HHS Public Access

Author manuscript

J Surg Oncol. Author manuscript; available in PMC 2019 September 01.

Published in final edited form as:

J Surg Oncol. 2018 September ; 118(3): 455–462. doi:10.1002/jso.25183.

Impact of neoadjuvant therapy on postoperative outcomes after pancreaticoduodenectomy

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Abstract

Background: Surgical resection provides the only potentially curative treatment for pancreatic cancer. Neoadjuvant chemotherapy and/or radiation (NAT) is used to downstage patients with borderline resectable tumors. The objective of this study was to examine the postoperative morbidity and mortality of NAT after pancreaticoduodenectomy (PD) for pancreatic ductal adenocarcinoma (PDA).

Methods: Using the ACS-NSQIP Targeted Pancreatectomy data, we identified patients who underwent a PD for PDA from 2014–2015. Patients were grouped by receipt of NAT 90-days prior to PD. Bivariable and multivariable analyses was used to compare postoperative outcomes.

Results: A total of 3,748 patients with PDA underwent PD; 926 (24.7%) received NAT. Those in the NAT group had more major vein resections, and longer operating times (all $p<0.001$). On pathologic staging, those in the NAT group had smaller tumors (T1 10.9% vs 5.1%, $p<0.001$) and fewer nodes positive (N0 49% vs 28%, $p<0.001$). There were no differences in 30-day postoperative mortality or overall complications. On multivariable analysis, patients who received NAT had a lower likelihood of pancreatic fistula (OR 0.67, $p<0.001$).

Conclusion: NAT does not increase the overall postoperative morbidity or mortality of PD for PDA. There is a decreased likelihood of pancreatic fistulas in patients that receive neoadjuvant therapy.

Keywords

Neoadjuvant therapy; pancreatic cancer; pancreaticoduodenectomy outcomes; Whipple postoperative complications; postoperative pancreatic fistula

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Introduction

Pancreatic adenocarcinoma is the third leading cause of cancer death in the United States.[1,2] A pancreaticoduodenectomy is most commonly performed for patients with adenocarcinoma in the head or neck of the pancreas. The goal of surgery for pancreatic cancer is to obtain a complete (R0) resection; those that do not receive a R0 resection have earlier recurrence and shorter survival.[3–5] Unfortunately, at the time of diagnosis, only 15–20% of patients with adenocarcinoma of the pancreas are candidates for potentially curative surgery due to advanced disease.[6]

Some patients with pancreatic cancer present with borderline resectable tumors. The most recent consensus definition of borderline resectable pancreatic cancer includes anatomical considerations (contact with less than 180 degrees of the superior mesenteric artery and/or celiac artery, short segment contact with the common hepatic artery, and contact or occlusion with the superior mesenteric vein-portal vein confluence with adequate vein proximal and distal for reconstruction), high-risk biologic features, and patient performance status.[7,8] All of these factors make upfront surgery risky, and studies have shown that these patients benefit from neoadjuvant chemotherapy and radiation.[8,9] As a result, the current National Comprehensive Cancer Network (NCCN) guidelines recommend neoadjuvant chemotherapy and chemoradiation for patients with borderline resectable disease.[10]

Initially, neoadjuvant therapy was mainly utilized at large academic centers specializing in pancreatic cancer, and most published studies evaluating the perioperative morbidity and mortality following neoadjuvant therapy for pancreatic cancer have come from these centers.[11] The majority of these single center studies have found no difference between neoadjuvant therapy and initial surgery approaches in terms of postoperative pancreatic fistula formation or total complications.[11,12] For example, in 2015 Cooper et al. published their study using the American College of Surgeons-National Surgical Quality Improvement Project (ACS-NSQIP) Pancreatectomy Demonstration Project pilot data to examine national rates of postoperative complications after neoadjuvant therapy. No difference in the overall postoperative complication rates was identified between groups in that study.[13] However, the sample size of that study was small and the rate of neoadjuvant therapy was still quite low. Since that time, the use of neoadjuvant therapy has become much more widespread and the number of hospitals participating in the ACS-NSQIP Targeted Pancreatectomy database has also increased substantially. As a result, this current study examines whether the findings, specifically the impact of neoadjuvant therapy on 30-day postoperative mortality and morbidity, hold true across this larger population of patients and hospitals.

Material and Methods

Data and Population

One-hundred and twenty de-identified hospitals in the United States contribute data to the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) and the Targeted Pancreatectomy data program. This program collects 36 additional pancreas specific variables in addition to those captured by the standard ACS-NSQIP

program. Patients undergoing a pancreaticoduodenectomy for pancreatic adenocarcinoma between January 1, 2014 to December 31, 2015 were identified in the ACS-NSQIP Targeted Pancreatectomy Participant Use Data Files (PUF) (N= 5,559). This cohort of patients was identified by Current Procedural Terminology (CPT) codes for pancreaticoduodenectomy (48150, 48152, 48153, and 48154) and with a histology diagnosis of pancreatic adenocarcinoma (N= 3,777). Patients were excluded if they had missing data for preoperative chemotherapy or radiation therapy (N= 29). The ACS-NSQIP and the hospitals participating in the ACS-NSQIP 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 the authors. The University of North Carolina Institutional Review Board deemed this study exempt from further review.

Variables and Outcomes

Patients were divided into two groups: those that received neoadjuvant therapy, and those that had initial surgery. We defined neoadjuvant therapy as any chemotherapy and/or radiation therapy occurring in the 90-days prior to the index operation. The ACS-NSQIP database does not specify the chemotherapy drug regimen, radiation dose, or duration of treatment. Variables extracted from the ACS-NSQIP database included demographics, preoperative risk factors, intraoperative factors, and 30-day postoperative outcomes classified according to the ACS-NSQIP PUF definitions.[14] The primary outcome of interest was 30-day postoperative mortality after pancreaticoduodenectomy for pancreatic adenocarcinoma. The cohort sample size allowed for a 90% power (alpha=0.05) to detect an absolute difference of 2% based on the cohort size (924 in the neoadjuvant group and 2,822 in the initial surgery group), assuming a 30-day mortality of 2%. The secondary outcome was 30-day postoperative complications. Pancreas specific complications included pancreatic fistula, and delayed gastric emptying. Pancreatic fistula is defined by ACS-NSQIP as persistent drainage of amylase rich fluid requiring continued operative drain placement for greater than 7 days, percutaneous drainage, or reoperation. Pancreatic fistula complications were categorized to the International Study Group for Pancreatic Fistula (ISGPF) grades A, B, or C based on available information.[15] Other postoperative complications included superficial and deep surgical site infections, organ space surgical site infection, wound dehiscence, pneumonia, pulmonary embolism/deep vein thromboembolism, unplanned intubation, renal insufficiency/renal failure, urinary tract infection, stroke, cardiac arrest, myocardial infarction, Clostridium difficile, transfusion, sepsis/septic shock, take back to the operating room, and 30-day readmission. Complications were transformed into categorical variables based on their Clavien-Dindo classification (grades 1–5) (Appendix A).[16] Complications were considered minor if they were Clavien-Dindo grades 1–2, and severe if they were grades 3–5.

Statistical Analysis

Chi-square and Student’s t-tests for categorical and continuous variables were used to compare patient demographics, preoperative risk factors, and intraoperative characteristics between the neoadjuvant therapy and initial surgery groups. Thirty-day postoperative outcomes were initially analyzed using unadjusted, bivariate analyses with chi-square and Student’s t-test. Intraoperative and postoperative outcomes that were statistically significant

on bivariate analysis were assessed using multivariable logistic regression. Each model was adjusted for age, sex, body mass index (BMI), preoperative steroid use, wound classification, operative time, preoperative biliary stenting, preoperative jaundice, preoperative albumin, preoperative anemia, pancreatic duct size, gland texture, presence of pancreatic fistula, and operative reconstruction (i.e. pylorus-sparing pancreaticoduodenectomy, and pancreaticojejunal vs pancreaticogastrostomy). Presence of pancreatic fistula was removed from the pancreatic fistula model. Each model was tested for effect-measure modification using likelihood ratio tests by creating interaction terms between receipt of neoadjuvant therapy and clinically significant covariates. Clostridium difficile postoperative complication was dropped from the analysis due to 45% missing values. Listwise deletion method was used for analysis of variables if less than 5% of the data was missing. Variables with greater than 5% missing data were reported in the tables and identified as “missing/unknown”. Statistical significance was set at $p<0.05$ and all tests were 2-sided. All analysis was conducted using STATA 14.1 (StataCorp, Inc., College Station, TX).

Results

A total of 3,748 patients underwent a pancreaticoduodenectomy (Figure 1). Of these patients, 926 (24.7%) received neoadjuvant therapy, with 506 (13.5%) receiving only chemotherapy, 28 (0.8%) receiving only radiation, and 392 (10.5%) receiving chemotherapy and radiation. Patients who received neoadjuvant therapy were more likely to be younger, non-Hispanic white, have normal BMI, have used preoperative steroids, have a higher preoperative albumin, have a biliary stent at the time of surgery, have less preoperative jaundice and have less preoperative hypertension compared to the initial surgery group (all $p<0.015$, Table 2). Although the majority of patients in both groups underwent an open pancreaticoduodenectomy, there was a larger proportion of patients in the neoadjuvant therapy group who underwent a robotic procedure (4.8% vs 3.3%, $p=0.035$) compared to the initial surgery group. The neoadjuvant group also required more major vein resections (35.8% vs 17.6%, $p<0.001$). Thus not surprisingly, the mean operative time was longer by 51 minutes in the neoadjuvant group (413 vs 364 minutes, $p<0.001$). The neoadjuvant group had more patients with a hard pancreas (66.5% vs 53.2%, $p<0.001$). Post-surgical pathology revealed smaller tumor size, and negative lymph nodes in the neoadjuvant therapy group ($p<0.001$, Table 3). Length of stay was shorter for the neoadjuvant therapy group than the initial surgery group (mean 9.7 vs 10.9, $p<0.001$).

The 30-day mortality was similar between the neoadjuvant therapy group and the initial surgery group (1.7% vs 2%, $p=0.622$). There was no difference in 30-day overall complications or readmission rates between the two groups (Table 3). After stratifying complications based on Clavien-Dindo Grade, there was no statistically significant difference in complications between the groups. On bivariate analyses of individual complications, there were statistically significant differences in postoperative complications for organ space surgical site infection, pneumonia, postoperative blood transfusion, pancreatic fistula and delayed gastric emptying between the neoadjuvant therapy and initial surgery groups (Table 3). There were significantly fewer organs space surgical site infections, pneumonias, pancreatic fistulas, and delayed gastric emptying in the neoadjuvant group. The neoadjuvant group had both fewer grade A (6% vs 10%, $p<0.001$) and grade C

(0.2% vs 1.2%) pancreatic fistulas complications. The neoadjuvant group did have higher rates of blood transfusion within 72 hours of the pancreaticoduodenectomy.

On multivariable logistic regression analysis, individuals who had neoadjuvant therapy were less likely to have a pancreatic fistula complication (OR, 0.67; 95% CI, 0.49–0.92; p=0.015) after controlling for clinically and statistically significant preoperative and operative characteristics (Table 3). Independent predictors for the development of a pancreatic fistula in addition to initial surgery included, having a preoperative biliary stent, having a small pancreatic duct (<3mm), having soft pancreatic tissue intraoperatively compared to hard, and having a longer operation (Table 4). After controlling for clinically and statistically significant perioperative characteristics, there was no statistically significant association between receipt of neoadjuvant therapy and organ space surgical site infection, pneumonia, delayed gastric emptying, or need for blood.

Discussion

Neoadjuvant therapy is increasingly being utilized in borderline resectable and locally advanced pancreatic cancer to improve margin negative resection rates or increase resectability, particularly in high-volume and academic centers.[17–19] One meta-analysis found 43% of patients with borderline resectable and locally advanced disease were able to be resected after preoperative FOLFIRINOX with or without radiation, with a complete resection (R0) rate of 85%.[17] Similarly, another systematic review of locally advanced pancreatic cancer patients found that 28% underwent resection after FOLFIRINOX with or without radiation, with a 77% R0 resection rate.[18] Consistent with these prior studies, this study demonstrated that patients treated with neoadjuvant therapy had smaller tumors and fewer nodes positive on pathologic staging compared to patients treated with surgery first (see Table 2), supporting the idea that neoadjuvant therapy results in downstaging of the tumor. Still, there are no published randomized control trials comparing neoadjuvant therapy to initial surgery in borderline resectable patients, so the best approach remains disputed.

Neoadjuvant therapy may have benefits beyond making an R0 resection possible. At the time of diagnosis, pancreatic cancer is a systemic disease and requires not only local control but also systemic treatment with chemotherapy to improve survival.[20] However, only 57.7% of patients receive adjuvant chemotherapy after curative-intent pancreatic resection.[21] Among patients that have a serious postoperative complication, only 43.6% receive adjuvant therapy.[21] Neoadjuvant therapy ensures that systemic therapy is not delayed or omitted due to prolonged postoperative recovery. Neoadjuvant therapy may also identify patients that would not benefit from surgical resection due to rapidly progressive metastatic disease.[22] Approximately 25% of patients who undergo preoperative chemotherapy or chemoradiation for pancreatic cancer do not undergo resection due to either preoperative disease progression, decline in performance status, or extrapancreatic disease found at the time of surgery.[22–24]

Despite these potential advantages, concerns remain regarding higher rates of perioperative complications in patients undergoing neoadjuvant therapy.[11,25,26] However, existing data do not support this concern. Two separate single high-volume center studies found no

difference in 90-day postoperative morbidity or mortality.[27,28] Prior ACS-NSQIP studies examined this on a national level but these studies had limitations. The first study using the ACS-NSQIP Targeted Pancreatectomy was limited in its conclusions due to the combination of both pancreaticoduodenectomy and distal pancreatectomy patients and the small proportion of patients that received neoadjuvant therapy (12.7%).[13] Other studies using the ACS-NSQIP data found no difference in overall morbidity and mortality, but were not able to capture pancreas specific complications (i.e. pancreatic fistula, and delayed gastric emptying).[29,30] This current study is unique in that we examined pancreaticoduodenectomy in the setting of neoadjuvant therapy across 120 hospitals in the modern era of pancreatic surgery. We found no statistically significant differences in mortality, overall complications, and major or minor complications between the initial surgery and neoadjuvant therapy groups.

Overall there was a pancreatic fistula rate of 13.4%, which is concordant with the previously published studies.[31] Postoperative pancreatic fistula was associated with preoperative biliary stenting, having a soft pancreas, small pancreatic duct (<3mm), longer operative time, and initial surgery (compared to neoadjuvant therapy). Patients who received neoadjuvant therapy (compared to initial surgery) had a decreased the likelihood of developing a pancreatic fistula, even after controlling for the other common risk factors.[32,33] Decreased pancreatic fistula rates in patients who receive neoadjuvant therapy is in alignment with previous single-center reports.[28,34] The proposed mechanism is impairment of pancreatic function and induction of pancreatic fibrosis, making the pancreas more favorable for pancreatic ductal anastomosis.[35] Additionally, intraoperative characteristic of having a soft pancreas and pancreatic duct size <3mm were even more strongly associated with developing a pancreatic fistula than exposure to neoadjuvant therapy alone. This is consistent with previous single-center studies that have shown that a fatty pancreas and lack of pancreatic fibrosis were significant risk factors for pancreatic fistula development.[36,37]

The rate of neoadjuvant therapy documented in this study (approximately 25% of patients undergoing a pancreaticoduodenectomy for pancreatic adenocarcinoma) was much higher than what had been previously reported.[29,30,38] The increased use may reflect increased adoption of neoadjuvant therapy for resectable pancreatic cancer patients in addition to borderline resectable and locally advanced disease. Alternatively, there could be selection bias as the high-volume pancreas centers that tend to participate in the ACS NSQIP Pancreas Group may also be more likely to be both early adopters of innovation such as neoadjuvant therapy.

There are some other limitations of these data, largely due to the limitations of registry data. The ACS-NSQIP Targeted Pancreatectomy data do not capture details such as chemotherapy drug regimen, radiation dosing, or duration of treatment, so we cannot determine the granular details of the planned therapy, or if patients completed a full course of treatment. In addition, as ACS-NSQIP data only capture surgical outcomes up to 30 days from the index operation; however, a prior single center study that followed patients out to 90-days after surgery found no difference in morbidity or mortality after neoadjuvant chemoradiation.[27] Finally, we were unable to adjust for surgeon, center, or center volume leaving the

possibility that differences in outcomes between the neoadjuvant group and the surgery first group may have been in part due to differential use of neoadjuvant therapy amongst high and low volume providers.

Despite these limitations, our study has many strengths. The cohort is comprised of over 900 patients who underwent neoadjuvant therapy after pancreaticoduodenectomy at 120 hospitals, allowing for a broader examination of outcomes compared to previous single center studies. Additionally, we were able to evaluate pancreas specific complications (i.e. pancreatic fistula, and delayed gastric emptying) that are often not captured with large database studies.

Conclusion

Neoadjuvant therapy does not appear to increase the 30-day overall postoperative morbidity or mortality of a pancreaticoduodenectomy for adenocarcinoma of the pancreas, and in fact, patients receiving neoadjuvant therapy have a decreased likelihood of pancreatic fistula. Despite the increased utilization of neoadjuvant therapy, prospective randomized trials are needed to establish the best approach for sequencing of therapy for the different subsets of patients with resectable, borderline resectable, and locally advanced pancreatic cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Grant Support:

This work is supported by the Cancer Care Quality Research Training Program from a National Institutes of Health grant R25CA116339.

Disclosures and Funding Sources: The authors have no disclosures relevant to the research covered in this submitted manuscript.

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Synopsis for Table of Contents:

Neoadjuvant chemotherapy and radiation are increasingly utilized in pancreatic cancer. This article examines the postoperative morbidity and mortality of neoadjuvant therapy following pancreaticoduodenectomy for pancreatic adenocarcinoma.

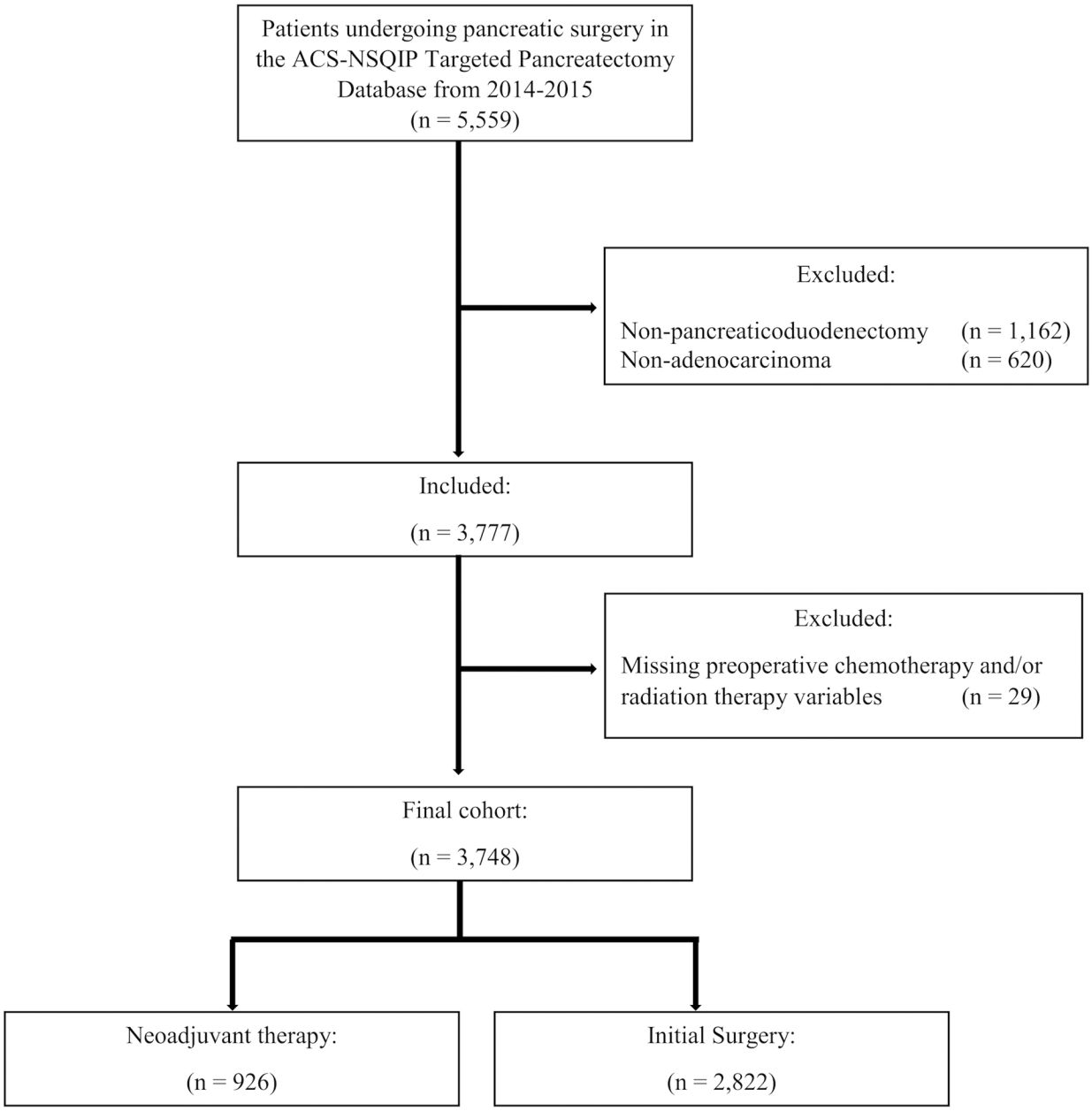

Figure 1:
CONSORT Diagram

Table 1.

Demographics and Preoperative Characteristics of Patients with Adenocarcinoma of the Pancreas Undergoing a Pancreaticoduodenectomy from 2014–2015 in the ACS-NSQIP Targeted Pancreatectomy Database

	Neoadjuvant Therapy N=926	**Initial Surgery N=2,822**	**p-value**
Age, mean (IQR)	**64 (57–71)**	**67 (60–74)**	**<0.001**
Male, n(%)	**456 (49.2%)**	**1,536 (54.4%)**	**0.006**
Race/Ethnicity, n(%)			
NHW	717 (79.1%)	2,001 (73.2%)	ref.
NHB	**138 (15.3%)**	**497 (18.2%)**	**0.013**
Hispanic	28 (3.1%)	116 (4.2%)	0.062
Asian	**20 (2.2%)**	**110 (4%)**	**0.005**
AI/NA	3 (0.3%)	11 (0.4%)	0.671
BMI, n(%)			
Normal	350 (37.8%)	892 (31.8%)	ref.
Underweight	16 (1.7%)	46 (1.6%)	0.685
Overweight	**323 (34.9%)**	**1,047 (37.3%)**	**0.007**
Obese	**237 (25.6%)**	**824 (29.3%)**	**0.001**
Smokers, n(%)	168 (18.1%)	503 (17.8%)	0.826
Diabetes, n(%)	267 (28.8%)	767 (27.2%)	0.328
Hypertension, n(%)	**455 (49.1%)**	**1,560 (55.3%)**	**0.001**
CHF, n(%)	1 (0.1%)	12 (0.4%)	0.154
COPD, n(%)	39 (4.2%)	133 (4.6%)	0.585
Functional Status, n (%)			
Independent	919 (99.4%)	2,783 (99%)	ref.
Partially Dependent	5 (0.5%)	27 (1%)	0.23
Totally Dependent	1 (0.1%)	0	0.082
Preoperative steroid use, n (%)	**31 (3.4%)**	**53 (1.9%)**	**0.009**
>10% weight loss ǂ, n (%)	186 (20.1%)	609 (21.6%)	0.335
Albumin, median (IQR)	**3.8 (3.4–4.1)**	**3.7 (3.3–4.1)**	**<0.001**
Albumin <3.5 g/dL	**235 (26.6%)**	**932 (35.4%)**	**<0.001**
Albumin >3.5 g/dL	**649 (73.4%)**	**1,703 (64.6%)**	
Bilirubin, median (IQR)	**0.4 (0.3–0.6)**	**1.2 (0.6–3.5)**	**<0.001**
Anemia, n(%)	**438 (48.0%)**	**1,162 (41.8%)**	**0.001**
Jaundice, n(%)	**332 (36.2%)**	**1,920 (68.5%)**	**<0.001**
Biliary stent, n(%)	**612 (66.1%)**	**1,744 (61.8%)**	**0.019**
ASA, n(%)			
1	1 (0.1%)	3 (0.1%)	0.996
2	166 (17.9%)	550 (19.5%)	0.287
3	694 (75.0%)	2,070 (73.4%)	ref.
4	65 (7%)	197 (7%)	0.915

IQR Interquartile Range; *BMI* body mass index, Normal (18.5–24.9), Underweight (<18.5), Overweight (25–29.9), Obese (>30); NHW non-Hispanic white; NHB non-Hispanic black; *AI/NA* American Indian/Native Alaskan; *ASA* American Society of Anesthesia physical status classification; *CHF* congestive heart failure; *COPD* chronic obstructive pulmonary disease;

‡ weight loss 6 months prior to operation

Table 2.

Operative Characteristics of Patients with Adenocarcinoma of the Pancreas Undergoing a Pancreaticoduodenectomy

	Neoadjuvant Therapy N=926	Initial Surgery N=2,828	p-value
T Stag, n(%)			
T0	**22 (2.4%)**	**2 (0.1%)**	**<0.001**
Tis	2 (0.2%)	3 (0.1%)	0.384
T1	**99 (11%)**	**142 (5.1%)**	**<0.001**
T2	71 (7.9%)	292 (10.5%)	0.094
T3	**682 (75.7%)**	**2,222 (79.6%)**	ref.
T4	**25 (2.8%)**	**129 (4.6%)**	**0.038**
N Stage, n(%)			**<0.001**
N0	442 (49%)	777 (28%)	
N1	460 (51%)	2,002 (72%)	
M Stage, n(%)			0.855
M0	839 (98.2%)	2,496 (98.2%)	
M1	15 (1.8%)	47 (1.8%)	
Total operating time (min.), median (IQR)	**399.5 (322–484)**	**354 (274–437)**	**<0.001**
Operative approach, n(%)			
Open	846 (91.4%)	2,620 (92.9%)	ref.
Laparoscopic	36 (3.9%)	110 (3.9%)	0.945
Robotic	**44 (4.8%)**	**92 (3.3%)**	**0.035**
Wound Class			
Clean	13 (1.4%)	44 (1.6%)	0.851
Clean-contaminated	732 (79.1%)	2,334 (82.7%)	ref.
Contaminated	**154 (16.7%)**	**332 (11.8%)**	**<0.001**
Dirty	27 (2.9%)	112 (4.0%)	0.227
Resection, n(%)			
Artery	59 (6.4%)	148 (5.3%)	0.211
Vein	**329 (35.8%)**	**487 (17.6%)**	**<0.001**
Pylorus-preserving surgery, n (%)	**322 (34.77%)**	**1,172 (41.5%)**	**<0.001**
Reconstruction, n(%)			
Pancreaticojejunal duct-to-mucosal	772 (89.4%)	2,340 (87.7%)	ref.
Pancreaticojejunal invagination	81 (9.4%)	262 (9.8%)	0.627
Pancreaticogastrostomy	**11 (1.3%)**	**66 (2.5%)**	**0.034**
Gland texture, n(%)			
Hard	469 (66.5%)	1,071 (53.2%)	ref
Intermediate	78 (11.1%)	226 (11.2%)	0.094
Soft	**158 (22.4%)**	**716 (35.6%)**	**<0.001**
Missing/Unknown	221	809	
Pancreatic duct size, n(%)			
<3 mm	190 (26.1%)	507 (23.8%)	0.354

	Neoadjuvant Therapy N=926	Initial Surgery N=2,828	p-value
3–6 mm	401 (55.2%)	1,177 (55.3%)	ref
>6 mm	136 (18.7%)	445 (20.9%)	0.339
Missing/Unknown	199	693	

Table 3.

Postoperative Complications for Patients with Adenocarcinoma of the Pancreas after Pancreaticoduodenectomy within 30-days of the procedure

	Neoadjuvant Therapy N= 926	Initial Surgery N= 2,822	p-value
Postoperative death, n (%)	16 (1.7%)	56 (2.0%)	0.622
Overall complication, n (%)	517 (55.8%)	1,554 (55.1%)	0.685
30-day Readmission, n (%)	154 (16.6%)	424 (15.0%)	0.24
Superficial SSI, n (%)	89 (9.6%)	253 (9.0%)	0.554
Deep incisional SSI, n (%)	20 (2.2%)	59 (2.1%)	0.899
Organ space SSI, n (%)	**76 (8.2%)**	**321 (11.4%)**	**0.007**
UTI, n (%)	40 (4.3%)	92 (3.3%)	0.129
Pneumonia, n (%)	**21 (2.3%)**	**108 (3.8%)**	**0.024**
Pulmonary embolism, n (%)	6 (0.7%)	35 (1.2%)	0.133
DVT, n (%)	27 (2.9%)	79 (2.8%)	0.853
Sepsis, n (%)	74 (8.0%)	232 (8.2%)	0.825
Septic Shock, n (%)	26 (2.8%)	84 (3.0%)	0.792
Acute renal insufficiency, n (%)	2 (0.2%)	19 (0.7%)	0.106
Acute renal failure, n (%)	5 (0.5%)	26 (0.9%)	0.266
Stroke, n (%)	1 (0.1%)	9 (0.3%)	0.28
Myocardial infarction, n (%)	6 (0.7%)	27 (1.0%)	0.383
Cardiac Arrest, n (%)	8 (0.9%)	35 (1.2%)	0.351
Wound dehiscence, n (%)	9 (1.0%)	34 (1.2%)	0.564
Reoperation, n (%)	49 (5.3%)	157 (5.5%)	0.784
Pancreatic fistula, n (%)	**85 (9.2%)**	**414 (14.8%)**	**<0.001**
Grade A (ISGPF)	**55 (6.0%)**	**278 (10.0%)**	**< 0.001**
Grade B (ISGPF)	28 (3.0%)	104 (3.7%)	0.331
Grade C (ISGPF)	**2 (0.2%)**	**32 (1.2%)**	**0.01**
Delayed gastric emptying, n (%)	**125 (13.8%)**	**481 (17.6%)**	**0.008**
Percutaneous drainage, n (%)	91 (10.0%)	297 (10.8%)	0.473
Perioperative transfusion, n (%)	**255 (27.5%)**	**596 (21.1%)**	**<0.001**
Clavien-Dino Complication, n (%)			
Grade 1	2 (0.2%)	19 (0.7%)	0.106
Grade 2	430 (46.4%)	1,247 (44.2%)	0.233
Grade 3	117 (12.6%)	419 (14.9%)	0.095
Grade 4	54 (5.8%)	192 (6.8%)	0.3
Grade 5 (death)	16 (1.7%)	56 (2.0%)	0.622
Complication, n (%)			
Minor (Clavien-Dino 1–2)	426 (46%)	1,232 (43.7%)	0.212
Severe (Clavien-Dino 3–5)	155 (16.7%)	516 (18.3%)	0.287

SSI surgical site infection; *UTI* urinary tract infection; *DVT* deep venous thrombus; *ISGPF* International Study Group for Pancreatic Fistula

Table 4.

Odds Ratios for 30-day Postoperative Complications for Patients with Adenocarcinoma of the Pancreas after Pancreaticoduodenectomy

	Crude		Adjusted*	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Organ space SSI				
Neoadjuvant Therapy	**0.70 (0.54, 0.91)**	**0.007**	0.86 (0.63–1.17)	0.353
Initial Surgery	1.0, Ref		Ref.	
Pneumonia				
Neoadjuvant Therapy	**0.58 (0.36, 0.94)**	**0.026**	1.15 (0.59–2.27)	0.681
Initial Surgery	Ref.		Ref.	
Pancreatic fistula				
Neoadjuvant Therapy	**0.66 (0.50–0.88)**	**<0.001**	**0.67 (0.49–0.92)**	**0.015**
Initial Surgery	Ref.		Ref.	
Delayed gastric emptying				
Neoadjuvant Therapy	**0.75 (0.61–0.93)**	**0.008**	0.80 (0.59–1.06)	0.124
Initial Surgery	Ref.		Ref.	
Perioperative transfusion				
Neoadjuvant Therapy	**1.42 (1.20–1.68)**	**<0.001**	1.12 (0.88–1.43)	0.344
Initial Surgery	Ref.		Ref.	

SSI surgical site infection; *CI* confidence interval;

* Odds Ratio was adjusted for: age, sex, body mass index, preoperative steroid use, wound classification, operative time (hours), preoperative biliary stenting, preoperative jaundice, preoperative albumin, preoperative anemia, pancreatic duct size, gland texture, presence of pancreatic fistula, and operative reconstruction (i.e. pylorus-sparing pancreaticoduodenectomy, and pancreaticojejunal vs pancreaticogastrostomy

Table 5:

Independent Predictors of Pancreatic Fistula

Risk Factor (Ref)	OR	95% CI	p-value
Neoadjuvant (Initial surgery)	0.67	0.49–0.92	0.015
Pre-op biliary stent (none)	1.3	1.01–1.69	0.043
<3mm pancreatic duct (3–6mm duct)	1.45	1.08–1.96	0.014
Soft pancreatic texture (Hard)	2.97	2.33–3.78	<0.001
Time (hours)	1.06	1.00–1.12	0.035

In addition to variables listed, model controls for: age, sex, body mass index, preoperative steroid use, wound classification, preoperative jaundice, preoperative albumin, preoperative anemia, and operative reconstruction.