



Reducing the risk of postoperative pancreatic fistula in radical gastrectomy: pre-assessment with computed tomography for the diagnosis of pancreatic steatosis

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Abstract

Purpose To determine whether pancreatic steatosis (PS) is associated with the risk of postoperative pancreatic fistula (POPF) after radical gastrectomy, and if so, to investigate whether pre-assessment by diagnostic imaging can mitigate the risk.

Methods The clinical records of 276 patients with cStage I gastric cancer who underwent laparoscopic gastrectomy with D1 + lymphadenectomy between 2012 and 2015 were reviewed. In the first phase up to July 2013 ($n = 138$), PS was classified from computed tomography (CT) findings into type S (superficial fat deposition) or type D (diffuse fatty replacement) and examined for association with POPF. In the second phase ($n = 138$), the preoperative CT assessment of PS was routinized. Separate samples from pancreatoduodenectomy consistent with each type were histologically examined.

Results In the first phase, the incidence of POPF was significantly higher in group S, but not in group D, compared with normal pancreas (16.3% and 9.1% vs. 3.6%, respectively; $P = 0.03$). The drain amylase level was lowest in group D, reflecting exocrine insufficiency. Histologically, the loose connective-tissue space between the fat infiltrating the pancreas and the peripancreatic fat containing the lymph nodes was unclear in type D but conserved in type S. In the second phase, surgery was performed with more intention on accurately tracing the dissection plane and significantly lowered incidence of POPF in Group S (16.3% to 2.1%; $P = 0.047$).

Conclusion Peripancreatic lymphadenectomy is more challenging and likely to cause POPF in patients with PS. However, the risk may be reduced using appropriate dissection techniques based on the CT pre-assessment findings.

Keywords Gastric cancer · Lymph node dissection · Pancreatic steatosis · Postoperative pancreatic fistula · Visceral obesity

Introduction

Postoperative pancreatic fistula (POPF) is a frequent and serious complication after radical gastrectomy [1–3]. One of the mechanisms suggested for POPF formation is

intraperitoneal lipolysis due to leakage of exocrine enzymes associated with pancreatic parenchymal injury [4]. As causative external or technical factors, direct compression of the pancreas or thermal damage to it associated with the use of electro-surgical devices such as electrocautery and ultrasonic instruments may exacerbate pancreatic juice leakage [5–9]. As a causative internal factor, visceral obesity is reported to be associated with an increased risk of developing POPF, probably due to difficulties in dissecting the peripancreatic lymph nodes (LNs) [10, 11].

Excess visceral fat causes lipid infiltration of organs such as the liver (known as non-alcoholic steatohepatitis or fatty liver disease), striated muscle, heart, and pancreas [12, 13]. Recent evidence suggests that pancreatic steatosis (PS), a general term for pancreatic fat accumulation, plays a role in type 2 diabetes, pancreatic exocrine dysfunction, acute pancreatitis, and pancreatic cancer [14–16]. In pancreatoduodenectomy, PS is considered a more reliable risk factor

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for leakage from the pancreatojejunostomy that causes POPF than in the normal pancreas [17, 18]. However, to date, there is no clear evidence that PS is involved in the development of POPF even in gastrectomy that is not accompanied by anastomosis with the pancreas.

In gastric cancer surgery, lymphadenectomy around the pancreas is important to spare the organ from the mesogastrium [19, 20]. Its safety is assured by sharp dissection of the loose connective-tissue space that interfaces between the pancreas and peripancreatic fat (PPF) that contains the regional LNs of the stomach [21]. Several reports have demonstrated that magnified images obtained by laparoscopy enable safe LN dissection while avoiding pancreatic damage [22, 23]. Therefore, it can be hypothesized that the obscuration of the dissection plane associated with PS can result in damage to the pancreatic parenchyma, leading to POPF.

The aim of this study was to determine whether PS is associated with the risk of POPF following radical gastrectomy, and if so, to investigate whether the risk can be mitigated by pre-assessment using diagnostic computed tomography (CT) imaging.

Materials and methods

Patients

In this retrospective study, demographic and perioperative characteristics were collected for analysis from the perioperative records of 276 patients with clinically suspected stage I gastric cancer who underwent laparoscopic distal or total gastrectomy with D1 or D1 + lymphadenectomy between January 2012 and January 2015 at Toranomon Hospital in Tokyo, Japan. Patients with advanced cancer or who received neoadjuvant chemotherapy were excluded to avoid the effects of complicated lymph node dissection on the development of POPF. Table 1 shows the characteristics of patients in this series, their oncological background, type of operation performed, and postoperative morbidity as determined by the Clavien-Dindo classification [24]. The detailed technique of the lymphadenectomy performed has been reported elsewhere [22, 23, 25–27].

In the first phase of this study, 138 patients who underwent surgery before July 2013 were analyzed to examine whether PS is associated with the risk of POPF. In the second phase from August 2013 to July 2015, we routinely evaluated PS preoperatively on CT images for all patients ($n = 138$). All surgeries were performed by one of two surgeons (HS and SH) certified according to the endoscopic surgical skill qualification guidelines of the Japan Society for Endoscopic Surgery. This study was approved by the Ethics Committee of Toranomon Hospital.

Table 1 Patient background, oncological characteristics, and postoperative morbidity ($n = 276$)

Characteristics	Value
Sex, male/female (%male)	179/97 (64.9)
Age, years, mean (SD)	64.7 (11.3)
Body mass index, kg/m ² , mean (SD)	22.8 (3.4)
Histology, pap/tub1/tub2/por1/por2/sig/muc/other	2/60/74/82/53/1/4
Type, 0-I/0-IIa/0-IIb/0-IIc/0-III/1/2/3/other	4/38/10/212/0/2/6/3/1
Operative procedure, distal/total	223/53
LN dissection, D1/D1 +	6/270
Number of LNs harvested, median (range)	51 (15–131)
pT, 1a/1b/2/3/4	126/123/23/3/1
pN, 0/1/2/3	251/12/11/2
pStage, IA/IB/IIA/IIB/IIIA/IIIB/IIIC	128/24/16/5/2/0/1
Morbidity, CD II/IIIa/IIIb/IVa	
Pancreatic fistula	7/5/1/2
Anastomotic leakage	0/2/0/0
Bleeding	0/0/0/0
Surgical site infection	1/0/0/0
Pneumonia	7/0/0/0
Ileus	0/1/0/0

CD, Clavien-Dindo classification

Classification of steatosis from CT images

Preoperative images obtained from contrast-enhanced CT were used to evaluate PS in each patient. As a control, we used images of normal pancreas, which has an even and dense parenchyma with a smooth surface (Fig. 1a). PS was classified into two types according to the degree and distribution of low attenuation corresponding to the fat components [28–31]: type S denoting superficial fat deposition with an irregular but dense parenchymal surface (Fig. 1b); and type D denoting diffuse fatty replacement with low attenuation areas unevenly distributed throughout the parenchyma (Fig. 1c). The classification was determined by two surgeons blinded to the presence/absence of subsequent POPF.

Definition of POPF

POPF was assessed in accordance with the International Study Group on Pancreatic Surgery (ISGPS) definition and grading of postoperative pancreatic fistula [32]. Patients who needed persistent drainage for more than 3 weeks or repositioning of the operatively placed drains through interventional, image-guided means were graded as B POPF; those who required reoperation, who had organ failure, or who died were graded as C POPF. Patients with biochemical leak (concentration of amylase in abdominal drainage fluid more

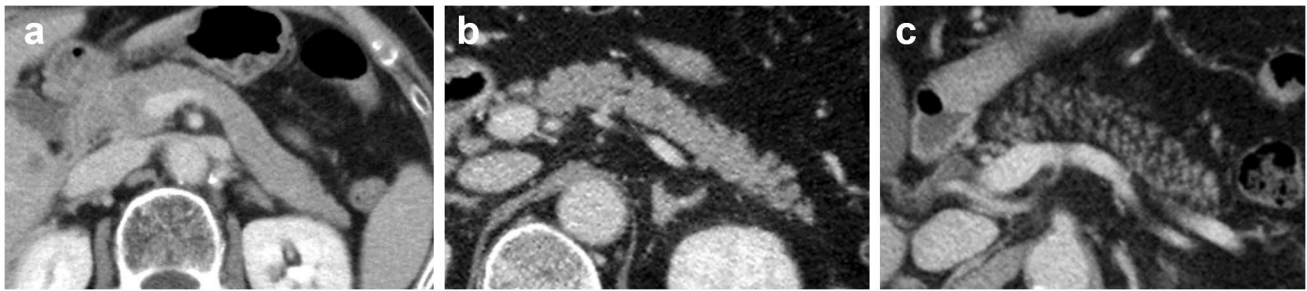


Fig. 1 Preoperative computed tomography images of histology of the pancreas. **a** Normal pancreas showing an even and dense parenchyma with a smooth surface. **b** Pancreatic steatosis (PS) classified as type S showing superficial fat deposition with an irregular but dense

parenchymal surface. **c** PS classified as type D showing diffuse fatty replacement with unevenly distributed low attenuation areas throughout the parenchyma

than 3 times the upper limit of the institutional normal serum value) were excluded from the analysis of POPF incidence because it has no clinical importance.

Histologic analysis

Distribution of fat accumulation in the pancreas and consistency of the fascial interface with PPF were histologically investigated using separate samples from patients with cancer of the pancreatic head after pancreatoduodenectomy. Each of three surgical specimens that were determined to be consistent with normal pancreas, PS type S, or PS type D based on the above-mentioned CT criteria was fixed using a standard mixture containing 10% formalin, embedded in 10% gelatin, sliced into 4-mm-thick sagittal sections, and then mounted on slides for hematoxylin and eosin staining.

Statistical analysis

To compare between the groups, we used Welch's *t*-test or Wilcoxon's rank-sum test for continuous variables expressed as means and standard deviations (SD) or medians and ranges, respectively, and we used Fisher's exact test for categorical variables. Statistical significance was set at $P < 0.05$. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 24 (IBM Corp., Armonk, NY).

Results

Incidence of POPF in the first phase

In the first phase of this study, the clinical records were analyzed to examine whether PS is associated with the risk of POPF. Mean age was 63.8 ± 10.7 years and mean BMI was 23.0 ± 3.8 . Among the 138 patients in this phase, 106 underwent distal gastrectomy and 32 underwent total gastrectomy.

Table 2 shows their baseline characteristics. Eighty-four patients had normal pancreas (group N) and 54 had PS, 43 with type S (group S) and 11 with type D (group D). There was no significant difference in sex distribution between the groups. Patients in group S were significantly older than patients in group N ($P < 0.01$). Mean BMI was significantly higher in groups S and D than in group N ($P = 0.04$ and $P = 0.02$, respectively). Mean operating time was significantly longer in group S than in group N ($P = 0.01$). Intraoperative blood loss did not differ significantly between the groups. On postoperative day 1, the drain amylase level was significantly lower in group D than in group N. The incidence of POPF with ISGPS grade B/C was significantly higher in group S (7/43, 16.3%; $P = 0.03$), but not significantly so in group D, compared with group N. There was no significant difference in the number of LNs harvested between the groups.

Differences in histological features

To investigate why the risk of POPF differed depending on the presence and type of PS, we compared histological features with the separate samples obtained from patients with cancer of the pancreatic head after pancreatoduodenectomy. Figure 2 shows macroscopic and microscopic findings of representative cases. In normal pancreas, the contour of the parenchyma is smooth and a clear boundary is apparent with PPF, which differs in color from the pancreas (Fig. 2a). Microscopically, pancreatic exocrine acinar cells form a lobular structure, in which branches of the pancreatic duct and blood vessels are evident. They are encapsulated as a whole and interface with the loose connective-tissue space seen between the pancreas and PPF that contains the LNs (Fig. 2b).

In PS type S, the contour of the parenchyma is rough and irregular. A thick fat layer deposited on the surface of the parenchyma infiltrates along the interstices of the lobules like a fjord. However, a clear boundary is still apparent

Table 2 Background characteristics of patients in the first phase of the study ($n = 138$) and incidence of POPF according to PS type

	Type N ($n = 84$)	Type S ($n = 43$)	Type D ($n = 11$)	<i>P</i> -value (N vs S)	<i>P</i> -value (N vs D)
Sex, male/female (%male)	54/30 (64.3)	30/13 (69.8)	7/4 (63.6)	0.27	0.48
Age, years, mean (SD)	61.8 (10.9)	68.3 (9.3)	65.3 (6.8)	<0.01	0.12
Body mass index, kg/m ² , mean (SD)	22.6 (3.3)	23.6 (3.1)	24.6 (2.6)	0.04	0.02
Operating time, min, mean (SD)	281 (67)	320 (72)	303 (58)	0.01	0.21
Intraoperative blood loss, mL, median (range)	50 (0–550)	71 (0–400)	25 (0–450)	0.42	0.49
Amylase concentration in drainage fluid, POD 1, IU/L, median (range)	734 (94–8,326)	675 (187–16,566)	460 (242–1,617)	0.16	<0.01
Amylase concentration in drainage fluid, POD 3, IU/L, median (range)	235 (33–3,620)	161 (25–29,607)	127 (62–517)	0.14	0.20
ISGPS grade					
Biochemical leak	19	4	2		
B	2	5	1		
C	1	2	0		
B + C (%POPF yes)	3 (3.6)	7 (16.3)	1 (9.1)	0.03	0.42
Number of LNs harvested, median (range)	56 (13–131)	54 (22–102)	54 (45–83)	0.18	0.44

ISGPS, International Study Group on Pancreatic Surgery; LNs, lymph nodes; POD, postoperative day; POPF, postoperative pancreatic fistula; PS, pancreatic steatosis; type D, PS with diffuse fatty replacement; type N, normal pancreas; type S, PS with superficial fat deposition

between the fat deposit and the PPF (Fig. 2c). Microscopic findings reveal that, like normal pancreas, the loose connective-tissue space between the pancreas and PPF remains. Branches of the pancreatic duct and blood vessels are buried in the fat deposit encapsulated with the loose connective-tissue, but they are not evident within the PPF (Fig. 2d).

In type D PS, the pancreatic parenchyma, whose stroma is filled with infiltrating fatty replacement, shows a marbled pattern macroscopically (Fig. 2e). Unlike the other two histological types, however, the boundary with the PPF is unclear. Microscopically, the fat deposit on the pancreatic surface is not encapsulated, and the loose connective-tissue space between the pancreas and PPF is no longer apparent (Fig. 2f). Figure 3 shows schematic diagrams of the histological features of the pancreas and PPF in the normal pancreas and two PS types.

Histology-based LN dissection in PS type S

The histological evidence obtained in the first phase informed our surgical approach, making us more cautious of the loose connective-tissue space during peripancreatic LN dissection. Figure 4 shows laparoscopic images of infrapyloric lymphadenectomy in patients with PS type S. Applying optimal countertraction to the PPF to be removed expands the loose connective-tissue space widely between the pancreatic surface and PPF to enable dissection (Fig. 4a). As a result, the superficial fat deposit can be separated from the pancreas as a different component and left on the remnant side (see Fig. 4b for a close-up view). Desired dissectible planes also become apparent on the

lateral side of the right gastroepiploic vein (Fig. 4c and d). After completion of lymphadenectomy, the dissection planes of both the removed PPF and the spared pancreas are coated with glossy connective tissue (Fig. 4e). Exposing the parenchyma is avoided by optimal dissection, namely, by not removing the fat deposit deeply from the pancreatic surface (see Fig. 4f for a close-up view).

Incidence of POPF in the second phase

In the second phase of the study, we routinely evaluated PS preoperatively on CT images for all patients. Table 3 shows the characteristics and POPF incidence of the 138 patients who underwent surgery during this second phase. Seventy-two patients had normal pancreas, 47 had PS type S, and 19 had PS type D; the proportions for the three groups were almost the same as in the first phase. Again, mean BMI was significantly higher in groups S and D than in group N (both $P < 0.01$). Despite performing the surgery more carefully, total operating time in group S was not much longer overall. The drain amylase level on postoperative day 3 tended to be lower in group D than in group N, but not significantly so. Only one patient in group S experienced POPF, indicating incidence was significantly decreased to 2.1% in this second phase ($P = 0.047$ compared with the first phase). Number of LNs harvested did not differ significantly between the groups, and the number harvested in group S was not lower than that in the first phase ($P = 0.14$).

Fig. 2 Representative macroscopic and microscopic findings of samples obtained from pancreatoduodenectomy determined to be consistent with normal pancreas, pancreatic steatosis (PS) type S, and PS type D. **a** Sagittal section of the normal pancreas. The contour of the parenchyma is smooth and a clear boundary with peri-pancreatic fat (PPF) is evident (white arrowheads). **b** Tissue section of the inset in **a**. Pancreatic exocrine acinar cells form a dense lobular structure, and a loose connective-tissue space between PPF containing lymph nodes (LNs) is evident (black arrowheads). P, pancreatic duct; V, vein. **c** Sagittal section of the pancreas categorized as PS type S. The contour of parenchyma is rough and irregular. A thick fat layer is deposited on the surface of the parenchyma and infiltrates along the interstices of the lobules (*), but a clear boundary with the PPF is conserved (white arrowheads). **d** Tissue section of the inset in **c**. Loose connective-tissue space with PPF remains visible (black arrowheads). Branches of the pancreatic duct and blood vessels are buried in the fat deposit. A, artery. **e** Sagittal section of the pancreas categorized as PS type D. A marble pattern of the pancreatic parenchyma, whose stroma is filled by infiltrating fat replacement, is evident. Note, the boundary with the PPF is unclear. **f** Tissue section of the inset in **e**. The fat deposit on the pancreatic surface is not encapsulated, and the loose connective-tissue interface between the PPF is obscure

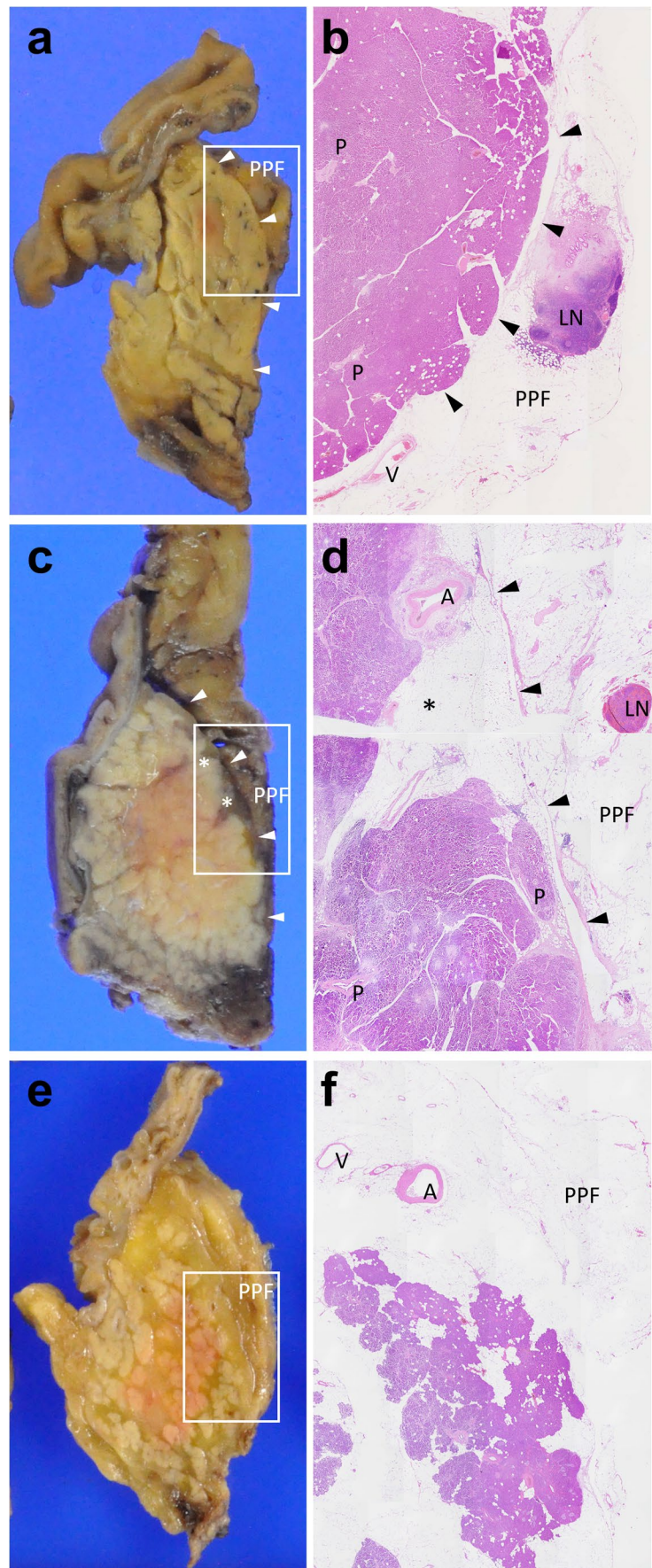
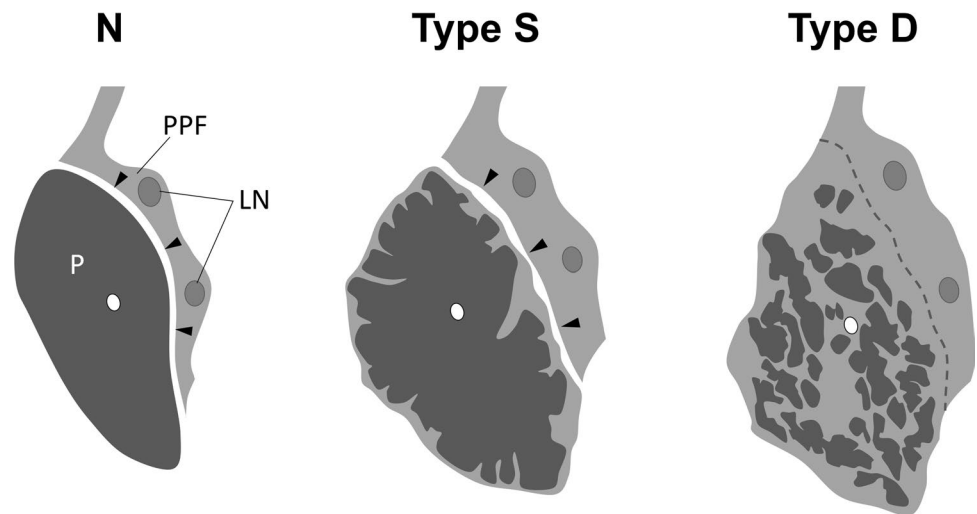


Fig. 3 Schematic diagrams showing the histological features of the pancreas and peripancreatic fat (PPF) in the normal pancreas (N) and two pancreatic steatosis (PS) types. Broken line in PS type D indicates the unclear loose connective-tissue interface, which is apparent in N and is still conserved in PS type S (arrowheads). LN, lymph node; P, pancreatic parenchyma



Discussion

In the first phase of this study, we found an increased risk of POPF with PS present preoperatively. When PS was broadly classified into two histological types on preoperative CT images, POPF was significantly more common in patients with superficial fat deposit (type S), but not with diffuse fatty replacement (type D), compared with patients with normal pancreas. In the second phase, when the preoperative CT assessment of PS was routinized, surgery was performed with more intention on accurately tracing the dissection plane and significantly lowered the incidence of POPF in patients with PS type S. Thus, PS may be a largely avoidable risk factor for POPF after radical gastrectomy.

Pathological fatty replacement has been referred to variously as pancreatic lipomatosis, fatty infiltration, and fatty pancreas, among other terms [14–16]. PS is a general term that can be used for all forms of pancreatic fat accumulation [14]. In the liver, hepatocytes accumulate fat in intracellular lipid droplets; in the pancreas, lipids are mainly stored in adipocytes, which infiltrate the parenchyma [33]. Aging and overweight, especially visceral obesity, are most associated with this condition [14–16, 34, 35]. One of the mechanisms suggested is the failure of lipid regulation to prevent lipid overload and fat apoptosis in certain organs in sarcopenia caused by aging and metabolic syndrome [36]. In both our study phases as well, patients in groups S and D were older and had a higher BMI than those in group N. PS is most often found using modern imaging technology such as ultrasonography [37] and magnetic resonance imaging [17]. With CT, focal PS can be seen as the separation of parenchymal lobules, with intermixed areas of lower attenuation corresponding to the fat components [28], and the individual lobules become more apparent as PS progresses [29]. Fatty infiltration of the pancreas is generally a diffuse process, but it may be unevenly distributed in the pancreas, usually

most prominently in the anterior aspect of the head of the pancreas [30, 31]. Thus, the presence of PS confers some risk for infrapyloric LN dissection in gastric cancer surgery.

In the first phase of this study, 31.1% of patients had PS type S, 16.3% of whom experienced grade 2 or higher POPF. This high incidence might have resulted from our attempts to remove fat deposits deeply from the pancreatic surface, thereby exposing the parenchyma to thermal damage from the energy device and causing pancreatic enzymes to leak. The unavoidable need for coagulation hemostasis at the parenchymal surface may also have increased the damage. As reported previously, lipolysis and proteolysis resulting from leaked pancreatic enzymes are thought to form abscesses at the surgical site and exacerbate pancreatitis and systemic inflammation [38, 39]. With the introduction of laparoscopic gastrectomy, surgeons have aimed for complete removal of peripancreatic adipose tissue to achieve more accurate LN dissection under the magnified image provided by the endoscope. However, evidence from a recent Japanese nationwide survey has revealed a somewhat higher incidence of POPF in laparoscopic gastrectomy than in open surgery [40]. At the very least, when performing prophylactic LN dissection, we need to keep in mind the optimal dissection planes on the surface of the pancreas.

In the embryonic stage, the primordium of the pancreas arises from the duodenal wall [41], grows between the layers of the mesoduodenum, and eventually extends into the dorsal mesogastrium [20, 42]. During this process, areolar interfaces consisting of connective tissue, referred to as the investing fascia [21], are formed to encapsulate the parenchyma and give the organ shape. During surgery, the investing fascia provides our desired dissection plane, allowing us to isolate the PPF containing the LNs with a connective tissue coating [19, 22]. In the present study, we found that this fascial interface is histologically conserved in PS type S and that the risk of POPF could be mitigated by sharp

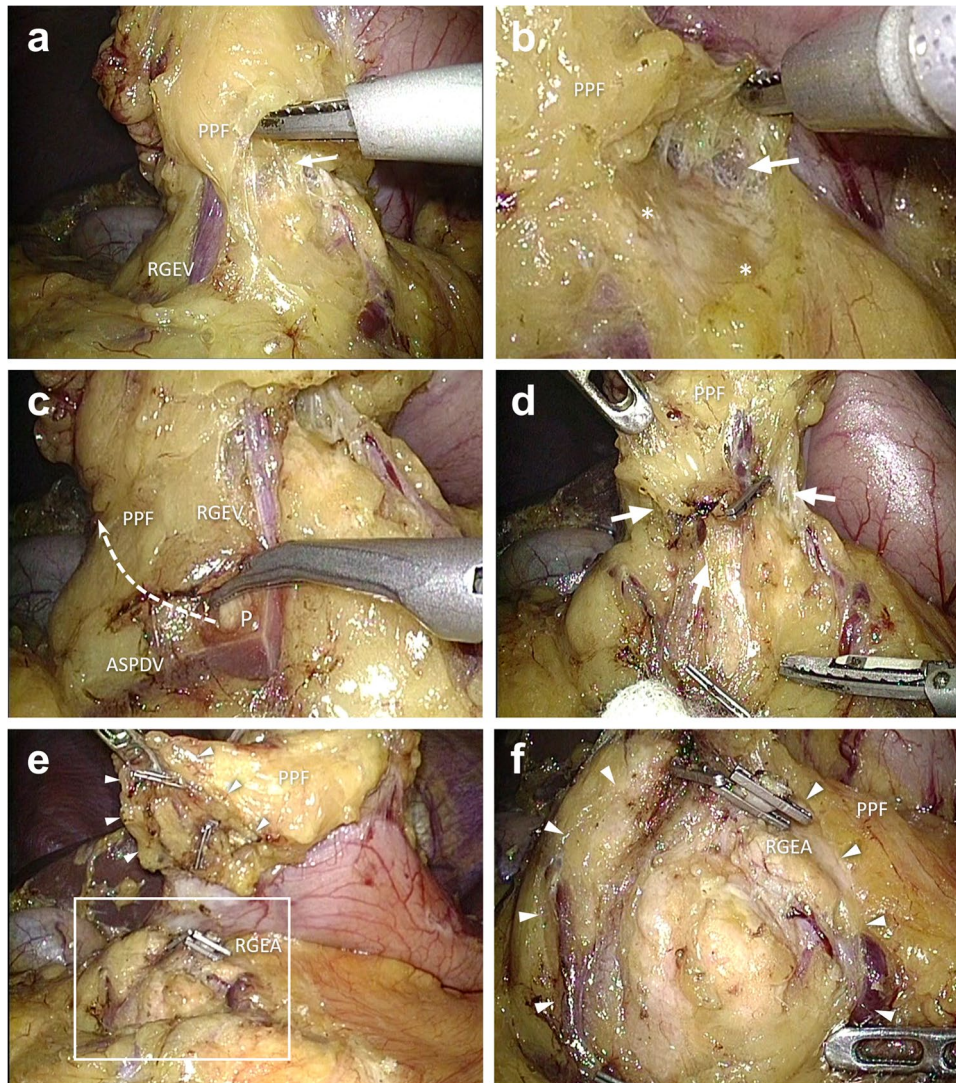


Fig. 4 Operative images during infrapyloric lymphadenectomy performed with more focus on tracing the dissectible planes in a patient with pancreatic steatosis type S. **a** Dissecting the medial side of the anterior surface of the pancreas head. The loose connective-tissue space between the pancreas and peripancreatic fat (PPF) is expanded (arrow). RGEV, right gastroepiploic vein. **b** A close-up view of the dissection plane in **a**. Note that the fat deposits infiltrating along the interstices of the lobules remain (*), while the PPF is dissected by tracing the loose connective-tissue space (arrow). **c** Dissecting the lateral side of the pancreas head. Dissection forceps inserted into the loose connective-tissue space reveal the surface of the pancreas (P) at the confluence of the anterior superior pancreaticoduodenal vein

(ASPDV). Broken arrow indicates the upcoming excision margin of the PPF. **d** Dissecting the PPF upwards after dividing the RGEV. The loose connective-tissue space between the pancreas and PPF is further expanded (arrows). **e** After infrapyloric lymphadenectomy is completed, the dissection plane of the removed PPF is coated with glossy connective tissue (arrowheads). RGEA, right gastroepiploic artery. **f** A close-up view of the inset in **e**. The dissection plane of the pancreas is also coated with glossy connective tissue (arrowheads). Note that exposing the parenchyma was avoided by optimal dissection, where the fat deposit was not removed deeply from the pancreatic surface

dissection of the loose connective-tissue space seen in the magnified laparoscopic image. In principle, lymphatic channels are not present in the fat components infiltrating the pancreas, so their removal should not contribute to improving the accuracy of LN dissection [43]. Indeed, the median number of retrieved LNs in our second phase was not lower than that in our first phase. Thus, maintaining the dissectible plane between the pancreas and PPF will be important for

safe and ontologically sufficient LN dissection, especially in obese patients.

Endocrine and exocrine function of the pancreas may be associated with fat accumulation in islet and acinar cells [44]. At present, there is insufficient evidence to conclude that PS causes pancreatic b-cell dysfunction leading to impaired insulin secretion in the context of insulin resistance [14, 45], although several reports have suggested that

Table 3 Background characteristics of patients in the second phase of the study ($n = 138$) and incidence of POPF according to PS type

	Type N ($n = 72$)	Type S ($n = 47$)	Type D ($n = 19$)	<i>P</i> -value (N vs S)	<i>P</i> -value (N vs D)
Sex, male/female (%male)	41/31 (56.9)	34/13 (72.3)	13/6 (68.4)	0.09	0.37
Age, years, mean (SD)	63.7 (12.0)	68.0 (11.3)	67.7 (9.3)	0.06	0.06
Body mass index, kg/m ² , mean (SD)	21.4 (3.5)	23.6 (2.5)	24.3 (3.5)	< 0.01	< 0.01
Operating time, min, mean (SD)	313 (62)	337 (69)	342 (69)	0.07	0.06
Intraoperative blood loss, mL, median (range)	37 (0–350)	50 (0–857)	50 (0–200)	0.04	0.23
Amylase concentration in drainage fluid, POD 1, IU/L, median (range)	744 (29–11,833)	796 (163–6,107)	629 (262–3,382)	0.34	0.42
Amylase concentration in drainage fluid, POD 3, IU/L, median (range)	166 (62–5,488)	213 (26–5,861)	111 (39–519)	0.32	0.09
ISGPS grade					
Biochemical leak	14	7	2		
B	3	1	0		
C	0	0	0		
B + C (%POPF yes)	3 (4.2)	1 (2.1)	0 (0.0)	0.57	0.37
Number of LNs harvested, median (range)	50 (15–117)	47 (19–95)	46 (26–90)	0.34	0.12

ISGPS, International Study Group on Pancreatic Surgery; LNs, lymph nodes; POD, postoperative day; POPF, postoperative pancreatic fistula; PS, pancreatic steatosis; type D, PS with diffuse fatty replacement; type N, normal pancreas; type S, PS with superficial fat deposition)

PS is present in the prediabetic phase and the amount of pancreatic fat increases prior to the onset of type 2 diabetes mellitus [46, 47]. In contrast, it is widely accepted that PS correlates with a reduction in pancreatic exocrine enzymes [14, 29], such as elastase-1 [48] and amylase [49]. The proposed mechanism involves the negative paracrine effect of pancreatic adipocytes on acinar cells, which serves to reduce the exocrine function [14]. These reports are consistent with our finding that the drain amylase levels in group D were consistently lower than those in the other groups. This may be one of the reasons why the risk of PS type D in the development of POPF was consistently low throughout our study period, despite histologically obscure dissectible planes.

This study has some limitations. First, the prediction of PS type S from preoperative CT images is qualitative and it is therefore difficult to definitively distinguish type S from type D. Due to the various stages of PS, the obscurity of the areolar interface observed in type D may not be even, depending on whether the fatty sparing is mild or severe. However, regardless of the type, it would be possible to determine a safe resection margin by understanding the histology of PS, predicting the pattern of fat deposition by preoperative CT in each patient, and performing surgery. Second, the learning curve effect cannot be completely excluded. The occurrence of postoperative complications can be affected by the skills and experience of the surgeons, assistants, or both. Although all of the gastrectomies analyzed in this study were performed by qualified surgeons, the drawback of comparing outcomes across different time periods is that these confounding factors are not adjusted for. Therefore, it may be difficult to conclude that the lower

incidence of POPF was the result of performing lymphadenectomy focused on dissectible planes alone. However, among various complex factors, PS is related to patient background such as visceral obesity and age, and it is one of the risks that can be predicted from CT images before surgery. A report on human error states that nearly 30% of surgical complications are caused by misrecognition during the operation [50]. For patients who have been diagnosed with PS, it is important that surgery is performed with awareness and caution so as not to damage the pancreatic parenchyma.

Conclusion

Peripancreatic lymphadenectomy is more challenging and likely to cause POPF in patients with PS. There is a higher risk of POPF with superficial fat deposits than with diffuse fatty replacement with exocrine insufficiency. However, the risk may be reduced by using appropriate dissection techniques that are selected based on the preoperative CT findings, which themselves can enhance surgical cognition during peripancreatic LN dissection.

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Authors' contributions Study conception and design: Kobayashi N and Shinohara H; acquisition of data: Kobayashi N and Haruta S; analysis

and interpretation of data: Kobayashi N and Shinohara H; drafting of manuscript: Shinohara H; critical revision of manuscript: Udagawa H and Ueno M.

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Data availability The datasets generated during and/or analyzed during the current study are not publicly available due to the medical data including participants' personal data.

Code availability Not applicable.

Declarations

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Written informed consent was obtained from all subjects for participation in and publication of this study.

Conflict of interest The authors declare no competing interests.

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