The influence of transection site on the development of pancreatic fistula in patients undergoing distal pancreatectomy: A review of 294 consecutive cases

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Background. *Pancreatic fistula (PF) is a significant cause of morbidity in patients undergoing distal pancreatectomy (DP), with an incidence of 15–40%. It remains unclear if the location of pancreatic transection affects the rate of PF occurrence. This study examines the correlation between the transection site of the pancreas during DP and the incidence of PF.*

Methods. *All cases of DP from October 2005 to January 2012 were reviewed retrospectively from an institutional review board-approved database at the Thomas Jefferson University Hospital. Patient demographics and perioperative outcomes were analyzed. The pancreatic transection location was determined by review of operative reports, and then dichotomized into 2 groups: neck/body or tail. PF were graded following the International Study Group on Pancreatic Fistula guidelines.*

Results. *During the study period, 294 DP were performed with 244 pancreas transections at the neck/body and 50 at the tail. Of the 294 patients, 52 (17.7%) developed a postoperative PF. The incidence of PF after transection at the tail of the pancreas was higher (28%) when compared with transection at the neck/body (15.6%;* P = *.04). When stratified by PF grade, grade A PF occurred more commonly when transection of the gland was at the tail (22% tail vs 8.2% neck/body;* P = *.007); however, no difference was found for grade B/C PF (6% tail vs 7.4% neck/body;* P = *1).*

Conclusion. *Our data suggest that PF occurs more often when the tail is transected during DP, although the majority are low grade and of minimal clinical significance. More severe PF occurred equally between the transection sites. (Surgery 2015;157:1080-7.)*

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Distal pancreatectomy (DP), or resection of the pancreas to the left of the mesoportal confluence, is a common operative procedure used to treat both benign and malignant diseases of the body and tail of the pancreas. Although mortality rates for major pancreatic resections have improved to <5% (1% for DP in recent years), morbidity rates have remained relatively unchanged, and have a significant effect on patient recovery and quality of life.[1] Pancreatic fistula (PF), defined as a parenchymal leak of amylase-rich fluid (>3 times the serum level on or after postoperative day 3),[2] remains among the most significant causes of morbidity after DP with a reported frequency of 15–40% in published studies.[2-4] Aside from being a major source of morbidity alone, PF is also associated with an increased risk of other related complications, such as delayed gastric emptying, intraabdominal abscess, wound infection, pulmonary complications, and visceral artery pseudoaneurysm development. PF results in prolonged postoperative hospital stays, increased readmission rates, and a delay to the commencement of adjuvant treatment (in patients with malignant disease).[5-7]

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In an effort to reduce the rate of PF after DP, many groups have attempted different pancreatic stump closure and/or transection techniques.[2,8,9] Traditionally, parenchymal transection with a scalpel or electrocautery was followed by direct ligation of the pancreatic duct and horizontal mattress suture closure of the pancreatic stump. More recently, and in conjunction with the advent of minimally invasive surgical techniques, transection and ligation of the pancreas is also being performed with gastrointestinal staplers with or without staple line reinforcement. Many adjuncts to decrease PF have been tried. Unfortunately, the data have not shown a clear consensus as to the optimal technique for gland closure, with various studies conflicting on the efficacy of each method.

To date, very little attention has been given to the site of pancreas transection during DP as a risk factor for PF formation. We hypothesized that the site of pancreatic transection during DP would likely affect postoperative PF rates and reviewed our large experience with DP to that end.

METHODS

All cases of DP at the Thomas Jefferson University Hospital (TJUH) from October 2005 to January 2012 were retrospectively reviewed, querying our institutional review board–approved, prospectively maintained pancreatic surgery database. Patients were excluded if they had prior pancreatic surgery or history of a previous PF. At TJUH, DP was performed by either cautery transection with direct duct ligation and mattress sutured remnant gland closure or by the use of a gastrointestinal stapler device with or without buttress material (Seamguard, Gore, Flagstaff, AZ). The decision where to transect the pancreas was made intraoperatively by the attending surgeon based on the location of the pathologic abnormality and with the objective of obtaining clear resection margins. Operative notes, patient charts, laboratory values, imaging studies, pathology reports, and discharge summaries were analyzed to assess pancreas transection location and perioperative outcomes. Location of transection was regionally defined as either "neck/body" (at or around the portal confluence or celiac axis) or "tail" (to the left of the celiac axis; Fig 1).

The International Study Group on Pancreatic Fistula grading system was used to classify PF as 1 of 3 grades: A, B, or C.[2] In brief, grade A PF are often asymptomatic and typically present only with either amylase-rich fluid collections or drainage of amylase rich fluid via operatively placed drains.

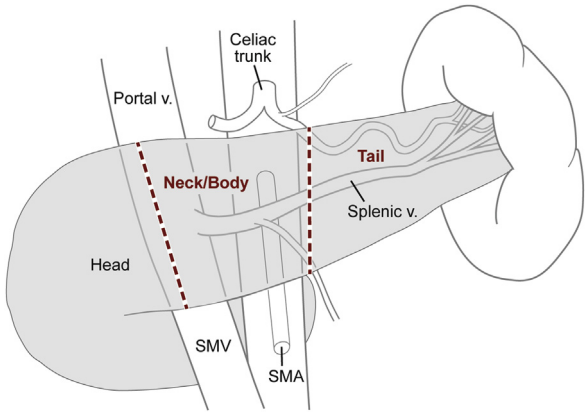


Fig 1. Anatomic determination between neck/body and tail transections. *SMA*, Superior mesenteric artery; *SMV*, superior mesenteric vein; *v.*, vein.

These PF typically do not require an alteration in postoperative management. Grade B PF include fistulae that alter clinical management by use of parental nutrition, antibiotics, or additional drainage. At our institution, all patients with amylase-rich fluid in an operatively placed drain after postoperative day 3 receive octreotide (per our standardized post-DP pathway),[10] regardless of PF severity, and so the use of somatostatin analog was not considered in our grading using the International Study Group on Pancreatic Fistula criteria. Grade C fistulae are the most severe, often requiring extensive intervention to address persistent leakage or life-threatening sequelae. Drain amylase values were only measured if clinical suspicion for PF was present. Upon documentation of a leak, octreotide 250 μg was administered subcutaneously every 8 hours for a total of 6 doses. Additionally, 20 mg of Sandostatin LAR, a long-acting depot formulation of octreotide, was given once intramuscularly upon initial finding of the leak. The dosage is the same for all patients. All complications that arose secondary to PF were treated with standard medical care for the complication at hand.

Statistical analysis of the groups was performed. Categorical outcome variables were compared by use of the Fisher exact test. Continuous outcome variables reported between groups were analyzed using the Kruskal–Wallis test. Logistic regression was used to determine adjusted estimates of association between PF and various patient and procedure characteristics. Variables were included in the full model if they were associated with PF in univariable analysis with $P < .20$, or if they were known to be associated with PF from previous

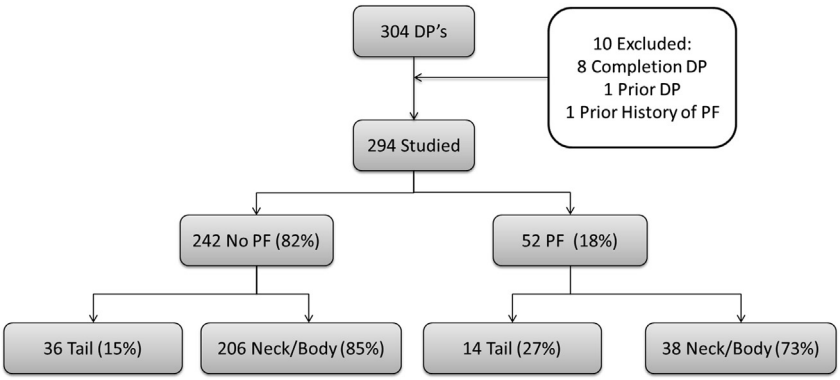


Fig 2. Study schema. *DP*, Distal pancreatectomy; *PF*, pancreatic fistula.

reports. A backward elimination model selection procedure was used to sequentially remove nonsignificant terms until all variables were significant with $P < .10$.

RESULTS

During the 76-month inclusion period, 304 consecutive DP were performed at TJUH. After excluding 10 cases (9 with prior pancreatic resections and 1 with a preoperative chronic PF), 294 were eligible for this study and had their perioperative history reviewed and analyzed (Fig 2).

The patient cohort was composed of 125 men (43%) and 169 women (57%), with a median age of 62 years (range, 19–89). The most common indications for DP were cystic disease/neoplasms (41%), pancreatic ductal adenocarcinoma (28%), neuroendocrine tumors (21%), and pancreatitis (5%; Table I). Of the 294 DP performed, 244 were transected at the neck/body (83%), and 50 were divided at the tail (17%; Table II).

Of the 294 patients, 52 (17.7%) developed a PF postoperatively: 31 grade A (11%) and 21 grade B/C (7%; Table II). There was a significantly higher rate of PF when transection of the pancreas occurred at the tail (28%), as compared with the neck/body (15.6%; $P = .04$). Grade A fistulae occurred more commonly in the tail region (22%) compared with the neck/body region (8.2%; $P = .007$). However, the occurrence of grade B/C fistulae did not differ based on the location of transection (6% at the tail vs 7.4% at neck/body; $P = 1$). Patients with grade A PF developed a transient increase in amylase-rich fluid drain output and recovered uneventfully. Those patients with grade B/C fistulae often had clinical signs of pancreatic leakage, sepsis, increased duration of stay and/or readmission. The most severe fistulae were treated with percutaneous drainage of intra-abdominal fluid collections or reoperation before a successful recovery.

The rate of PF development with direct suture ligation of the pancreatic duct and horizontal mattress closure was 14.1%, whereas the incidence of PF when stapled, with or without reinforcement, was 22.1% ($P = .09$). Grade A PF had an incidence of 8% with cautery and direct ligation with mattress closure as compared with 13.7% with stapler transection ($P = .12$). Grade B/C PF developed in 6.1% of cases after cautery, direct ligation, and mattress closure, and 8.4% when stapled ($P = .49$).

Of the 294 patients, 50 (17%) underwent laparoscopic DP with 40% of them developing a PF, compared with 13.1% for patients undergoing an open DP ($P < .001$; Table I). Grade A PF occurred in 32% of laparoscopic patients, compared with 6.1% of open surgery patients ($P < .001$). No difference was observed in the occurrence of grade B/C fistulae with a rate of 8% in laparoscopic patients and 6.7% in open patients ($P = .49$).

Patients who underwent DP for cystic disease had the highest PF rates of any pathologic entity (21.5%; $P = .16$). Additionally, patients who developed a PF trended toward greater intraoperative blood loss (250 vs 325 mL; $P = .34$; Table I).

Postoperative complications are tabulated and summarized in Table III. Delayed gastric emptying, wound infection, intraabdominal abscess, and pulmonary complications had the highest incidence, with each occurring significantly more frequently in patients with PF. Concordantly, postoperative hospital duration of stay and readmission rates were greater in patients with PF regardless of grade. The median duration of stay for a non-PF

Table I. Patient demographics and perioperative variables

		PF (n = *52*)		*Grade A* (n = *31*)		*Grade B/C* (n = *21*)	
Total (n = *294*)	*No PF* (n = *242*)		P *value*		P *value**		P *value**
Age (y), median (range)	63.5 (22–89)	59 (19–81)	.012	61 (40–81)	.21	57 (19–78)	.008
Gender (% male)	100 (41%)	25 (48%)	.44	14 (45%)	.70	11 (52%)	.36
EBL (mL), median (range)	250 (25–8,400)	325 (25–25,000)	.34	300 (25–4,500)	.76	375 (25–25,000)	.22
CEA (median, range)	1.6 (0.1–278)	1.7 (0.5–17)	.85	1.6 (0.5–5.8)	.48	2.4 (0.6–17.1)	.17
BMI (median, range)	26.8 (9.4–56.4)	28.4 (18–43.2)	.076	28.5 (21.2–39.8)	.005	28.1 (18–43.2)	.58
Diabetes	54 (22%)	10 (20%)	.71	6 (19%)	.82	4 (20%)	1
Smoking	56 (23%)	7 (15%)	.18	6 (19%)	.82	1 (5%)	.085
Method							
Laparoscopic (n = 50)	30	20 (38%)	<.0001	16 (52%)	<.0001	4 (19%)	.49
Open (n = 244)	212	32 (62%)		15 (48%)		17 (81%)	
Indication, n (%)							
Cystic disease	95 (39%)	26 (50%)	.16	17 (55%)	.12	9 (43%)	.82
PDA	71 (29%)	11 (21%)	.24	5 (16%)	.14	6 (29%)	1
Endocrine tumor	52 (22%)	11 (21%)	1	8 (26%)	.65	3 (14%)	.58
Pancreatitis	14 (6%)	0 (0%)	.14	0 (0%)	.23	0 (0%)	.39
Miscellaneous	10 (4%)	4 (8%)	.28	1 (3%)	1	3 (14%)	.07

*Compared with No PF.
Fistula grading per ISGPF criteria; α = .05.
BMI, Body mass index; *CEA*, carcinoembryonic antigen; *EBL*, estimated blood loss; *PDA*, pancreatic ductal adenocarcinoma; *PF*, pancreatic fistula.

Table II. Pancreatic fistula (PF) rates and site of transection

Total (n = *294*)	*No PF* (n = *242*)	*All PF* (n = *52*)		*Grade A* (n = *31*)		*Grade B/C* (n = *21*)	
Neck/body (n = 244)	206	38	15.6%	20	8.2%	18	7.4%
Tail (n = 50)	36	14	28%	11	22%	3	6%
P value		.043		.007		1	

patient was 5 days, whereas a patient with a grade A PF was 6 days (P = .029) and that of a grade B/C PF patient was 8 days (P < .001). The readmission rate was also found to be significantly greater in PF patients (40%) compared with those without a PF (12%; P < .001; Table III). Patients with grade B/C PF had a high readmission rate (81%, P < .001), whereas the readmission rate of grade A PF patients (13%) was not found to be different than non-PF patients (P = .53).

Logistic regression analysis found 3 variables associated with the development of PF at the P < .1 level, namely, EBL, laparoscopy, and preoperative smoking (Table IV). Increased EBL (odds ratio [OR], 1.87; P = .002) and a laparoscopic operation (OR, 12.37; P < .001) were associated with an increased risk of PF development, while a history of smoking was found to be protective (OR, 0.44; P = .089).

DISCUSSION

Reducing the rate of postoperative PF after DP remains a formidable task. Although some risk factors for the development of PF are known, little has been written on the role of pancreatic gland transection site in fistula formation. Our group reviewed our experience with 294 consecutive DPs and analyzed whether site of transection (neck/body vs tail) influenced PF rates. Our institution's total PF rate was 17.7%, which is consistent with most high-volume pancreatic surgery centers (documented rates in the literature between 15 and 40%).[1] Overall, 60% of these PF were grade A (31/52) and 40% were grade B/C (21/52). Fistulae that occurred when transection took place at the neck/body of the pancreas were almost evenly split between grade A and grade B/C, whereas fistulae occurring at the tail were almost 4 times more likely to be grade A as grade B/C.

Table III. Postoperative variables

Total (n = *294*)	*No PF* (n = *242*)	*PF* (n = *52*)	P *value*	*Grade A* (n = *31*)	P *value**	*Grade B/C* (n = *21*)	P *value**
Complications, *n* (%)†	76 (31%)	25 (48%)	.02	9 (29%)	.84	16 (76%)	<.001
DGE	10 (4%)	6 (12%)	.044	1 (3%)	1	5 (24%)	.003
Wound infection	14 (6%)	11 (21%)	<.001	1 (3%)	1	10 (48%)	<.001
Intraabdominal abscess	2 (0.8%)	12 (23%)	<.001	1 (3%)	.31	11 (52%)	<.001
Pulmonary	14 (6%)	8 (15%)	.035	2 (6%)	1	6 (29%)	.002
Duration of stay (d), median (range)	5 (3–24)	6 (4–22)	<.001	6 (4–15)	.029	8 (4–22)	<.001
Readmission, *n* (%)	29 (12%)	21 (40%)	<.001	4 (13%)	.53	17 (81%)	<.001

*Compared with No PF.
†Number of patients with one or more complications not including PF.
Fistula grading per ISGPF criteria; $\alpha = .05$.
DGE, Delayed gastric emptying.

Table IV. Multivariable logistic regression (PF vs no PF; $n = 257$)

Variable	*Measurement*	*Odds ratio (95% CI)*	P *value*
Full model			
Age	Per year	0.98 (0.95, 1.008)	.16
BMI	Per unit	1.01 (0.95, 1.07)	.74
EBL (log)	Per unit	1.87 (1.25, 2.80)	.002
Diabetes	Y vs N	0.99 (0.40, 2.49)	.98
Laparoscopy	Y vs N	11.27 (3.53, 36.03)	<.001
Location	Tail vs Neck/Body	1.49 (0.59, 3.81)	.40
Smoking	Y vs N	0.43 (0.16, 1.14)	.089
Method	Stapler vs Cautery/Suture	0.93 (0.37, 2.35)	.87
Indication	PDA vs cystic disease	0.80 (0.31, 2.08)	.65
Reduced model after backward elimination			
EBL (log)	Per unit	1.87 (1.27, 2.74)	.002
Laparoscopy	Y vs N	12.37 (4.55, 33.61)	<.001
Smoking	Y vs N	0.44 (0.17, 1.13)	.089

BMI, Body mass index; *EBL*, estimated blood loss; *PDA*, pancreatic ductal adenocarcinoma.

These data suggest that PF development may be attributed (at least in part) to the volume of residual gland remaining after extirpation of the pathologic specimen. Two groups have studied the relationship between the volume of residual pancreatic gland and the development of PF, and both studies suggested a higher PF rate with increased residual gland volume.[11,12] It is theorized that a larger residual gland may generate a greater intraductal pressure (and this increased pressure may overcome the duct/gland ligation).[13]

Furthermore, in most instances the further to the left the pancreas is transected the smaller the diameter of pancreatic duct that is ligated (with the average diameter of the pancreatic duct at the body being 3 vs 1.6 mm at the tail).[14] This narrowed duct may be more technically difficult to ligate effectively. Callery et al[15] reported that there was an increase in the odds of developing a PF for each millimeter decrease in diameter of the pancreatic duct at the transection site during pancreaticoduodenectomy (PD).

Another confounding factor in the development of PF after DP is the technique used to ligate the gland. Although a considerable amount of research has focused on the technical aspects of pancreatic transection and stump closure techniques, no consensus has yet been reached as to the optimal method.[16-19] The data from our cohort demonstrate a trend toward greater PF rate for stapled DP (22%), compared with direct suture ligation and mattress closure (14%), although this finding did not attain significance ($P = .09$). Grade A PF rates showed a similar trend accounting for the overall difference noted, whereas the grade B/C PF rates were nearly identical when comparing direct suture ligation and mattress closure with stapling. Also, we noted no difference

was seen in PF with and without staple-line reinforcement (27% vs 20.2%, respectively; $P = .48$). There has been no consensus achieved in the literature regarding staple line reinforcement.[9,20,21]

Although the majority of the DPs at our institution were performed via an open approach, minimally invasive resections were associated with an increase in the PF rate. These findings are in contrast with those of other groups who have found no difference in PF rates when comparing laparoscopic with open DP.[22-24] On multivariate analysis, the use of laparoscopy was found to be the most significant independent predictive variable associated with PF (OR, 12.37; $P < .001$). Although grade A PF were more common in the minimally invasive group, serious fistulae (grade B/C PF) had a similar incidence between open and laparoscopic techniques. Perhaps this is owing to the primary finding of more grade A PF occurring with tail transections, which is often the location of transection in a laparoscopic DP. It will be of interest to revisit these findings in the future as robotic and laparoscopic DP are becoming more common.

Additional factors have been suggested to impact PF development. Pancreatic texture has long been speculated to play a role in the development and severity of PF, with multiple studies in PD demonstrating that soft texture glands having a significantly greater risk of PF compared with glands of hard texture.[25-27] Pancreas gland texture in the upstream gland in a PD depends on the pathologic abnormality and resultant PD obstruction, whereas in DP the abnormal area in the vast majority of cases is being resected so the remnant gland is typically a soft, normal texture.[27,28] Because of this, it is less likely that gland texture differences play as significant a role in DP postoperative PF compared with PD. Our study failed to reveal a difference in leak rates based on pathologic entity.

Intraoperative blood loss is known as a risk factor for the development of PF. It is speculated that ischemia after increased blood loss may lead to poor wound healing, increasing the risk of pancreatic leak.[15,29] We found that the patients with any grade PF and those patients with more severe grade B/C fistulae trended toward a greater EBL. In the multivariate logistic regression model, EBL was a significant factor in the development of PF (OR, 1.87; $P = .002$). Despite this, it is important to recognize that other factors, such as the extent of disease, operative time, and complexity, may serve as confounders in this analysis of EBL.[30]

In our series, patients who developed PF had a significantly increased risk of developing delayed gastric emptying, intraabdominal abscess, wound infection, and pulmonary complications (Table III). In addition, PF patients had a significantly longer postoperative hospital duration of stay and higher readmission rate. Fong et al[31] recently described PF as an independent predictive factor for hospital readmission after PD. Two associated complications of PF—intraabdominal abscess and wound infection—were additional risk factors for readmission in their study.[31]

This study was subject to a number of limitations. First, the retrospective nature of our data collection may not allow us to identify fully and report all variables and outcomes, including, but not limited to, gland texture and the condition of the pancreatic duct. Second, there was lack of a uniform technique for gland transection over the 6 years reviewed among the 7 surgeons who performed DP in the study. Third, this paper did not focus on long-term endocrine outcomes such as glycemic control and insulin use. However, this issue was addressed by our group in another study[32] that reported a significant risk in the development of new-onset diabetes in patients after DP. Fourth, the determination of the transection location was based upon review of operative notes and preoperative and postoperative imaging. Although all records were reviewed independently by 2 separate authors, the determined results would have been more valid if the transection location had been reported prospectively. The authors reviewing these data were blinded to the patient's postoperative PF status while analyzing all of the other variables until final compilation of the data for analysis. Also, designating the transection location in relation to the celiac axis, although not as exact as direct measurement of gland volume or pancreatic length, was chosen owing to its easily reproducible nature in assessing gland transection location intraoperatively (in a retrospective fashion).

Despite these limitations, our study represents a large cohort of consecutive patients who underwent DP, and suggests that grade A PF occur more commonly when the pancreas is transected at the tail. Grade B/C PF occur at equivalent rates regardless of transection site.

While transection site historically has not been a well-described factor in PF occurrence, our study suggests that surgeons should consider the importance of the site of transection in affecting PF rates. Although our results showed a significant increase in the rate of PF when the pancreas is transected at the tail, we do not advocate that all

DP be performed exclusively over the superior mesenteric vein axis given that the majority of PF that developed were minor and do not change clinical management or outcomes. There remain many opportunities to decrement PF rates after DP, and we would suggest that transection site should be considered as a variable in future studies of PF.

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