

ORIGINAL ARTICLE

Thirty-day outcomes underestimate endocrine and exocrine insufficiency after pancreatic resection

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Abstract

Background: Long-term incidence of endocrine and exocrine insufficiency after pancreatectomy is poorly described. We analyze the long-term risks of pancreatic insufficiency after pancreatectomy.

Methods: Subjects who underwent pancreatectomy from 2002 to 2012 were identified from a prospective database (n = 227). Subjects who underwent total pancreatectomy or pancreatitis surgery were excluded. New post-operative endocrine and exocrine insufficiency was defined as the need for new pharmacologic intervention within 1000 days from resection.

Results: 28 (16%) of 178 subjects without pre-existing endocrine insufficiency developed post-operative endocrine insufficiency: 7 (25%) did so within 30 days, 8 (29%) between 30 and 90 days, and 13 (46%) after 90 days. 94 (43%) of 214 subjects without pre-operative exocrine insufficiency developed exocrine insufficiency: 20 (21%) did so within 30 days, 29 (31%) between 30 and 90 days, and 45 (48%) after 90 days. Adjuvant radiation was associated with new endocrine insufficiency. On multivariate regression, pancreaticoduodenectomy and chemotherapy were associated with a greater risk of exocrine insufficiency.

Conclusion: Reporting 30-day functional outcomes for pancreatic resection is insufficient, as nearly 45% of subjects who develop disease do so after 90 days. Reporting of at least 90-day outcomes may more reliably assess risk for post-operative endocrine and exocrine insufficiency.

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Introduction

Pancreatectomy has been increasingly utilized in recent decades for both benign and malignant entities. Owing to the refinement of surgical technique as well as improvement in patient selection and perioperative care, pancreatic resection can be performed safely with a morbidity rate of 4.6–46%.^{1,2} While the use of parenchymal-preserving resections such as enucleation and central pancreatectomy aim to reduce the risk of post-operative endocrine and exocrine insufficiency, these complications still result in a detrimental impact on quality of life.

While many studies have reported these complications, few have excluded pancreatitis patients, who are more prone to these specific complications and biasing the outcomes. Even fewer have reported long-term outcomes. The presence of such data may allow for a more accurate means of educating patient about long-term risks following resection.

A study of the Society of Thoracic Surgery (STS) mortality database revealed significantly greater mortality after lung resection at 90 days compared to 30 days,³ suggesting that standard 30-day outcome reporting is inadequate. Work in hepatic resection demonstrated that 30-day reporting of mortality may be misleading. The authors proposed that perioperative outcomes for hepatic resection should be reported with the 90-day benchmark.⁴ However, such a study has not been reported

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following pancreatic surgery, which may limit physicians from appropriately educating their patients preoperatively about these potential risks.

In light of the limited data, we aim to report the short- and long-term incidence of new endocrine and exocrine insufficiency after pancreatic resection for non-pancreatitis etiologies. We also seek to determine if the standard reporting of 30-day outcomes for these complications is sufficient and to identify predictive factors for new post-operative endocrine and exocrine insufficiency after pancreatectomy.

Methods

Subjects who underwent pancreatic resection from January 2002 to December 2012 at a tertiary care center were identified from a prospectively maintained pancreatic surgery database. Subjects who underwent total pancreatectomy or surgery for pancreatitis were excluded. Demographic, histopathologic, operative, perioperative, and follow-up data were collected. The study was conducted according to institutional human research committee procedures, and was reviewed and approved by the University of Massachusetts Medical School Institutional Review Board.

Development of pancreatic insufficiency was defined by the need for new pharmacological intervention, such as pancreatic enzymes, insulin or oral hypoglycemic medications that persisted beyond discharge after initial surgery. Subjects who received insulin in the immediate perioperative period that was not continued at discharge were excluded. Initiation of pancreatic enzymes by members of the pancreatic team involved in the subject's care was based on symptom development or on serologic data (such as new hyperglycemia). Data on subjects with pre-resection endocrine and exocrine insufficiency (such as need for escalation or continuation of medication) were collected. However, these data are not included in the current analysis and are not considered "new onset." Subjects who developed pancreatic insufficiency within 1000 days were included in analysis. The median time to development of pancreatic insufficiency was calculated from the first post-operative day to the first date of newly documented pharmacological initiation.

Statistical analyses were performed using Intercooled Stata software, version 12.0 (StataCorp, College Station, TX). Categorical variables were analyzed utilizing Fisher's Exact test and Pearson's chi-squared test. Continuous variables were analyzed using the student t-test for variables with a normal distribution, and the Mann-Whitney rank sum test for variables without normal distribution. Univariate variables with statistical significance were included in the multivariate model. Statistical significance was accepted at a p-value of less than 0.05.

Results

Patient and tumor characteristics

Of the 239 subjects who underwent pancreatic resection from January 2002 to December 2012, 12 subjects were excluded due to the presence of total pancreatectomy ($n = 5$) or surgery for pancreatitis ($n = 7$). A total of 227 subjects were analyzed (Fig. 1). The mean age was 62 years old (range: 22–88 years). Median follow-up was 21 months (range: 0–114 months). The majority were females ($n = 120$, 53%). Tumors were most commonly located at the pancreatic head ($n = 150$, 66%), followed by body (15%) and tail (12%). One hundred and fifty nine (70%) subjects underwent pancreaticoduodenectomy (PD), while 63 (28%) subjects had distal pancreatectomy (DP), and 5 (2%) underwent enucleation (Table 1).

Seventy-two (32%) were found to have non-invasive disease, including intraductal papillary mucinous neoplasm ($n = 35$, 15%), serous cystadenoma (4%), mucinous cystadenoma (3%) and gastrointestinal stromal tumor (1%). The majority ($n = 155$, 68%) had malignant disease, most commonly pancreatic ductal adenocarcinoma (PDAC; 44%), ampullary adenocarcinoma (12%), neuroendocrine carcinoma (6%) and cholangiocarcinoma (4%; Table 1).

Mean tumor size was 3.0 cm (range: 0.2 cm–17.0 cm). Fifty-seven (25%) subjects were incidentally found to have pancreatitis on pathologic analysis, but surgery was not performed for this indication. Eighteen (8%) subjects underwent neoadjuvant chemotherapy, and 109 (48%) underwent adjuvant chemotherapy. Seventeen (8%) underwent neoadjuvant radiation therapy while 80 (35%) underwent adjuvant radiation therapy (Table 1).

Incidence of post-operative pancreatic endocrine and exocrine insufficiency

Forty-seven (21%) subjects had preoperative endocrine insufficiency and need for pharmacologic intervention. Of the remaining previously unaffected ($n = 180$), two were excluded due to development beyond 1000 days. Twenty-eight (16%) developed post-operative endocrine insufficiency with a median time to development of 72 days (range: 0–906 days) and were included in the analysis. Of these, 7 (25%) subjects did so within 30 days, 8 (29%) between 30 and 90 days and 13 (46%) after 90 days (Fig. 1).

Ten subjects had pre-existing exocrine insufficiency. Of the previously unaffected subjects ($n = 217$), three were excluded from analysis due to time to disease. Ninety-four (43%) subjects developed exocrine insufficiency over a median of 75 days (range: 0–881 days). Twenty (21%) subjects developed the deficiency within 30 days of resection, whereas 31% ($n = 29$) between 30 and 90 days of resection, and 48% ($n = 45$) after 90 days (Fig. 1).

Of the 122 new events of pancreatic endocrine and exocrine insufficiency, 78% of these events ($n = 95$) developed after the

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