

ROUND 1

Reviewer 1 Comments:

The authors carefully analyzed the data of patients listed in the 2015-2019 NSQIP data set who received a pancreaticoduodenectomy for pancreatic adenocarcinoma. Two groups were formed based off neoadjuvant radiotherapy status. I think the conclusions drawn from this grouping are not in line with the current clinical treatment background. Neoadjuvant chemotherapy has become the treatment of choice for borderline resectable pancreatic cancer and has begun to be used in patients with resectable pancreatic cancer who may have a poor prognosis. I recommend that the control cohort be neoadjuvant chemotherapy patients.

Answer: We thank the reviewer for this recommendation. Making the control group patients who receive neoadjuvant chemotherapy would change the scope of the paper, making it address the question of whether neoadjuvant radiotherapy results in better or worse outcomes than neoadjuvant chemotherapy. Our goal for this analysis was instead to isolate outcomes associated with the administration of radiotherapy, and identify if its use is safe and effective for patients with pancreatic adenocarcinoma. We purposefully avoided comparative analysis regarding modalities of neoadjuvant therapy, because we felt that this would detract from the purpose of the study.

In addition to the above mentioned, there are two other questions. 1. The intraoperative difficulty of borderline resectable pancreatic cancer was significantly greater than that of resectable pancreatic cancer. There was no subgroup analysis for this in the two cohorts, and the results would be biased.

The study did not directly compare the resection of borderline resectable pancreatic adenocarcinoma to resectable pancreatic adenocarcinoma. Although the reviewer is correct in implying that neoadjuvant therapy is usually used for borderline resectable pancreatic adenocarcinoma, we did not specifically separate the two study groups based on whether the patients had borderline-resectable pancreatic adenocarcinoma or not. Instead, the two study groups were based on whether or not neoadjuvant radiotherapy was used.

It is a reasonable inference (but not confirmed in the analysis) that the neoadjuvant radiotherapy group would have more borderline resectable patients in it than the surgery alone group. It is also reasonable to say that surgically treating borderline resectable pancreatic adenocarcinoma is "harder" (ie potentially longer operative times and higher intraoperative bloodloss) than surgically treating resectable pancreatic adenocarcinoma, regardless of the use of neoadjuvant therapy. If we understand the reviewers comment correctly, he/she is stating that a discrepancy in the number of borderline-resectable cases in each study group may be confounding our data. This is a reasonable conclusion. The nature of the NISQIP dataset is such that it is impossible to discern whether a patient has borderline-resectable pancreatic adenocarcinoma or not. We tried to combat this confounding effect in our multivariable analysis, by controlling for "resection of artery or vein" an "T-stage, N-stage" in our model. The inability

to completely control for the effect that borderline-resectable pancreatic cancer has on the difficulty of the surgery is a limitation of the study. The manuscript has been updated to reflect this limitation.

2. In “introduction” part, there mentioned “Despite the purported benefits, neoadjuvant therapy is still regarded with caution and its use remains low in the United States[13]”. I believe the original article refers to the current status of neoadjuvant therapy in resectable pancreatic cancer.

Taken directly from the cited article, “Current guidelines state that either immediate surgical resection or NT [neoadjuvant therapy] followed by surgical resection can be considered but utilization of NT for PDAC [pancreatic ductal adenocarcinoma] in the United States remains low despite the theoretical and empiric advantages of NT”. The statement made in our manuscript reflects what was stated in the cited article. Both the cited article and our manuscript indicate that neoadjuvant therapy use is limited for all pancreatic adenocarcinoma, and not just for resectable pancreatic adenocarcinoma.

Reviewer 2 Comments:

The authors reported the association between neoadjuvant radiotherapy and 30-day morbidity and mortality outcomes among patients receiving a pancreaticoduodenectomy for pancreatic adenocarcinoma, compared to surgical resection alone. This study is the first time that such associations have been reported using multivariable analysis with patients receiving only neoadjuvant radiotherapy. It was found a statistically significant increase in total operative time and perioperative transfusion requirements among patients receiving neoadjuvant radiation therapy compared to just surgery alone. Their findings are consistent with those of previous similar studies. Based on the discussion provided, here are some suggestions for further discussion or analysis: 1. The dose of radiotherapy was not mentioned in this study. I speculate that different doses of radiation may affect the outcome of the treatment.

The reviewer is correct; the doses of radiotherapy may impact the outcomes, but this data is not available in the NISQIP database and is therefore impossible to control for.

2. Compared with patients undergoing surgery without radiotherapy, patients undergoing neoadjuvant radiotherapy were more likely to be younger, female, non-Hispanic white, diabetic, and of normal body weight, and more likely to have a lower T-stage, a lower N-stage, receive an elective surgery, have a higher wound class, etc. Further study is warranted to determine whether these factors may affect the occurrence of organ space infection and pancreatic fistula. Therefore, I suggest that multivariable regression analysis should be

carried out with organ space infection rate and pancreatic fistula rate as dependent variables, including age, gender, ethnicity, diabetes status and weight status, T stage, N stage, wound grade, pancreatic duct size, and preoperative radiotherapy as independent variables. This analysis is necessary to confirm that direct surgery is an independent risk factor for organ space infection and pancreatic fistula.

In our analysis, we did perform multivariable regression analysis to isolate the effect that radiotherapy had on pancreatic fistula rates and organ space infection rates. In the footnotes for Table 4, the odds ratio derived for both the organ space infections and the pancreatic fistulas controlled for differences in age, race, BMI, diabetes, steroids, wound class, ASA class, surgical approach, resection of artery or vein. While we could have adjusted for other mentioned variables like T-stage, N-stage, weight, etc., we felt that this was too extensive for a subgroup analysis.

3. The term "the two study groups" used in this article can easily be understood as two different research institutions conducting this study, and it is recommended to use "two groups of cases" or other more appropriate names.

We feel that "two study groups" is standard nomenclature to describe two different subgroups being compared in an analysis. We make it clear that only one research group conducted this study. The recommended "two groups of cases" is rarely used in the literature.

4. In Discussion, second paragraph, lines 7-10, "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 lower than the rate in patients who progressed directly to surgery [21]." Reference [21], Czosnyka et al. (2017) reported "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). <https://doi.org/10.1016/j.hpb.2017.07.001>

This is an accurate statement. The manuscript was adjusted to properly reflect the findings of the cited work.

ROUND 2

Revision #2

Revision #1 Comment and response

Comment: Compared with patients undergoing surgery without radiotherapy, patients undergoing neoadjuvant radiotherapy were more likely to be younger, female, non-Hispanic white, diabetic, and of normal body weight, and more likely to have a lower T-stage, a lower N-stage, receive an elective surgery, have a higher wound class, etc. Further study is warranted to determine whether these factors may affect the occurrence of organ space infection and pancreatic fistula. Therefore, I suggest that multivariable regression analysis should be carried out with organ space infection rate and pancreatic fistula rate as dependent variables, including age, gender, ethnicity, diabetes status and weight status, T stage, N stage, wound grade, pancreatic duct size, and preoperative radiotherapy as independent variables. This analysis is necessary to confirm that direct surgery is an independent risk factor for organ space infection and pancreatic fistula.

Response: *In our analysis, we did perform multivariable regression analysis to isolate the effect that radiotherapy had on pancreatic fistula rates and organ space infection rates. In the footnotes for Table 4, the odds ratio derived for both the organ space infections and the pancreatic fistulas controlled for differences in age, race, BMI, diabetes, steroids, wound class, ASA class, surgical approach, resection of artery or vein. While we could have adjusted for other mentioned variables like T-stage, N-stage, weight, etc., we felt that this was too extensive for a subgroup analysis.*

Revision #2 Comment and response

Comment: The author avoids my serious concerns raised, "comment 2". The response does not address my doubts.

Response: *We apologize for not adequately addressing the reviewer's concerns. We did not state, nor did we mean to imply, that that direct surgery was an independent risk factor for organ space infection and pancreatic fistula formation. We merely stated that, when controlling for differences in age, race, BMI, diabetes, steroids, wound class, ASA class, surgical approach, and resection of artery or vein, patients undergoing neoadjuvant radiotherapy were statistically less likely to acquire an organ space infection or a pancreatic fistula when compared with patients who underwent surgery alone. While the reviewer is correct that additional analysis would be required to prove that direct surgery is an independent risk factor for organ space infection and pancreatic fistula formation, we chose not to perform this analysis as we felt that this was beyond the scope of the manuscript. We wanted our manuscript to specifically highlight the differences in 30-day morbidities between patients who received neoadjuvant radiotherapy prior to surgery, compared with patients who just received surgery alone. We did not seek to identify independent risk factors for organ space infections and pancreatic fistula formation.*