ORIGINAL ARTICLE

Long-term health after pancreatic surgery: the view from 9.5 years

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Abstract

Background: Discussing the impact of pancreatic surgery on long-term health is poorly understood, but necessary for informed consent. Given the increased number of pancreatic operations being performed annually, further investigation is necessary.

Methods: Patients surviving longer than 5 years after pancreatic surgery were surveyed for post-operative hospitalizations, operations, pain, nutrition and diabetes. Variables were analyzed according to patient and peri-operative variables, and validated using medical records.

Results: Eighty individuals completed the survey; median follow-up was 9.5 years (IQR:6.43,12.73). 47.5% underwent a pancreatoduodenectomy, and 25.0% a distal pancreatectomy; 40.0% had adenocarcinoma. 57.1% reported long-term weight loss, of which 65.9% was unintentional. While 1.3% took pancreatic enzymes before surgery, 38.8% utilized after. 12.5% had diabetes before, and 28.6% after surgery; 22 of 30 patients required insulin replacement therapy (73.3%). 41.3% reported hospitalizations, 17.5% required endoscopies and 28.8% additional operations after full recovery. Need for additional interventions were not related to pathology or post-operative complications, but were more common among patients undergoing a Whipple.

Conclusion: More than half of patients will have a long-term medical complication attributable to pancreatectomy. In comparison to the literature, it may be inferred that consequences occur within the first few years after surgery, and do not compound over time.

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Introduction

Pancreatic surgery is historically associated with considerable morbidity and mortality. In spite of this, the annual number of pancreatic operations for premalignant and malignant lesions of the pancreas is increasing.[1–4] Although the 5-year survival rate remains low for pancreatic cancer, the absolute number of long-term pancreatic cancer survivors will increase. Furthermore, the lifespan of patients with resected benign neoplasms is expected to be normal. This necessitates an emphasis on counseling patients regarding the impact of pancreatectomy[4]

In addition to the usual perioperative risks and complications, patients should be well-informed and have full understanding about the long-term outcome and potential changes in their health. Some of the long-term complications are incisional hernia, endocrine and exocrine insufficiency, anastomotic site ulcer, and bile duct and pancreatic duct strictures. These complications may have various consequences such as hospitalization, endoscopic and/or radiologic interventions, and repeat operations. However, most literature on postpancreatectomy complications focus on the first 12–18 months.[5–15]

It is critical to investigate the long-term health status of survivors of pancreatectomy and the complications they experience attributable to their original operation. The aim of the current study was to identify long-term complications among patients surviving greater than five years from pancreatic surgery for benign and malignant indications.

Methods

This study was approved by the Columbia University Irving Medical Center (CUIMC) Institutional Review Board. Data of

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patients who received pancreatic surgery at CUIMC between July 2008 and May 2012 were searched from a prospectively maintained Pancreatic Center database. Pancreatic surgery was defined as pancreatoduodenectomy, distal pancreatectomy, central pancreatectomy, and total pancreatectomy. Pancreatic surgeries for pancreatitis were excluded.

Patients who were alive for more than 5 years after full recovery were identified and were contacted by telephone between 2017 and 2018. Those who could be reached were informed about the study and survey. Patients who were interested were sent a recruitment letter, a consent form, and a modified Columbia University Cancer Center Demographic Survey (supplement material 1).

The survey was used to identify any hospitalization, additional operation, interventional procedures, analgesia utilization, nutritional status, and diabetes status. The survey explicitly directed consented patients to fill out any complications, operations, and procedures after 90-days or full recovery from their original pancreatic surgery. In addition to the survey responses, electronic medical records of the patients were reviewed for preoperative baseline data, operative data, and long-term follow data to validate and/or supplement patients' reports.

Continuous variables, reported as median and interquartile range (IQR), were compared between groups using the non-parametric Wilcoxon rank-sum tests. Categorical variables were summarized as frequency and percentages and compared using Pearson's Chi squared or Fisher's exact tests. The result was considered statistically significant when p-value was <0.050. All analyses were performed using Stata 15 (StataCorp, College Station, TX).

Results

Patients and demographics

A total of 870 pancreatic operations were performed for benign or malignant lesions between July 2008 and May 2012; 292 were believed to be alive per the database. After calling, 87 patients were found to be deceased and 106 could not be contacted and were considered lost to follow-up. Of the 99 accrued patients, 80 patients (81%) completed surveys. The median follow-up period was 9.5 years (IQR: 6.4, 12.7). The median age was 72.9 years (IQR: 45.9, 88.3). Forty-three patients were female (53.8%), and 64 (80.0%) were Caucasian. Thirty-eight patients (47.5%) underwent a pancreatoduodenectomy, 20 (25.0%) a distal pancreatectomy, 11 (13.8%) a central pancreatectomy, and 11 (13.8%) a total pancreatectomy. In terms of pathology, 37 patients (46.3%) had cystic neoplasms, 32 (40.0%) had pancreatic ductal adenocarcinoma, and 11 (13.7%) had neuroendocrine tumors (Table 1).

Table 1 General demographics and clinical features

	N (%)
Age at operation, median (IQR)	64.3 (37.9, 77.9)
Sex	
Male	37 (46.2)
Female	43 (53.8)
Race	
Caucasian	64 (80.0)
Non-Caucasian	16 (20.0)
Operation	
Pancreatoduodenectomy	38 (47.5)
Distal pancreatectomy	20 (25.0)
Central pancreatectomy	11 (13.8)
Total pancreatectomy	11 (13.8)
Pathology	
Pancreatic ductal adenocarcinoma	32 (40.0)
Pancreas cystic lesion	37 (46.3)
Neuroendocrine tumor	11 (13.8)

Long-term nutritional health and endocrine/exocrine function

According to anesthesia records, the median weight at pancreatectomy was 74.8 kg (IQR: 53.5, 108.9), which decreased to a median of 70.3 kg (IQR: 51.7, 102.1) at the time of survey. Although this matched difference was significant ($p < 0.001$), it did not statistically differ by operation performed ($p = 0.572$) (Table 2). Among 77 respondents, 44 (57.1%) reported weight loss, of who 65.9% (n = 29) reported the weight loss to be unintentional. Weight gain was reported in 22 patients (28.6%), 86.4% reported to be unintentional. Weight loss was most frequently observed among total pancreatectomy (72.7%) and pancreatoduodenectomy (64.9%) patients, and least likely among central pancreatectomy (30.0%) patients. Weight gain was most frequent in central pancreatectomy (40.0%) patients.

Ten patients had diabetes at the time of their pancreatic operation, whereas 20 patients newly developed diabetes postoperatively. Of the 30 diabetic patients, 22 required insulin replacement. The incidence of newly developed diabetes among those who were not diabetic before surgery was 28.6%. Whereas 9 out of 36 pancreatoduodenectomy patients and 5 of 17 distal pancreatectomy patients newly developed diabetes, none of central pancreatectomy patients did ($p = 0.141$). Of 11 total pancreatectomy patients, 5 had diabetes at the time of surgery, and the remaining 6 developed diabetes after surgery (Table 2).

Excluding total pancreatectomy patients, 11 of 19 diabetic patients required insulin. Of all the diabetic patients, 21 patients reported hypoglycemic episodes (<70 mg/dL): 15 (51.7%) infrequently, 3 (10.3%) monthly, and 3 (10.3%) weekly. Regarding long-term diabetes complications, 2 patients reported retinopathy, 7 reported neuropathy, 3 reported both retinopathy and neuropathy, and no patients reported peripheral vascular disease. This was not significantly different if diabetes developed pre- or post-operatively ($p = 0.576$).

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Table 2 Summary of weight, and endocrine and exocrine function related to pancreatic operation

	Total (n = 80)	Operation type				
		PD (n = 38)	DP (n = 20)	CP (n = 11)	TP (n = 11)	p-value
Weight (kg)						
At surgery	74.8 (53.5, 108.9)	69.8 (54.4102.1)	82.1 (73.5,90.7)	67.4 (63.5,68.0)	72.1 (68.0,74.8)	
At present	70.3 (51.7, 102.1)[a]	68.0 (54.4, 92.1)	77.6 (68.0,92.9)	68.1 59.9,68.0)	65.8 (63.5, 74.8)	
Change in weight	(n = 77)	(n = 37)	(n = 19)	(n = 10)	(n = 11)	
Decreased	44 (57.1)	24	9	3	8	0.572
Similar	11 (14.3)	3	3	3	2	
Increased	22 (28.6)	10	7	4	1	
Diabetes (preop)						
Yes	10 (12.5)	2	3	0	5	
No	70 (87.5)	36	17	11	6	
Diabetes (postop)	(n = 70)	(n = 36)	(n = 17)	(n = 11)	(n = 6)	
New	20 (28.6)	9	5	0	6	0.140[b]
No	50 (71.4)	27	12	11	0	
PERT (at present)	31 (38.8)	15	4	1	11	0.098[b]

PD, pancreatoduodenectomy; DP, distal pancreatectomy; CP, central pancreatectomy; TP, total pancreatectomy; PERT, pancreatic enzyme replacement therapy.
Continuous variables presented as median and IQR, and categorical variables presented as frequency and percentage.
[a] p<0.001.
[b] total pancreatectomy excluded.

Only one patient reported having pancreatic enzyme replacement therapy (PERT) at the time of the operation, whereas 31 patients (38.8%) reported requiring PERT at present. All total pancreatectomy patients required PERT due to absence of exocrine function. In other pancreatectomies, pancreatoduodenectomy patients were most likely to require PERT, while central pancreatectomy patients were least likely. Excluding total pancreatectomy, there was no significant difference across the type of operation (p = 0.098) (Table 2).

Hospitalizations for medical management and analgesia requirement after complete recovery

Thirty-three patients (41.3%) reported a median of 2 hospitalizations related to their pancreatectomy after full recovery, ranging from 1 to 11 hospitalizations. Patients who underwent pancreatoduodenectomy had significantly more hospitalizations (24 of 38 patients) than patients undergoing other operations such as distal pancreatectomy, central pancreatectomy, total pancreatectomy (p < 0.001) (Table 3).

For pancreatoduodenectomy patients, the most common cause of hospitalization was pancreatitis followed by small bowel obstruction, gastrointestinal hemorrhage, and cholangitis. Less than 20% of patients who underwent distal and central pancreatectomy required hospitalization. Among total pancreatectomy patients, 5 patients required hospitalization and they were all related to poor glycemic control. Four hospitalizations were due to hypoglycemia and one due to hyperglycemia (Table 3).

Six patients (7.5%) reported long-term use of analgesic medications. Five patients (13.2%) had underwent pancreatoduodenectomy, and one (5.0%) a distal pancreatectomy (p = 0.606). Half of these patients reported using narcotics, whereas the remaining reported using non-steroidal anti-inflammatory drugs (Table 3).

Procedures and operations after complete recovery

Fourteen patients (17.5%) required a median of 2 endoscopic retrograde cholangiopancreatographies (ERCP) (IQR 1, 3) for stricture concerns (n = 7), pancreatitis (n = 4), or surveillance (n = 3). Two pancreatoduodenectomy patients and one total pancreatectomy patient were stented for hepaticojejunostomy strictures. In addition, 2 pancreatoduodenectomy patients received endoscopic balloon dilation for pancreaticojejunostomy and gastrojejunostomy strictures (Table 4).

Twenty-three patients (28.8%) required additional abdominal operations that were reported to be related to their pancreatic surgery (Table 4). Patients who underwent pancreatoduodenectomy were significantly more likely to undergo repeat abdominal operations than those underwent other types of pancreatectomy (p = 0.019). Incisional hernia repair was the most frequent operation across all types of pancreatectomy, with a median of 16.0 months from the primary surgery to repair. There was no association between incisional hernia or anastomotic strictures and perioperative Clavien-Dindo grade 2–4 complications.

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Table 3 Hospitalization for medical treatment and analgesic requirements related to pancreatic operation

	Total (n = 80)	Operation type				
		PD (n = 38)	DP (n = 20)	CP (n = 11)	TP (n = 11)	p-value
Hospitalizations	33 (41.3)	24	2	2	5	<0.001
Etiology						
Small bowel obstruction	6 (7.5)	4	1	1	0	
GI hemorrhage	4 (5.0)	4	0	0	0	
Pancreatitis	6 (7.5)	6	0	0	0	
Cholangitis	2 (2.5)	1	0	1	0	
Dysglycemia	6 (7.5)	0	1	0	5	
Hypoglycemia	5 (6.3)	0	1	0	4	
Hyperglycemia	1 (1.3)	0	0	0	1	
Other	9 (11.3)	9	0	0	0	
Analgesia	6 (7.5)	5	1	0	0	0.606

PD, pancreatoduodenectomy; DP, distal pancreatectomy; CP, central pancreatectomy; TP, total pancreatectomy; GI, gastrointestinal.
In parenthesis are percentages.

Table 4 Additional procedures and operations related to pancreatic operation

	Total (n = 80)	Operation type				
		PD (n = 38)	DP (n = 20)	CP (n = 11)	TP (n = 11)	p-value
ERCP	14 (17.5)	11	2	0	1	0.202
Operation	23 (28.8)	16	1	3	3	0.019
Incisional hernia	16 (20.0)	10	1	2	3	
Small bowel obstruction	2 (2.5)	2	0	0	0	
GJ revision	2 (2.5)	2	–	–	0	
PJ revision	3 (3.8)	2	–	1	–	

PD, pancreatoduodenectomy; DP, distal pancreatectomy; CP, central pancreatectomy; TP, total pancreatectomy; ERCP, endoscopic retrograde cholangiopancreatography; GJ, gastrojejunostomy; PJ, pancreaticojejunostomy.
In parenthesis are percentages.

Discussion

This study examined the health of patients a median of 9.5 years after pancreatic surgery, focusing on conditions affected by pancreatic function and the type of pancreatectomy. Past literature has primarily focused on outcomes less than 2 years from surgery, and has not queried related hospitalizations, interventions and operations after recovery from pancreatectomy. Doctors and patients need to understand the long-term outcomes of these operations because they are being performed more frequently, and patients are living longer. By studying patients undergoing different types of pancreatectomy for a range of indications, we were able to better understand pancreas-related health. Reported long-term consequences included unintentional weight loss, new dependence on insulin, repeated hospitalizations for glycemic control and gastrointestinal problems, and abdominal operations, namely hernias. Patients who recovered from a Whipple or total pancreatectomy were more affected than central and distal pancreatectomies. Weight loss and diabetic medications were compared against pre-operative data, and the majority of self-reported interventions/operations were validated against hospital record.

At clinics, patients often express concern about their weight in the years after pancreatic surgery. When comparing weight by age and gender, current weights were indeed less than national averages reported by the National Center for Health Statistics.[16] With regard to women, the 7 participants between 40 and 59 years had a mean body weight of 77.0 kg and the 34 participants 60 years or over had a mean body weight of 63.9 kg compared to 80.0 kg and 75.5 kg, respectively, for same-aged women. With regard to men, the 6 participants between 40 and 59 years had a mean body weight of 89.7 kg and the 31 participants of 60 years or over had a mean body weight of 76.6 kg, compared to 91.1 kg and 88.3 kg, respectively, for same-aged men. This demonstrates a nearly 12 kg difference for both men and women over 60 years of age between national averages and those reported in this study Although it can be argued patients may be biased toward self-reporting lower weights, this is countered by the overwhelming majority reporting their current weight to be unintentional.

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The frequency of newly developed diabetes after pancreatoduodenectomy was consistent with past reports, ranging from 0 to 50%,[9–12,17] as was that after distal pancreatectomy.[12–14] It is recognized that postpancreatectomy diabetes mellitus is associated with the amount of parenchyma resected, viability of remnant pancreas, chronic pancreatitis, age, and other comorbidities.[8–10,18,19] Considering this and that no patient who underwent central pancreatectomy developed diabetes, the importance of tailoring operations cannot be over emphasized. When planning a pancreatectomy, efforts should be directed at preserving parenchyma and function within the boundary of oncologic safety.

That the rate of new onset diabetes, excluding total pancreatectomies, was 21.9% by a median of 9.5 years after surgery is very concerning, given this is more than twice the 9.1% incidence in the general adult population in the United States.[20] This demonstrates the burden of diabetes in these patients relative to the general population. Furthermore, even after excluding total pancreatectomies, more than half of the diabetic patients required insulin replacement therapy. This compares unfavorably to the 5.2–10.9% of the adults in the United States diagnosed with diabetes who use insulin.[21]

Retinopathy and neuropathy occurred in 5 and 10 patients among 30 diabetic patients, respectively. The incidence of retinopathy was lower than the reported 25–30%, and that of neuropathy was comparable to the 30.6% reported.[22–25] Overall, 12 of 30 diabetic patients manifested microvascular complications which is a significant number of patients. Therefore, meticulous monitoring and early management should be initiated. In addition, further studies are needed to understand the nature and the course of diabetes in pancreatectomy patients.

Hospitalizations for varying reasons after complete recovery from pancreatic operations occurred in 41%. Hospitalizations were higher among patients who underwent pancreatoduodenectomy or total pancreatectomy. This may be attributable to more extensive anatomical and functional changes caused by these operations. It should be also noted that all the reasons for hospitalization in total pancreatectomy patients were related to dysglycemia. Thus, patients should be informed of the risks, appropriately selected for this operation, and well educated on glucose control before and after total pancreatectomy.

Among long-term survivors, 17.5% of the patients required an ERCP procedure at least once. Aanastomotic stricture was the most frequent reason for ERCP. As pancreatoduodenectomy requires a minimum of 3 anastomoses, ERCP was mostly performed in these patients. The reported rate of hepaticojejunostomy and pancreaticojejunostomy stricture is 2.5–8% and 3–11%, respectively.[6,7,15] The frequency of ERCPs this long after pancreatic surgery has not been previously reported to our knowledge. The 5.0% incidence of stent placement and balloon dilation in this study may be indicative of stricture formation and lies within the previously mentioned rates reported in the literatures. The high utilization of ERCP in this series contrasts with the low rate of operative management, because endoscopic interventions are preferred at our institution, and operating reserved for interventional failure.

Additional operations were required in 28.8% of the patients; incisional hernia repairs were the most frequent. Incisional hernia was not associated with a specific type of operation, nor was it related to the length of hospitalization or perioperative complications. In this study, the incidence of incisional hernia was 20.0% and the repair was performed at a median of 16.0 months for patients undergoing repair at our institution. This rate is almost double of 11.6% reported in a recent study by Chen-Xu and colleagues.[5] The lower rate of hernia repair after a distal pancreatectomy was likely due to 35% of distal pancreatectomies being performed laparoscopically.

An important limitation of the study was self-reporting of retrospective events. Thus, patients may not have accurately remembered complications or incorrectly attributed hospitalizations and interventions to their pancreatic operation. In order to improve the quality of the collected data, 60% of the operations and hospitalizations were validated against the online medical record and clinic notes. The additional 40% of reported events occurred outside of our health system. Furthermore, it would be important to also query radiologic interventional procedures such as percutaneous transhepatic cholangiography and biliary drainage, medications related to ulcer prophylaxis, and timing of events for future studies. Lastly, the size of cohort is not as large as anticipated, however considering outcomes of pancreatic malignancy and the design of this study, it was difficult to collect a larger cohort. Multicenter studies or studies using nationwide database may overcome this limitation. Despite these limitations, this is the largest and longest study to specifically understand the impact that pancreatic operations have on patient health to date.

Long-term health status and complications are important to discuss with patients as part of informed consent. Many will experience unintentional weight loss in the long-term. A third of patients who undergo a pancreatic operation may require another operation. Patients who undergo pancreatoduodenectomy are more likely to require ERCPs or have structural issues related to their new anatomy. Rates of many complications in this study were comparable to those reported through 12–24 months in previous investigations postoperatively.[5–15,26] It may be inferred that many long-term consequences of pancreatectomy occur within the first two years after surgery, and do not continue to compound over time. This is an important finding and needs further validation.

This study provides new insights and guidance for physicians educating their patients about the long-term effects of pancreatic surgery. This is especially important as the number of prophylactic operations increases in patients expected to have a normal life expectancy.

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Conflict of interest

None to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2020.08.017.

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