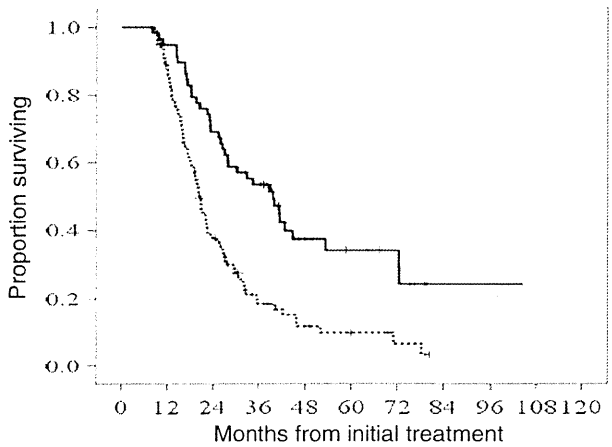
without the respective risk characteristics (hazard ratio range 1.209–1.800, all $p < 0.05$). Data were further stratified by known clinical predictors of survival, and adjuvant surgery was protective and statistically significant among each risk group. A multivariate analysis using clinical predictors obtained by univariate analysis showed that the adjuvant surgery group, a decrease of tumor markers during non-surgical anti-cancer treatments, dose of gemcitabine (≤28 g), and RECIST evaluation (PR/CR) were significant favorable factors for survival (Table 6).



	1y	2y	3y	4y	5y	death
Adjuvant surgery (n=58)						
OS (%)	95	69	53	37	34	37/58
Patient at risk	55	40	30	12	8	
Control (n=101)						
OS	88	38	18	12	10	83/101
Patient at risk	85	35	13	7	4	

Fig. 1 Comparison of the overall survival curves between the adjuvant surgery (*solid line*) and control groups (*broken line*). The overall survival rates at 1, 3, and 5 years were 95, 53, and 34 % in the adjuvant surgery group, and 88, 18, and 10 % in the control group, respectively, and the median survival time was 39.7 months in the adjuvant surgery group and 20.8 months in the control group. The survival curve in the adjuvant surgery group was significantly better than that in the control group ($p < 0.0001$)

Cox proportion-hazard model analysis stratified over the propensity score

Propensity scores were calculated using multivariate logistic regression with calculation of the conditional probabilities for the adjuvant surgery group to adjust for the significant differences in the clinical backgrounds between two groups. A Cox proportional-hazard model analysis stratified over the propensity score was performed to account for the non-randomized provision of adjuvant surgery. Table 7 demonstrates that the adjuvant surgery group was a significant independent prognostic variable with an adjusted hazard ratio (95 % confidence interval) of 0.569 (0.36–0.89).

Optimal timing of adjuvant surgery in this study

Figure 2a shows that the longer the duration of the initial treatment prior to surgical resection, the longer the survival time. Figure 2b shows comparisons of the survival curves of adjuvant surgery according to the time from the initial treatment to surgical resection; group A, over 365 days after the initial treatment ($n = 12$); group B, between 241 and 365 days ($n = 26$); group C, between 180 and 240 days after initial treatment ($n = 20$); control group (group D, $n = 101$). Although there was no difference in the survival curves between groups C and D ($p = 0.795$), significant differences were found in the survival curve between groups B and C or D ($p < 0.0001$), and between groups A and B, C, or D ($p < 0.005$). The overall survival rate in group A + B was statistically better than in group C ($p < 0.0001$). There was no difference in the primary site of recurrence (60 % distant organ metastasis and 40 % loco-regional recurrence) between groups A + B and C.

Discussion

A multicenter survey organized by JSHBPS collected 159 initially unresectable pancreatic cancer patients with

Table 4 Univariate and multivariate analyses for overall survival in the adjuvant surgery group

Parameter	Univariate analysis		Multivariate analysis	
	Hazard ratio (95 % CI)	*p* value	Hazard ratio (95 % CI)	*p* value
<240 days vs. ≥ 240 days until operation	0.237 (0.118–0.473)	<0.0001	0.332 (0.150–0.734)	0.006
Negative vs. positive LN metastasis	0.487 (0.243–0.947)	0.042	0.547 (0.264–1.132)	0.104
Dose of gemcitabine (≤28 g vs. >28 g)	0.399 (0.202–0.785)	0.008	0.603 (0.275–1.321)	0.206

CI confidence interval, *LN* lymph node

Table 5 Univariate Cox proportional-hazard analysis for overall survival: association between overall survival and patient, tumor, and treatment characteristics

Variable	No. (%) Ad vs. CTR	MST (months) Ad vs. CTR	2-year OS (%) Ad vs. CTR	5-year OS (%) Ad vs. CTR	Estimate	SE	*P*	Hazard ratio (95 % CI)
Group	58 vs. 101	39.7 vs. 20.8	69 vs. 38	34 vs. 10	−0.862	0.202	<0.0001	0.422 (0.284–0.627)
Sex					−0.165	0.289	0.385	0.848 (0.585–1.230)
Male	37 vs. 59	34 vs. 20	76 vs. 36	56 vs. 9				
Female	21 vs. 42	72 vs. 21	65 vs. 39	20 vs. 10				
Age					0.010	0.010	0.321	1.010 (0.990–1.030)
<65 years	38 vs. 51	40 vs. 21	69 vs. 40	34 vs. 12				
≥65 years	20 vs. 50	34 vs. 20	70 vs. 36	36 vs. 14				
Reason for UN					0.379	0.186	0.041	1.461 (1.016–2.102)
Met	17 vs. 45	39 vs. 19	77 vs. 33	30 vs. 6				
LA	41 vs. 56	41 vs. 22	66 vs. 41	40 vs. 13				
Peritoneal met					0.256	0.131	0.052	1.291 (0.998–1.671)
Presence	1 vs. 17	15 vs. 20	0 vs. 35	0 vs. 12				
None	57 vs. 84	40 vs. 21	70 vs. 38	35 vs. 9				
Tumor size					0.210	0.183	0.253	1.233 (0.861–1.766)
<34 mm	37 vs. 44	40 vs. 20	62 vs. 37	28 vs. 16				
≥34 mm	21 vs. 57	41 vs. 21	81 vs. 38	45 vs. 5				
Tumor location					0.224	0.184	0.224	1.250 (0.872–1.793)
Ph	31 vs. 50	41 vs. 21	74 vs. 45	34 vs. 10				
Pbt	27 vs. 51	28 vs. 20	63 vs. 30	33 vs. 10				
Tumor marker					0.868	0.395	0.028	2.382 (1.098–5.165)
Decrease or no tumor marker	54 vs. 97	40 vs. 21	72 vs. 39	35 vs. 13				
Increase	4 vs. 4	18 vs. 13	25 vs. 0	0 vs. 0				
Chemotherapy					0.152	0.305	0.618	1.165 (0.64–2.119)
GEM base	53 vs. 89	39 vs. 20	66 vs. 39	33 vs. 8				
Others	5 vs. 12	43 vs. 16	80 vs. 30	40 vs. 20				
Dose of GEM					0.588	0.185	0.001	1.800 (1.253–2.586)
<28 g	29 vs. 51	28 vs. 18	55 vs. 20	18 vs. 9				
≥28 g	29 vs. 50	53 vs. 26	83 vs. 54	48 vs. 7				
Dose of S-1					0.131	0.184	0.476	1.140 (0.796–1.633)
<5600 mg	32 vs. 49	28 vs. 22	59 vs. 45	39 vs. 13				
≥5600 mg	26 vs. 52	40 vs. 20	81 vs 31	34 vs. 7				
Radiotherapy					0.280	0.210	0.184	1.323 (0.876–1.998)
None	32 vs. 82	41 vs. 20	78 vs. 40	31 vs. 4				
Done	26 vs. 19	27 vs. 21	58 vs. 29	37 vs. 23				
TNM					−0.548	0.285	0.055	0.578 (0.331–1.012)
II	10 vs. 14	53 vs. 27	80 vs. 55	40 vs. 25				
III/IV	48 vs. 87	39 vs. 20	67 vs. 32	35 vs. 7				
RECIST					0.668	0.186	<0.0001	1.950 (1.355–2.806)
SD	12 vs. 61	20 vs. 20	42 vs. 33	25 vs. 4				
CR/PR	46 vs. 40	41 vs. 22	76 vs. 44	36 vs. 17				

MST median survival time, *OS* overall survival rate, *SE* standard error, *CI* confidence interval, *Ad* adjuvant surgery group, *CTR* control group, *Surg* surgery, *UN* unresectability, *met* metastasis, *Ph* pancreas head, *Pbt* pancreas body and tail, *CA19-9* carbohydrate antigen 19-9, *GEM* gemcitabine, *RECIST* Response Evaluation Criteria In Solid Tumors, *CR* complete response, *PR* partial response, *SD* stable disease

Table 6 Multivariate Cox proportional-hazard analysis for overall survival

Variable	Estimate	SE	*P*	Hazard ratio (95 % CI)
Adjuvant surgery vs. control	−0.757	0.233	0.001	0.469 (0.297–0.741)
Dose of gemcitabine (≤28 g vs. >28 g)	−0.598	0.190	0.002	0.550 (0.379–0.798)
Tumor marker (decrease or no tumor marker vs. increase)	0.944	0.420	0.025	2.570 (1.128–5.855)
RECIST (SD vs. CR/PR)	0.484	0.199	0.015	1.623 (1.099–2.395)
Tumor size (<34 mm vs. ≥34 mm)	0.034	0.195	0.862	1.035 (0.706–1.517)
Reason for unresectability (met vs. locally advanced)	0.332	0.223	0.136	1.394 (0.901–2.158)
TNM (III/IV vs. II)	−0.396	0.302	0.189	0.673 (0.372–1.216)
Peritoneal metastasis or not	−0.047	0.309	0.880	0.954 (0.521–1.749)

RECIST Response Evaluation Criteria In Solid Tumors, *CI* confidence interval, *CR* complete response, *PR* partial response, *SD* stable disease, *met* distant organ metastasis

Table 7 Propensity-score adjusted stratified multivariate Cox proportional-hazard analysis

Variable	Estimate	SE	*P*	Hazard ratio (95 % CI)
Ad surg vs. control	−0.563	0.229	0.01	0.569 (0.36–0.89)
Propensity score				
2nd 25 % vs. Lowest 25 %	−0.159	0.249	0.52	0.853 (0.52–1.39)
3rd 25 % vs. Lowest 25 %	−0.933	0.291	<0.01	0.393 (0.22–0.70)
Highest 25 % vs. Lowest 25 %	−0.727	0.293	0.01	0.483 (0.27–0.86)

CI confidence interval, *Ad surg* adjuvant surgery

favorable response to non-surgical anti-cancer treatments over 6 months after the initial treatment between 2001 and 2009. Fifty-eight patients underwent "adjuvant surgery", and the residual 101 patients who did not undergo adjuvant surgery served as a control group. The first clinical question of this survey was whether the addition of adjuvant surgery is safe treatment. The surgical mortality and morbidity in this study were 1.7 and 47 %, respectively, which was similar to the previous reports in initially resectable pancreatic cancer patients [17, 18], in spite of a more extensive/aggressive surgical approach (69 % of combined organ or vascular resection rate in this study). The second clinical question of this survey was whether additional adjuvant surgery is an effective treatment. Surprisingly, the overall survival rates at 1, 3, and 5 years from the initial treatment were 95, 53, and 34 %, respectively, in this highly selected group of patients, under a median observation period of 54 months (26–125), which was significantly better than those (88, 18, and 10 %) in the control group. The unadjusted and propensity-score adjusted stratified multivariate analyses showed adjuvant surgery to be a significant independent factor for overall survival. Furthermore, favorable survival rates were observed among all risk-stratified subgroups with the addition of adjuvant surgery.

Appropriate surgical management for the patients with initially unresectable pancreatic cancer is less clear. There are some reports from several groups on the use of chemo(radio)therapy to downstage unresectable pancreatic cancer to resectable disease [19–23]. They reported that the median survival time after surgery in these patients with unresectable tumor at presentation is 23.6 months [11, 19–24]. These results appear to be at least comparable to those reported with surgery alone or surgery plus postoperative adjuvant treatment in resectable patients [12]. The Memorial Sloan–Kettering Cancer Center (MSKCC) group reported that 36 patients who were able to undergo surgical resection following treatment of initial stage III pancreatic cancer experienced survival similar to those who were initially resectable as a matched control [24]. The current study found that the longer the median time from the initial therapy to surgical resection, the longer the median postoperative follow-up, and the higher the frequency of concomitant vascular resection, relative to the results from the MSKCC group. A major difference from the previous reports in this study is the investigation of the clinical safety and efficacy of adjuvant surgery in this highly selected group of patients in comparison to patients who did not undergo adjuvant surgery.

This study definitively selected patients at the initial detection of progressive disease during multimodal treatment over 6 months, and at the detection of occult distant organ metastasis during surgical exploration. Moreover, any patients with a poor functional status were also excluded in the process of non-surgical anticancer treatments. Therefore, 58 patients in the adjuvant surgery group were regard as "super-responders" to non-surgical anticancer treatments. This retrospective patient selection is one of the limitations of this study. The other limitation is

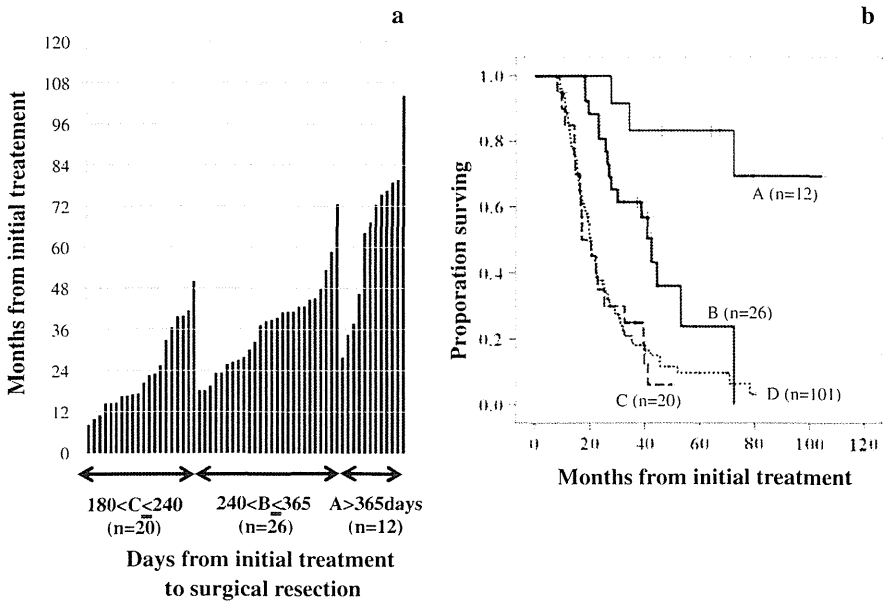


Fig. 2 Survival time and curves according to time from initial treatment to surgical resection. **a** Survival time in each patient. Group A, 12 patients who underwent adjuvant surgery more than 365 days after initial treatment; Group B, 26 patients who underwent adjuvant surgery between 241 and 365 days; Group C, 20 patients who underwent adjuvant surgery between 180 and 240 days. **b** Comparisons of the survival curves of adjuvant surgery more than 365 days after the initial treatment [$n = 12$, group A, median survival time (MST) not reached], between 241 and 365 days ($n = 26$, group B, MST 43 months), between 180 and 240 days after initial treatment ($n = 20$, group C, MST 17 months), and the control group ($n = 101$, group D, MST 20 months). Although there was no difference in the survival curves between groups C and D ($p = 0.795$), significant differences were found in the survival curve between groups B and C or D ($p < 0.0001$), and between groups A and B, C, or D ($p < 0.005$). The overall survival rate in group A + B was significantly better than in group C ($p < 0.0001$). The dose of gemcitabine and S-1, and the tumor diameter, in group A + B were significantly greater than those in group C ($p < 0.05$) but there were no significant differences in other clinical parameters

that the criteria used to select patients who were eligible for surgical exploration during non-surgical anticancer treatments differed among institutions. The 58 patients in the adjuvant surgery group were collected from 39 hospitals over 8 years, and thus the average number was 1.2 cases per hospital. Moreover, it should be noted that a significantly higher rate of peritoneal metastasis was found in the control group.

Donahue et al. [25] reported that patients with initially unresectable pancreaticobiliary malignant tumors should be selected for surgery on the basis of lack of disease progression, good functional status, and a decrease in the CA19-9 level rather than of evidence that vessel involvement has disappeared on computed tomography or magnetic resonance imaging. The third clinical question is the optimal time for adjuvant surgery in this patient population. When should the shrunken tumor be removed in the process of maintaining chemotherapy and/or radiation therapy? The sub-group analysis according to the time from the initial treatment to surgical resection showed significant favorable differences in the overall survival rates in patients who were able to undergo adjuvant surgery more than 240 days after initial treatment. Therefore, the recommended optimal time for adjuvant surgery is at least 240 days after the initial treatment. A longer duration of non-surgical anti-cancer treatment may be associated with better patient selection, greater doses of chemotherapy, a higher rate of PR/CR, and lower levels of tumor markers, thus resulting in a better prognosis of patients, since a certain period of observation time allows for the identification of progressive disease or poor surgical candidates. The primary findings of this study indicate the importance of finding the appropriate non-surgical anticancer treatments for effective tumor downsizing over at least 240 days after the initial treatment.

The adjuvant surgery group underwent major pancreatic resection with concomitant other organ and/or vascular resection in 69 % of patients. It is technically possible to perform extensive resections with vein and/or arterial reconstruction, but concomitant arterial resection remains controversial because it is associated with a high morbidity [26–28]. Laurence et al. [28] reported that an increased risk of perioperative death appears to be associated with resection performed in patients with initially designated

unresectable tumors prior to neoadjuvant chemoradiation therapy. Nakao et al. [29] reported that pancreatectomy with portal vein resection can be performed safely, and long-term survival is observed in selected patients. The current study found no significant difference in overall survival or morbidity and mortality between those receiving concomitant resection or not. Therefore, the results from this study demonstrated that concomitant resections of other organs and vessels were safely performed with special caution.

In conclusion, adjuvant surgery for initially unresectable pancreatic cancer patients with a long-term favorable response to non-surgical anticancer treatments is considered to be a safe and effective treatment. The overall survival rate from the initial treatment was extremely high, especially in patients who received non-surgical anti-cancer treatment for more than 240 days. Adjuvant surgery can occupy an important position in multimodal therapy for patients with initially unresectable pancreatic cancer.

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Conflicts of interest The authors have no commercial affiliations that might pose any conflicts of interest in connection with this study.

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ORIGINAL ARTICLE

Risk factor analysis and prevention of postoperative pancreatic fistula after distal pancreatectomy with stapler use

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Abstract
Background Postoperative pancreatic fistula (POPF) is a major, intractable complication after distal pancreatectomy (DP). Risk factor evaluation and prevention of this complication are important tasks for pancreatic surgeons.
Methods One hundred and six patients who underwent DP using a stapler for pancreatic division were retrospectively investigated. The relationship between clinicopathological factors and the incidence of POPF was statistically analyzed.
Results Clinically relevant, Grade B or C POPF by International Study Group of Pancreatic Fistula criteria occurred in 52 patients (49.1 %). Age, American Society of Anesthesiologists score, body mass index, and concomitant gastrointestinal tract resection did not influence the incidence of POPF. Use of a double-row stapler and a thick pancreatic stump were significant risk factors for POPF in multivariate analysis. Compression index was also shown to be an important factor in cases in which the pancreas was divided by a stapler.
Conclusions The most important risk factor for POPF after DP was suggested to be the thickness of the pancreatic stump, reflecting the volume of remnant pancreas. A triple-row stapler seemed to be superior to a double-row stapler in preventing POPF. However, triple-row stapler use in a thick pancreas is considered to be a future problem to be solved.

Keywords Distal pancreatectomy · Pancreatic fistula · Stapler · Pancreatic thickness · Compression index

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Introduction

Although operative management and techniques in pancreatic surgery have progressed in the last several decades, postoperative pancreatic fistula (POPF) remains a devastating complication, because it is intractable, needs prolonged drain insertion, and can lead to further morbidity and mortality. It is generally reported that the incidence of POPF after distal pancreatectomy (DP) is 5–40 % following the establishment of the International Study Group of Pancreatic Fistula (ISGPF) criteria [1–4]. Various reports have discussed the risk factors for POPF after DP, and surgical techniques for pancreatic division have been attempted to prevent POPF, but promising management still does not exist [2, 4–13]. The DISPACT study, a recent large randomized controlled trial that examined the efficacy of stapler versus hand-sewn closure, showed that stapler closure did not reduce the rate of POPF, with a POPF rate of 32 % in the stapler group and 28 % in the hand-sewn group [14]. A recent meta-analysis also showed

a similar risk of POPF occurrence, with 22.1 % in the stapler group and 31.2 % in the suture group [3]. The risk factors and prevention of POPF after DP seem to depend on the technique of division and closure of the pancreatic remnant, unless coverage or anastomosis to the stump is established. Dividing the pancreas by stapler is still common because of convenience, with advances in the devices for the field of abdominal surgery, and will continue to be required because of the wider indication for endoscopic surgery. Few reports have been published on whether the type of stapler, double-row or triple-row, influences POPF after DP. This study examined risk factors that may be associated with the occurrence of POPF after DP using a stapler for division of the pancreas, and analyzed the impact of the type of stapler.

Methods

Patients and clinical data collection

One hundred and forty consecutive patients who underwent DP at the National Cancer Center Hospital East between August 2006 and December 2011 were retrospectively investigated. Clinicopathological data were reviewed from the medical records. Twenty-one patients who underwent insertion of an open drain intraoperatively and 13 patients who underwent pancreatic resection, not with a stapler but with laparosonic coagulating shears (LCS) or knife, were excluded. An open drain was considered to be a risk for retrograde intra-abdominal infection, which is related to the risk of POPF, as we reported in a previous study [15]. Patient characteristics are shown in Table 1. The study was approved by the institutional review board of the National Cancer Center.

Operative techniques

After dissection of the peripancreatic space, ligation of the splenic artery and vein, and lymphadenectomy as needed, the pancreas was divided by one of the following techniques: double-row stapler (Proximate reloadable stapler, TLH 60; Ethicon Endo-Surgery, Cincinnati, OH, USA) with LCS or knife, or triple-row stapler (Echelon 60 mm; Ethicon Endo-Surgery, GIA Universal or Endo-GIA Ultra tri staple 60 mm; Covidien, North Haven, CT, USA). The resection site was usually above the portal vein–superior mesenteric vein (PV-SMV) axis, preserving an adequate surgical margin. The type of stapler was selected at the surgeon's discretion as well as based on changing trends. The cartridge height of the stapler was selected according to the pancreatic texture or thickness by rough intraoperative estimation. Main pancreatic duct (MPD) ligation or absorbable polyglycolic acid reinforcement felt was used for division using a double-row stapler as an additional technique in particular cases.

Gastrointestinal (GI) tract resection was performed in cases in which there appeared to be invasion by pancreatic cancer or in which it was difficult to dissect and preserve intestines, or that harbored gastric cancer. All patients underwent placement of two closed suction drains, one at the pancreatic stump and the other in the left subphrenic space. Operative data are shown in Table 2.

Perioperative management

Drainage data of amylase level (D-Amy, IU/ml) and culture results were evaluated on postoperative day (POD) 1, 3, 5, and 7. An oral diet was restarted on POD4 in general, regardless of whether POPF existed or not. A first generation cefem was used for perioperative antibiotic

Table 1 Patient characteristics

	POPF Grade B/C (n = 52)	None or POPF Grade A (n = 54)
Age (years)	61.9 ± 13.8	65.4 ± 11.9
Sex (male)	36 (69.2 %)	33 (61.1 %)
BMI (kg/m^2)	22.2 ± 3.4	21.0 ± 2.9
ASA score (1/2/3/4)	14/35/5	23/25/4
Preoperative serum albumin (mg/dl)	4.0 ± 0.5	4.0 ± 0.5
Diabetes	11 (21.2 %)	13 (24.1 %)
Smoking history	29 (55.8 %)	22 (40.7 %)
Neoadjuvant chemotherapy	0 (0.0 %)	3 (5.6 %)
Histopathological diagnosis		
Malignant disease	46 (88.5 %)	51 (94.4 %)
Pancreatic cancer	31 (59.6 %)	35 (64.8 %)
Gastric cancer	13 (25.0 %)	14 (25.9 %)
Metastatic disease	2 (3.8 %)	2 (3.7 %)
Benign disease	6 (11.5 %)	3 (5.6 %)

POPF postoperative pancreatic fistula, *BMI* body mass index, *ASA* American Society of Anesthesiologists

Table 2 Operative factors

	POPF Grade B/C ($n = 52$)	None or POPF Grade A ($n = 54$)
DP		
+Splenectomy	50 (96.2 %)	52 (96.3 %)
+GI tract resection	17 (32.7 %)	20 (37.0 %)
Gastrectomy	15 (28.8 %)	19 (35.2 %)
Jejunal resection	2 (3.8 %)	3 (5.6 %)
Colectomy	4 (7.7 %)	1 (1.9 %)
+SMA perineural dissection	12 (23.1 %)	13 (24.1 %)
+PV resection	1 (1.9 %)	1 (1.9 %)
+Celiac axis resection	3 (5.8 %)	1 (1.9 %)
+Para-aortic lymph node dissection	3 (5.8 %)	0 (0.0 %)
Type of stapler (double-row/triple-row)	47/5	40/14
Pancreatic resection site: near above PV-SMV	37 (71.2 %)	39 (72.2 %)
Additional MPD ligation after pancreatic resection	5 (9.6 %)	8 (14.8 %)
Absorbable PGA reinforcement felt use	10 (19.2 %)	8 (14.8 %)
Operation time (min)	224 ± 74	222 ± 82
Blood loss (ml)	632 ± 415	675 ± 887

POPF postoperative pancreatic fistula, *DP* distal pancreatectomy, *GI* gastrointestinal, *SMA* superior mesenteric artery, *PV* portal vein, *SMV* superior mesenteric vein, *MPD* main pancreatic duct, *PGA* polyglycolic acid

prophylaxis. Somatostatin analogues were never administered perioperatively in an attempt to prevent or treat POPF. Drains were removed when the drainage fluid did not show extremely high D-Amy or sign of infection after POD5. Drain replacement via the ordinary tract created at operation was performed under fluorography on POD7–14, in order to prevent drain occlusion and achieve effective drainage in cases that showed signs of infection in the drainage fluid.

Pancreatic factors

The configuration of the pancreatic stump was evaluated in detail. Thickness, width, and main pancreatic duct diameter (MPDd) were defined as shown in Fig. 1. The pancreatic parenchyma was considered to be the difference between the whole pancreatic stump and MPD. Each parameter was calculated on the assumption that the pancreas was an ellipse, and the MPD a circle. The pancreatic resection site was reviewed, and these parameters were measured using 2-mm-slice high-resolution multi-detector CT. Compression index was defined as the ratio of stapler height at closure to stump thickness.

Definitions of POPF

POPF was basically diagnosed according to the ISGPF criteria: Grade A: transient fistula with no clinical effect, with D-Amy greater than 3 times the upper normal serum value on or after POD3; Grade B: requiring change in management (e.g. drain replacement with prolonged drain insertion); Grade C: requiring major change in clinical management (clinical stability may be borderline and more aggressive intervention needed, e.g., intra-abdominal hemorrhage). The POPF cases in this study were considered to be "clinically relevant", consistent with Grade B or C of the ISGPF criteria.

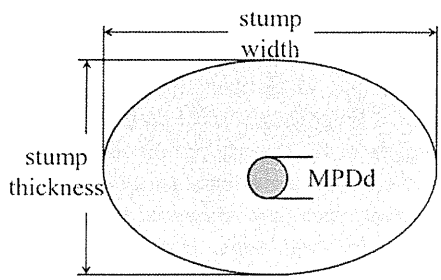

Fig. 1 Configuration of the pancreatic stump. MPDd (mm): main pancreatic duct diameter; parenchymal thickness (mm): stump thickness – MPDd; MPD area (mm^2): 1/4 × MPDd × MPDd × π; stump area (mm^2): 1/4 × stump width × stump thickness × π; parenchymal area (mm^2): stump area – MPD area

Statistical analysis

Patient characteristics, operative factors, and pancreatic measurements were compared between patients who did and did not experience "clinically relevant" POPF. Pancreatic measurements were compared using the Mann–Whitney *U* test to screen out covariates that could be associated with POPF. Categorical variables are summarized as numbers and percentages, and continuous variables are presented as mean ± SD.

Univariate and multivariate logistic regression analyses were conducted to identify independent risk factors for POPF. Covariates known to be risk factors for POPF were included [4, 16–21]. Furthermore, we evaluated whether the compression index would change the result of regression analyses, by substituting it for stump thickness. All statistical analyses were performed using SAS Release 9.3 (SAS Institute, Inc., Cary, NC, USA). All P values were based on two-sided statistical tests, setting the significance level as 0.05.

Results

Fifty-two patients (49.1 %) had "clinically relevant" POPF, which corresponded to Grade B of the ISGPF definition. No patient with Grade C was identified. Grade A was observed in 24 patients. There were 6 patients with wound infection, 3 with pneumonia, and 4 with delayed gastric emptying.

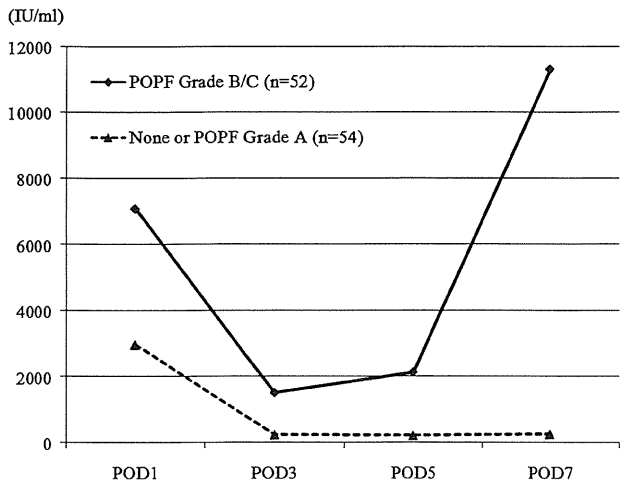

Fig. 2 Relationship between drainage data of amylase level (D-Amy) on each postoperative day (POD) and POPF D-Amy in the POPF Grade B/C group on POD1, 3, 5, and 7. There was a gradual decreased in the None or POPF Grade A group, but a gradual increased in the POPF Grade B/C group

Drainage data

Figure 2 shows the drainage data of both groups. D-Amy in the POPF Grade B/C group was significantly higher than that in the None or POPF Grade A group on POD1, 3, 5, and 7. It decreased gradually in the None or POPF Grade A group, while it gradually increased in the POPF Grade B/C group.

Pancreatic measurements

The correlation between pancreatic stump measurement data and clinically relevant POPF is shown in Table 3. Parenchymal thickness was the most significant factor in the POPF Grade B/C group, followed by parenchymal area, stump thickness, and stump area. Of these, stump thickness was representatively used in multivariate analyses.

Multivariate analyses for risk factors for clinically relevant POPF

As shown in Table 4, double-row stapler use and stump thickness were significant risk factors for POPF Grade B/C. Age, ASA score, body mass index (BMI), and concomitant GI tract resection were not significant in both univariate and multivariate analyses. The results of ancillary multivariate analysis are shown in Table 5, which substituted the compression index for the stump thickness. In spite of the missing data of compression index, double-row stapler use and compression index were significant risk factors for POPF Grade B/C.

Table 3 Pancreatic measurements

	POPF Grade B/C (n = 52)	None or POPF Grade A (n = 54)	P
MPDd (mm)	2.0 ± 0.7	2.7 ± 2.2	0.284
Stump thickness (mm)	12.9 ± 3.8	11.1 ± 3.4	0.017*
Stump width (mm)	31.0 ± 7.6	12.5 ± 8.7	0.273
Parenchymal thickness (mm)	10.9 ± 3.9	8.3 ± 3.6	0.001*
Stump area (mm^2)	322.3 ± 144.8	257.5 ± 107.4	0.025*
MPD area (mm^2)	3.6 ± 2.6	9.6 ± 21.0	0.284
Parenchymal area (mm^2)	318.7 ± 145.2	247.9 ± 103.0	0.012*
Compression index[a]	0.19 ± 0.08	0.16 ± 0.06	0.029*

POPF postoperative pancreatic fistula, *MPD* main pancreatic duct, *MPDd* main pancreatic duct diameter

* $P < 0.05$

[a] Compression index was defined as the ratio of stapler height at closure to stump thickness

Table 4 Analysis of risk factors for POPF Grade B/C ($n = 106$)

	Univariate analysis	Multivariate analysis		
	P	Odds ratio	95 % CI	*P*
Age ≥65 (years)	0.448	0.97	0.39–2.44	0.951
ASA score 2 or 3	0.050	0.51	0.20–1.33	0.168
BMI ≥25 (kg/m^2)	0.341	2.11	0.53–8.33	0.287
Concomitant GI tract resection	0.639	0.86	0.35–2.15	0.755
Double-row stapler	0.035*	3.85	1.19–12.50	0.024*
Stump thickness	0.012*	1.14	1.01–1.28	0.032*

POPF postoperative pancreatic fistula, *CI* confidence interval, *ASA* American Society of Anesthesiologists, *BMI* body mass index, *GI* gastrointestinal

* $P < 0.05$

Table 5 Analysis of risk factors for POPF Grade B/C including "compression index" instead of stump thickness ($n = 85$)

	Univariate analysis	Multivariate analysis		
	P	Odds ratio	95 % CI	*P*
Age ≥65 (years)	0.448	0.96	0.39–2.44	0.931
ASA score 2 or 3	0.050	0.46	0.20–1.33	0.146
BMI ≥25 (kg/m^2)	0.341	1.78	0.53–8.33	0.456
Concomitant GI tract resection	0.639	0.81	0.35–2.15	0.692
Double-row stapler	0.035*	3.85	1.19–12.50	0.032*
Compression index[a]	0.029*	5.00	1.28–20.00	0.020*

POPF postoperative pancreatic fistula, *CI* confidence interval, *ASA* American Society of Anesthesiologists, *BMI* body mass index, *GI* gastrointestinal

* $P < 0.05$

[a] Compression index was defined as the ratio of stapler height at closure to stump thickness

Discussion

The incidence of clinically relevant POPF after DP in this study was relatively high compared with previous reports [1–4]. There are various considerations in the interpretation of POPF, even after the establishment of the ISGPF criteria. POPF is typically confirmed in cases in which the drainage fluid shows a so-called wine red color, high D-Amy, and subsequent signs of infection of characteristic partially granular and purulent fluid as a result of saponification. However, it is sometimes difficult to make the clinical judgment of whether to carry out prolonged drain insertion to drain septic fluid, in particular in cases where it is difficult to distinguish POPF from other infective conditions. Controversial cases, for example, those without a markedly high D-Amy but requiring drain replacement because of subtle signs of infection, were included in POPF Grade B in this study, because intra-abdominal abscess drainage from a drain inserted near the pancreatic stump could be assumed to be due to POPF, unless another apparent cause of drain infection were detected. Of 52 Grade B cases, 8 did not show even ISGPF Grade A findings on POD 3 but were considered to be Grade B during the entire clinical course. To elucidate whether the preceding origin was pancreatic leakage or intra-abdominal infection is occasionally difficult. Patients who underwent GI tract resection did not show a significantly higher incidence of POPF, which suggests that possible contamination due to GI tract resection did not influence POPF.

In the drainage data, median D-Amy decreased in both groups during POD1–3, although D-Amy in the POPF Grade B/C group remained high and increased significantly even after POD5 (Fig. 2). The mechanism of clinically problematic POPF after DP was hypothesized to be that retrograde drain infection occurred subsequently in the situation of amylase-rich fluid collection, which could easily give rise to tissue injury or decrease host resistance, local anti-inflammatory factors, and the nutritional state. Although drain insertion might be necessary for only a few early postoperative days, in order to prevent dispersion of amylase-rich pancreatic juice from the stump and to allow the diagnosis of POPF after DP, the drain should be removed as early as possible, in consideration of wound healing and retrograde infection. The most important point in reducing the incidence of POPF is to close the entire pancreatic stump completely at operation.

Risk factors for clinically relevant POPF after DP have been reported in many papers. Male sex, younger age, high BMI, diabetes, large volume of pancreatic remnant, longer operation time, additional procedures, extended lymphadenectomy, and staple size of 4.1 mm were previously reported to be associated with higher risk [4, 16–21].

The texture of the resection site of the pancreas in DP is generally not affected by chronic inflammation and is considered to be healthy and exocrine-functional, because the disease is always located peripheral to the resection line. Instead, stump thickness, parenchymal thickness, stump area, and parenchymal area were significant risk factors for POPF, and parenchymal thickness and parenchymal area, which reflected the parenchymal volume, showed the lowest and second lowest *P* values in univariate analyses (Table 3). Abundant pancreatic parenchyma is essentially considered to have rich pancreatic exocrine function, as Frozanpor et al. [16] reported that a large volume of remnant pancreatic gland increased the risk of POPF. We chose just stump thickness in multivariate analyses as an index of remnant pancreatic volume because it is simple and easy to understand. The key to reducing the POPF rate after DP suggested by multivariate analysis was closure of the pancreatic remnant, especially in a pancreas with abundant and highly-functioning exocrine gland.

Previous studies on stapler use for pancreatic transection have reported various results, "beneficial" [6, 10], "hazardous" [18], or "disputable" [2, 3, 14]. The study by Bassi et al. [10] is the only randomized controlled trial, and reported that the stapler technique showed better results in comparison to suture closure, with a POPF rate of 14 versus 33 %. The merits of a stapler are considered to be convenience and possibility of simultaneous closure of the pancreatic parenchyma and MPD. Several types of stapler were used in the present study. TLH was used in order to adjust the staple height to accommodate tissue thickness. The staple height when closed varied from 1.5 to 2.5 mm. Another type of stapler, a triple-row cartridge with a cutter, was applied for both transection and closure, with selection of the stapler height according to the texture and thickness. The staple height when open/closed is 2.5 mm/1.0 mm in the white, 3.5 mm/1.5 mm in the blue, 3.8 mm/1.8 mm in the gold, and 4.1 mm/2.0 mm in the green cartridge of Echelon or GIA Universal, and 2.0–3.0 mm/0.75–1.5 mm in the camel, 3.0–4.0 mm/1.5–2.25 mm in the purple, and 4.0–5.0 mm/2.25–3.0 mm in the black cartridge of Endo-GIA Ultra Tri-Staple, which has a broader range of staple height. There is some literature about the indication for stapler use for pancreatic division. Kah Heng et al. [22] reported that the use of a stapler on a soft pancreas led to a high risk of POPF after DP. Eguchi et al. [19] reported that applying a stapler for a pancreatic stump thickness of more than 13 mm had a significant risk of POPF.

The results of the present study suggested that a triple-row stapler was safer than a double-row stapler, although our experience was limited. The indication, knack, and technique of a triple-row stapler should be considered in its use, because there has been increasing interest in performing laparoscopic pancreatic resection. Nakamura et al. [23] emphasized the importance of prolonged peri-firing compression which effectively prevented POPF after laparoscopic DP. Sepesi et al. [24] reported the importance of selection of the stapler's height. Okano et al. [25] noted that the "slow parenchymal flattening technique" should be useful to reduce the thickness of the pancreatic parenchyma. It is estimated from these studies that instant and violent compression by a stapler seems to cause crushing and tearing of the capsule of the pancreatic remnant and the development of POPF. Persistent exposure of pancreatic juice from small branches in the cut end of the torn capsule is suspected to contribute to MPD failure, resulting in major leakage. Although the remnant pancreas is usually highly-functional "soft pancreas", not only the tactile sensation but also the vulnerability of the remnant pancreas should be considered an important factor.

The compression index, which is defined as stump thickness divided by the stapler height when closed, was also a significant risk factor. This suggests that selection of stapler height according to the individual pancreatic thickness or texture would be important in preventing POPF. However, it was difficult to set the cut-off value of stump thickness or compression index for preventing POPF statistically. The compression index analyzed in this study was produced by using a mixture of double-row and triple-row staplers. Prospective collection of data from triple-row staplers not only in low risk pancreas but also in thick pancreatic stump, with appropriate staple height and unified technique, and understanding the compression index in triple-row stapler use is awaited. Limitations of this study are the retrospective design of the study, single center experience, selection of the type of stapler by trend, and possible bias of increasing experience over time.

Detailed preoperative evaluation of the remnant pancreatic parenchyma at the planned resection site by imaging modalities would mean that a suitable stapler could be used that would not tear the normal pancreatic capsule. A "high risk" pancreas with abundant parenchyma might be safely transected not only by a triple-row stapler but also by additional procedures, such as coverage, anastomosis, or transpapillary stenting [5, 7–9, 12, 13, 18]. Failure of the pancreatic stump due to pancreatic ductal back pressure in the early postoperative period was reported by Hashimoto et al. [26]. They stated that low pancreatic ductal back pressure was secured by preoperative endoscopic decompression of Wirsung's duct, and that it was worsened by intravenous opioid use.

Moreover, the detailed procedures of compressing, dividing, and closing the pancreatic remnant, by applying devices without injury to the remnant pancreatic capsule, based on the patient's individual pancreatic characteristics, are considered to be mandatory for the prevention of clinically relevant POPF after DP.

Conclusions

Clinically relevant POPF after DP still occurs with high frequency. The most important risk factor was suggested to be the thickness of the pancreatic stump. A triple-row stapler was shown to be superior to a double-row stapler in the prevention of POPF. Appropriate application of devices according to the remnant volume of the individual pancreas and further experience of triple-row stapler use with gentle maneuvering are urgently needed.

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ORIGINAL ARTICLE

Schematic Pancreatic Configuration: A Risk Assessment for Postoperative Pancreatic Fistula After Pancreaticoduodenectomy

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Abstract
Introduction Postoperative pancreatic fistula (POPF) remains a serious complication after pancreaticoduodenectomy (PD). Preoperative risk assessment of POPF is desirable in careful preparation for operation. The aim of this study was to assess simple and accurate risk factors for clinically relevant POPF based on a schematic understanding of the pancreatic configuration using preoperative multidetector computed tomography.
Methods Three hundred and eighteen consecutive patients who underwent PD in the National Cancer Center Hospital East between November 2006 and March 2013 were investigated. Pre-, intra-, and postoperative clinicopathological findings as well as pancreatic configuration data were analyzed for the risk of clinically relevant POPF. POPF was defined according to the International Study Group of Pancreatic Fistula classification. POPF grade A occurred in 52 patients (16.4 %), grade B in 84 (26.4 %), and grade C in 6 (1.9 %).
Conclusions Independent risk factors for POPF grade B/C included main pancreatic duct diameter (MPDd) < 2 mm ($P = 0.001$), parenchymal thickness ≥ 8 mm ($P = 0.018$), not performing portal vein/superior mesenteric vein resection ($P = 0.004$), and amylase level of drainage fluid on postoperative day 3 ≥ 375 IU/L ($P < 0.001$). Pancreatic configuration data including MPDd and parenchymal thickness were good indicators of clinically relevant POPF.

Keywords Postoperative pancreatic fistula · Pancreaticoduodenectomy · Pancreatic configuration · Main pancreatic duct diameter · Parenchymal thickness

Introduction

Postoperative pancreatic fistula (POPF) is still a devastating complication after pancreaticoduodenectomy (PD), because it is intractable, needs prolonged drain insertion, and can lead to further morbidity and mortality. It is generally reported that the incidence of clinically relevant POPF after PD is 7.6–36.4 %,[1–5] in accordance with the definition of the International Study Group of Pancreatic Fistula (ISGPF).[6] To reduce the incidence of POPF after PD, accurate preoperative assessment of POPF risk, as well as appropriate surgical techniques and perioperative management especially for high-risk cases, is required. Preoperative assessment of risk factors in a simple, objective way could be utilized in a widespread manner. For instance, a surgical trial with stratification of patients according to the definitive POPF risk may enhance the statistical power for a specific procedure.

Multidetector computed tomography (MDCT) to create a picture of the pancreas may express the POPF risk inherent in the pancreas. A small main pancreatic duct (MPD) is widely accepted as a significant risk factor for POPF after PD,[5,7–16] and so is a thick pancreas for POPF after distal pancreatectomy,[17,18] both of which can be demonstrated quite simply by MDCT. Schematic understanding of the pancreatic configuration by referring to preoperative MDCT findings, as established in our previous study of distal pancreatectomy,[18] may enable evaluation of preoperative risk factors for POPF after PD. The aims of this study were to assess simple and objective parameters using preoperative MDCT, compare their prognostic value for clinically relevant POPF with that of other preoperative, intraoperative, and postoperative parameters, and educe accurate risk factors available preoperatively.

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Materials and Methods

Patients and Clinical Data Collection

Three hundred and eighteen consecutive patients who underwent PD with curative intent at the National Cancer Center Hospital East between November 2006 and March 2013 were retrospectively investigated. Clinicopathological data were reviewed from the medical records. All patients underwent preoperative contrast-enhanced MDCT focusing on the pancreas and surrounding region as a part of the diagnostic workup, and PD was indicated for suspected malignancy. During this period, the reconstruction method for the remnant pancreas and postoperative management were standardized. The study was approved by the institutional review board of the National Cancer Center.

Operative Techniques

Subtotal stomach-preserving PD was performed in most of the cases, whereas conventional resection with antrectomy was performed particularly in cases with a gastric tumor. D2 lymphadenectomy was routinely performed with skeletonization of the arteries of the hepatoduodenal ligament, and removal of the retroportal pancreatic lamina on the right aspect of the mesenteric artery, paraaortic lymph node sampling, or extended resection including adjacent organs was performed based on the surgeon's decision to achieve curative resection. The pancreas was divided using a scalpel, ultrasonically activated device, or a combination of both. Segmental resection of the portal vein (PV) and/or superior mesenteric vein (SMV) was performed when a periampullary tumor was inseparable from the vein. For reconstruction, end-to-side pancreaticojejunostomy was performed using the modified technique first described by Kakita et al.[19] (Fig. 1). For the outer layer, two to four interrupted sutures penetrating the pancreatic parenchyma and picking up the seromuscular layer of the jejunum were placed using 3–0 nonabsorbable monofilament sutures with a straightened needle. Next, the pancreatic duct and full thickness jejunal wall were fixed as the inner layer with 8 to 14 interrupted stitches using 5–0 or 6–0 absorbable monofilament sutures, according to the size of the MPD. Then approximation of the jejunal wall and the pancreatic stump was accomplished with ligation of the outer layer stitches to cover fully the cut surface of the pancreas. A 6-Fr short internal drainage tube was placed through the pancreatic duct with an anchoring suture using one of the inner layer stitches, except in cases with an exceedingly dilated MPD. The number of stitches and the size of the suture material were at the surgeon's discretion for each case. No autologous grafts, artificial grafts, or sealing agents were applied in covering the anastomosis. Jackson–Pratt-type closed suction drains were placed near the pancreaticojejunal and choledochojejunal anastomoses, avoiding direct contact with vascular structures. Pancreatic consistency, especially at the pancreatic resection site, was evaluated subjectively as soft or hard by the surgeon during the operation.

Perioperative Management

D-Amy (in International units per liter) and drainage fluid culture were evaluated on POD 1, 3, and 5 and as necessary. Drains were removed when the drainage fluid did not show high D-Amy or signs of infection after POD 3–6. In cases showing signs of infection in the drainage fluid, drain replacement via the ordinary tract created at operation was performed under fluorography on POD 7–10, to prevent drain occlusion and achieve effective drainage. Postoperative CT was not planned routinely but was carried out if clinical symptoms suggested an intraabdominal inflammatory complication. In cases with drainage failure, percutaneous drainage was facilitated by CT or ultrasonographic guidance. An oral diet was restarted on POD 3 in general, and was not prohibited unless delayed gastric emptying or anastomotic failure in the digestive passage was diagnosed radiologically. Somatostatin and its analogs were never administered perioperatively in an attempt to prevent or treat POPF. Readmission for surgical complications within 30 days after discharge was evaluated. The POPF cases focused on in this study were "clinically relevant," consistent with grades B and C of the ISGPF criteria.

Schematic Understanding of Pancreatic Configuration

The configuration of the pancreatic stump was evaluated in detail.[18] The pancreatic stump was recognized as an eclipse, the MPD as a circle, and the parenchyma as the difference between the whole stump and MPD, as shown in Fig. 2. Parameters including stump thickness, stump width, and MPD diameter (MPDd) were measured using axial and coronal 2-mm-slice high-resolution MDCT, at the pancreatic resection site, which was determined with reference to the positional relationship with the adjacent vessels (Fig. 3). Pancreatic thickness was considered to be the length of the pancreas in an approximately ventrodorsal direction and vertical to the MPD, whereas pancreatic width was considered to be the length of the pancreas in an approximately cephalocaudal direction and vertical to the pancreatic thickness. Parameters including parenchymal thickness, parenchymal width, MPD area, stump area, and parenchymal area were defined and calculated using each formula (Fig. 2). The resection site was determined mainly by preoperative MDCT, confirmed by intraoperative ultrasound, and occasionally changed to a distal site because of the finding of microscopic malignancy in a frozen biopsy of the stump, with consideration of obtaining a secure tumor margin and the remnant pancreatic volume.

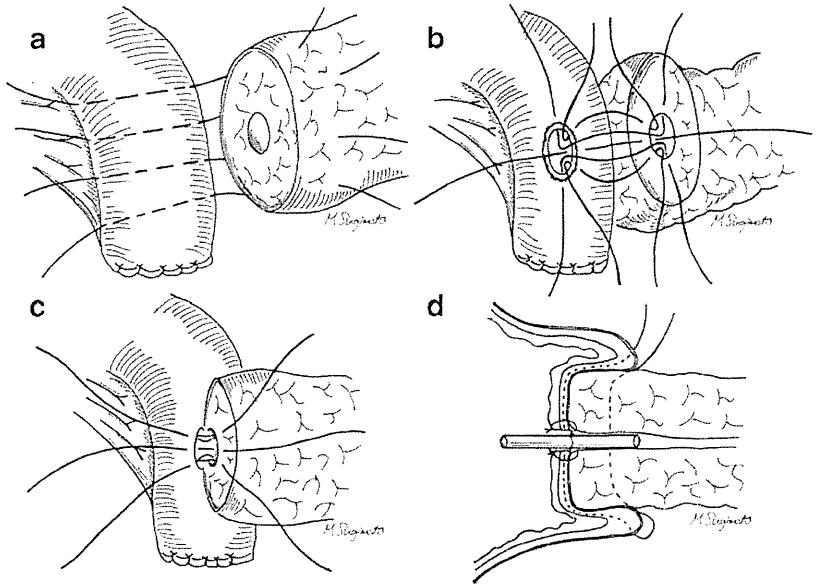

Fig. 1 Reconstructive procedure of end-to-side pancreaticoduodenectomy. **a** Four interrupted sutures penetrating the pancreatic parenchyma and picking up the seromuscular layer of the jejunum were placed for the outer layer, using 3–0 nonabsorbable monofilament sutures with a straightened needle. **b** The posterior wall of the pancreatic duct and full thickness jejunal wall were fixed as the inner layer with five interrupted stitches using 5–0 absorbable monofilament sutures. Outer layer stiches are omitted in figure. **c** The anterior wall of the inner layer of pancreatic duct and full thickness jejunal wall were fixed with three interrupted stitches using 5–0 absorbable monofilament sutures. Outer layer stiches are omitted in figure. **d** Approximation of the jejunal wall and the pancreatic stump was accomplished with ligation of the outer layer stitches to fully cover the cut surface of the pancreas. A 6-Fr short internal drainage tube was placed through the pancreatic duct with an anchoring suture using one of the inner layer stitches

Statistical Analysis

Preoperative patient characteristics, pancreatic configuration data, intraoperative factors, and D-Amy, representing postoperative data, were compared between patients who did and did not experience clinically relevant POPF in univariate logistic regression analysis. Covariates reported to be risk factors for POPF were included.[3–5,7–16,20–23] Categorical variables are summarized as numbers and percentages, and continuous variables are presented as median±standard deviation. Pre- and intraoperative factors achieving statistical significance at a 0.1 level in univariate analysis were included in multivariate analysis. Receiver operating characteristic (ROC) curves were used and area under the curve (AUC) was analyzed, to determine the cut-off value with sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy, and to identify especially predictive variables in pancreatic configuration data. One postoperative parameter, among D-Amy on POD 1, 3, and 5, was also included in multivariate analysis, although it was not considered causative or predictive. Then multivariate logistic regression analysis was conducted to identify independent risk factors or associated parameters for POPF grade B/C during the perioperative period. Odds ratios (OR) with 95 % confidence intervals (95 % CI) were obtained. All *P* values were based on two-sided statistical tests, setting the significance level as 0.05. All statistical analyses were performed using SPSS Statistics version 19.0 software (SPSS, Chicago, IL, USA).

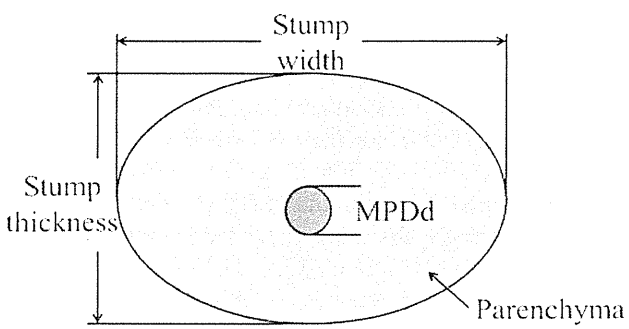

Fig. 2 Schematic configuration of pancreatic stump. *MPDd* main pancreatic duct diameter (in millimeters). *parenchymal thickness* stump thickness−MPDd (in millimeters), *parenchymal width* stump width−MPDd (in millimeters), *MPD area* 1/4×MPDd×MPDd×π (in square millimeters), *stump area* 1/4×stump width×stump thickness×π (in square millimeters), *parenchymal area* stump area−MPD area (in square millimeters)

Results

Postoperative Outcome

The postoperative course with respect to POPF in 318 patients is tabulated in Table 1. POPF grade A was observed in 52 cases (16.4 %), grade B in 84 cases (26.4 %), and grade C in 6

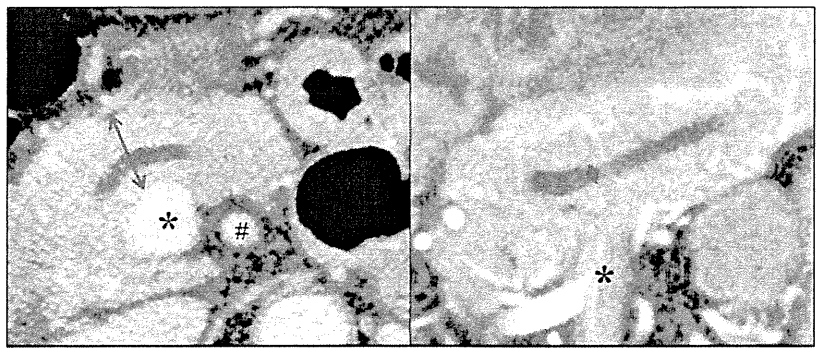

Fig. 3 Assessment of pancreatic thickness and main pancreatic duct by preoperative MDCT. Pancreatic thickness and main pancreatic duct diameter (*MPDd*) were measured at the resection site in axial (*left*) and coronal (*right*) views of preoperative MDCT. *Large arrow* pancreatic thickness; *small arrow* MPDd. *Asterisk* denotes superior mesenteric vein. *Number sign* denotes superior mesenteric artery

cases (1.9 %). Patients with POPF grade B/C experienced prolonged drain insertion (29±21 vs. 6±5 days), higher need for percutaneous drainage (22.2 vs. 2.3 %), prolonged postoperative hospital stay (33±20 vs. 13±12 days), and higher mortality (2.2 vs. 0.0 %), compared with patients who did not develop POPF (POPF grade A/none). Reoperation was never performed with an intention to manage POPF. The detailed reasons for 30-day readmission were mild transient anorexia in three patients, cholangitis in two, and delayed gastric emptying in two, with POPF grade A/none, whereas intraabdominal bleeding (POPF grade C) in one patient with POPF grade B/C. Both of the mortality cases underwent radiologic intervention for aneurysmal rupture induced by POPF and died of subsequent liver failure.

Evaluation of Risks for Clinically Relevant POPF

Factors reported or assumed to be associated with clinically relevant POPF after PD were compared between the patient groups with POPF grade A/none and POPF grade B/C by univariate analysis (Tables 2). Of the preoperative factors, patients with high BMI and pathological condition other than pancreatic cancer had a significantly higher incidence of POPF grade B/C ($P<0.001$ and $P<0.001$), whereas patients without diabetes showed a tendency for a higher incidence ($P=0.051$). Of the pancreatic configuration data, MPDd, stump width, parenchymal thickness, parenchymal width, and parenchymal area differed significantly between patients with POPF grade A/none and POPF grade B/C ($P<0.001$, $P=0.003$, $P<0.001$, $P<0.001$, and $P<0.001$, respectively). ROC curves for pancreatic configuration data are shown in Fig. 4. Values of AUC in these data were as follows; MPDd, 0.764; stump thickness, 0.523, stump width, 0.614; parenchymal thickness, 0.709; parenchymal width, 0.687; stump area, 0.589; and parenchymal area, 0.656. These results indicated that parameters with "fair accuracy" were MPDd and parenchymal thickness (AUC≥0.700). When a cut-off value of 2 mm was applied for MPDd, sensitivity was 42.2 %; specificity, 89.5 %; PPV, 61.3 %; NPV, 79.7 %; and accuracy 76.1 %, whereas sensitivity was 68.9 %; specificity, 71.9 %; PPV, 49.2 %; NPV, 85.4 %; and accuracy, 71.1 % when the cut-off value was 3 mm. When a cut-off value of 8 mm was applied for parenchymal thickness, sensitivity was 71.1 %; specificity, 64.5 %; PPV, 44.1 %; NPV, 85.0 %; and accuracy, 66.4 %. Of the intraoperative factors, soft pancreas and not performing PV/SMV resection were significantly associated with clinically relevant POPF ($P<0.001$ and $P=0.001$, respectively). Of the postoperative data, D-Amy on POD 1, 3, and 5 differed significantly between patients with POPF grade A/none and POPF grade B/C ($P=0.005$, $P<0.001$, and $P<0.001$, respectively). D-Amy on POD 3≥375 was considered to be most strongly associated with POPF grade B/C, because it is the criterion for POPF grade A. BMI≥25 kg/m^2, absence of diabetes, pathological condition other than pancreatic cancer, MPDd<2 mm, parenchymal thickness≥8 mm, soft pancreas, not performing PV/SMV resection, and POD 3 D-Amy≥375 IU/L were included in multivariate analysis of POPF grade B/C. Independent risk factors for clinically relevant POPF were MPDd<2 mm (OR, 3.589 (95 % CI, 1.665–7.737), $P=0.001$), parenchymal thickness≥8 mm

Table 1 Postoperative outcome after PD

	Overall ($n=318$)	POPF grade A/none ($n=228$)	POPF grade B/C ($n=90$)
Drain insertion (days)	7±17	6±5	29±21
Percutaneous drainage	25 (7.9 %)	5 (2.3 %)	20 (22.2 %)
Reoperation	3 (0.9 %)	2 (0.9 %)	1 (1.1 %)
Postoperative hospital stay (days)	15±18	13±12	33±20
30-day readmission	8 (2.5 %)	7 (3.1 %)	1 (1.1 %)
Mortality	2 (0.6 %)	0 (0.0 %)	2 (2.2 %)

PD pancreaticoduodenectomy, *POPF* postoperative pancreatic fistula

Table 2 Characteristics of patients and univariate analysis of risk factors for clinically relevant POPF after PD

Parameter	Overall (n=318)	POPF grade A/none (n=228)	POPF grade B/C (n=90)	P
Preoperative factors				
Age	69±11	69±11	70±10	0.489
Sex (male)	207 (65.1 %)	149 (68.3 %)	58 (64.4 %)	0.879
BMI (kg/m^2)	21.5±3.1	21.0±3.0	22.8±3.1	<0.001*
ASA score (1/2/3)	109/192/17	77/138/13	32/54/4	0.607
Diabetes	73 (23.0 %)	59 (27.1 %)	14 (15.6 %)	0.051
Coronary artery disease	18 (5.7 %)	12 (5.5 %)	6 (6.7 %)	0.626
Preoperative biliary drainage	161 (50.6 %)	121 (55.5 %)	40 (44.4 %)	0.167
Preoperative therapy	12 (3.8 %)	11 (5.0 %)	1 (1.1 %)	0.152
Albumin (g/dL)	3.8±0.4	3.8±0.4	3.9±0.5	0.958
Creatinine (mg/dL)	0.8±0.2	0.7±0.2	0.8±0.2	0.581
Pathological diagnosis (pancreatic cancer)	158 (49.7 %)	131 (60.1 %)	27 (30.0 %)	<0.001*
Pancreatic configuration data				
MPDd (mm)	3.8±3.4	4.7±3.6	2.2±1.7	<0.001*
Stump thickness (mm)	12.4±3.7	12.4±3.9	13.0±3.3	0.941
Stump width (mm)	24.0±6.3	24.0±6.4	27.0±5.7	0.003*
Parenchymal thickness (mm)	7.7±3.7	7.0±3.5	9.9±3.5	<0.001*
Parenchymal width (mm)	20.5±7.9	19.3±8.0	24.4±6.3	<0.001*
Stump area (mm^2)	235.2±99.5	230.8±104.3	255.9±84.5	0.086
Parenchymal area (mm^2)	211.9±91.1	199.6±90.5	247.3±84.9	<0.001*
Intraoperative factors				
Soft pancreas	172 (54.1 %)	99 (45.4 %)	73 (81.1 %)	<0.001*
Extended lymph node dissection	14 (4.4 %)	9 (4.1 %)	5 (5.6 %)	0.531
Pancreatic resection at PV-SMV level	272 (85.5 %)	194 (89.0 %)	78 (86.7 %)	0.676
PV/SMV resection	61 (19.2 %)	55 (25.2 %)	6 (6.7 %)	0.001*
Operation time (min)	363±76	361±79	366±70	0.774
Estimated blood loss (mL)	812±669	802±651	844±711	0.230
Transfusion	52 (16.4 %)	37 (17.0 %)	15 (16.7 %)	0.924
Postoperative data				
POD 1 D-Amy (IU/L)	2,029±48,783	462±36,399	13,530±68,325	0.005*
POD 3 D-Amy (IU/L)	134±5,666	51±2,183	1,964±9,696	0.001*
POD 5 D-Amy (IU/L)	107±12,385	46±2,439	1,267±21,583	0.001*

Differences between the two groups were evaluated using logistic regression analyses

POPF postoperative pancreatic fistula, *PD* pancreaticoduodenectomy, *BMI* body mass index, *ASA* American Society of Anesthesiologists, *MPDd* main pancreatic duct diameter, *PV/SMV* portal vein and/or superior mesenteric vein, *POD* postoperative day, *D-Amy* amylase level of drainage fluid

*P<0.05

(2.214 (1.146–4.278), P=0.018), not performing PV/SMV resection (5.564 (1.721–17.994), P=0.004), and POD 3 D-Amy ≥ 375 IU/L (13.044 (6.114–27.826), P<0.001) (Table 3).

Validation of Combination of Pancreatic Configuration Data as Risk Factor for Clinically Relevant POPF

There were 43 patients (13.5 %) with both MPDd<2 mm and parenchymal thickness≥8 mm. They were significantly associated with POPF grade B/C (9.458 (4.576–19.545), P<0.001), with sensitivity, 34.4 %; specificity, 94.7 %; PPV, 72.1 %; NPV, 78.5 %; and accuracy, 77.7 %.

Discussion

The present study investigated predictive factors for clinically relevant POPF after PD, and demonstrated the significance of schematic understanding of pancreatic configuration as a preoperative risk factor. Soft pancreatic texture has been widely recognized as an important risk factor, but is problematic as it

Table 3 Multivariate analysis of risk factors for clinically relevant POPF after PD (n=318)

Parameter	OR	95 % CI	P
BMI≥25 kg/m^2	2.137	0.897–5.095	0.087
Absence of diabetes	1.367	0.568–3.293	0.486
Pathological condition other than pancreatic cancer	0.467	0.183–1.187	0.110
MPDd<2 mm	3.589	1.665–7.737	0.001*
Parenchymal thickness≥8 mm	2.214	1.146–4.278	0.018*
Soft pancreas	1.317	0.497–3.492	0.580
Not performing PV/SMV resection	5.564	1.721–17.994	0.004*
POD 3 D-Amy≥375 IU/L	13.044	6.114–27.826	<0.001*

Independent risk factors for clinically relevant POPF were evaluated using logistic regression analysis

POPF postoperative pancreatic fistula, *PD* pancreaticoduodenectomy, *OR* odds ratio, *95 % CI* 95 % confidence interval, *BMI* body mass index, *MPDd* main pancreatic duct diameter, *PV/SMV* portal vein and/or superior mesenteric vein, *POD* postoperative day, *D-Amy* amylase level of drainage fluid

*P<0.05

is revealed intraoperatively in a subjective way, lacks quantitative analysis, and has imperfect predictive value. Recent Japanese multicenter data from 1,239 patients showed that clinically relevant POPF occurred in 142 (21.9 %) of 648 cases with soft pancreas and 36 (6.1 %) of 591 cases with hard pancreas.[3] Clinical parameters including D-Amy and blood test data in the postoperative period can be the basis

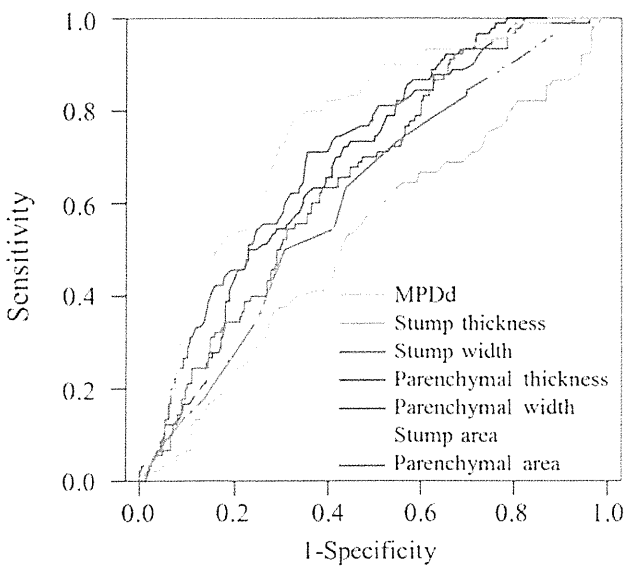

Fig. 4 ROC curves for risk of clinically relevant POPF grade B/C after PD in schematic pancreatic configuration data. Values of AUC: MPDd, 0.764; stump thickness, 0.523, stump width, 0.614; parenchymal thickness, 0.709; parenchymal width, 0.687; stump area, 0.589; parenchymal area, 0.656. *POPF* postoperative pancreatic fistula, *PD* pancreaticoduodenectomy, *MPDd* main pancreatic duct diameter

for early drain removal[24] or an early marker of latent fistula, and possibly reflect other ominous clinical conditions. D-Amy is of course a reliable postoperative factor associated with POPF,[3,20] because D-Amy on POD 3 is itself a definitive ISGPF criterion. Conversely, accurate and reliable risk factors for POPF that can be detected preoperatively will allow pancreatic surgeons to carry out preventive measures against postoperative complications. This study indicates the utility of schematic pancreatic configuration data as a prognostic marker for POPF after PD. MPDd, stump width, parenchymal thickness, parenchymal width, and parenchymal area were significantly correlated with POPF grade B/C in univariate analysis. AUC to determine the cut-off value showed that MPDd and parenchymal thickness were especially important among the pancreatic configuration data. A cut-off value of 2 mm for MPDs was more accurate than that of 3 mm, and it seemed to be a good clinical benchmark of difficult anastomosis in our operative setting. Thick pancreatic parenchyma with well-preserved exocrine function and small MPDd, which made the anastomotic technique physically difficult, might frequently result in leakage of pancreatic juice, injury of the anastomotic tissue, and infection, and lead to clinically relevant POPF. These two parameters were independent predictive factors, as were not performing PV/SMV resection and high D-Amy on POD 3, and surpassed soft pancreatic consistency in multivariate analysis. The combination of MPD< 2 mm and parenchymal thickness≥8 mm showed high specificity (94.7 %) and NPV (78.5 %). Preoperative MDCT is expected to allow earlier and more objective and precise measurement of pancreatic configuration data than were other methods of measurement, such as intraoperative ultrasound or direct measurement of the stump or resected specimen with a ruler.

Regarding other options using imaging modalities, Tajima et al.[25,26] reported that the time-signal intensity curve profile correlated with fibrosis of the pancreas in a dynamic MRI study, and a relationship between fibrosis and MPD dilation was suggested.[26] Atrophic pancreas caused by chronic inflammation revealed increased fibrosis, decreased exocrine function, and a low risk of POPF.[27,28] Conversely, Mathur et al. reported that patients with fatty pancreas had increased risk of POPF and showed decreased pancreatic fibrosis, blood vessel density, and MPDd.[29] MPDd and parenchymal thickness assessed by preoperative MDCT might be accurate indicators of the degree of fibrosis and fatty infiltration of the pancreas. Investigating the relationships among pancreatic configuration data, detailed histopathological findings, and operative outcome should be the next concern. Parameters such as the absence of diabetes, high BMI, pathological condition other than pancreatic cancer, soft pancreatic consistency, and not performing PV/SMV resection might be associated with histopathological alteration of the pancreatic parenchyma.

The incidence of clinically relevant POPF in the current study seemed to be relatively high.[1–5] Although evaluation of POPF using the definition of the ISGPF is convenient and important in the worldwide effort to reduce complications, there may still exist dilemmas and inter-institutional differences in its interpretation and application. In some cases, it is difficult to identify the origin of intraabdominal infection as POPF or another cause. We have a policy of drain management to perform an exchange procedure under fluorography on POD 7–10 in cases in which signs of infection are observed in the drainage fluid. Patients who underwent exchange procedure were considered to be grade B, even if the true origin was unclear. Our patient population had a relatively low rate of reoperation (1.0 %), 30-day readmission (2.5 %), and mortality (0.6 %).[1,30,31] Aggressive management to obtain effective drainage was given priority to reduce septic and lethal complications in our institution.

There are some limitations to our study. First, although we tried to standardize the surgical management in this single institution study and identify objective preoperative predictors of POPF, this study should be reproduced. Second, the shape of the actual surgical stump is not exactly elliptical, and that of the MPD is not a circle. The pancreatic parenchymal area at the resection site calculated on the basis that schematic configuration did not express POPF risk as accurately as did parenchymal thickness. The schematic pancreatic configuration was a good indicator of the risk of clinically relevant POPF; however, a volumetric imaging modality may have superiority in meticulous evaluation of the pancreatic configuration and volume.[32,33] Last, in cases in which the extent of tumor was beyond expectation, remeasurement by MDCT should be performed at the modified resection site intraoperatively, although these cases were rare. In fact, in most cases (85.5 %), the pancreas was divided at the PV/SMV level, which was consistent with the assessment by preoperative MDCT. Imaging modalities that facilitate more convenient and precise rendering ability and reflect the histopathological findings and function of the remnant pancreas are anticipated in the near future.

Appropriate surgical technique and perioperative management as well as understanding accurate risk factors are mandatory to reduce POPF. Efforts to reduce the incidence of POPF have encompassed various modifications of the anastomotic technique and pharmacological measures, pancreaticogastrostomy or pancreaticojejunostomy, duct-to-mucosa, invagination, the use of stents, internal or external drainage, application of topical agents to the anastomotic site, placement of an autologous graft such as omentum or falciform ligament on the anastomotic site, and prophylactic administration of somatostatin or its analog.[16,34–38] Preoperative patient stratification using accurate risk factors may lead to careful management in high-risk patients, and well-designed surgical trials can be exploited to improve the surgical technique and perioperative management. Pancreatic configuration data based on preoperative MDCT may be useful to evaluate the risk of POPF accurately, simply, and objectively. In the future, we believe that the reconstruction technique should be tailored to the individual patient according to the definitive risk of POPF.

Conclusions

MPDd and parenchymal thickness were identified as independent risk factors for clinically relevant POPF after PD, based on a schematic understanding of the pancreatic configuration. These parameters were assessed by preoperative MDCT in a simple and objective way, and the prognostic value was comparable to that of other preoperative, intraoperative, and even postoperative risk factors. The combination of MPDd<2 mm and parenchymal thickness≥8 mm was significantly associated with clinically relevant POPF, with high accuracy.

Conflict of interest None

Sources of funding for research and/or publication None

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