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ORIGINAL ARTICLE

The Effect of Pancreaticojejunostomy Technique on Fistula Formation Following Pancreaticoduodenectomy in the Soft Pancreas

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Abstract

Introduction A soft pancreas has been associated with an increased risk of post-operative pancreatic fistula formation. Few studies have evaluated the effect of anastomotic technique (duct to mucosa vs invagination) on fistula formation. This study aims to compare the effect of anastomotic technique on fistula formation among patients with a soft pancreas in a large multiinstitutional database.

Methods The targeted pancreas module of the American College of Surgeons–National Surgical Quality Improvement Program (NSQIP) Database was used. All patients with a soft pancreas who underwent pancreaticoduodenectomy from 2014 to 2015 were identified. Demographic data, comorbid conditions, operative variables, and 30-day outcomes were compared using univariate and multivariable analyses.

Results A total of 975 patients met inclusion criteria. Eight-hundred fifty four (88%) underwent a duct to mucosa pancreaticojejunostomy technique and 121 (12%) underwent invagination. Patients who underwent invagination had higher 30-day mortality (5.8% vs 1.4%, $p < 0.01$), higher fistula formation (38% vs 25%, $p < 0.01$), and more often had percutaneous drain placement post-operatively (27% vs 14%, $p < 0.01$). Following multivariable analysis, invagination remained associated with pancreatic fistula formation (OR 2.5, CI 1.4–4.3) and post-operative percutaneous drain placement (OR 1.8, CI 1.1–2.9).

Conclusion Invagination technique for pancreaticojejunostomy in patients with a soft pancreas is associated with increased rates of pancreatic fistula. Surgeons should consider utilizing a duct to mucosa technique when feasible to decrease morbidity following pancreaticoduodenectomy in this patient population.

Keywords Post-operative pancreatic fistula · Pancreaticojejunostomy · NSQIP

Introduction

Pancreaticoduodenectomy is a complex surgical procedure requiring advanced skill to achieve successful outcomes. Although mortality rates are low, major morbidity remains a challenge in the care of these patients. Post-operative pancreatic fistula is a major morbidity associated with pancreaticoduodenectomy with rates as high as 10 to 20%.[1] The International Study Group on Pancreatic Fistulas defines post-operative pancreatic fistula by a drain amylase greater than three times the serum level on or after post-operative day 3.[2]

Multiple risk factors for post-operative pancreatic fistula have been identified, including small pancreatic duct and a soft pancreatic texture.[3–6] Pancreaticojejunal anastomosis can be accomplished by either a duct-to-mucosa or invagination technique.[7] Previous studies have attempted to determine if one technique is superior to the other; however, these studies

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are limited due to their small sample size, single-institutional nature, lack of standardization, and conflicting results.[8–10] No studies have independently assessed the effect of anastomotic technique in patients with a soft pancreas.

This study aims to compare outcomes between duct-to-mucosa and invagination techniques for patients undergoing pancreaticoduodenectomy with a soft pancreas in a large multiinstitutional database. We hypothesize that among patients with a soft pancreas, an invagination technique will be associated with higher perioperative fistula rates.

Methods

Patients

The targeted pancreas module of the American College of Surgeons–National Surgical Quality Improvement Project (NSQIP) Database was utilized. The targeted pancreas NSQIP module is a national clinical registry developed in 2011, which collects demographic data, operative details, and 30-day outcomes from patients undergoing surgical procedures at more than 100 self-selected hospitals. Further information is available at www.facs.org/quality-programs/acs-nsqip.

In this study, we identified all patients undergoing pancreaticoduodenectomy who had a soft pancreas as described by the NSQIP definition from 2014 to 2015. Patients who underwent distal pancreatectomy ($N = 1852$) and pancreaticogastrostomy ($N = 101$) and those without documented reconstruction ($N = 193$) were excluded.

Variables

Patient demographic data and comorbid conditions were compared between those who underwent duct to mucosa vs invagination anastomosis. Smoking was defined as current tobacco use. Glomerular filtration rate (GFR; mL/min per 1.73m^2) was calculated in accordance with the Modification of Diet in Renal Disease (MDRD) equation, and chronic kidney disease was identified according the Kidney Disease: Improving Global Outcomes (KDIGO) and Acute Kidney Injury Network (AKIN) Clinical Practice Guidelines.[11] Body mass index (BMI) was categorized as normal (18.5 to 30 kg/m^2), obese (greater than 30 kg/m^2), or underweight (less than 18.5 kg/m^2). Normal BMI was used as the reference group.

The NSQIP definition for pancreatic fistula was used. This is defined as persistent drainage of amylase-rich fluid (greater than three times serum level) beyond post-operative day three (in concordance with the International Study Group on Pancreatic Fistulas) or clinical documentation by the attending surgeon of a pancreatic fistula. Additionally, the fistula must have required drainage, reoperation, or nothing per mouth status with total parenteral nutrition.

Operative variables were also evaluated. Open operations were defined as any procedure completed in an open fashion, including planned open operations or conversion to open. Chemotherapy and radiation therapy in the 90 days prior to operation was documented. Pre-operative obstructive jaundice was defined by a bilirubin greater than 2 mg/dL in the 90 days prior to surgery. Pancreatic duct size and gland texture were classified according to NSQIP variables. Gland texture was extracted from documentation by the physician in the operative report. Duct size was grouped by NSQIP as < 3, 3–6, or > 6 mm. A duct of 3 to 6 mm was used as a reference group in multivariable analysis.

All outcomes measured occurred within 30 days post-operatively. Delayed gastric emptying was defined as gastrostomy tube to external drainage after post-operative day 7, nasogastric tube present or reinserted after day 7, or no oral intake by post-operative day 14. Wound complications were defined as any superficial, deep incisional, or organ space infection.

Statistics Analysis

Univariate analysis was completed using chi-square and Fisher exact test for categorical variables. The Student's *t* test and Mann-Whitney *U* test were utilized to evaluate continuous variables according to the normalcy of distribution of data. All variables had less than 5% missing data, except for duct size (10%). Independent predictors of pancreatic fistula formation were established using multivariable regression. The Hosmer-Lemshow goodness of fit test was used to evaluate each module. A p value of < 0.05 was considered significant. All statistical analysis was performed using the SPSS statistical package (version 21.0). The institutional review board of George Washington University Medical Center approved this study. The hospitals participating in the ACS-NSQIP Database are the source of the data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by this study.

Results

Baseline Characteristics

We identified 975 patients, of whom 854 (88%) underwent duct to mucosa anastomotic technique and 121 (12%) underwent invagination. There were no differences in age, sex, or any other demographic variables between the two groups (Table 1). Comorbid conditions including smoking, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), and hypertension (HTN) were also similar.

Table 1 Patient demographics and comorbidities

	Duct to mucosa ($N = 854$)	Invagination ($N = 121$)	P value
Age—mean (SD)	63.9 (11)	62.8 (12)	0.26
Male sex	454 (53)	55 (45)	0.11
Body mass index			0.07
Normal (18.5–30)	580 (68)	87 (73)	
Obese (> 30)	254 (29)	27 (22)	
Underweight (< 18.5)	15 (1.8)	5 (4.2)	
Diabetes mellitus	180 (21)	18 (14)	0.11
Smoke (current)	152 (17)	25 (20)	0.45
Chronic obstructive pulmonary disease	51 (6)	3 (2.5)	0.11
Congestive heart failure	4 (0.5)	0 (0)	1.00
Hypertension	458 (53)	61 (50)	0.51
eGFR—median	82 (65–99)	84 (61–103)	0.58
GFR < 60	138 (16)	25 (21)	0.22

SD standard deviation, eGFR estimated glomerular filtration rate

Operative Characteristics

The majority of operations were performed via an open approach (Table 2). Duct size differed between cohorts, while operative time was similar. Malignant tumors were also similar between the two groups. There was no statistical significant difference in rates of preoperative stent placement, preoperative jaundice, or vascular reconstruction.

Outcomes

Patients who underwent an invagination technique had a statistically significant greater morbidity and mortality (Table 3). Mortality was 5.8% among those who underwent an invagination technique, as compared to 1.4% with a duct to mucosa technique ($p < 0.01$). Total hospital length of stay was also higher for patients with an invagination anastomosis (10 days vs 9 days, $p < 0.01$). Additionally, patients with an invagination pancreaticojejunostomy had higher rates of post-operative fistula (38% vs 25%, $p < 0.01$) and need for percutaneous drain after surgery (27% vs 14%, $p < 0.01$).

In multivariable analysis, after controlling for duct size and other variables, invagination was an independent risk factor for pancreatic fistula (OR 2.5, CI 1.4–4.3) and percutaneous drain placement (OR 1.8, CI 1.1–2.9) (Tables 4 and 5).

Discussion

Our study found that among patients with a soft pancreas, the invagination technique is an independent risk factor for pancreatic fistula. The optimal anastomotic technique for pancreaticojejunostomy is widely debated within the literature. Bai et al. in a single-center, single-surgeon, randomized control trial found higher rates of clinical relevant fistulas in patients treated with invagination when compared to duct to

Table 2 Operative characteristics

	Duct to mucosa ($N = 854$)	Invagination ($N = 121$)	P value
Open	795 (93)	119 (98)	*0.03*
Pre-op stent	362 (44)	47 (45)	0.79
Pre-op jaundice	357 (42)	51 (42)	0.91
Pre-op chemotherapy	79 (9.3)	10 (8.3)	0.72
Pre-op radiation	19 (2.2)	4 (3.3)	0.47
Duct size (in mm)			*< 0.01*
3–6	377 (48)	31 (29)	
< 3	316 (41)	70 (67)	
> 6	78 (10)	3 (2.9)	
Vascular reconstruction	88 (10)	8 (6.7)	0.21
Operative time (min)	351 (280–440)	346 (293–418)	0.86
Malignant	620 (72)	88 (72)	0.98

p value of < 0.05 was considered significant as indicated in italics

Table 3 Outcomes

	Duct to mucosa ($N = 854$)	Invagination ($N = 121$)	P value
30-day mortality	12 (1.4)	7 (5.8)	*< 0.01*
Total hospital LOS	9 (7–14)	10 (7–16)	*< 0.01*
Any wound infection	254 (29)	35 (28)	0.85
Pneumonia	28 (3.3)	5 (4.1)	0.63
Reintubation	36 (4.2)	9 (7.4)	0.11
Fail to wean ventilator	28 (3.3)	6 (5.0)	0.35
Myocardial infarction	8 (0.9)	1 (0.8)	0.91
Cardiac arrest	7 (0.8)	3 (2.5)	0.09
DVT/PE	29 (3.4)	7 (5.8)	0.19
Percutaneous drain	119 (14)	31 (27)	*< 0.01*
Return to OR	41 (4.8)	9 (7.4)	0.29
Still in hospital at 30 days	20 (2.3)	4 (3.3)	0.52
Delayed gastric emptying	130 (16)	23 (20)	0.25
Fistula	216 (25)	46 (38)	*< 0.01*

p value of < 0.05 was considered significant as indicated in italics

LOS length of stay, DVT/PE deep vein thrombosis or pulmonary embolism, OR operating room

mucosa.[10] A second randomized controlled trial by Fragulidis et al. also found higher rates of pancreatic fistula when invagination technique was used, although in this study gland texture was not controlled for.[12] Alternatively, Berguer et al. identified higher rates of fistula formation among patients who underwent a duct to mucosa anastomosis when compared to invagination.[7] Limitations for these studies include a single-center nature, small sample size, and a lack of generalizability. But perhaps most importantly, these studies included all patients and were not limited to patients with a soft gland texture, who are at highest risk for pancreatic fistula formation.

Pancreas texture has been identified as a risk factor for pancreatic fistula by several authors.[13,14] Small pancreatic duct size (< 3 mm) has also been associated with higher fistula rates.[15,16] This may be explained by the technical challenge of sewing small ducts and an increased risk of a resulting obstruction.[17] Given the significant effect duct size on fistula formation, our study adjusted for duct size in multivariable analysis. After accounting for duct size, we found that the invagination technique was associated with an increased risk of pancreatic fistula formation. Based on these results, duct to mucosa anastomosis may be preferred over invagination in a soft pancreas when technically feasible. Identifying patients who are at high risk for pancreatic fistula following pancreaticoduodenectomy may help surgeons anticipate and identify fistulas, and implement management strategies to mitigate complications, thus improving outcomes in those undergoing pancreaticoduodenectomy.[18]

This study has various limitations. First, it contains generic limitations that apply to all large database studies, such as missing data, errors in coding, and limited variable definitions. However, NSQIP is widely audited to ensure the quality and accuracy of data. Second, this study utilized the NSQIP definition of pancreatic fistula, which includes those defined by International Study Group for Pancreatic Fistula and is unable to completely differentiate between categories. However, by

Table 4 Multivariable analysis

	Invagination Odds ratio (95% confidence interval)
30-day mortality	1.9 (0.5–6.4)
Return to operating room	1.4 (0.5–3.7)
Pancreatic fistula	*2.5 (1.4–4.3)*
Percutaneous drain	*1.8 (1.1–2.9)*
Delayed gastric emptying	1.1 (0.6–2.1)
Any wound	0.7 (0.4–1.2)

Table 5 Multivariable predictors of pancreatic fistula

	Odds ratio (95% confidence interval)
Age—increasing decade	1.2 (0.99–1.4)
Female gender	1.2 (0.8–1.6)
GFR < 60	0.8 (0.5–1.3)
Diabetes	0.9 (0.6–1.4)
Malignant indication	0.7 (0.5–0.99)
Pre-operative stent	0.9 (0.6–1.3)
Chemotherapy	0.7 (0.4–1.5)
Radiation	0.9 (0.2–3.0)
Open approach	1.1 (0.6–2.2)
Invagination technique	*1.8 (1.1–2.9)*
Small duct	*1.8 (1.3–2.6)*
Large duct	0.6 (0.3–1.1)

including only those fistulas of clinical consequence (necessitating reoperation, drainage, or NPO status with long-term parenteral nutrition), this study includes outcomes of greatest significance to patient care. Additionally, we were unable to account for surgeon specific bias, volume, and surgeon skill. Finally, this study was unable to assess the long-term effects of pancreatic fistulas or survival beyond 30 days, which is pertinent for oncologic outcomes.

Conclusion

Invagination technique for pancreaticojejunostomy is associated with increased rates of pancreatic fistula in patients with a soft pancreas after pancreaticoduodenectomy. In this patient population, surgeons should consider utilizing a duct to mucosa technique when feasible to decrease morbidity following pancreaticoduodenectomy.

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