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Proximal subtotal pancreatectomy as an alternative to total pancreatectomy for malnourished patients

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Abstract

Purpose To investigate whether proximal subtotal pancreatectomy (PSTP) is superior to total pancreatectomy (TP) for preserving postoperative endocrine function, and to identify the pre-operative risk factors influencing prognosis after TP and PSTP.

Methods The subjects of this retrospective study were patients who underwent TP ($n=15$) or PSTP ($n=16$) between 2008 and 2018 in our hospital. First, we compared the incidence of hypoglycemia within 30 days after surgery and the total daily amount of insulin needed in the 30 days after TP vs. PSTP. Then, we compared the prognoses between the groups.

Results The incidence of hypoglycemia in the 30 days after surgery was significantly lower in the PSTP group than in the TP group ($n=0$ vs. $n=5$; $p<0.001$). The total amount of daily insulin given was also significantly lower after PSTP than after TP: (0 units vs. 18 units, $p=0.001$). Lower lymphocyte counts ($p=0.014$), lower cholinesterase ($p=0.021$), and lower prognostic nutrition index ($p=0.021$) were identified as significant risk factors for hypoglycemia in the TP group. Low cholinesterase ($p=0.015$) and a low prognostic nutrition index ($p=0.048$) were significantly associated with an unfavorable prognosis in the TP group, but not in the PSTP group.

Conclusions PSTP may be a feasible alternative to TP to preserve endocrine function, especially for malnourished patients.

Keywords Proximal subtotal pancreatectomy · Total pancreatectomy · Prognostic nutrition index

Introduction

Total pancreatectomy (TP) can be conducted safely with low postoperative mortality and morbidity similar to other pancreatectomies [1, 2]. The surgical indications for TP have extended to include diffuse pancreatic disease such as chronic pancreatitis, multicentric pancreatic neuroendocrine tumors, pancreatic cancer [3, 4], and multifocal intraductal papillary mucinous neoplasms (IPMNs) [5]. However, the postoperative nutritional support and treatments are challenging because of the complete obliteration of both exocrine and endocrine functions [6, 7]. Despite recent advances in insulin formulations such as improved long- and short-acting insulin and a new injectable synthetic analog of human amylin [8], the risk of hypoglycemic episodes is still high and can result in death. Conversely, the supplementation of high-quality pancreatic enzymes to improve malabsorption after TP is well-established. However, we sometimes encounter patients with refractory malnutrition caused by severe malabsorption and steatorrhea after TP, resulting in poor postoperative outcomes.

Our institution has tried to avert TP, especially for patients with pancreatic ductal adenocarcinoma (PDAC), to prioritize postoperative adjuvant therapies and patient quality of life (QOL). For instance, we reported a new surgical technique of pancreaticoduodenectomy (PD) with splenic artery resection (PD–SAR) for PDAC of the head and/or body invading the root of the splenic artery, which contributes significantly to maintaining postoperative endocrine functions [9]. We also perform a surgical procedure called

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"proximal subtotal pancreatectomy (PSTP)" with invagination for pancreatointestinal anastomosis, especially for pancreatic head/body tumors extending to the tail. Recently, we reported the preliminary data of a comparative study between PSTP and TP, which suggested that the amount of insulin given and the frequency of hypoglycemic episodes in patients who underwent PSTP was significantly lower than in those who underwent TP [10]. However, there has been no clinical study done to compare postsurgical outcomes such as endocrine function and prognosis between PSTP and TP.

When we focus on nutritional status, the prognostic nutrition index (PNI), as reported originally by Buzby et al. [11] in 1980, is often used to predict postoperative complications after abdominal and thoracic surgery. In 1984 Onodera et al. modified the PNI to make it much simpler to use [12]. In addition to its use as a predictor of postoperative complications, Onodera's PNI is used widely as a prognostic factor for patients with various malignancies [13–16]. However, the association between postoperative outcomes after TP and pre-operative nutritional makers, including the PNI, has yet to be elucidated.

We conducted the present study to investigate the hypothesis that PSTP is superior to TP for the preservation of postoperative endocrine function, and to identify the preoperative factors influencing the postoperative prognosis after TP and PSTP. To our knowledge, this is the first report to identify the usefulness of PSTP as an alternative to TP, and the importance of pre-operative nutritional factors for predicting postoperative outcome after TP, which might support the surgeon's pre-operative decision about which patients are likely to tolerate TP.

Patients and methods

The subjects of this study were 15 patients who underwent TP (for pancreatic ductal adenocarcinoma (PDAC) in 7 patients, intraductal papillary mucinous carcinoma (IPMC) in 7 patients, and intraductal papillary mucinous adenoma (IPMA) in 1 patient) and 16 patients who underwent PSTP (for PDAC in 14 patients and for IPMC in 2 patients), between August, 2008 and December, 2018, in our hospital. We compared the incidence of hypoglycemia within 30 days after surgery and the total amount of insulin needed within 30 days after surgery between the TP and PSTP groups. In the TP group, we conducted a risk analysis to identify the predictors of postoperative hypoglycemic episodes. We also compared survival between the two groups. The prognostic factors of the overall 31 patients were assessed by uni- and multivariate analyses, and those of TP or PSTP groups were further evaluated according to the age, gender, diabetes, BMI, and pre-operative white blood cell count, lymphocyte count, hemoglobin level, albumin level, cholinesterase level, total cholesterol level, triglyceride level, amylase level, PNI, CA19-9 level, and any pre-operative treatment. Hypoglycemia is defined by an arbitrary plasma glucose level of < 3.9 mmol/l (70 mg/dl), which is the level below which activation of the counter-regulatory hormone response occurs in most adults. In terms of postoperative glycemic control, one international unit (IU) of rapid-acting insulin per 10 g of carbohydrate was added to the parental nutrition to compensate the basal insulin requirement. Besides this infusion, sliding scale protocols were used for bolus insulin release. The infusion was discontinued when sufficient oral intake had recovered, when the administration of long-acting insulin was initiated instead.

This is a retrospective study and the protocol was approved by the medical ethics committee of Mie University Hospital (No 2857) and performed in accordance with the ethical standards established in the 1964 Declaration of Helsinki.

Surgical procedure of PSTP and TP

Stitzenberg et al. [17] defined PSTP as a type of pancreaticoduodenectomy in which the residual pancreatic tissue was insufficient to permit pancreaticojejunostomy. In the present study, PSTP was defined as pancreaticoduodenectomy in which the pancreatic resection line was made on the far-left side of the above superior mesenteric artery (SMA) and the remnant small pancreas and jejunum were anastomosed by the invaginated pancreatojejunostomy instead of by an over-sewn stump closure (Fig. 1). In both PSTP and TP for pancreatic tumors including PDAC, the concept of a medial-to-lateral mesenteric approach has been adopted, regardless of proximal or distal pancreatectomy, as so-called "antegrade en-bloc pancreatectomy" since April, 2005 [18]. In both PSTP and TP, a feeding jejunostomy tube was placed intraoperatively for early postoperative enteral nutrition. A single abdominal drain was inserted through the foramen of Winslow near the site of pancreaticojejunostomy and left in place until postoperative day (POD) 5, as long as the drain discharge was clear and its amylase level was less than three times higher than the upper limit of the serum amylase level (132U/ml).

Assessment for pancreatic fistula

In all patients who underwent PSTP, the amylase activities of the abdominal drainage fluid and serum were measured on PODs 3–7. Pancreatic fistula was defined and graded according to the International Study Group on Pancreatic Fistula classification [19].

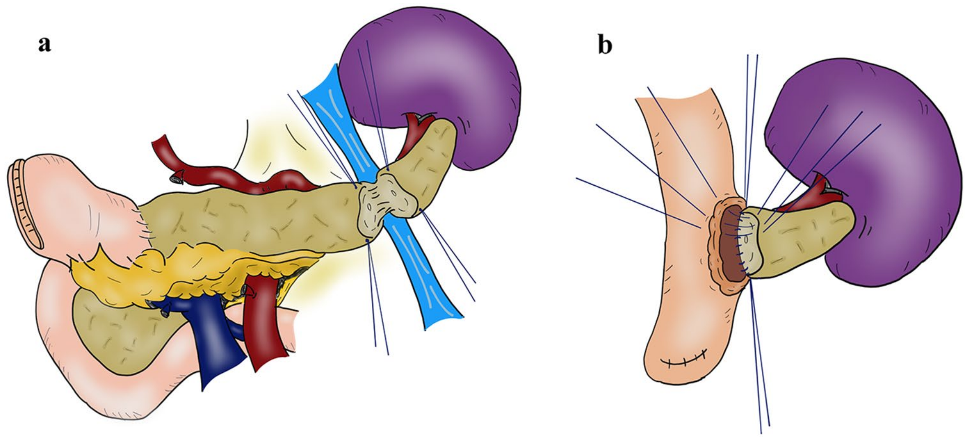

Fig. 1 Schemas of proximal subtotal pancreatectomy. **a** A cut line of pancreatectomy, **b** a schema of pancreatojejunostomy with invagination method

Statistical analysis

Continuous and categorical variables are expressed as the median value with the range or mean value with standard deviation, if appropriate. They were compared using the Mann–Whitney *U* test and the Chi-squared test, respectively. Overall survival was calculated by the Kaplan–Meier method and compared between the groups using the log-rank test. Factors affecting overall survival were analyzed using the Cox proportional hazards model. In multivariate analysis, logistic regression and the Cox proportional hazards model were used to identify the risk factor of hypoglycemia and prognosis, respectively. Only variables with a p value of less than 0.05 by univariate analysis were included in the multivariate analysis. In the present study, the continuous values were used directly throughout the analysis. Cut-off values for cholinesterase and PNI were calculated using a software tool (Evaluate Cutpoints) [20] and the values were dichotomized for further survival analyses using the Kaplan–Meier method. All statistical analyses were performed using IBM SPSS Statistics for Macintosh, (version 24; IBM Corp., Armonk, NY, USA). A p value of <0.05 was considered significant.

Results

Table 1 summarizes the background and pre-operative clinical findings of the patients in the two groups. There were no significant differences between the groups in age, gender, or BMI. The incidence of pre-operative diabetes requiring insulin was significantly higher in the TP group than the PSTP group ($p=0.029$). The number of patients with PDAC was significantly higher in the PSTP group ($p=0.027$). In terms of tumor locations, 60% (9/15) and 69% (11/16) of tumors were located predominantly in the pancreatic head (Ph) in the TP and PSTP groups, respectively. In PSTP, the splenic vein/portal vein confluence and splenic artery were resected in 10 and 5 patients, respectively. There was no difference in the rate of preoperative chemoradiotherapy and primary disease (malignancy/benign) between the groups. There were no significant differences in surgical outcomes, including median operation time and blood loss, except for remnant pancreatic volume. The median remnant pancreatic volume was only 4.3 (1.1–7.5) ml based on the postoperative CT volumetry. In PSTP, there was one case (6.3%) of grade B or C pancreatic fistula. The incidence of hypoglycemia within 30 days of surgery was significantly lower in the PSTP group than in the TP group (0 vs. 5, $p<0.001$; Table 1).

We performed uni-and multivariate analyses to identify the risk factors for postoperative hypoglycemia occurring >5 times within a month, which identified only a low PNI ($p=0.036$) and TP ($p=0.038$) as independent risk factors for hypoglycemia (Table 2). As the incidence of postoperative hypoglycemia was very low, we conducted a subgroup analysis in the TP group and found that the pre-operative lymphocyte counts ($p=0.014$), pre-operative cholinesterase ($p=0.021$), and pre-operative prognostic nutrition index ($p=0.021$) were significantly lower in the patients with postoperative hypoglycemia >5 times within a month (Table 3). The total amount of daily insulin usage was also significantly lower after PSTP than after TP: at 1 month (8.7 ± 13.0 vs 22.7 ± 9.0, $p=0.004$), 3 months (4.0 ± 9.9 vs 23.2 ± 10.2, $p=0.00026$), 6 months (2.9 ± 8.7 vs 25.4 vs 9.1, $p=0.001$), and 12 months (4.3 ± 10.7 vs 27.3 ± 16.8, $p=0.014$) (Fig. 2).

The median survival time (MST) and overall survival (OS) were comparable between the TP and PSTP groups, being 57.8 months vs. 38.1 months and 63.6% vs 52.5%, respectively ($p=0.992$) (Fig. 3a). When we focused on the 21 PDAC patients who underwent TP ($n=7$) or PSTP ($n=14$), the MST and OS did not differ significantly, being 21.4 months vs. 25.9 months and 38.1% vs. 50.0%, respectively ($p=0.349$) (Fig. 3b). To assess the significant prognostic factors of patients who underwent TP or PSTP, uni- and multivariate analyses were conducted, which identified a lower PNI ($p=0.004$) as an unfavorable predictor (Table 4).

Table 1 Comparison of clinical backgrounds and incidence of hypoglycemia within 30 days after surgery between the total pancreatectomy (TP) and proximal subtotal pancreatectomy (PSTP) groups

	TP ($n=15$)	PSTP ($n=16$)	p value
Pre-operative variables			
Age (years)	67.0 (61–83)	69.0 (40–77)	0.626
Gender (male/female)	11/4	7/9	0.281
BMI (kg/m^2)	20.0 (13.5–25.5)	22.3 (17.3–27.4)	0.098
Diabetes mellitus (yes/no)	**13/2**	**4/12**	**0.003**
Pre-operative insulin (yes/no)	**10/5**	**2/14**	**0.009**
Pre-operative chemoradiotherapy (yes/no)	4/11	10/6	0.093
Primary disease (malignancy/benign)	14/1	14/2	0.800
Diagnosis (PDAC/IPMC/IPMA)	**7/7/1**	**14/0/2**	**0.027**
Location of tumor (Phbt/Phb/Ph/Pbt/Pb/Pt)	4/0/9/1/0/1	2/2/11/0/1/0	0.984
Pre-operative completion pancreatectomy (yes/no)	**9/6**	**1/15**	**0.009**
White blood cell count (/mm^2)	5540 (2320–10,400)	4865 (2540–8350)	0.129
Lymphocyte count (/mm^2)	1460 (390–3070)	1080 (320–2300)	0.512
Albumin (g/dl)	4.0 (2.6–4.7)	4.2 (2.8–4.6)	0.119
Hemoglobin (g/dl)	**11.0 (7.9–14.6)**	**12.4 (11.3–14.3)**	**0.033**
Cholinesterase (U/l)	214 (48–448)	289 (133–407)	0.129
Serum amylase (U/l)	**88 (37–205)**	**56.5 (25–170)**	**0.008**
Triglyceride (mg/dl)	102 (28–148)	93 (53–429)	0.572
Prognostic nutrition index	46.0 (29.1–57.8)	47.9 (29.6–53.5)	0.870
CA19-9 (U/ml)	44.4 (1.0–426.4)	44.1 (4.7–1053.2)	0.914
Intra-operative variables			
Operation time (min)	481 (218–727)	565 (393–769)	0.140
Blood loss (g)	961 (38–4790)	770 (80–4739)	0.922
Remnant pancreatic volume (cm^2)	**0 (0–0)**	**4.3 (1.1–7.5)**	**< 0.0001**
Incidence of hypoglycemia	**5.0 (0–23)**	**0 (0–7)**	**< 0.001**

Significant values are given bold at $p<0.05$

TP total pancreatectomy, *PSTP* proximal subtotal pancreatectomy, *PDAC* pancreatic ductal adenocarcinoma, *IPMC* intraductal papillary mucinous carcinoma, *IPMA* intraductal papillary mucinous adenoma, *BMI* body mass index, *CA19-9* carbohydrate antigen 19–9

Regarding prognostic factors influencing OS after TP vs. PSTP according to univariate analysis, no significant factor was identified in the 16 PSTP patients (Table 5). Conversely, preoperative cholinesterase ($p=0.015$) and pre-operative prognostic nutrition index ($p=0.048$) were identified as significant prognostic factors after surgery in the 15 TP patients (Table 6).

The best cut-off values contributing to OS in the TP group were 180 U/L for cholinesterase and 40 for PNI. Figure 4 compares OS according to the significant prognostic factors for the TP patients. The MST for patients with a high pre-operative cholinesterase ≥ 180 U/L ($n=10$) was significantly better than that for those with a low pre-operative cholinesterase < 180 U/L ($n=5$) (75.0 vs. 6.4 months, $p=0.001$; Fig. 4a) and that for those with a high PNI ≥ 40 ($n=11$) was significantly better than that for those with a low PNI < 40 ($n=4$) (75.0 vs. 6.4 months, $p=0.027$; Fig. 4b).

Moreover, because multivariate analysis identified the PNI as the only independent prognostic factor after TP and PSTP, we compared the PNI in the two groups, 1, 3, 6 and 12 months after surgery. Indeed, the PNI was statistically comparable between the TP and PSTP groups at 1 month (TP:40.4 ± 4.7 vs PSTP:39.1 ± 4.8, $p=0.516$) and 12 months (TP:45.6 ± 4.5 vs PSTP:43.6 ± 3.3, $p=0.481$), but not at 3 months (TP:43.9 ± 7.8 vs PSTP:38.9 ± 5.9, $p=0.032$) and 6 months (TP: 45.7 ± 6.7 vs PSTP:38.5 ± 8.6, $p=0.016$) (Supplementary Fig. 1).

Discussion

The important findings of the present study were as follows: first, PSTP contributed more than TP to the preservation of postoperative endocrine function; second, patients with malnutrition tended to be more prone to hypoglycemic episodes after TP than well-nutritional patients; third, the survival outcomes of the patients in the TP and PSTP groups were comparable regardless of malignancy; and fourth, survival outcomes after TP were significantly worse in the malnourished patients (PNI < 40, cholinesterase < 180U/l) than in

Table 2 Uni- and multivariate analyses to identify the risk factors for postoperative hypoglycemia > 5 times within 1 month

Total = 31 patients	Univariate analysis			Multivariate analysis		
	Hypoglycemia (> 5 times within 30 days) $n = 8$	Hypoglycemia (≤ 5 times within 30 days) $n = 23$	*p* value	Odd's ratio	95%CI	*p* value
Pre-operative variables						
Age (years)	70.5 (62–83)	66.0 (40–77)	0.110			
Gender (male/female)	5/3	14/9	0.947			
BMI (kg/m^2)	16.9 (13.5–25.6)	22.2 (17.3–27.4)	0.132			
Diabetes mellitus (yes/no)	6/2	11/12	0.275			
Pre-operative insulin (yes/no)	3/5	9/14	0.947			
Pre-operative chemoradiotherapy (yes/no)	1/7	13/10	0.067			
Primary disease (malignancy/benign)	8/0	20/3	0.611			
Diagnosis (PDAC/IPMC/IPMA)	3/4/1	16/2/5	0.255			
Albumin (g/dl)	3.5 (2.6–4.3)	4.2 (2.8–4.7)	0.067			
Hemoglobin (g/dl)	11.1 (7.9–14.6)	12.2 (7.9–14.3)	0.132			
White blood cell count (/mm^2)	4845 (2320–10,400)	5540 (3810–9870)	0.295			
Lymphocyte count (/mm^2)	**910 (390–1570)**	**1370 (320–3070)**	**0.027**			
Cholinesterase (U/l)	**180 (48–302)**	**277 (173–448)**	**0.020**	–	–	–
Serum amylase (U/l)	78 (32–205)	69 (25–170)	0.611			
Triglyceride (mg/dl)	**64 (28–134)**	**102 (53–429)**	**0.030**	–	–	–
Prognostic nutrition index	**41.0 (29.1–50.3)**	**48.6 (29.6–57.8)**	**0.021**	**0.853**	**0.736–0.989**	**0.036**
CA19-9 (U/ml)	53.4 (1.0–426.4)	44.4 (4.7–1053)	0.842			
Intra-operative variables						
Operation time (min)	526 (365–769)	525 (218–740)	0.877			
Blood loss (g)	1241 (38–3400)	750 (54–4790)	0.386			
TP/PSTP	**7/1**	**8/15**	**0.026**	**16.68**	**1.17–238.8**	**0.038**
Remnant pancreatic volume	0 (0–6.6)	2.6 (0–7.5)	0.054			

Significant values are given bold at $p < 0.05$

TP total pancreatectomy, *PSTP* proximal subtotal pancreatectomy, *BMI* body mass index, *PDAC* pancreatic ductal adenocarcinoma, *IPMC* intraductal papillary mucinous carcinoma, *IPMA* intraductal papillary mucinous adenoma, *CA19-9* carbohydrate antigen 19-9, *CI* confidence interval

those who were well-nourished, although these variables were not recognized as an unfavorable prognostic factor in the PSTP group.

Unlike the patients who underwent TP, which obliterates the pancreatic hormones, including insulin, glucagon and other islet regulation peptides, our results indicated that endocrine function was significantly preserved in the patients who underwent PSTP, as evidenced by the low incidence of postoperative hypoglycemic episodes and less need for insulin administration in the initial 12 months after surgery. The reason for this could be explained by the distribution of islet cells in the pancreas. Wittingen et al. [21] evaluated the relative concentrations in various parts of the pancreas and found that the islet concentration (45.7 ± 17.0 per circular cross Sect. 6 mm in diameter) in the tail is significantly greater than the concentration in the head (25.5 ± 9.9) and body (28.1 ± 8.8). In our study, the remnant volume of pancreas after PSTP was only 4.3 ml on the basis of CT volumetry, but there could be a significant number of islet cells remaining even in such a small remnant pancreas, leading to the amelioration of endocrine crisis. Moreover, the prevalence of pre-operative diabetes mellitus (DM) was significantly lower in the PSTP group than in the TP group (Table 1), which means that islet cells might be well-preserved even in a small remnant pancreas. However, as we could not evaluate the histology of the pancreatic stump, further study is needed to confirm our conjecture.

Episodes of hypoglycemia after TP remain a threat for both patients and surgeons; therefore, identifying the pre-operative risk factors for hypoglycemia after TP is very important. Our study found that a low lymphocyte count, low serum cholinesterase level, and low PNI were associated with frequent episodes of hypoglycemia (> 5 times within 30 days). Advanced age, frailty, ethnicity (African American), chronic renal failure, depression, and dementia have all been reported as global risk factors of frequent hypoglycemic episodes during the treatment of DM [22–24]. Among these well-known risk factors for

Table 3 Comparison of clinical backgrounds of patients who experienced postoperative hypoglycemia > 5 times within a month or less after total pancreatectomy (TP)

TP ($n = 15$)	Hypoglycemia (> 5 times within a month) $n = 7$	Hypoglycemia (≤times within a month) $n = 8$	p value
Pre-operative variables			
Age (years)	70.0 (62–83)	65.5 (61–75)	0.189
Gender (male/female)	5/2	6/2	0.955
BMI (kg/m^2)	16.7 (13.5–25.5)	21.9 (18.0–24.6)	0.094
Diabetes mellitus (yes/no)	6/1	7/1	0.955
Preoperative insulin (yes/no)	3/4	7/1	0.152
Preoperative chemoradiotherapy (yes/no)	1/6	3/5	0.463
Primary disease (malignancy/benign)	7/0	7/1	0.694
Diagnosis (PDAC/IPMC/IPMA)	5/2/0	3/4/1	0.316
Albumin (g/dl)	3.2 (2.6–4.3)	4.1 (3.1–4.7)	0.232
Hemoglobin (g/dl)	10.7 (7.9–14.6)	11.5 (7.9–13.2)	0.694
White blood cell count (/mm^2)	5090 (2320–10,400)	6050 (4730–9870)	0.121
Lymphocyte count (/mm^2)	830 (390–1570)	2285 (660–3070)	0.014
Cholinesterase (U/l)	**179 (48–293)**	**273 (173–448)**	**0.021**
Serum amylase (U/l)	88 (37–205)	92 (50–169)	0.955
Triglyceride (mg/dl)	52 (28–134)	107 (63–148)	0.072
Prognostic nutrition index	**36.2 (29.1–50.3)**	**51.4 (44.3–57.8)**	**0.021**
CA19-9 (U/ml)	77.1 (1.0–426.4)	44.4 (8.6–252)	0.536
Intraoperative variables			
Operation time (min)	481 (365–769)	491 (218–727)	0.694
Blood loss (g)	1482 (38–3400)	765 (54–4790)	0.463

Significant values are given bold at $p < 0.05$

BMI body mass index, *PDAC* pancreatic ductal adenocarcinoma, *IPMC* intraductal papillary mucinous carcinoma, *IPMA* intraductal papillary mucinous adenoma, *CA19-9*: carbohydrate antigen 19-9

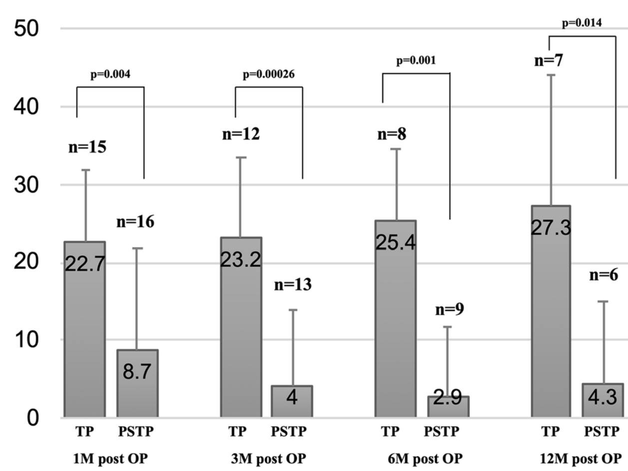

Fig. 2 Comparison of insulin usage between TP and PSTP groups from 1 to 12 months after surgery. The total amount of daily insulin usage was significantly lower in PSTP than in TP at 1 month (8.7 ± 13.0 versus 22.7 ± 9.0, $p = 0.004$), 3 months (4.0 ± 9.9 versus 23.2 ± 10.2, $p = 0.00026$), 6 months (2.9 ± 8.7 versus 25.4 versus 9.1, $p = 0.001$), and 12 months (4.3 ± 10.7 versus 27.3 ± 16.8, $p = 0.014$) after surgery. *TP* total pancreatectomy, *PSTP* proximal subtotal pancreatectomy, *OP* operation

hypoglycemic episodes, frailty is considered to be associated with under-nourished older people [23]. The results of these reports are consistent with our data, which identified that malnourished patients suffered more frequent hypoglycemia episodes after TP; however, there are no reports proposing the importance of measuring the pre-operative PNI and cholinesterase levels of patients scheduled to undergo TP.

Apart from the common nutritional indicators (serum prealbumin, albumin, cholesterol and lymphocyte count), cholinesterase and PNI have also been identified as risk factors for hypoglycemic episodes, suggesting their possible role as a marker of nutritional status [25]. Patients who are under-nourished pre-operatively metabolize by decomposing body fat and ketone bodies as energy sources. In these patients, hepatic glycogen, which is necessary for glucogenesis, is considered to be much more depleted than in well-nourished patients. A previous study found that insulin sensitivity was significantly increased in rat-starved skeletal muscle [26], suggesting that it was also potentially increased in the skeletal muscle cells of under-nutritional patients. Thus, we conjectured that hypoglycemia might be caused by the decreased glucogenesis, increased insulin sensitivity, and lack of counter regulatory hormone that often occur after TP.

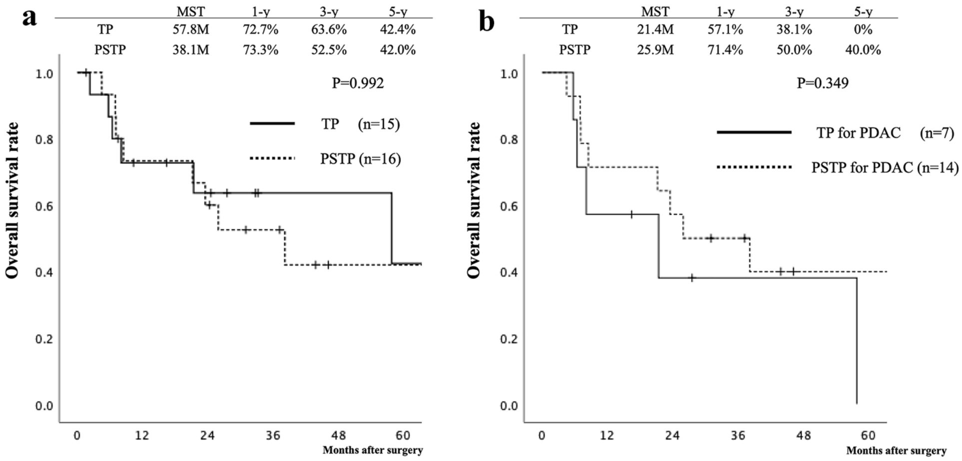

Fig. 3 Comparison of overall survival rates between TP and PSTP groups. Median survival time (MST) and overall survival (OS) were comparable between the patients who underwent TP and PSTP: MST:57.8 months versus 38.1 months and 3-year OS: 63.6% versus 52.5% ($p=0.992$) (**a**). When we focused on the 21 PDAC patients who underwent TP ($n=7$) and PSTP ($n=14$), MST and OS did not differ significantly: MST:21.4 months vs. 25.9 months and 3-year OS: 38.1% vs. 50.0% ($p=0.349$) (**b**). *TP* total pancreatectomy, *PSTP* proximal subtotal pancreatectomy, *PDAC* pancreatic adenocarcinoma, *IPMN* intraductal papillary mucinous carcinoma, *IPMA* intraductal papillary mucinous adenoma

Table 4 Uni- and multivariate analyses to identify the prognostic factors of the 31 patients who underwent total pancreatectomy (TP) or proximal subtotal pancreatectomy (PSTP)

TP and PSTP ($n=31$)	Univariate			Multivariate		
	HR	95% CI	*p* value	Hazard ratio	95% CI	*p* value
Preoperative variables						
Age (years)	1.001	0.931–1.078	0.969			
Gender (male/female)	1.704	0.577–5.029	0.335			
BMI (kg/m^2)	1.031	0.878–1.210	0.713			
Diabetes mellitus (yes/no)	0.923	0.331–2.575	0.878			
Pre-operative insulin (yes/no)	0.584	0.185–1.840	0.358			
Pre-operative chemoradiotherapy (yes/no)	1.534	0.545–4.318	0.418			
Primary disease (malignancy/benign)	24.474	0.013–44,653	0.404			
White blood cell count (/mm^2)	1.000	1.000–1.000	0.631			
Lymphocyte count (/mm^2)	0.999	0.998–1.000	0.047			
Albumin (g/dl)	0.426	0.169–1.070	0.069			
Hemoglobin (g/dl)	0.974	0.742–1.278	0.848			
Cholinesterase (U/l)	0.991	0.984–0.998	0.010	–	–	–
Serum amylase (U/l)	0.992	0.977–1.006	0.271			
Prognostic nutrition index	**0.895**	**0.830–0.965**	**0.004**	**0.895**	**0.830–0.965**	**0.004**
CA19-9 (U/ml)	1.002	1.000–1.004	0.081			
Total cholesterol (mg/dl)	0.997	0.980–1.005	0.237			
Triglyceride (mg/dl)	0.989	0.976–1.003	0.120			
Intra-operative variables						
Operation time (min)	1.004	1.000–1.008	0.069			
Blood loss (g)	1.000	1.000–1.000	0.458			
TP/PSTP	1.400	0.491–3.993	0.529			
Remnant pancreatic volume (cm^3)	1.025	0.834–1.261	0.812			

Significant values are given bold at $p<0.05$

BMI body mass index, *CA19-9* carbohydrate antigen 19-9, *TP* total pancreatectomy, *PSTP* proximal subtotal pancreatectomy, *CI* confidence interval

Table 5 Cox regression analysis to identify prognostic factors in the 16 patients who underwent proximal subtotal pancreatectomy (PSTP)

PSTP ($n = 16$)			
	HR	95% CI	*p* value
Preoperative variables			
Age (years)	0.949	0.873–1.032	0.433
Gender (male/female)	1.447	0.359–5.830	0.603
BMI (kg/m^2)	1.024	0.862–1.024	0.862
Diabetes mellitus (yes/no)	1.771	0.341–9.199	0.497
Preoperative insulin (yes/no)	1.551	0.185–12.989	0.686
Preoperative chemoradiotherapy (yes/no)	3.933	0.483–32.031	0.201
Primary disease (malignancy/benign)	22.922	0.000–9,137,434	0.634
White blood cell count (/mm^2)	1.000	0.999–1.001	0.599
Lymphocyte count (/mm^2)	0.999	0.998–1.001	0.377
Albumin (g/dl)	0.733	0.183–2.940	0.661
Hemoglobin (g/dl)	0.942	0.449–1.975	0.873
Cholinesterase (U/l)	0.994	0.986–1.003	0.223
Serum amylase (U/l)	0.987	0.959–1.017	0.394
Prognostic nutrition index	0.951	0.858–1.053	0.333
CA19-9 (U/ml)	1.002	1.000–1.005	0.051
Total cholesterol (mg/dl)	0.997	0.979–1.016	0.763
Triglyceride (mg/dl)	0.989	0.972–1.007	0.233
Intra-operative variables			
Operation time (min)	1.002	0.996–1.008	0.463
Blood loss (g)	1.000	1.000–1.001	0.464
Remnant pancreatic volume (cm^3)	0.729	0.485–1.095	0.128

BMI body mass index, *CA19-9* carbohydrate antigen 19-9, *CI* confidence interval

Hypoglycemia is common in hospitalized patients and associated with high mortality in severely ill patients [27]. Although the survival rate of the PSTP patients was similar to that of the patients who underwent TP in this study, it tended to be superior in the PSTP group when we focused on the 21 PDAC patients (Fig. 3b). In PDAC patients, preoperative exocrine dysfunction caused by pancreatic duct obstruction often results in malnutrition and the subsequent intra-operative dissection of peri-SMA neuro-plexus induces refractory severe diarrhea [28]. In this situation, TP necessitates strict management of diabetes and dangerous episodes of hypoglycemia caused by a complete absence of pancreatic hormones, including insulin, glucagon, and other islet regulation peptides [9]. Moreover, the lack of pancreatic digestive enzymes exacerbates malabsorption with diarrhea and steatorrhea [29]. It has been conjectured that glycemic control and nutritional maintenance could have a potential impact on long-term survival after TP, but nutritional support of malnourished patients can be challenging, especially after TP.

In the present study, PNI < 40 and cholinesterase < 180U/l were identified as unfavorable prognostic factors after TP regardless of the primary disease. In the clinical setting, the surgeon's decision about whether to perform TP should not be based solely on surgical resectability, but also take into account the condition of the host; that is, if the patient can withstand the physiological challenge of surgery. In malnourished patients, early intervention with nutritional support and rehabilitation might improve their PNI before surgery, but it is difficult to conduct, especially for patients with malignant disease, who require prompt surgical intervention. We consider that TP is contraindicated for patients with a low PNI and low cholinesterase levels, even if it seems to be indicated based on tumor factors. In the present study, PNI and cholinesterase levels were not recognized as unfavorable prognostic factors for the patients who underwent PSTP, although these factors were comparable pre-operatively in the two groups, suggesting that even small remnant pancreatic parenchyma might compensate both endo- and exocrine insufficiency after PSTP. Taken together, PSTP could be regarded as a feasible alternative for these malnourished patients.

In pancreatectomy for PDAC, peripancreatic lymphadenectomy is essential for complete tumor removal. In the PSTP group, we did not perform lymphadenectomy around the splenic hilum, as usually included in the resected specimen of TP. There was one case of lymph node metastasis in the splenic hilum in a patient who underwent TP in the present study; however, this tumor was regarded as far advanced PDAC occupying the entire pancreas with massive lymph

Table 6 Cox regression analysis to identify prognostic factors in the 15 patients who underwent total pancreatectomy (TP)

TP ($n = 15$)	HR	95% CI	p value
Pre-operative variables			
Age (years)	1.088	0.958–1.236	0.193
Gender (male/female)	3.027	0.357–25.636	0.310
BMI (kg/m^2)	0.935	0.763–1.145	0.515
Diabetes mellitus (yes/no)	0.690	0.077–6.204	0.741
Preoperative insulin (yes/no)	0.349	0.087–1.791	0.228
Preoperative chemoradiotherapy (yes/no)	1.099	0.201–6.022	0.913
Primary disease (malignancy/benign)	38.450	0.006–253,983	0.416
Diagnosis PDAC/IPMC/IPMA	1.033	0.372–2.871	0.950
White blood cell count (/mm^2)	1.000	0.999–1.000	0.701
Lymphocyte count (/mm^2)	0.999	0.998–1.000	0.098
Albumin (g/dl)	0.213	0.126–1.587	0.213
Hemoglobin (g/dl)	1.024	0.727–1.442	0.891
Cholinesterase (U/l)	**0.985**	**0.973–0.997**	**0.015**
Serum amylase (U/l)	0.999	0.981–1.018	0.952
Prognostic nutrition index	**0.900**	**0.810–0.999**	**0.048**
CA19-9 (U/ml)	1.003	0.998–1.008	0.286
Total cholesterol (mg/dl)	0.988	0.968–1.009	0.267
Triglyceride (mg/dl)	0.984	0.961–1007	0.178
Intra-operative variables			
Operation time (min)	1.003	0.997–1.010	0.335
Blood loss (g)	1.000	1.000–1.001	0.237

Significant values are given bold at $p < 0.05$

BMI body mass index, *PDAC* pancreatic ductal adenocarcinoma, *IPMC* intraductal papillary mucinous carcinoma, *IPMA* intraductal papillary mucinous adenoma, *CA19-9* carbohydrate antigen 19-9, *CI* confidence interval

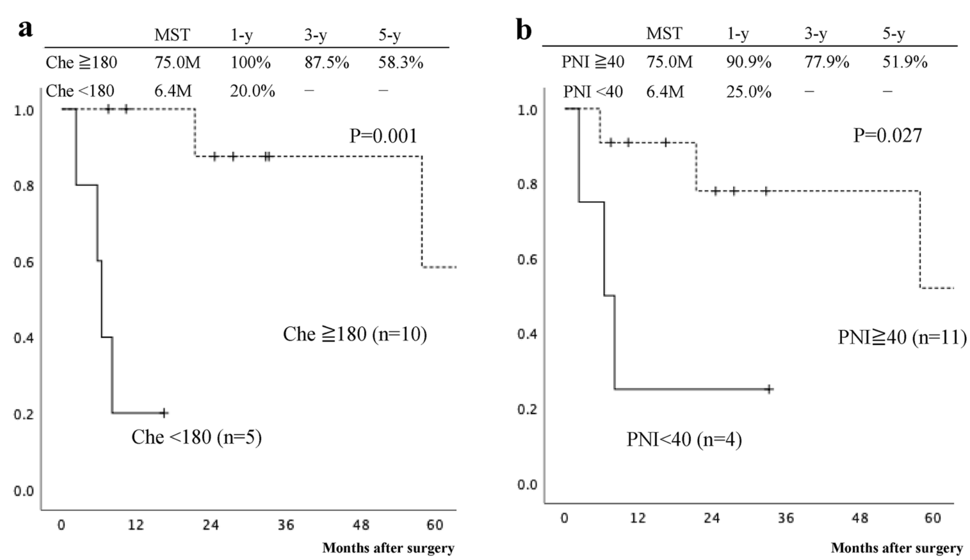

Fig. 4 Comparison of overall survival rates in TP group according to the cholinesterase level a and prognostic nutrition index b. The MST in patients with a high pre-operative cholinesterase ≥ 180 U/L ($n = 10$) was significantly better than in those with a low pre-operative cholinesterase < 180 U/L ($n = 5$) (75.0 vs. 6.4 months, $p = 0.001$) as shown in Fig. 3a. The MST in patients with a high PNI ≥ 40 ($n = 11$) was significantly better than in those with a low PNI < 40 ($n = 4$) (75.0 vs. 6.4 months, $p = 0.044$) as shown in Fig. 3b. *Che* cholinesterase, *PNI* prognostic nutrition index

node metastases, contraindicating PSTP. We considered that PSTP should be indicated for tumors located mainly in Ph, Pb, or Phb, but not in Pbth, Pbt, or Pt. Therefore, lymphadenectomy of the splenic hilum is probably not always necessary in PSTP because it is not performed in conventional pancreaticoduodenectomy, but further case accumulation is needed to clarify this.

Regarding the long-term nutritional status, we could not find any superiority of the PSTP group over the TP group in terms of postoperative PNI in the 12 months after surgery. Nevertheless, the prevalence of PDAC was significantly higher in the PSTP group than in the TP group. In other words, postoperative recurrence and adjuvant chemotherapies might negatively influence the PNI and serum cholinesterase level for a long-term period after PSTP.

The present study has several limitations. First, the number of subjects was small and further case accumulation or multicenter analyses are needed to show the true value of PSTP. Second, this was a retrospective analysis, so we could not monitor the long-term outcomes of hypoglycemia from 3 to 12 months in several patients. Nonetheless, our study highlights the usefulness of the PNI and cholinesterase level to predict whether patients will tolerate TP, and the feasibility of PSTP as an alternative for patients who are not suitable candidates for TP.

In conclusion, the indications for TP must be evaluated carefully for patients with malnutrition and PSTP should be considered a good alternative procedure for such patients.

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Declarations

Conflict of interest We have no competing interests to declare.

Ethics approval and consent to participate This retrospective study was approved by the ethics committee of Mie University Hospital and conducted in accordance with the principles of the Declaration of Helsinki. As a retrospective cohort study, the ethics committee waived the need for informed consent and there was an opt-out option.

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