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Neoadjuvant radiation therapy prior to a pancreaticoduodenectomy for adenocarcinoma is associated with longer operative times and higher perioperative blood loss

Neoadjuvant radiation effect on pancreaticoduodenectomy

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## **Abstract**

### **BACKGROUND**

Pancreatic adenocarcinoma today represents the fourth most common cause of cancer-related death in the United States. In patients with “borderline resectable” disease, current National Comprehensive Cancer Center guidelines recommend the use of neoadjuvant chemoradiation prior to a pancreaticoduodenectomy. Although neoadjuvant radiotherapy may improve negative margin resection rate, it is theorized that its administration increases operative times and complexity.

### **AIM**

This study investigated the association between neoadjuvant radiotherapy and 30-day morbidity and mortality outcomes among patients receiving a pancreaticoduodenectomy for pancreatic adenocarcinoma.

### **METHODS**

Patients listed in the 2015-2019 National Surgical Quality Improvement Program (NSQIP) data set who received a pancreaticoduodenectomy for pancreatic adenocarcinoma were divided into two groups based off neoadjuvant radiotherapy status. Multivariable regression was used to determine if there is a significant correlation between neoadjuvant radiotherapy, perioperative blood transfusion status, total operative time, and other perioperative outcomes.

### **RESULTS**

Out of the 11,458 patients included in the study, 1,470 (12.8%) underwent neoadjuvant radiotherapy. Patients who received neoadjuvant radiotherapy were significantly more likely to require a perioperative blood transfusion (aOR = 1.58, 95%CI = 1.37, 1.82,  $p < 0.001$ ) and have longer surgeries (IRR = 1.14, 95%CI = 1.11, 1.16,  $p < 0.001$ ), while simultaneously having lower rates of organ space infections (aOR = 0.80, 95%CI = 0.66,

0.97,  $P = 0.02$ ) and pancreatic fistula formation (aOR = 0.50, 95%CI = 0.40, 0.63,  $p < 0.001$ ) compared to those that underwent surgery alone.

## CONCLUSION

Neoadjuvant radiotherapy, while not associated with increased mortality, will impact the complexity of surgical resection in patients with pancreatic adenocarcinoma.

**Key Words:** Pancreaticoduodenectomy; Pancreatic adenocarcinoma; Neoadjuvant chemoradiation; National Surgical Quality Improvement Program; Whipple procedure; Operative Time

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**Core Tip:** In this retrospective study, we use a national database to investigate the impact that neoadjuvant radiotherapy has on intraoperative and 30-day post-operative outcomes among patients undergoing surgical resection for pancreatic adenocarcinoma. We found that neoadjuvant radiotherapy was associated with longer operative times and the more frequent need for perioperative blood transfusions, but not with increased 30-day mortality. Neoadjuvant radiotherapy was also associated with a lower number of organ space infections and post-operative pancreatic fistula formation. Taken together, these results work to highlight the challenges that surgeons may face when operating in previously irradiated fields.

<sup>1</sup>

## INTRODUCTION

Pancreatic adenocarcinoma today represents the fourth most common cause of cancer-related death in the United States. In patients suffering from the disease, an R0 resection

is the primary and preferred method of treatment <sup>[1,2]</sup>. While this is often obtainable in patients with early-stage pancreatic malignancies, roughly 85 percent of patients present with disease that is not amenable to cure with surgical resection alone <sup>[3]</sup>. The tumors in many of these patients are considered borderline resectable, defined by National Comprehensive Cancer Network (NCCN) guidelines as <sup>3</sup> contact with 180 degrees or less of the superior mesenteric artery or the celiac artery, contact with the common hepatic artery, and/or contact with the superior mesenteric vein/portal vein resulting in contour irregularity or vein thrombosis <sup>[4]</sup>. According to the NCCN guidelines, such cancers may benefit from treatment with neoadjuvant therapy in the form of chemoradiation <sup>[5]</sup>.

When compared to adjuvant therapy, neoadjuvant chemoradiation has the theoretical benefit of testing for chemosensitivity, increasing the control of micrometastases and circulating tumor cells, ensuring a higher rate of systemic therapy completion, potentially downstaging a disease to make it amenable to surgical therapy, and reducing pancreatic leak rates <sup>[6-8]</sup>. Multiple studies have demonstrated the morbidity benefits that comes with neoadjuvant treatment of patients with borderline resectable pancreatic adenocarcinoma prior to surgery compared with just surgical treatment alone. Among others, these benefits include a decrease in tumor size at the time of surgery, decreased number of positive lymph nodes, fewer organ space infections, and fewer post-operative pancreatic fistulae <sup>[9-12]</sup>.

Despite the purported benefits, neoadjuvant therapy is still regarded with caution and its use remains low in the United States <sup>[13]</sup>. It is theorized that neoadjuvant therapy increases the rate of gastrointestinal toxicity and impairs post-operative wound healing, which can result in preoperative decompensation and subsequent post-operative morbidities. Neoadjuvant therapy can also theoretically delay definitive surgical resection, which can lead to the development of metastatic disease in non-responders. Radiotherapy, in particular, has been associated with disruption of the pancreatic tissue planes, which is thought to make eventual surgical resection more difficult <sup>[14]</sup>. Numerous studies have contradicted these ideas, showing that neoadjuvant

therapy results in little to no intra- and post-operative increases in morbidity and mortality [9,10,15]. To date, however, many of these prior studies are plagued by single institution analysis with small sample sizes. These samples are even smaller when looking at the number of participants who received neoadjuvant radiotherapy, as chemotherapy remains the lion's share of neoadjuvant therapy. The aim of this study is to investigate the effects that neoadjuvant radiation therapy has on both intra-operative and 30-day postoperative morbidities using a nation-wide dataset. We specifically hypothesize that among patients receiving a pancreaticoduodenectomy for pancreatic adenocarcinoma, those that also undergo neoadjuvant radiotherapy are more likely to have longer operative times and a perioperative transfusion compared with those who simply receive surgery alone.

## **MATERIALS AND METHODS**

### *Study Design and Participants:*

We performed a cross sectional study utilizing data from the American College of Surgeons (ACS) National Surgery Quality Improvement Program (NSQIP) database from January 1, 2015 to December 31, 2019. Data from the standard public use file was merged with that from the NSQIP Targeted Pancreatectomy Participant Use Data Files (a separate collection of pancreas-specific variables) using the CASEID variable. Patients greater than 18 years old who had a histological diagnosis of pancreatic adenocarcinoma and underwent a pancreaticoduodenectomy were included in this study. Patients undergoing resection were identified by one or more of the following additional CPT codes: 48150, 48152, 48153, 48154. This study was exempt from our Institutional Review Board review since the data was de-identified and obtained from a participant use data file.

### *Variables:*

From the patients included in the study, two groups were formed based on the independent variable of interest: those that received neoadjuvant radiotherapy prior to

a pancreaticoduodenectomy, and those that had progressed directly to surgery. For the purposes of this study, neoadjuvant radiotherapy was defined as those receiving treatments within 90 days of the index operation. The primary outcomes of interest were perioperative blood transfusions (defined by the need for a blood transfusion within 72 hrs of surgery start time; OTHBLEED variable) and total operative time (defined by operative time in minutes; OPTIME variable). The secondary outcomes of interest were 30-day post-operative morbidities and mortality. Specific variables included rate of the following: wound dehiscence, ventilator dependence, stroke, myocardial infarction (MI), deep venous thrombosis (DVT), pulmonary embolism (PE), pneumonia, urinary tract infection (UTI), septic shock, superficial surgical site infection (SSI), organ space SSI, 30-day re-operation, 30-day mortality, 30-day readmission, renal failure, hospital length of stay, duration of pancreatic drain, pancreatic fistula, and delay gastric emptying. Pancreatic fistulae were defined according to the International Study Group for Pancreatic Fistula grading scheme [16].

#### *Statistical Analysis:*

StataSE was used for statistical analysis. Descriptive statistics including mean/SD for normally distributed continuous variables, median/interquartile range for skewed continuous variables, and number/percentage for categorical variables. We assessed bi-variable differences in outcomes between patients with upfront surgery and neoadjuvant radiotherapy with surgery using the chi-squared test, univariable logistic regression, and Fisher's exact test for categorical variables. Two-tailed Student's t-tests for continuous variables. Variables that were statistically associated ( $\alpha < 0.05$ ) with both the outcome and the independent variable, as well as those that were predicted theoretical confounders, were included in multivariate regression analysis. Multivariable negative binomial regression was used for the total operative time variable, and multivariable logistic regression was used for the remaining secondary variables. We used stepwise, backward selection and tested full/reduced models with the likelihood ratio test to determine the most parsimonious model. For 30-day outcome

variables occurring less than 5% of the time, multivariable regression was not performed. For variables missing less than 5% of data, the listwise deletion method was used. Variables missing greater than 5% of data were reported as “unknown” in the tables.

## **RESULTS**

Query of the ACS-NSQIP database identified a total of 11,775 patients who underwent surgery for pancreatic adenocarcinoma from 2015 to 2019. Patients who had data missing with regards to neoadjuvant radiation therapy status, and patients in whom surgical site infections were reported upon admission, were excluded from the analysis. This left a final cohort of 11,458 patients. The cohort was then split into two study groups based off neoadjuvant radiotherapy exposure. 1,470 patients (12.8%) received neoadjuvant radiation therapy, compared with 9,988 (87.2%) patients who proceeded directly to surgery (Figure 1).

Patients undergoing neoadjuvant radiotherapy were more likely to be younger, female, non-Hispanic white, diabetic, and of normal body weight (all  $p \leq 0.04$ ). Conversely, patients undergoing surgery without radiotherapy were more likely to be Hispanic, overweight/obese, and jaundiced (all  $p \leq 0.002$ ). They were also more likely to have chronic obstructive pulmonary disease (COPD), dyspnea, and hypertension (all  $p \leq 0.05$ ) (Table 1).

With regards to tumor characteristics and operative approaches, patients receiving neoadjuvant radiotherapy were more likely to have a lower T-stage, a lower N-stage, receive an elective surgery, have a higher wound class, and have a smaller pancreatic duct size (all  $p < 0.04$ ). Such patients were also more likely to undergo an open surgical approach that involved resection of an artery or vein (all  $p \leq 0.001$ ) (Table 2).

Within the first 30 days following surgery, bi-variable statistical analysis revealed that patients receiving surgical treatment only were more likely to experience a myocardial infarction, a pulmonary embolism, pneumonia, an organ space infection,



delayed gastric emptying, and a pancreatic fistula (all  $p \leq 0.035$ ). Such patients also had a higher 30-day mortality rate, a longer hospital stay, a drain that remained in place after 30 days, and a longer total operative time (all  $p \leq 0.041$ ). Patients undergoing neoadjuvant radiation were more likely to receive a DVT and receive a perioperative transfusion (all  $p \leq 0.024$ ). On multivariate analysis of the 30-day outcomes that occurred at a rate of greater than 5% in both study groups, neoadjuvant radiotherapy was associated with longer total operative times and the need for a perioperative transfusion. Patients undergoing neoadjuvant radiotherapy, however, were statistically less likely to acquire an organ space infection or a pancreatic fistula when compared with patients who underwent surgery alone (Table 3, Table 4). While total hospital stay, presence of drain on post-operative day (POD) 30, and delayed gastric emptying occurred at significantly lower rates in the neoadjuvant therapy group upon univariate statistical analysis, this difference was not statistically significant on multivariable analysis.

## **DISCUSSION**

In the past, numerous studies have implicated single and multi-agent neoadjuvant chemotherapy with both tumor downstaging and an increased rate of R0 resections [17,18]. In comparison with neoadjuvant chemotherapy, however, evidence demonstrating similar advantages with neoadjuvant radiation therapy has been somewhat sparse. In 2019, Jiang *et al* used the NCDB database to show an increased R0 resection and overall survival rate among patients that utilized neoadjuvant stereotactic body radiation therapy (SBRT) in addition to neoadjuvant chemotherapy compared to just neoadjuvant chemotherapy alone [19]. A paper by Chung *et al* showed that higher doses of radiation (ie. intensity-modulate radiation therapy, or IMRT) corresponded to increased 1 year survival and progression-free survival with no significant increase in short or long-term side effects [20]. Upon initial analysis of our study data, we found that patients undergoing neoadjuvant radiotherapy prior to surgery had smaller tumors and less positive lymph nodes on pathologic staging compared with those undergoing

surgery alone. This suggests that neoadjuvant therapy successfully worked to downstage the tumors prior to surgical re-section. Although this effect could be confounded by the substantial difference in baseline demographic data between the two study groups, these results are nearly identical to those found in similarly designed NSQIP studies comparing neoadjuvant chemoradiation to surgery alone [9].

When examining our two primary outcome variables, we found a statistically significant increase in total operative time and perioperative transfusion requirements among patients receiving neoadjuvant radiation therapy compared to just surgery alone. This is the first time that such associations have been reported using multivariable analysis with patients receiving only neoadjuvant radiotherapy (vs neoadjuvant radiotherapy and/or chemotherapy). An analysis of 2005-2010 NSQIP data from Cho *et al* found similar results, but with bi-variable analysis only [14]. Similarly, a study using NSQIP data from 2014 to 2015 showed that the perioperative transfusion requirement rate among patients receiving neoadjuvant therapy (chemotherapy and/or radiotherapy) was significantly higher than the rate in patients who progressed directly to surgery [21]. In 2021, Krell *et al* showed that (with propensity score matching) there were increased total operative times and more frequent perioperative blood transfusions among those receiving neoadjuvant therapy (chemotherapy and/or radiotherapy) prior to surgery compared to those undergoing surgery alone [22].

Previously, it has been suggested that these differences in perioperative blood transfusions and total operative time are secondary to an increase in the number of borderline resectable cancers in the neoadjuvant therapy groups [14]. By definition, these tumors involve major blood vessels and usually require more complex dissections when compared to lower stage tumors. While the increased number of vascular resections within our neoadjuvant therapy group supports this conclusion, an alternative explanation may be that neoadjuvant radiotherapy itself impacts the complexity of the eventual surgical resection. Histologic evaluation of pancreatic tumors before and after neoadjuvant chemoradiation has shown a significant increase in the ratio of fibrosis to neoplastic cells, indicating a change in the tissue character following neoadjuvant

therapy <sup>[23]</sup>. While such fibrosis has been theorized to be protective against post-operative complications like pancreatic fistulae formation, its distortional effect on classic tissue planes may make the surgery itself more difficult <sup>[24]</sup>. It is important for the operating surgeon to keep this in mind, as it may impact both the procedure type (ie open *vs* minimally invasive) and the expected post-operative complications.

Overall, the 30-day post-operative complication and morbidity rates were similar between both study groups. Of the variables that were analyzed using multivariable regression, only organ space infections and pancreatic fistula rates were significantly different between the two study groups. Numerous studies have detailed the decreased rate of both variables in patients receiving neoadjuvant therapy, suggesting that neoadjuvant radiotherapy may have a small positive effect on short term post-operative morbidity <sup>[9,10,14,21,25]</sup>.

Although the data provided in this study lends credence to the safety and efficacy of neoadjuvant radiotherapy, there are some limitations to keep in mind. Data regarding the specific details of neoadjuvant radiotherapy regimen used (duration, intensity, timing prior to surgery) is not available within the NSQIP database, making it impossible to account for related confounding factors in our data analysis. Additionally, NSQIP only collects data on post-operative outcomes that occur within 30 days of the index operation, making the results of this study difficult to extrapolate over a longer-term period. Facility and surgeon data are also not reported in NSQIP, which again may represent confounding factors that our analysis did not consider. Finally, it is impossible to determine whether a patient's tumor is resectable or borderline resectable (per NCCN guidelines) based on the information reported in NSQIP. As surgeries may be more difficult in borderline resectable patients, this represents a further confounding factor that could not be completely controlled for.

## **CONCLUSION**

The results of this study contribute to the notion that neoadjuvant radiotherapy is both safe and effective to use prior to a pancreaticoduodenectomy for pancreatic

adenocarcinoma. The study does, however, suggest that adverse intraoperative outcomes like total operative time and perioperative transfusion requirements may be increased among patients receiving surgery for cancer resection after neoadjuvant radiotherapy. Surgeons are encouraged to keep in mind the potential positive and negative effects that neoadjuvant radiotherapy has on the complexity of the eventual surgery when it is performed.

## **ARTICLE HIGHLIGHTS**

### ***Research background***

**1** Pancreatic adenocarcinoma today represents the fourth most common cause of cancer-related death in the United States. In addition to neoadjuvant chemotherapy, neoadjuvant radiotherapy may improve negative margin resection rates. This study seeks to investigate the safety and efficacy of neoadjuvant radiotherapy in patients with pancreatic adenocarcinoma.

### ***Research motivation***

By better clarifying the benefits and drawbacks that are associated with neoadjuvant radiotherapy administration in patients with pancreatic adenocarcinoma, practitioners can make informed decisions regarding its use.

### ***Research objectives***

The primary objective of the study was to investigate the effect that neoadjuvant radiotherapy has on both intra-operative and 30-day postoperative morbidities in patients with pancreatic adenocarcinoma.

### ***Research methods***

Using 2015-2019 data from the National Surgical Quality Improvement Program data set, we divided **1** pancreatic adenocarcinoma patients into two groups based on neoadjuvant radiotherapy status. We then performed univariable and multivariable

analysis **to** identify differences in baseline characteristics and outcomes between the two groups.

### ***Research results***

When compared to patients with pancreatic adenocarcinoma who underwent surgical resection alone, patients who underwent neoadjuvant radiotherapy were more likely to have longer surgeries and higher perioperative blood loss. The neoadjuvant radiotherapy patients were also less likely to have organ space infections and pancreatic fistulae formation.

### ***Research conclusions***

Neoadjuvant radiotherapy has significant effects on intraoperative and 30-day postoperative morbidity in patients with pancreatic adenocarcinoma. It may make eventual surgical resection of the cancer more complex.

### ***Research perspectives***

Future research should focus on finding new methods that work to minimize the negative side effects associated with neoadjuvant radiotherapy in patients with pancreatic adenocarcinoma.

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