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Tobacco Smoking Associated with Increased Anastomotic Disruption Following Pancreaticoduodenectomy

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Abstract

Introduction: The effect of cigarette smoking on postoperative morbidity following pancreaticoduodenectomy (PD) for cancer is unclear. We hypothesize that smoking is associated with higher morbidity following PD.

Materials and Methods: A retrospective review of patients undergoing PD for cancer from 2010–2016 at a single institution was performed. Patients that had never smoked were compared to current or past smokers with at least 1 pack-year history. Univariate and multivariable analyses were performed.

Results: 252 patients met inclusion criteria. On univariate analysis, there was a significant difference between smokers and never-smokers in age at diagnosis (65.5 versus 68.6 years, p=0.013), and fistula rate (28.5% versus 16.2%, p=0.024). Male sex was significantly associated with fistula rate compared to female sex (15.5% vs 7.1%, p=0.023). Comparing males and females separately, smoking correlated with higher fistula development only in the male cohort (22.5% versus 5.8%, p=0.016 in men and 7.3% versus 9.1%, p=1.00 in women). On multivariable analysis, current and past smoking was independently predictive of developing a fistula: OR of 2.038 (p=0.030). For current and past-smokers, male sex was an independent risk factor for developing a fistula: OR 2.817 (p=0.022). There were no other significant differences between groups in rates of postoperative complications.

Conclusions: Smoking status is independently predictive of postoperative pancreatic fistula following PD for cancer. Among smokers, male sex is an independent risk factor for fistula. Further studies are needed to determine if smoking cessation before surgery decreases this risk, and if so, the optimal duration of cessation.

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Contributions

Dr. Rozich and Dr. Morris were the primary authors of the manuscript. Dr. Landmann assisted with statistical analysis, gathering data, and contributed to writing both the abstract and the manuscript. Dr. Butler and Dr. Bonds were both involved in gathering data and editing the abstract and manuscript. Dr. Fischer provided statistical analysis and edited both the abstract and the manuscript. Dr. Postier performed the majority of the surgical cases and edited both the abstract and the manuscript.

Disclosure

The authors reported no proprietary or commercial interest in any product mentioned or concept discussed in this article.

Keywords

Tobacco; smoking; pancreaticoduodenectomy; pancreas cancer; pancreatic fistula; complications

Introduction

Pancreatic cancer is the 4th leading cause of cancer related deaths in the United States, with one of the lowest 5-year survival rates at only 8% (1). Pancreaticoduodenectomy (PD) remains the mainstay of treatment for cancer of the pancreatic head, and while operative mortality has decreased throughout the years, morbidity remains high (38–44%) (2–4). Numerous investigators have demonstrated significant correlations between patient specific characteristics and increased risk of complications after PD (5–15). However, many of these risk factors, such as obesity, are difficult to modify in a short period of time, and some, such as having congestive heart failure, are impossible to modify.

Several studies have demonstrated that tobacco smokers have an increased risk for the development of pancreatic ductal adenocarcinoma (PDAC) (16), making it likely that many patients who present for consideration of PD for PDAC will be smokers. Active smoking is a potential risk factor for postoperative morbidity that patients can change in a short period of time, making it critical for us to better understand the relationship between smoking and outcomes for patients undergoing PD. Most surgeons encourage smoking cessation prior to operative intervention for many reasons. Yet, available evidence regarding the effects of smoking on complications rates following PD is unclear. Furthermore, current studies have not specifically focused on analyzing smoking as a primary risk factor for complications.

The aim of this study is to investigate the relationship between current and past smoking with postoperative morbidity including POPF in patients undergoing resection for pancreatic cancer. We hypothesize that smoking will be independently associated with increased overall morbidity, and specifically increased POPF rates, following PD for PDAC and other related cancers.

Methods

Study design

We conducted a retrospective chart review of patients with PDAC treated with PD for curative intent at the University of Oklahoma Medical Center from January 1, 2010 to December 31, 2016. Patients with peri-ampullary carcinoma and distal cholangiocarcinoma who underwent PD were also included. Patients without adequate clinic and hospital records were excluded. Patients were divided into groups based on smoking status: never-smokers vs those with at least 1 pack-year smoking history or current-smokers with at least 1 pack-year smoking history. The study design was in accordance with STROBE guidelines (17). Approval from the University of Oklahoma Health Sciences Center Institutional Review Board with a waiver of informed consent was obtained.

Preoperative and intraoperative variables

Data were gathered from inpatient and outpatient electronic medical records. Demographic data included age at primary diagnosis, sex, preoperative albumin, Body Mass Index (BMI) at the time of surgery, major medical comorbidities, past surgical history, neoadjuvant chemotherapy and radiation therapy, and smoking status, including current versus past smoking, overall duration in pack-years and time elapsed since cessation if applicable. Operative data were gathered from dictated operative notes, anesthesia records, and blood bank records. Pathologic data was collected from pathology reports and included margin status, TNM classification, and presence or absence of both lymphovascular and perineural invasion.

Operative Technique

All pancreaticoduodenectomies were performed by two senior staff surgeons. All surgeries were performed open, with antecolic duodenojejunostomies or gastrojejunostomies. Pancreaticojejunostomy anastomoses were typically performed in a two-layer duct-to-mucosa fashion if the pancreatic duct was able to be identified intraoperatively and was estimated to be of adequate size (>3mm). If ducts were estimated to be ≤3mm or unable to identified, an invaginated pancreaticojejunostomy was typically performed. However, the decision of which anastomotic technique to use was ultimately left to the operating surgeon's discretion. Both surgeons left two 19-French round Blake drains: one positioned behind the pancreaticojejunostomy and one behind the hepaticojejunostomy. Drains were left in place until output was ≤ 30 milliliters per day or at the discretion of the attending surgeon. Drain fluid was routinely analyzed for amylase content on postoperative day 3. Pancreatic parenchymal texture was not regularly documented in operative reports but was captured in this study when available. Similarly, pancreatic duct size was not routinely documented, but was obtained when available from operative reports, official imaging reports, and endoscopic retrograde cholangiopancreatography procedure notes.

Postoperative Outcome

Information regarding postoperative complications and morbidity was gathered from a review of daily progress notes, discharge summaries, clinic follow up notes, inpatient and outpatient laboratory data, imaging reports, pathology and microbiology samples, and blood bank records. POPF grade was defined using the International Study Group of Pancreatic Fistula (ISGPF) (18) classification scheme and calculated with the International Study Group of Pancreatic Surgery (ISGPS) online calculator for leak found on the Pancreas Club website. Delayed gastric emptying (DGE) was also defined and stratified using ISGPF criteria (19). Length of stay was measured in days from the date of surgery to the date of hospital discharge. Readmission was defined as admittance after initial discharge within 30 days of the primary operative intervention for sequelae directly relating to the operation. Death data was collected using the United States Social Security Death Index, as well as hospital death notes and death certificates found in clinic records.

Statistics

Univariate analysis using Chi-squared or Fisher's exact test, Student's *t* and Mann Whitney rank sum analyses were performed for categorical, mean and median values, respectively. All variables significantly associated with POPF identified on univariate analysis were then analyzed using multivariable binary logistic regression modeling. All statistics were performed using SPSS version 24 (IBM Corp., Armonk, NY). All tests were two-tailed and p-values of less than or equal to 0.05 were considered significant.

Results

Adult patients who underwent PD for PDAC, distal cholangiocarcinoma, and peri-ampullary carcinoma from January 1, 2010 to December 31, 2016 at the University of Oklahoma Medical Center were analyzed. A total of 252 patients met inclusion criteria, with demographic data depicted in Table 1. Four patients had insufficient data to accurately quantify their smoking history by pack-years but had other relevant data so were included in the overall analysis.

There was a slight male predominance with 114 women (45%) and 138 (55%) men, and significantly more men were current or past-smokers than women (88 (64%) men vs 49 (36%) women, p=0.003). Additionally, male smokers had significantly higher average quantity of pack-years smoked versus female smokers, 21 vs 12.5, p=0.004 (Table 2). Smokers were significantly younger than non-smokers at diagnosis. There was no difference between smokers and non-smokers in the following potential patient-specific risk factors: preoperative BMI, rate of preoperative albumin level <3.5, presence of diabetes mellitus, jaundice, history of abdominal surgery, neoadjuvant chemotherapy and/or radiation therapy. There was a trend toward higher ASA scores and the presence of more than one comorbidity in past or current-smokers, but these differences were not statistically significant. Unsurprisingly, smokers were more likely to have a diagnosis of coronary artery disease (CAD) compared to never-smokers, 26 (19.0%) vs 7 (6.3%), p=0.004. In terms of peri-operative risk factors for complications, the groups were also similar. Specifically, there were no significant differences between the groups in in estimated blood loss, distribution of pathology (PDAC vs distal cholangiocarcinoma vs peri-ampullary carcinoma), final pathologic stage, or rate of margin positivity (Table 3).

There was no significant difference between these two groups in the incidence of the following complications: DGE, pneumonia, urinary tract infections, intra-abdominal abscesses, or bacteremia/fungemia. Length of hospital stay was also similar between the two groups. Both groups had similar numbers of patients discharged home versus to a skilled nursing facility, long-term acute care hospitals, or physical rehabilitation centers postoperatively. Additionally, postoperative morbidity quantified by Clavien-Dindo scores (20) were not significantly different between the two groups. 90-day mortality was similar between groups, with 15 (13.5%) deaths within 90 days in the never-smoking group compared to 14 (10.2%) in the smoking group, p=0.422. Interestingly, and somewhat counterintuitively, current and past-smokers had a lower 30-day mortality compared to never-smokers, 5 (3.6%) vs 11 (9.9%) p=0.046.

Overall, 57 (22.6%) patients suffered POPF, with 38 (15.1%) being clinically significant B and C fistulas. On univariate analysis, current or past-smokers had a higher overall rate of POPF compared with never-smokers (28.5% vs 16.2%, p=0.024). When we examined the rates of only clinically significant fistulae, we found a higher rate of B and C fistulae among smokers (18.2%) vs never-smokers (11.7%) but this was no longer statistically significant (p=0.155). Overall fistula rate in current-smokers was 36.4% versus a rate of 26.0% in previous-smokers, which was also not significantly different (p=0.273). In order to determine if there was a dose effect for smoking, smokers having greater than 20 pack-year smoking history were compared to those with 20 or less pack-year history. No difference was found between the fistula rates of these groups (>20 pack-years: 30.7% vs ≤20 pack-years: 27.7%, p=0.839).

As previously stated, pancreatic parenchymal texture and duct size were not consistently documented in operative reports, however, parenchymal texture was reported for 82 (32.5%) patients and duct size was reported for 122 (48.4%) patients. The average duct size for the entire population was 7.2mm. Duct size was stratified into two groups, with ≤3mm classified as small and >3mm labeled as large. There was no significant difference in duct size between smokers and never-smokers (Table 4). Importantly, there was no significant correlation between duct size and total fistula rate (small duct: 12 (9.8%) vs large duct: 18 (14.8%), p=0.332) or B/C fistula rate (small duct: 5 (4.1%) vs large duct: 12 (9.8%), p=0.749). There was also no significant difference in parenchymal texture between smokers and never-smokers. However, patients with soft pancreatic texture trended toward a higher overall fistula rate (soft: 13 (15.9%) vs firm: 6 (7.3%) vs inflamed: 1 (1.2%), p=0.069) and significantly higher B/C fistula rate (soft: 10 (12.2%) vs firm: 4 (4.9%) vs inflamed: 0, p=0.046).

For the entire population, fistula rate was found to be significantly higher in men as compared to women (Table 2). Among men, current or past smoking was found to be predictive of developing a POPF, with 31 (22.5%) male smokers developing POPF versus 8 (5.8%) male never-smokers, p=0.016. This relationship was not seen among women, as 8 (7.3%) current or past-smoking women developed POPF versus 10 (9.1%) of never-smoking women, p=1.00.

On multivariable analysis, male sex was found to be independently predictive of a higher rate of POPF among current or past-smokers only (HR=2.817 CI: 1.164–6.815, p=0.022), with age and preoperatively documented CAD failing to reach statistical significance. Among never-smokers, none of these variables were predictive of POPF (Table 5). For the entire population, multivariable analysis showed smoking status to be the only independent predictor of POPF (HR=2.038, CI: 1.067–3.896, p=0.03), with a potential trend toward male sex predicting higher fistula rate (HR=1.852, CI: 0.975–3.519 p=0.06). Preoperatively documented CAD (HR=2.301, CI: 0.824–6.426, p=0.112) and age (HR=1.004, CI: 0.973–1.037, p=0.792) both showed no significant influence on POPF rate.

Discussion

The objective of this study was to determine whether tobacco use negatively affects morbidity following PD for cancer. Our study found that smoking is an independent risk factor for the development of POPF (including biochemical leaks) following resection in patients with PDAC and peri-pancreatic cancers. When the analysis was performed with POPF defined as only the clinically significant Grade B or C fistulae, there was a trend towards higher fistula rate in smokers. Furthermore, we found that, among current and past-smokers, male sex was independently predictive of higher fistula rates, while this relationship was not demonstrated in never-smokers. No significant relationship between quantity smoked, quantified by pack-years, and postoperative morbidity was found. Additionally, while current tobacco smokers had higher POPF rates compared to previous smokers, this difference was not statistically significant, perhaps due to the sample size.

There are mixed findings in the literature regarding postoperative morbidity and tobacco smoking for pancreatic cancer patients. In a large, multi-institutional study from Japan, Aoki et al. found smoking (quantified by the Brinkman Index >600) to be one of fifteen independent risk factors for serious postoperative morbidity and an ISGPF grade C POPF (5). Conversely, Hu et al. showed no correlation with smoking and POPF in a single-institution retrospective review from China (6). Several other studies found no significant correlation between smoking and POPF (7–13). Interestingly, a study from the United Kingdom by Roberts et al. showed a lower fistula rate among smokers compared to past and never-smokers on univariate analysis only (11). There have also been studies showing a significant association between smoking and known risk factors for POPF, such as BMI (14), as well as factors protective against developing fistulas, including firm pancreas texture (12); both did not show an independent relationship between smoking and pancreatic leak rate.

Tobacco consumption is a known risk factor for progressive vascular atherosclerosis. In CAD, smoking has been found to cause platelet aggregation, endothelial injury resulting in dysfunction, and impaired vascular repair (21). It has also been linked to anastomotic leaks in colorectal literature (22). Kruschewski et al. drew a correlation between CAD as a marker for general atherosclerosis, suggesting a similar disease process perturbs the microvascular circulation of colorectal anastomoses. This relationship has been demonstrated in other studies as well (23). Indeed, Fawcet et al. demonstrated that smoking was correlated with microvascular disease of resected colonic specimens, and those with disease had statistically significant increases in anastomotic failures (24). Smoking is also commonly implicated in worse outcomes following microvascular anastomosis for free flaps (25). It is reasonable to conclude that microvascular disease and ischemia are responsible for small areas of focal tissue damage within and around the pancreaticojejunostomy, leading to subsequent partial anastomotic breakdown, impaired healing and ultimately increased POPF. CAD seems to be a marker for diffuse macro and microvascular disease, exacerbated by smoking (26). Our study found that current-smokers had a higher rate of POPF compared to past-smokers, although not statistically significant. Perhaps this suggests that the underlying pathology is more related to vascular disease from chronic insult as opposed to the acute effects of tobacco exposure. Thus, similar to peripheral and coronary artery disease, cessation of smoking does not completely reverse years of damage from chronic exposure.

POPF rates vary in the literature and range from 10–29% (15). This variability has been attenuated by the acceptance of the ISGPF criteria published by Bassi et al. (18), which was further standardized in our study using the POPF calculator on the Pancreas Club Inc. website, based on the ISGPS definitions. In 2016, the ISGPF updated the POPF definition, classifying grade A POPF as "biochemical leaks" and providing stricter criteria for grade B and C fistulas (27). While we included grade A fistulas in our analysis of POPFs, we also performed the analysis using the updated criteria for B and C fistulas separately as well. While no statistically significant difference between never-smokers and past/current-smokers was found, there was a trend toward higher B/C fistula rates in smokers compared to never-smokers, 25 (18.2%) vs 13 (11.7%), p=0.155. It is worth noting that by excluding "biochemical leaks", our findings lose statistical significance. This is likely due to our sample size. However, our data clearly demonstrate a relationship between anastomotic disruption and smoking status. Future studies with larger patient populations are important as further understanding the correlation between smoking and fistula rates has implications ranging from preoperative counseling, managing patient expectations, operative placement and positioning of drains, even influencing the decision of when to remove drains and discharge patients.

Our study found male sex is a risk factor for developing POPF on univariate analysis, similar to previous studies (5, 6, 8, 28, 29). Overall, men smoke at a higher rate than women, both throughout the country (16.7% vs 13.6%) (30), and in our study: 34.9% vs 19.4%, respectively. Additionally, men in our study were exposed to a significantly higher average quantity of cigarette use as quantified by pack-years compared to women. This increased tobacco exposure may partially explain why POPF rates were significantly higher in men compared to women. Although not statistically significant, a trend towards higher fistula rates in patients with preoperatively documented CAD was found. Also, as expected, we noted a significantly higher incidence of CAD in smokers compared to never-smokers. This suggests a common underlying pathology and echoes the findings of other studies where CAD was found to be associated with higher fistula rates (8, 31, 32). Furthermore, the prevalence of CAD trended higher in men compared to women, which may imply a higher incidence of diffuse macro and microvascular disease, contributing to the finding of higher fistula rates in men compared to women. This relationship is complex, and further studies may help explain these findings.

Our study has several limitations. The retrospective nature of the study limits the available data to what is reported in the medical records. However, our surgeons and medical oncologists keep detailed notes regarding smoking status, and we were able to obtain details of patients' smoking habits for all but 4 (1.6%) of our 252 patients. The retrospective nature of the study also limits our ability to detect POPFs. However, the regular use of postoperative drains and analysis of fluid amylase levels gives consistent, objective data for documenting fistulas. Those with clinically significant fistulas, ISGPF grades B and C, typically have documented evidence from a combination of imaging reports, intervention notes, and readmission and follow up data. Major postoperative complications requiring intervention, imaging, consultation, or prolongation of hospital stay were reliably documented. Additionally, while several previously studied risk factors for POPF, such as gland texture and pancreatic duct diameter, were not routinely documented in operative reports, they were included in our analysis for patients when available. While we did not find that pancreatic duct size was correlated with POPF rate, soft parenchymal gland texture was significantly associated with B/C POPFs. This is consistent with previous studies (7, 8, 12, 29). As there was no significant difference between never-smokers and smokers with regard to gland texture or duct size, it is unlikely this finding had a significant impact on the rate of POPF in smokers compared to never-smokers.

Lastly, the 30-day mortality rate in our study was found to be higher in never-smokers than in current and past-smokers. While the average age of the never-smoking patients who died at ≤30 days was greater than that of the smokers who died at ≤30 days (76 vs 69, respectively), no other difference was found to reasonably account for this disparity. A study by Lee et al (33) utilizing the NSQIP database found, for patients undergoing PD, age ≥80 years was an independent risk factor for higher 30-day mortality compared to <80 years, and age ≥70 had higher 30-day mortality compared to age <70 years on univariate analysis only. While this may provide a partial explanation for the significantly higher mortality in never-smoking patients, our overall 30-day mortality rate was high (7.5%) compared to rates quoted in the literature, ranging from 1–4% (33–37). Causes of death included aspiration related respiratory failure, overwhelming septic shock, hypoxemic respiratory failure, hemorrhagic shock, and cardiopulmonary arrest of unknown cause. Efforts to improve our pre- and postoperative care for pancreatic cancer patients continue to expand, including implementation of a multi-disciplinary tumor board, establishing a pre-habilitation program, participating in clinical trials, and improvements in postoperative care. Further efforts, such as establishing an institution-based Enhanced Recovery After Surgery (ERAS) program (38), may help improve our 30-day mortality rate.

Conclusion

Our study documents that current or previous smoking history is an independent risk factor for POPF following PD for PDAC and associated cancers. In addition, we found that male sex is an independent risk factor for POPF in current or past-smokers only. Smoking is a modifiable risk factor, and thus it is practical to encourage smoking cessation not only as it pertains to the development of pancreatic cancer, but many benefits to other organ systems as well. The lack of a clear relationship in our study between fistula rate and pack-years smoked, or previous smokers versus current smokers, could be due to sample size, but until clear data exists documenting that pre-operative cessation has no effects on post-operative morbidity, we will continue to encourage our patients to quit using tobacco. Clearly, however, larger studies will need to be performed to address whether smoking cessation before surgery results in improved outcomes for this disease and if so, what the optimal duration of cessation is to minimize postoperative morbidity.

Acknowledgment

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Table 1:

Demographic and Descriptive Data by Smoking Status

Variables	Total Population	Never Smokers (NS)	Current or Past-Smokers (S)	P Value (comparing NS to S)
n	252	111	137	
Female Sex (%)	114 (45)	61 (55)	49 (36)	**0.003**
Mean Age (y) (Range)	67 (39–90)	69 (44–90)	66 (39–87)	**0.013**†
Mean BMI (Range)	27.0 (14.9–51.4)	27.1 (14.9–43.7)	27.6 (17.7–51.4)	0.871†
<18	2	1	1	
18–25	97	47	50	
25–30	76	32	44	
>30	63	29	34	
ASA (II /III/IV) (%)	33/183/29 (13.1/72.6/11.5)	19/82/8 (17.1/73.9/7.2)	14/101/21 (10.2/73.7/15.3)	0.059
Albumin <3.5 (%)	107 (42.5)	54 (48.6)	53 (38.7)	0.156†
Comorbidity >1 (%)	150 (59.5)	60 (54.1)	90 (65.7)	0.068
CAD (%)	33 (13.1)	7 (6.3)	26 (19.0)	**0.004**
DM (%)	80 (31.7)	40 (36.0)	40 (29.2)	0.276
Jaundice (%)	108 (42.9)	47 (42.3)	61 (44.5)	0.797
Hx of Abd Surgery (%)	85 (33.7)	40 (36.0)	45 (32.8)	0.614
Neoadjuvant (%)				
Chemotherapy	41 (16.3)	17 (15.3)	24 (17.5)	0.732
Radiation Therapy	17 (6.7)	6 (5.4)	11 (8.0)	0.460

† = p-value for Students T-Test, BMI = body mass index (kg/m^2), ASA = American Society of Anesthesiology classification, CAD = coronary artery disease, DM = diabetes mellitus, Hx of abd surgery= history of abdominal surgery

Table 2:

Differences by Sex

Variables	Female (%)	Male (%)	P Value
n	114	138	
Mean Age	67	67	0.788 †
CAD Present	12 (10.5)	21 (15.2)	0.272
Smoking Status			**0.003**
Current/Past-Smoker	49 (43.0)	88 (63.8)	
Never-Smoker	61 (53.5)	50 (36.2)	
Pack-Years (range)	12.5 (1–60)	21 (1–120)	**0.004** †
POPF	18 (15.8)	39 (28.3)	**0.023**

† = p-value for Students T-Test, CAD = coronary artery disease, POPF = postoperative pancreatic fistula

Table 3:

Postoperative Outcomes by Smoking Status

Variables	Total Population	Never Smokers (NS)	Current or Past-Smokers (S)	P Value (comparing NS to S)
Avg EBL (mL) (Range)	856 (75–10000)	784 (100–8000)	923 (75–10000)	0.363[†]
Margin (R0/R1) (%)	192/60 (76.2/23.8)	89/22 (80.2/19.8)	102/35 (74.4/25.5)	0.363
Official Pathology (%)				0.651
PDAC	191 (75.8)	82 (73.9)	105 (76.6)	
Cholangiocarcinoma	13 (5.2)	6 (5.4)	7 (5.1)	
Peri-ampullary	48 (19.0)	20 (18)	28 (20.4)	
T stage (0/1/2/3/4) (%)	2/28/36/178/8 (1/11/14/71/3)	1/13/15/78/4 (1/12/13/70/4)	1/15/20/97/4 (1/11/14/71/3)	0.995
N stage (0/1) (%)	107/145 (42.5/57.5)	49/62 (44.1/55.9)	57/80 (41.6/58.4)	0.701
DGE (%)	140 (55.6)	63 (56.8)	77 (56.2)	1.00
POPF (%)	57 (22.6)	18 (16.2)	39 (28.5)	**0.024**
A	19 (7.5)	5 (4.5)	14 (10.2)	
B	29 (11.5)	11 (9.9)	18 (13.1)	0.155 B+C
C	9 (3.6)	2 (1.8)	7 (5.1)	
Clavien-Dindo (%)				0.156
0	66 (26.2)	34 (30.6)	32 (23.4)	
I	57 (22.6)	23 (20.7)	34 (24.8)	
II	77 (30.6)	37 (33.3)	39 (28.5)	
III A/B	17/9 (6.7/3.6)	5/2 (4.5/1.8)	12/7 (8.8/5.1)	
IV A/B	6/5 (2.4/2.0)	3/0 (2.7/0.0)	3/5 (2.2/3.6)	
V	15 (6.0)	7 (6.3)	5 (3.6)	
Infectious (%)	87 (34.5)	38 (34.2)	49 (35.8)	0.894
Pneumonia (%)	19 (7.5)	5 (4.5)	14 (10.2)	0.148
UTI (%)	27 (10.7)	13 (11.7)	14 (10.2)	0.838
Intra-abd Abscess (%)	19 (7.5)	6 (5.4)	13 (9.5)	0.337
Cardiac Complication	39 (15.5)	12 (10.8)	24 (17.5)	0.136
Bacter-/fungemia (%)	12 (4.8)	3 (2.7)	9 (6.6)	0.235
Avg LOS (days) (range)	13 (0–69)	12 (4–69)	13 (0–68)	0.343[†]
Disposition (%)				0.535
Home	206 (81.7)	92 (82.9)	113 (82.5)	
SNF/LTAC	6/10 (2.4/4.0)	3/2 (2.7/1.8)	3/8 (2.2/5.8)	
Rehab	14 (5.6)	7 (6.3)	7 (5.1)	
30-day Re-adm (%)	57 (22.6)	28 (25.2)	29 (21.2)	0.453
30-day Mortality (%)	19 (7.5)	11 (9.9)	5 (3.6)	**0.046**

Variables	Total Population	Never Smokers (NS)	Current or Past-Smokers (S)	P Value (comparing NS to S)
90-day Mortality (%)	32 (12.7)	15 (13.5)	14 (10.2)	0.422

† = p-value for Students T-Test, Avg EBL = average estimated blood loss, R0 = no residual tumor, R1 = microscopic residual tumor, DGE = delayed gastric emptying, POPF = postoperative pancreatic fistula, UTI = urinary tract infection, SNF = skilled nursing facility, LTAC = long-term acute care hospital, Re-adm = re-admission, Avg LOS = Average length of stay, PDAC = pancreatic ductal adenocarcinoma

Table 4:

Operative data by smoking status

Variables	Total Population	Never Smokers (NS)	Current or Past Smokers (S)	P Value (comparing NS to S)
Pancreas Texture	82	35	47	0.300
Soft	36 (43.9)	15 (42.9)	21 (44.7)	
Firm	33 (40.2)	12 (34.3)	21 (44.7)	
Inflamed	13 (15.9)	8 (22.9)	5 (10.6)	
Duct Size	122	54	68	0.354
≤3mm	40 (32.8)	14 (25.9)	26 (38.2)	
>3mm	82 (67.2)	40 (74.1)	42 (61.8)	
P-J Anastomosis	251	111	140	0.641
Duct-to-mucosa	199 (79.3)	87 (78.4)	112 (80.0)	
Invaginated	52 (20.7)	24 (21.6)	28 (20.0)	

P-J anastomosis = pancreaticojejunostomy, pylorus-preserving = pylorus preserving pancreaticoduodenectomy

Table 5:

Multivariable Analysis: Pancreatic Fistula Risk Never Smokers and Current/Past Smokers

Variables	Never Smokers OR (95% Confidence Interval)	Current/Past Smokers OR (95% Confidence Interval)
Age	0.980 (0.929–1.035, p=0.473)	1.016 (0.975–1.059, p= 0.458)
Sex (Male)	1.056 (0.378–2.946, p=0.917)	**2.817** (1.164–6.815, p=0.022)
CAD	0.000 (Not Estimable)	2.144 (0.723–6.355, p=0.480)

Binary logistic regression analysis