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ORIGINAL ARTICLE

Pancreatic adenocarcinoma: effects of neoadjuvant therapy on post-pancreatectomy outcomes – an American College of Surgeons National Surgical Quality Improvement Program targeted variable review

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Abstract

Background: As the incidence of pancreatic adenocarcinoma increases, so has the utilization of neoadjuvant therapy. The objective of this study was to evaluate outcomes in patients undergoing neoadjuvant therapy or surgery first for pancreatic adenocarcinoma.

Methods: The ACS-NSQIP 2014–2015 targeted pancreatectomy variables were queried for patients with pancreatic adenocarcinoma who underwent resection. Outcomes of those receiving neoadjuvant therapy were compared to surgery first using a multivariate, logistic regression model.

Results: 3408 patients underwent pancreatectomy; 2596 proximal pancreatectomies, 741 distal pancreatectomies, 64 total pancreatectomies and 7 other pancreatic procedures were performed. Of the 3408 patients identified, 934 (27.5%) received neoadjuvant therapy: 496 chemotherapy alone, 28 radiation alone, and 410 combined chemotherapy/radiation therapy. Overall morbidity and mortality were similar between patients receiving neoadjuvant therapy versus those who underwent surgery first. Neoadjuvant treatment was associated with lower rates of pancreatic fistulas (10.2% vs. 13.2%, $P = 0.017$), but higher intra/postoperative transfusion rates (27.4% vs. 20.3%, $P < 0.0001$).

Conclusions: Neoadjuvant therapy appeared to be safe prior to operative intervention as no difference in overall postoperative morbidity or mortality rates were identified. There were increased intra/postoperative transfusions in the neoadjuvant therapy group, but neoadjuvant therapy was associated with lower rates of pancreatic fistulas.

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Introduction

The incidence of pancreatic adenocarcinoma is increasing and is currently the 4th leading cause of cancer death in men and women.[1] Pancreatic adenocarcinoma remains difficult to treat, with a low overall 5-year survival rate of 7.7%.[2] A multidisciplinary approach using surgical resection, combined with chemotherapy and/or radiation therapy remains the only potentially curative approach. Significant improvements in surgical technique over the past 20 years have resulted in decreased mortality. In addition, more radical pancreatic resections with concomitant vascular resections and reconstructions are being

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performed. These advances have resulted in expansion of the population of patients able to receive potentially curative surgery.[3] Despite these improvements, postoperative morbidity rates following pancreatic resection remains high, ranging from 22% to 64%.[4]

National Comprehensive Cancer Network (NCCN) guidelines categorize pancreatic adenocarcinoma into resectable, borderline resectable, and unresectable disease. Surgery first is the current standard for therapy in patients with resectable disease, while neoadjuvant therapy followed by surgery is recommended for patients with borderline resectable disease.[5] Early reports of feasibility for neoadjuvant therapy exist.[6–8] The rationale for neoadjuvant therapy includes: (i) Increased probability of R0 resection, and (ii) Patient selection, neoadjuvant therapy allows for selection of patients with favorable tumor biology. Since these initial studies, the rates of neoadjuvant chemotherapy and chemoradiotherapy have increased.[9,10] Given its increased utilization, understanding the effect of neoadjuvant therapy on surgical recovery is necessary.

The aim of this study was to evaluate rates of postoperative morbidity and mortality for patients with pancreatic adenocarcinoma treated at all American College of Surgeons National Surgical Quality Improvement Program® (ACS NSQIP) hospitals with surgery first or surgery following neoadjuvant therapy using the general and pancreatic procedure-specific 2014 and 2015 NSQIP Participant Use Files (PUF).[11] We hypothesized that an increased rate of postoperative morbidity and mortality would be seen in the neoadjuvant therapy group.

Methods

The ACS-NSQIP is a multicenter database that collects demographic, preoperative, and procedural variables to provide risk-adjusted rates of postoperative morbidity and mortality.[12] The ACS NSQIP PUF files for 2014 and 2015 cases were queried to identify all patients with the diagnosis of pancreatic adenocarcinoma undergoing non-emergent pancreatectomies, with the following CPT codes: 48120, 48140, 48145, 48146, 48150, 48152, 48153, 48154, 48155 and 48999 (N = 3408, after excluding 19 patients missing neoadjuvant treatment status). In addition to the general ACS NSQIP dataset, targeted pancreatic-specific variables were also queried and merged with the general dataset. These variables included laparoscopic/minimally invasive surgery, preoperative obstructive jaundice, preoperative biliary stent, chemotherapy within 90 days, radiation therapy within 90 days, operative approach, pancreatic duct size, pancreatic gland texture, pancreatic reconstruction, gastrojejunostomy or duodenojejunostomy reconstruction, drain(s), drain type, vascular resection, postoperative day (POD) #1 highest drain amylase, highest drain amylase POD# 2–30, number of days with highest amylase level after surgery, number of days for last pancreatic drain removal after surgery, drain still present at POD# 30, pancreatic fistula, delayed gastric emptying, and percutaneous drainage. These variables are described and defined in the NSQIP 2014 and 2015 PUF user guides.[13] The pancreas-specific variables of neoadjuvant chemotherapy or radiation therapy 90 days prior to surgery were used to identify the neoadjuvant therapy group (n = 934, 27.5%). The neoadjuvant therapy group consisted of patients receiving chemotherapy alone, radiation therapy alone or combined therapy. Outcomes of those receiving neoadjuvant therapy were compared to those with no neoadjuvant therapy, referred to as the surgery first group.

Patient characteristics and outcomes were compared using standard non-parametric statistical techniques, including chi-square test, Fisher's exact test, and Wilcoxon Rank sum test. A multivariate, logistic regression model of post-surgical morbidity was constructed using all demographic and procedural variables found to be significantly associated with postoperative complications. Postoperative outcomes and complications included 30-day mortality, delayed gastric emptying, pancreatic fistula, reoperation, any surgical site infection, acute renal failure, pneumonia, pulmonary embolism, need for cardiopulmonary resuscitation, myocardial infarction, intra/postoperative transfusion, sepsis, septic shock, urinary tract infection (UTI), unplanned intubation, ventilator required for >48 h, venous thromboembolism (VTE), transfusion, and readmission. The primary endpoint of any postoperative morbidity was defined as experiencing one or more of the outcomes and complications listed above. These variables are described and defined in the NSQIP 2014 and 2015 PUF users guides.[13] Level of significance was defined as $P < 0.05$.

Results

During 2014 and 2015 NSQIP reporting cycles, 3408 patients underwent pancreatectomy for pancreatic adenocarcinoma. Of these, 2596 underwent proximal pancreatectomy, 741 underwent distal pancreatectomy, 64 underwent total pancreatectomy and seven underwent some other pancreatic procedure (1 excision of lesion, CPT 48120, and 6 other pancreas procedures, CPT 48999). Of the 3408 undergoing pancreatectomy, 934 (27.5%) received neoadjuvant therapy: 496 chemotherapy alone, 28 radiation alone, and 410 combined chemotherapy and radiation therapy.

Demographic and preoperative data are reported in Table 1. Overall, basic demographic and preoperative variables were similar between patients who underwent surgery first vs. neoadjuvant therapy. The neoadjuvant group was significantly younger compared to the surgery first group. Patients receiving neoadjuvant treatment were more likely to have insulin-dependent diabetes, but less likely to require medication for hypertension. The neoadjuvant therapy group was more likely to have undergone preoperative biliary stenting and have lower preoperative bilirubin levels. Those receiving neoadjuvant therapy were less likely to undergo a distal pancreatectomy as opposed to a proximal or total pancreatectomy, more likely to

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