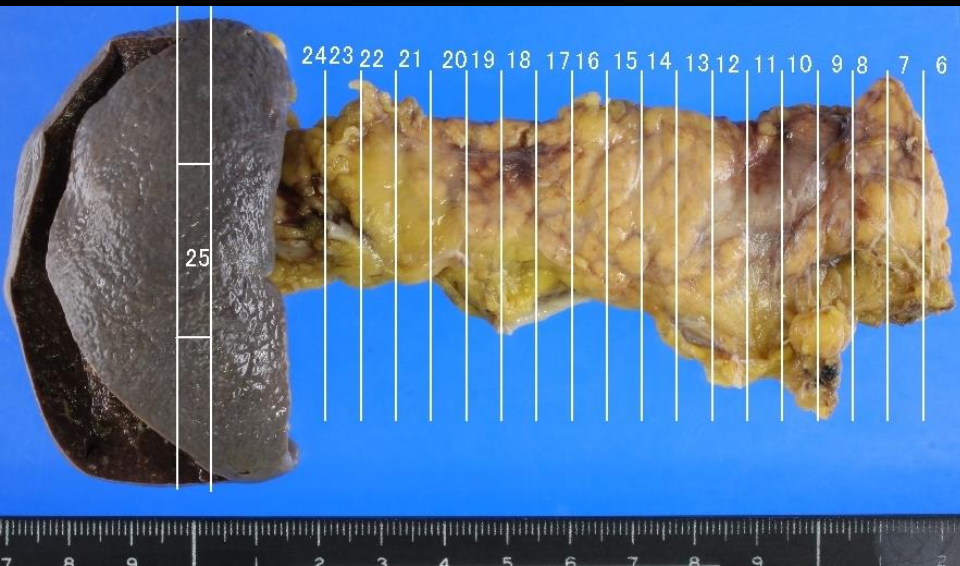
b. 24 June 2016

a. In 2008, the pancreas looks normal.

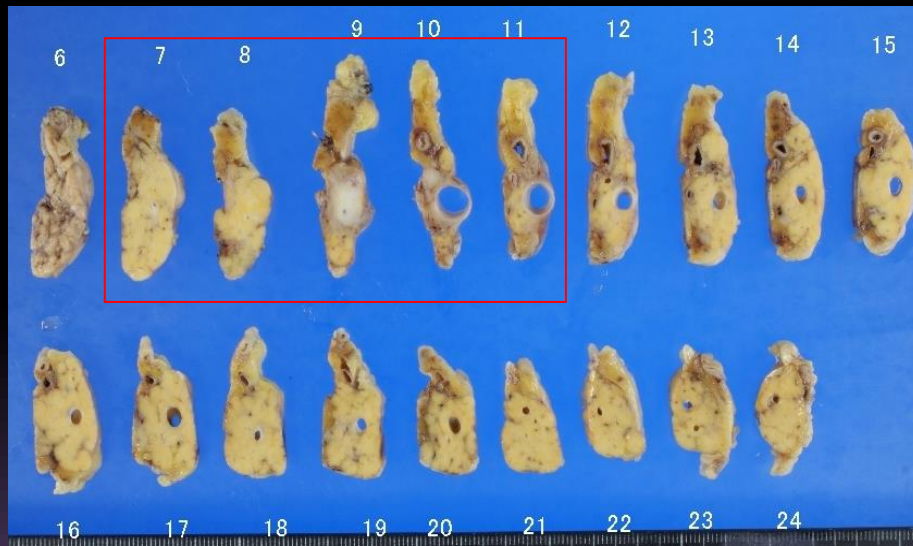
b. In 2016, The pancreatic body has K-shaped sign (arrows). Main pancreatic duct dilatation also occurs (arrowhead).

c. The main pancreatic duct dilatation is getting worse. The pancreatic cancer is visualized in front of it (arrow).

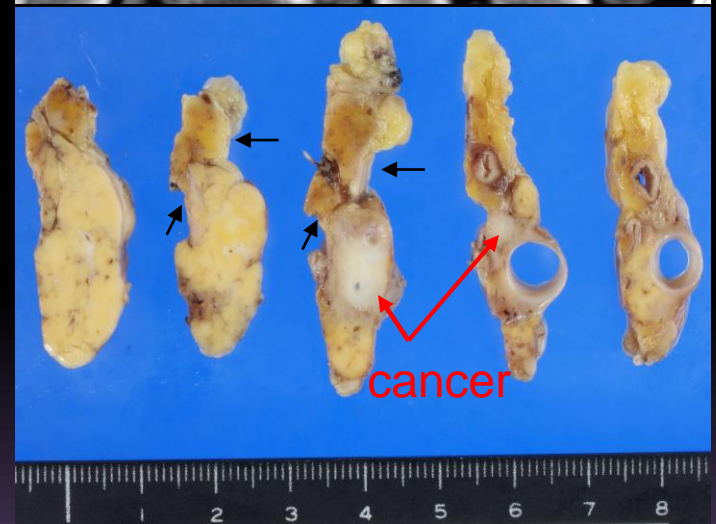
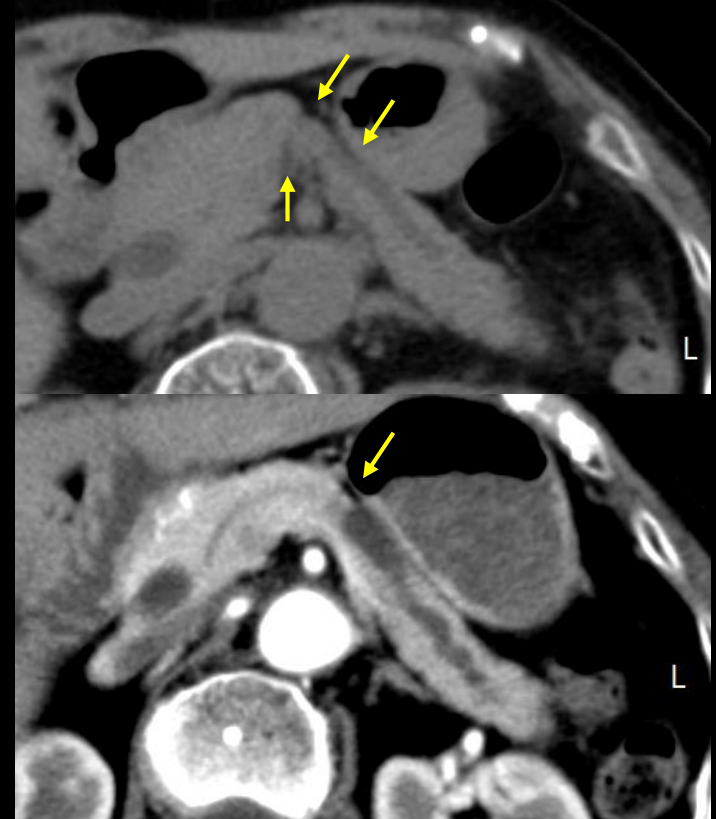
# Figure 5 (Pathology)



d. Pancreatic body and spleen

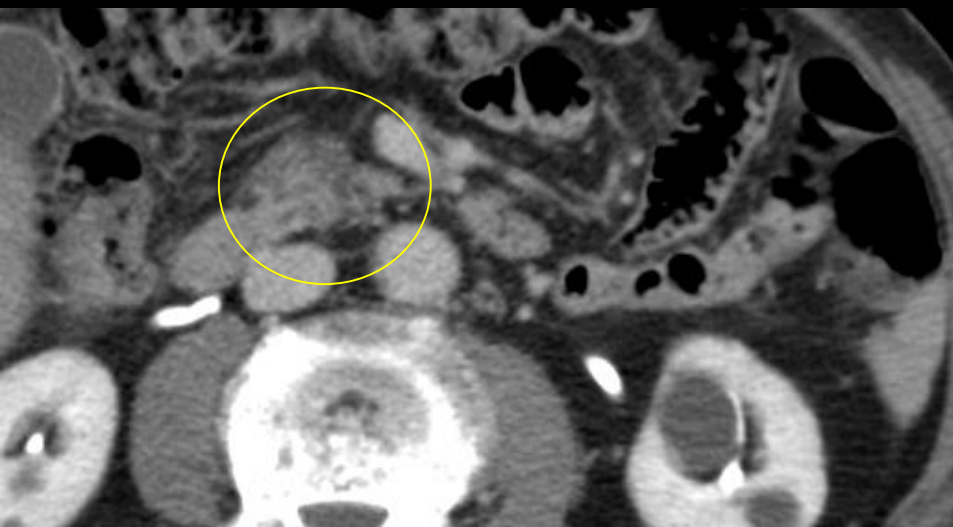


e. Macroscopic specimen

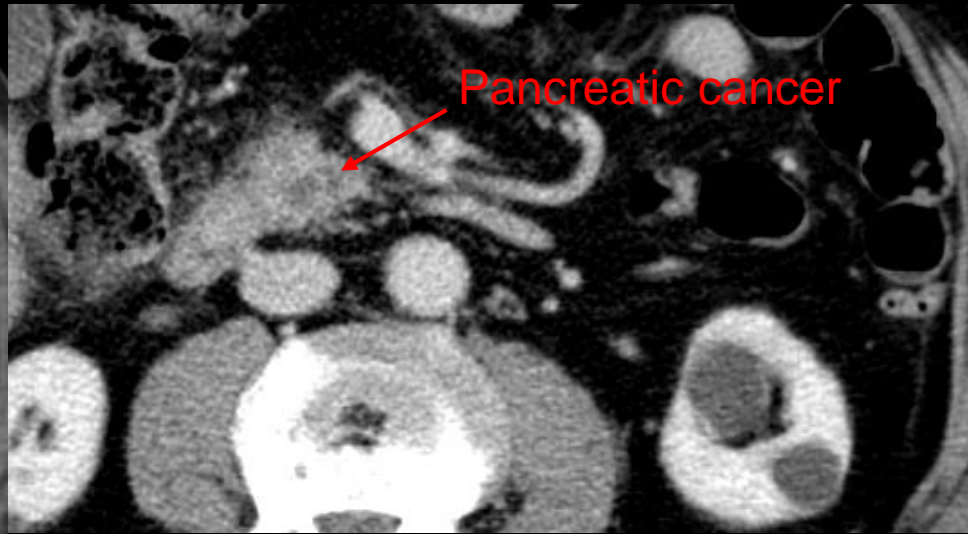


f. Rudimentary K-shaped sign (arrows)

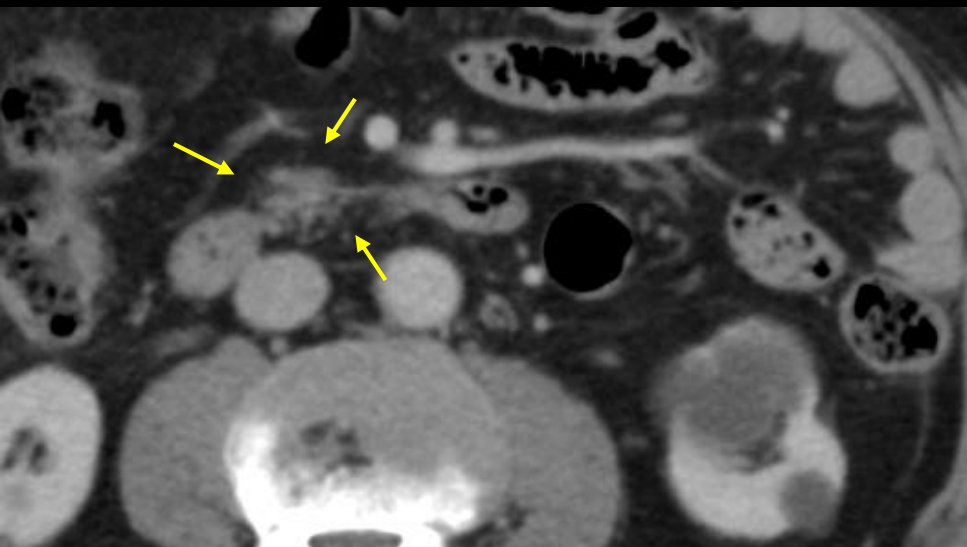
## Figure 6. Localized fatty change of the pancreas



a. 21 August 2014



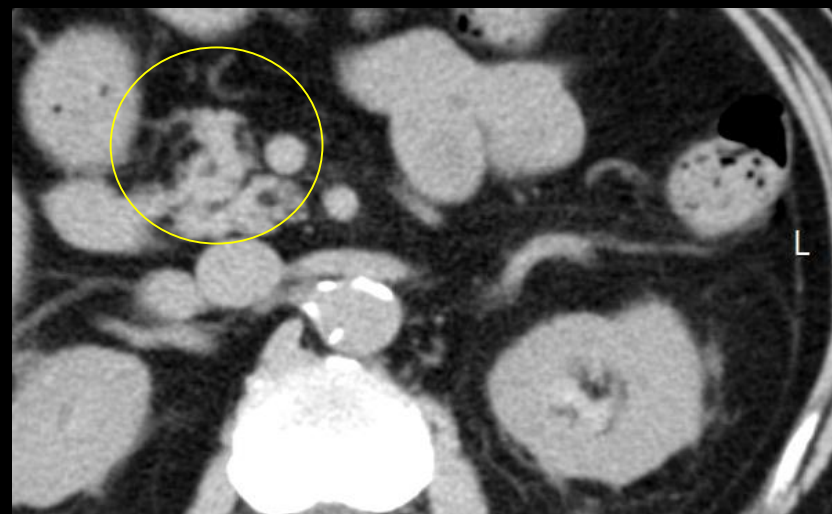
c. 10 January 2017



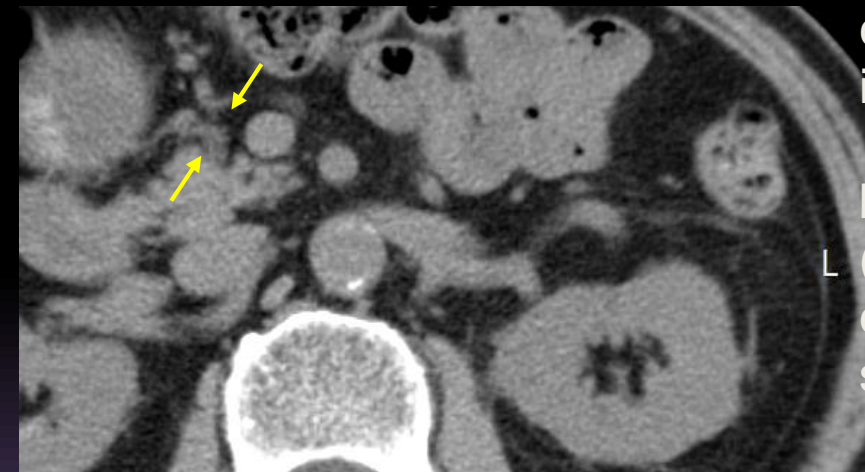
b. 5 July 2016

- a. The pancreatic head shows mixed high and low density suggestive of fatty Infiltration (Circle).
- b. About 2 years later, The pancreatic head is smaller than the previous CT (a). Localized fatty change of the pancreas is progressing (arrows).
- c. In 2017, low density mass suggestive of pancreatic cancer is visualized in that Localized fatty area (arrow).

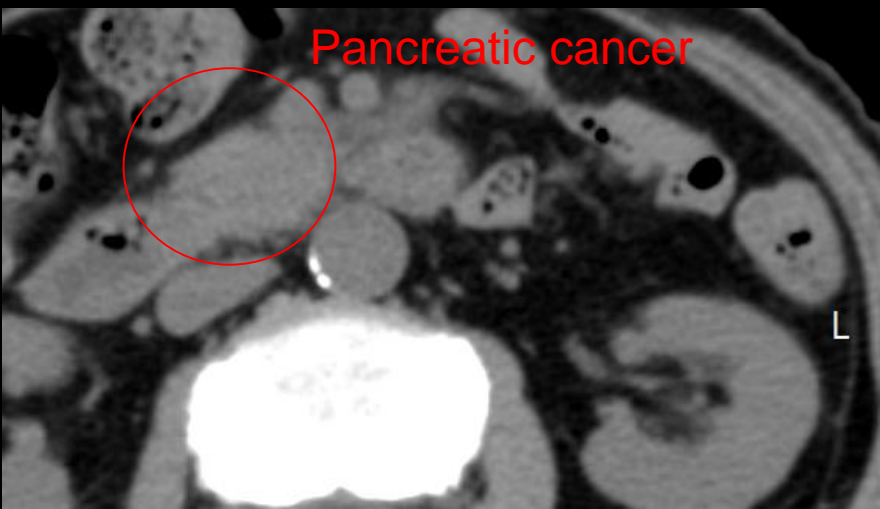
# Figure 7. Localized fatty change of pancreas in the uncinate



a. 15 November 2011



b. 12 June 2014



c. 23 February 2016

a. The pancreatic head shows Localized fatty change (circle). However, pancreatic head cancer is not detected.

b. That focal fatty change is getting progressing (arrows). It doesn't look K-shaped sign but extreme progression of the fatty change may suggest presence of the early pancreatic cancer.

c. Pancreatic head cancer occurs in that area (circle).

# Discussion

- Detection at an earlier stage is the cornerstones of reducing pancreatic cancer death rates. Also, earlier detection would allow the down staging of locally unresectable disease to allow resection, potentially reducing the risk of metastatic disease (1). Therefore, many researchers have tried to find features of an early stage of pancreatic cancer on several modalities for many years. For example, Gangi S et al (2) reported that pancreatic duct dilatation and cutoff were early findings associated with the development of pancreatic cancer and could be detected on CT with a high degree of reproducibility (2, 3). Although they didn't mention about how dilatation of the main pancreatic duct was abnormal, those pancreatic duct abnormalities they suggested have been one of the greatest key findings to detect pancreatic cancer. In our study, all patients with the pancreatic duct dilatation included the K-shaped sign. In addition, fifteen of the 32 patients had the K-shaped sign before the pancreatic duct dilatation appeared. It suggests that the K-shaped sign is an earlier sign of the pancreatic cancer than the pancreatic duct dilatation.

- In regard to the distribution of the K-shaped sign, it was well detected in the pancreatic body and head in our study. Pancreatic head and body were seen in a lot of slices on CT, so detecting the pancreatic shrinkage in those areas was easier than other areas on CT. However, the uncinate process of pancreas was different from other areas because of its individual difference. The pancreatic uncinate process is usually small and tends to have fatty change which is related or not related to pancreatic cancer. Therefore, the K-shaped sign may be difficult to form in the uncinate process of the pancreas.

# How is the K-shaped sign formed?

- From pathological findings, we assume the K-shaped sign consists of fatty infiltration of pancreas with unknown etiology. Interestingly, in our study, eight of the 32 patients had localized fatty change of pancreas in either head or uncinate although they didn't have the K-shaped sign, and pancreatic cancer arose from those areas. The localized fatty change of pancreas may be a part of the K-shaped sign.
- If we postulate that, we need to check how many normal people have fatty infiltration in their pancreas. Schwenzer NF et al (4) reported that fat deposits are larger in the body and tail than in the head of the pancreas. However, in our study, eight of the 32 patients had focal fatty change in their pancreatic head or uncinate process. Their study group consisted of all type 2 diabetes volunteers (only 5 of the 32 patients had diabetes in our study group), so other mechanisms such as vascular disorder might be added to the pancreas more than that of our study group.

- Saisho (5) reported that pancreas volume and pancreatic fat increase with obesity. Pancreatic fat is characterized by adipocyte infiltration in the interlobular and intralobular pancreas and called pancreatic steatosis (5, 6). That disease used to be considered an innocuous condition, a bystander of many underlying diseases, but now, evidence that pancreatic steatosis (strongly associated with obesity and the metabolic syndrome) has a role in type 2 diabetes mellitus, pancreatic exocrine dysfunction, acute pancreatitis, pancreatic cancer and the formation of pancreatic fistula after pancreatic surgery is emerging (5, 6). We are not sure how many patients we studied is called pancreatic steatosis nor how many pancreatic steatosis will progress to the pancreas cancer. However, a lot of fatty deposits may have a high potential for causing a pancreatic cancer.

- On the other hand, pancreatic cancer usually elicits an intense desmoplastic (stromal) reaction to pancreas (7, 8). This desmoplastic reaction is composed of fibroblasts, inflammatory cells, endothelial cells and a complex extracellular matrix, and is associated with significantly increased interstitial fluid pressure within the tumor. This elevated interstitial fluid pressure has been hypothesized to be an impediment to perfusion of the tumor, explaining the low attenuation seen on contrast enhanced CT and MRI imaging (7, 8). Stroma production is stimulated by cancer-cell derived growth factors including transforming growth factor- $\beta$  (TGF $\beta$ ), hepatocyte growth factor (HGF), fibroblast growth factor (FGF), insulin-like growth factor 1 (IGF-1) and epidermal growth factor (EGF) (9). The stroma can form up to 90% of the tumor volume, a property which is unique to pancreatic cancer (10).
- The K-shaped sign doesn't point out a pancreatic cancer itself (when the K-shaped sign appears, there is not the pancreatic cancer yet). So those growth factors and fibrotic change may not be related to the form of the K-shaped sign. To solve this mystery of the K-shaped sign, we should detect many pancreatic cancers such as carcinoma in situ of pancreas using the K-shaped sign, and compare CT findings with pathological findings.

# Limitations

- We know some limitations on our study.
- Firstly, our study was small. Secondly, if there is no CT which was taken before having pancreatic cancer, we are not able to detect the K-shaped sign. Thirdly, we don't know whether normal people have localized fatty change or not. Regarding this point, we need to make a control group which doesn't have any pancreatic disease.

# Conclusion

- In conclusion, the K-shaped sign is best sign for detecting a pancreatic abnormality which will become a cancer. It appears earlier than the pancreatic duct dilatation. The K-shaped sign consists of localized fatty infiltration into pancreas with unknown etiology. Pancreatic parenchyma is replaced with fatty deposits and shows the K-shaped sign in the pancreas, especially pancreatic body and head. Localized fatty change of pancreatic head and uncinate may be a part of the K-shaped sign.

# References

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