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High Surgical Morbidity Following Distal Pancreatectomy: Still an Unsolved Problem

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Abstract
Background High surgical morbidity following distal pancreatectomy, especially pancreatic fistula, remains an unsolved problem. The aim of this study was to identify potential risk factors for surgical morbidity with a focus on the development of pancreatic fistula.
Methods Clinicopathologic parameters were collected for 283 patients who underwent distal pancreatectomy between January 2000 and May 2010. Logistic regression analyses were performed to identify potential risk factors for surgical morbidity and pancreatic fistula.
Results Spleen-preserving pancreatectomy was carried out in 12% of all cases and multivisceral resections were performed in 37.8%. For closure of the pancreatic remnant, three different techniques were used: hand-sewn suture in 44.5%, pancreaticojejunal anastomosis in 24%, and closure by stapler in 31.5%. Overall morbidity and mortality were 53 and 3.5%. Surgical morbidity was observed in 50.2% of all cases and pancreatic fistula in 24%. The stapling group had significantly higher surgical morbidity at 65.2% ($p = 0.001$) and the most pancreatic fistulas, though this did not reach statistical significance ($p = 0.189$). Univariate and multivariate logistic analyses indicated that closure by stapler [odds ratio (OR) = 3.61; $p < 0.001$] is a risk factor for surgical morbidity.
Conclusion Closure of the pancreatic remnant by using a stapling device was associated with an increased risk of surgical morbidity. With an increasing number of laparoscopic distal pancreatectomies being performed, further studies analyzing the use of stapling devices and newer closure techniques are needed.

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Introduction

Distal pancreatectomy is the standard procedure for treating benign and malignant tumors or pancreatitis with or without pseudocysts in the body or the tail of the pancreas [1]. Advances in surgical technique have reduced the current mortality rate of pancreatic resections to below 5% in high-volume centers. Unfortunately, postoperative morbidity rates remain high, ranging from 22 to 64% [2–5]. The main cause of these high morbidity rates is pancreatic fistula, which can lead to intra-abdominal abscesses, insufficiency of anastomosis, hemorrhage, wound infection, sepsis, delayed gastric emptying (DGE), or ileus [6, 7]. The rate of pancreatic leakage after distal pancreatectomy is still up to 32% [8–10].

As yet the main causes of pancreatic fistula remain unclear. The main risk factors are considered to be associated with surgical technique and the operating experience of the surgeon. Many different surgical techniques for closure and sealing the pancreatic remnant have been developed for reducing postoperative complications. The three most commonly used techniques are hand-sewn suture, stapled closure methods [8, 11–13], and pancreaticoenteric anastomosis [7, 14, 15]. Validated recommendations or guidelines for closure of the pancreatic remnant do not exist, reflecting a lack of consensus regarding the optimal methods of pancreatic stump closure and perioperative management.

The objective of this study was to analyze factors influencing mortality and morbidity associated with distal pancreatectomy, especially regarding the formation of

pancreatic fistula, and with particular attention to the different techniques for closure of the pancreatic remnant.

Patients and methods

Data collection

Data were collected from January 2000 to May 2010 for 283 patients who underwent distal pancreatectomy at the University Hospital Hamburg-Eppendorf. Demographic and clinical data and details of the operative and postoperative courses were collected for each patient. Specifically, information regarding age, gender, indication for distal pancreatectomy, concomitant splenectomy, and method of closure of the pancreatic remnant was gathered.

Intraoperative and postoperative complications were recorded, with particular regard to pancreatic fistula, intraabdominal abscess, wound infection, DGE, bleeding, or anastomotic leak. Perioperative death was defined as any death that occurred within 30 days after distal pancreatectomy. DGE was defined as present when a nasogastric tube was needed for more than 10 days after surgery, the patient was unable to proceed to a regular diet within 10 days, or the patient vomited for more than three consecutive days after postoperative day 5.

Presence of a pancreatic fistula was defined according to the definition of the ISGPF [16], i.e., a drain output of any measurable volume of fluid on or after postoperative day 3 with an amylase content greater than three times the serum amylase activity. The postoperative pancreatic fistulas (POPF) were classified by grades A, B, and C according to the clinical impact on the patient's hospital course. The parenchymal texture was classified according to the Johns Hopkins experience as soft and hard, respectively [17].

Surgical procedures

The different closure techniques were performed without differences in distribution among the skilled senior surgeons. In benign diseases, distal pancreatectomy was performed with the aim to preserve the spleen. In malignant processes, the resection was accompanied by lymphadenectomy. This procedure comprised the resection of the nodal tissue along the hepatic artery, left gastric artery, the celiac axis, and the superior mesenteric vein, and the excision of all peripancreatic lymph nodes.

For closure of the pancreatic remnant, basically three different surgical techniques were used:

1. Pancreaticojejunal end-to-side anastomosis
2. Closure by hand-sewn suture. First, the pancreas was transected by knife or electrocautery. This was followed by identification of the main pancreatic duct and selective closure by single stitches using monofilament, nonabsorbable sutures (Prolene® 5-0). Finally, the remaining parenchyma of the pancreas remnant was closed using monofilament, nonabsorbable sutures (Prolene® 3-0).
3. Dissection and closure of the pancreatic parenchyma using a stapling device. TA 45/55 blue/green and GIA 45/55/75 blue/green staplers were used, depending on the texture of the parenchyma and the personal preference of the surgeon. In 37 cases, the procedure was followed by hand-sewn closure of the staple line using a monofilament, nonabsorbable suture (Prolene® 3-0) for reinforcing the closure line.

Hospital protocols

All patients received daily prophylactic subcutaneous low-molecular-weight heparin and gastric acid blocker. Perioperatively, antibiotics, i.e., cephalosporin and metronidazole, were routinely applied. Postoperative pain management included epidural anesthesia or patient-controlled analgesia, with administration of metamizole in defined 6-h intervals and additional piritramide intravenously or subcutaneously as required. Prophylactic octreotide medication was not administered routinely. Nasogastric tubes were placed in all patients during the operation and routinely removed on the first postoperative day (depending on the fluid volume). Two passive drains, one at the pancreatic remnant and the other in the pelvis, were routinely placed and removed depending on the volume and content of the fluid.

Depending on the health status of the patient, the extent and length of the operation, and the incidence of complications during the procedure, patients were transferred to an intensive care unit (ICU), an intermediate care (IMC) unit overnight, or back to the ward.

Statistical analysis

SPSS software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Descriptive statistics of the quantitative parameters age at operation, operative time, ICU/IMC stay, and postoperative hospital stay are presented as median. For comparison of subgroups according to the closure technique, Fisher's exact test was used. Operative time, ICU stay, and hospital stay were compared among the different closure groups using the Kruskal-Wallis test. Univariate and multivariate logistic regression analyses were performed to identify risk factors that are potentially associated with morbidity and especially pancreatic fistula. The relative risk was described using the estimated odds

ratio (OR) with a 95% confidence interval. Results were considered statistically significant at $p \leq 0.05$.

Results

Patient characteristics

Data were collected on 283 patients who underwent distal pancreatectomy between January 2000 and May 2010 at the Department of General, Visceral and Thoracic Surgery, University Hospital Hamburg-Eppendorf, Germany. There were 121 female patients (42.8%) and 162 male patients (57.2%). The median age of the patients at the time of operation was 56 years with a range of 16-83 years (Table 1). The main indications for distal pancreatectomy were malignant pancreatic tumor (46.3%, $N = 131$) followed by pancreatitis (38.9%, $N = 110$). More rarely, indications were benign pancreatic tumor (7.4%, $N = 21$), other tumors such as gastrointestinal stromal tumor (GIST) or lymphoma (6.4%, $N = 18$), and trauma (1%, $N = 3$). Malignancy in general was the indication for the procedure in 52.7% of patients ($N = 149$).

Table 1 Distal pancreatectomies ($N = 283$): demographic, clinical, and technical characteristics of patients and procedures

Age (years) [median (range)]	56 (16-83)
Sex [*N* (%)]	
Male	162 (57.2)
Female	121 (42.8)
Indication [*N* (%)]	
Pancreatic tumors	152 (53.7)
Benign	21 (7.4)
Malignant	131 (46.3)
Other tumors	18 (6.4)
Pancreatitis	110 (38.9)
Trauma	3 (1)
Malignancy [*N* (%)]	
Yes	149 (52.7)
No	134 (47.3)
Splenectomy [*N* (%)]	
Yes	249 (88)
No	34 (12)
Surgical technique [*N* (%)]	
Laparotomy	265 (93.6)
Laparoscopy	18 (6.4)
Type of closure [*N* (%)]	
Anastomosis	68 (24)
Suture	126 (44.5)
Stapler (± hand-sewn closure of staple line)	89 (31.5)
Multivisceral resection [*N* (%)]	107 (37.8)

Operative details

Of the distal pancreatectomies, 93.6% were carried out by laparotomy ($N = 265$). Laparoscopy was performed in only 6.4% of cases ($N = 18$). Concomitant splenectomy was carried out in 88% of cases ($N = 249$). Multivisceral resections were carried out in 37.8% of the patients ($N = 107$) and included stomach, small intestine, colon, spleen, liver, kidney, adrenal gland, diaphragm, and biliary tract and resection and reconstruction of major vessels such as the celiac artery, the hepatic artery, and the portal vein. The numbers of resected organs are given in Table 2.

Outcome analysis according to type of closure

For analysis of the outcomes after distal pancreatectomy according to the technique used to close the pancreatic remnant, all 283 patients were divided into three groups. A pancreaticojejunal anastomosis was created in 24% ($N = 68$), the pancreatic remnant was sealed by hand-sewn suture as described in the Methods section in 44.5% of all cases ($N = 126$), and transection and closure of the pancreas by means of a stapling device was performed in 31.5% of patients ($N = 89$). In 41.6% of the latter cases (37 of 89), the stapling line was closed by hand-sewn suture to reinforce the closure line. TA and GIA staplers were used in 56.2% ($N = 50$) and 43.8% ($N = 39$) of the 89 cases in which closure of the pancreatic remnant were performed by stapling device. Closure of the pancreatic remnant by hand-sewn suture was performed significantly more often on patients with pancreatitis ($p = 0.011$) and significantly more often during distal splenopancreatectomy ($p = 0.038$). However, with respect to high-risk indications such as malignant pancreatic tumors ($p = 0.432$) or high-risk procedures such as multivisceral resections ($p = 0.895$), no significant differences in closure techniques could be observed. In addition, there were no

Table 2 Distribution of resected organs in multivisceral distal pancreatectomies (107/283 patients, 37.8%)

Resected organs	*N*
Adrenal gland	39
Kidney	8
Stomach	57
Small intestine	31
Colon	39
Liver	47
Diaphragm	21
Biliary tract	13
Resection and reconstruction of celiac artery/hepatic artery/portal vein	18

significant differences between the three basic closure techniques concerning the texture of the pancreatic parenchyma ($p = 0.156$).

The median operative time was 249 min (range = 90–521 min). The significant shortest median operative time of 213 min (range 116–521 min, $p = 0.014$) was seen in the stapling group. All three closure types showed no significant difference with respect to the need for blood transfusion ($p = 0.318$).

The stapling group had a significantly higher overall morbidity (66.3%, $p = 0.003$) and surgical morbidity rate (65.2%, $p = 0.001$) compared with the suture and anastomosis groups. No significant differences between TA and GIA staplers were observed with respect to overall ($p = 0.155$) and surgical morbidity ($p = 0.247$).

Pancreatic fistulas developed in 24% of all patients ($N = 68$). According to the ISGPF grading classification, 44 grade A (64.7%), 21 grade B (30.9%), and 3 grade C (4.4%) fistulas were observed. There were slight differences between the different groups, with a rate of 19% in the suture group and a rate of 26.5% in the anastomosis group. The highest fistula rate was observed in the stapler group at 29.2%; this was not significantly different from the other groups ($p = 0.189$). Intra-abdominal abscesses and DGE developed significantly more often in the stapler group at 18% ($p < 0.001$) and 29.2% ($p = 0.009$), respectively.

Other surgical complications such as wound infection, bleeding, pancreatitis of the remnant, or sepsis were not significantly different between different closure method groups. Also, intensive care unit, intermediate care unit, and hospital stay and mortality rate did not differ significantly (Table 3).

Logistic regression analyses to identify risk factors for morbidity and pancreatic fistula

Univariate logistic regression analysis was carried out to identify potential risk factors associated with surgical morbidity (especially pancreatic fistula) following distal pancreatectomy.

Closure of the pancreatic remnant by means of a stapling device was associated with a 3.02-fold greater risk of surgical morbidity ($p = 0.001$). As might be expected, multivisceral resections and an operative time longer than 400 min were associated with an increased risk of surgical morbidity as well (Table 4). These three parameters remained significant in multivariate analysis and are independent risk factors for the development of surgical morbidity (Table 5).

In univariate logistic regression analyses concerning the development of pancreatic fistula, no parameter was revealed significantly as a potential risk factor (Table 6).

Discussion

In the present study, we found that the use of a stapling device for closure of the pancreatic remnant had the highest morbidity rate with the highest number of pancreatic fistulas compared with the use of hand-sewn sutures and pancreaticoenteric anastomosis. Statistical analyses indicated that stapling was an independent risk factor for surgical morbidity.

The closure of the pancreatic remnant has been suggested to be the main risk factor associated with the development of pancreatic leakage [7, 9, 13]. As yet, pancreatic fistulas remain a clinically important and unsolved problem. In recent studies the rates of pancreatic fistula have varied from 2 to 32% [6–9, 18]. These data accord well with our findings. However, one problem with published pancreatic fistula rates is the lack of a standard definition which makes comparisons inappropriate. In 2005, Bassi et al. [16], with the International Study Group on Pancreatic Fistulas (ISGPF), presented a classification for standardized definition of pancreatic fistula; we used this classification in the present study [16, 19, 20]. We suggest that the ISGPF standardization should be used in other studies for better comparison of pancreatic fistula rates.

So far, all reported technical variations have failed to reduce the pancreatic fistula rate, with most fistulas treated conservatively or with radiologically implanted drainage [21]. They are the main source of surgical morbidity as they lead to intra-abdominal abscesses, bleeding, pancreatitis, DGE and sepsis. A systematic review and meta-analysis by Knaebel et al. [6] reported overall morbidity rates that varied from 13.3 to 64%. In our study, an overall morbidity rate of 53% and a surgical morbidity rate of 50.2% were observed.

A recently published study by Seeliger et al. [9] reported that malignant disease showed a trend toward being a confounding variable for surgical morbidity. Our findings confirmed these results. Resections because of malignant pancreatic tumor as an indication had the highest surgical morbidity rate of 56.5% (74/131) in comparison to the other indications. There were no significant differences between the distribution of closure techniques and malignant pancreatic tumors as an indication ($p = 0.178$). Malignant pancreatic tumors are associated with several factors such as longer median operative time, greater need for blood transfusion, multivisceral resections and effects of other organ systems, which may explain these findings.

Several techniques for closure of the pancreatic remnant have been reported in the attempt to reduce surgical morbidity and especially the incidence of pancreatic fistula. These procedures include pancreaticoenteric anastomosis [14], hand-sewn suture with selective duct ligation, transection by stapling device [8, 11–13], and the use of

Table 3 Outcome after distal pancreatectomy depending on type of closure (283 patients)

	Anastomosis	Suture	Stapler	All	*p* value
Patients [*N* (% of total)]	68 (24)	126 (44.5)	89 (31.5)	283 (100)	
Indication					0.011
Benign pancreatic tumor	3 (14.3)	8 (38.1)	10 (47.6)	21 (7.4)	
Malignant pancreatic tumor	37 (28.2)	48 (36.6)	46 (35.2)	131 (46.3)	
Pancreatitis	25 (22.7)	62 (56.4)	23 (20.9)	110 (38.9)	
Others	3 (14.3)	8 (38.1)	10 (47.6)	21 (7.4)	
Texture of parenchyma					0.156
Soft	36 (21.9)	69 (42.1)	59 (36.0)	164 (58.0)	
Hard	32 (26.9)	57 (47.9)	30 (25.2)	119 (42.0)	
Extent of resection					0.038
Distal pancreatectomy	8 (23.6)	13 (38.2)	13 (38.2)	34 (12)	
Distal splenopancreatectomy	31 (21.8)	76 (53.5)	35 (24.7)	142 (50.2)	
Multivisceral resection	29 (27.1)	37 (34.6)	41 (38.3)	107 (37.8)	
Operative time (min) [median (range)]	286 (160–493)	255 (90–450)	213 (116–521)	249 (90–521)	0.014
Blood transfusion $\geq$ 2 PRBC [*N* (% of group)]	26 (38.2)	39 (31)	24 (27)	89 (31.4)	0.318
Overall morbidity [*N* (% of group)]	26 (38.2)	65 (51.6)	59 (66.3)	150 (53.0)	0.003
Surgical morbidity [*N* (% of group)]	26 (38.2)	58 (46)	58 (65.2)	142 (50.2)	0.001
Major complications					
Pancreatic fistula	18 (26.5)	24 (19)	26 (29.2)	68 (24)	0.189
Abscess	0 (0)	3 (2.4)	16 (18)	19 (6.7)	0.000
Bleeding	5 (7.4)	11 (8.7)	8 (9)	24 (8.5)	0.962
Sepsis	5 (7.4)	8 (6.3)	2 (2.2)	15 (5.3)	0.286
Minor complications					
Wound infection	8 (11.8)	5 (4)	8 (9)	21 (7.4)	0.088
Pancreatitis of the remnant	3 (4.4)	8 (6.3)	2 (2.2)	13 (4.6)	0.388
DGE	8 (11.8)	18 (14.3)	26 (29.2)	52 (18.4)	0.009
Nonsurgical morbidity [*N* (% of group)]	14 (20.6)	24 (19)	26 (29.2)	64 (22.6)	0.213
Relaparotomy [*N* (%)]	8 (11.8)	13 (10.3)	18 (20.2)	39 (13.8)	0.110
ICU/IMC unit stay (days)[median (range)]	1 (0–38)	1 (0–37)	1 (0–42)	1 (0–42)	0.873
ICU/IMC unit stay > 1 day [*N* (%)]	16 (23.5)	42 (33.3)	26 (29.2)	84 (29.7)	0.377
Mortality [*N* (%)]	3 (4.4)	5 (4)	2 (2.2)	10 (3.5)	0.720
Hospital stay (days) [median (range)]	18 (11–60)	17.5 (7–86)	15 (10–47)	16.5 (7–86)	0.219

PRBC packed red blood cells, *DGE* delayed gastric emptying, *ICU/IMC* intensive care unit/intermediate care

patches, meshes, ultrasonic dissection, or fibrin glue [22–25]. None could be considered the definitively optimal surgical procedure and the incidence of pancreatic fistula has not notably decreased in recent decades. In our study, pancreaticojejunal anastomosis, hand-sewn suture, and dissection by stapler were carried out, and pancreatic fistula occurred in 24% of all cases ($N = 68$). Several studies have favored closure by hand-sewn suture, which ideally should be combined with main duct ligation [7, 11]. In another study, pancreatic anastomosis was associated with the lowest number of pancreatic fistulas [14]. However, Kleeff et al. [7] recommend that pancreatic anastomosis should be performed only when there is indication of a pancreatic duct obstruction and if it can be carried out safely.

Another frequently used closure technique is pancreatic transection by means of a stapling device. In a systematic review and meta-analysis, the stapler closure technique was found to have the lowest pancreatic fistula rate and was favored for closure of the pancreatic remnant [6]. Nevertheless, a large cohort study from the same department suggested that stapler closure of the pancreatic remnant was associated with a significantly higher fistula rate [7].

In our study, hand-sewn suture, pancreatic anastomosis, and stapler closure were carried out in 44.5, 24, and 31.5% of patients, respectively. As might be expected, the shortest median operative time was observed in the stapler group and the longest median operative time was in the group who underwent pancreatic anastomosis ($p = 0.014$). On the other hand, the stapler group had a significantly higher

Table 4 Univariate logistic regression analysis of risk factors associated with surgical morbidity

Variable	OR	95% CI	*p* value
Age			
<50 years	Reference		
50 to <70 years	1.07	0.62–1.86	0.812
≥70 years	0.69	0.44–1.73	0.692
Gender			
Female	Reference		
Male	0.83	0.52–1.33	0.430
Indication			
Benign pancreatic tumor	Reference		
Malignant pancreatic tumor	2.11	0.82–5.43	0.122
Pancreatitis	1.46	0.56–3.79	0.441
Others	1.00	0.29–3.48	1.000
Closure			
Anastomosis	Reference		
Suture	1.38	0.76–2.52	0.296
Stapler	3.02	1.57–5.82	0.001
Extent of resection			
Spleen-preserving	Reference		
Distal splenopancreatectomy	1.82	0.82–4.00	0.139
Multivisceral	3.24	1.43–7.32	0.005
Blood transfusion			
<2 PRBC	Reference		
≥2 PRBC	1.25	0.75–2.06	0.392
Operative time			
<400 min	Reference		
≥400 min	4.66	1.53–14.22	0.007

CI confidence interval, *OR* odds ratio

Table 5 Multivariate logistic regression analysis of risk factors associated with surgical morbidity

Variable	OR	95% CI	*p* value
Closure			
Stapler vs. anastomosis	3.61	1.80–7.24	0.000
Extent of resection			
Multivisceral vs. distal pancreatectomy	2.78	1.17–6.56	0.020
Operative time			
≥400 min vs. <400 min	4.26	1.25–14.45	0.020

CI confidence interval, *OR* odds ratio

surgical morbidity rate of 65.2% compared with the other groups ($p = 0.001$). Moreover, the highest pancreatic fistula rate occurred in the stapler group at 29.2% ($p = 0.189$), and intra-abdominal abscesses and DGE developed significantly more often, in 18% ($p < 0.001$) and 29.2% ($p = 0.009$) of this group, respectively. These findings agree well with the results of recent studies by Kleeff et al. [7] and Ferrone et al. [26].

Table 6 Univariate logistic regression analysis of risk factors associated with pancreatic fistula

Variable	OR	95% CI	*p* value
Age			
<50 years	Reference		
≥50 to <70 years	0.62	0.33–1.15	0.126
≥70 years	0.51	0.22–1.15	0.103
Gender			
Female	Reference		
Male	0.68	0.39–1.18	0.167
Indication			
Benign pancreatic tumor	Reference		
Malignant pancreatic tumor	1.71	0.47–6.20	0.417
Pancreatitis	2.35	0.65–8.56	0.194
Others	1.88	0.39–9.12	0.436
Closure			
Anastomosis	Reference		
Suture	0.65	0.33–1.31	0.233
Stapler	1.15	0.57–2.32	0.705
Extent of resection			
Spleen-preserving	Reference		
Distal splenopancreatectomy	0.76	0.48–2.75	0.762
Multivisceral	0.89	0.36–2.24	0.803
Blood transfusion			
<2 PRBC	Reference		
≥2 PRBC	1.51	0.60–3.80	0.381
Operative time			
<400 min	Reference		
≥400 min	2.07	0.82–5.23	0.123

CI confidence interval, *OR* odds ratio

However, the best closure technique of the pancreatic remnant is still a matter of controversy. The results of a multicenter randomized controlled study that compared the outcome of stapler closure and hand-sewn suture are expected in 2011 [27, 28]. Support of our findings would emphasize the need for further studies that investigate new closure techniques. For example, the LigaSure® dissector (Covidien, Mansfield, MA, USA) has been used for resection of various organs [29, 30]. A recently published trial investigated the use of LigaSure and the development of pancreatic fistulas [31]. Pancreatic closure by LigaSure was compared with hand-sewn suture in an experimental animal model. None of the animals that underwent distal pancreatectomy by LigaSure developed pancreatic fistula. These are promising results that should be investigated by further studies in pancreatic surgery, especially with the increase in the number of laparoscopic distal

pancreatectomies being performed [32–34]. As stapling has been commonly used for pancreatic dissection, new sealing techniques need to be investigated considering that closure by stapler is associated with increased surgical morbidity.

Conclusion

In conclusion, closure of the pancreatic remnant by using a stapling device was associated with an increased risk of surgical morbidity but without statistical evidence for the development of pancreatic fistulas. Which method is best for closure of the pancreatic remnant remains unclear and needs to be determined by large prospective multicenter trials. In addition, new closure techniques need to be investigated in future studies.

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