**Peer Review File**

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**Response to Reviewer A**

**Comment 1: There is a typo in both the abstract and results section for this sentence "that received chemotherapy and 298 (42.3%) that did not receive chemotherapy"**
Thank you for noticing this typo. These sentences have now been amended.
Changes in the text: On page 3, lines 12-15, the previous sentence has been replaced by the following: "There were 698 patients with metastatic PASC available for analysis, including 400 patients (57.3%) who received chemotherapy and 298 patients (42.3%) who did not receive chemotherapy." Similarly, on page 6, lines 18-20, the sentence now reads: "After removing 31 patients who had missing data on chemotherapy, 698 patients were available for analysis: 400 patients (57.3%) who received chemotherapy and 298 patients (42.3%) who did not receive chemotherapy (Table 1)."

**Comment 2: The authors used the Charlson Deyo Comorbidity Index to characterize patients' comorbidity burden but proceed to refer to patients with ANY comorbidities as those with "major comorbidities"? Is this a fair characterization of all comorbidities captured in this index? Is a more detailed breakdown of which specific comorbidities patients had available?**
Thank you for your insightful comment.
Changes in the text: We have changed major comorbidities" to "any comorbidities" (page 3, line 17; page 7, line 4; page 7 line 16).
The Charlson Comorbidity Index includes myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular accident, COPD, dementia, connective tissue disease, peptic ulcer disease, liver disease, diabetes, hemiplegia, leukemia, lymphoma, solid tumor, and AIDS, as well as age. The NCDB does not provide individual breakdown, but rather provides the Charlson Devo Comorbidity Index which is validated to predict mortality. (Quan, 2011; Radanovic, 2013).

**Comment 3: Minor: would report p-values less than 0.001 as $p < 0.001$ vs "$p = <0.001$"**
Thank you for noticing this.
Changes in the text: We have made this correction (page 3, line 15 ,17, 19; page 7, line; 3, 4, 5, 16)

**Comment 4: Additional details on how key study variables are collected would be beneficial to the reader. For example, how is receipt of chemotherapy operationalized? Is it limited to some timeframe soon after the initial diagnosis per NCDB rules? Similarly, are income and insurance status evaluated when patients are first diagnosed and enter the database?**
Thank you for drawing our attention to these omissions. As soon as a patient received a single dose of chemotherapy, they were considered to have received chemotherapy. It is not limited to some timeframe soon after the initial diagnosis. Similarly, median household income and insurance status were taken from the time of diagnosis. All of this is important to note and the manuscript has been updated to reflect this information in the method section.
Changes in text: We have added the following sentence: "Patients were then categorized according to receipt of chemotherapy; as soon as a patient received a single dose of chemotherapy, they were considered to have received chemotherapy (page 5, line 18). We have also added the following sentence: "These variables were evaluated at the time of diagnosis" (page 6, line 1).

**Comment 5: Figure 1 - The Y-axis title in Figure 1 should be modified. Cumulative survival is not the statistic that is being displayed in the Kaplan-Meier curve.**
Thank you for drawing our attention to this error.
Changes in the text: Figure 1 has been changed such that the y-axis is now labeled "overall survival".

**Comment 6: There may other limitations to consider based on how the data are collected. In particular, immortal time bias may be of concern since those who receive treatment need to survive long enough to receive treatment. Is there any way to evaluate survival from the start of treatment for those who received chemotherapy? Additionally, given that age what a significant predictor of the receipt of chemotherapy do the authors believe that this is driven by physicians deciding there are no feasible treatment options or patients opting to forgo treatment given their age?**
Thank you for this insightful point. This is extremely important, especially in adjuvant studies where patients must survive the postoperative period in order to get chemotherapy. As for the metastatic setting, this may not be as impactful but is definitely a possibility as very nicely raised by the reviewer. In our experience, we have accounted for this bias in the adjuvant studies by excluding patients who had died within 30 days. However, in this manuscript excluding these patients would lead to a large drop out because of the very short survival in our population. Therefore, we approached it differently and we calculated the median time from starting chemotherapy and subtracted that from the median survival for the chemotherapy group. The median time to initiation of chemotherapy was 25 days (0.8 months). If overall survival was measured from the time of initiation of chemotherapy, it would be reduced from 5.3 months to 4.5 months. The 4.5 months is still significantly longer than the 1.5 months found in the group that did not receive chemotherapy.

In response to the reviewer's concern of age: Based on the database, it was not possible to determine if the decision was made by the patient or by the physician. Based on our clinical experience, it is usually a combination of both.
It is certainly possible that age is driving many decisions; however, we have accounted for age as a confounding variable in our analysis. In the Cox model, after adjusting for age, there was still a significant association.
Changes: We added the following sentence to the results section: "median time to initiation of chemotherapy was 25 days (0.8 months)" (page 7, line 1). We have also added the following to the limitations section of the discussion: "Third, the difference in survival could be skewed by immortal time bias. After accounting for time to chemotherapy initiation, there seems to be a persistent association between receipt of chemotherapy and survival" (page 11, lines 1-3).

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**Response to Reviewer B**

**Comment 1: This manuscript is an interesting compilation of data from the National Cancer Data Base on the rare pancreatic cancer PASC. As PASC is a rare cancer, the fact that it is a retrospective report would not be considered a problem. The focus of the manuscript may be to provide strategy options for what to do to improve survival for PASC, but it was limited to the obvious benefits of chemotherapy with a poor prognosis and listed its menu of regimens.**
**The manuscript also lacked important information including each imaging of PASC and metastasis lesion, the details of pathology, performance status, chemotherapy regimen details, and the presence or absence of radiation therapy. The manuscript fails to verify prognosis based on such information.**

Thank you for your excellent insight in noting that site of metastasis should be included. We reviewed the data set again and found that this information was available. This information was added.
Changes in text: Below is an abridged version of Table 1 with the sites of metastasis added.

| | Chemotherapy | | |
|---|---|---|---|
| Variable | Yes (n = 400) | No (n = 298) | p -value |
| Site of metastasis | | | |
| Bone | 10 (4.2%) | 11 (6.5%) | 0.524 |
| Brain | 0 (0.0%) | 2 (1.2%) | 0.195 |
| Liver | 200 (83.7%) | 135 (80.4%) | 0.557 |
| Lung | 33 (13.8%) | 30 (17.9%) | 0.95 |

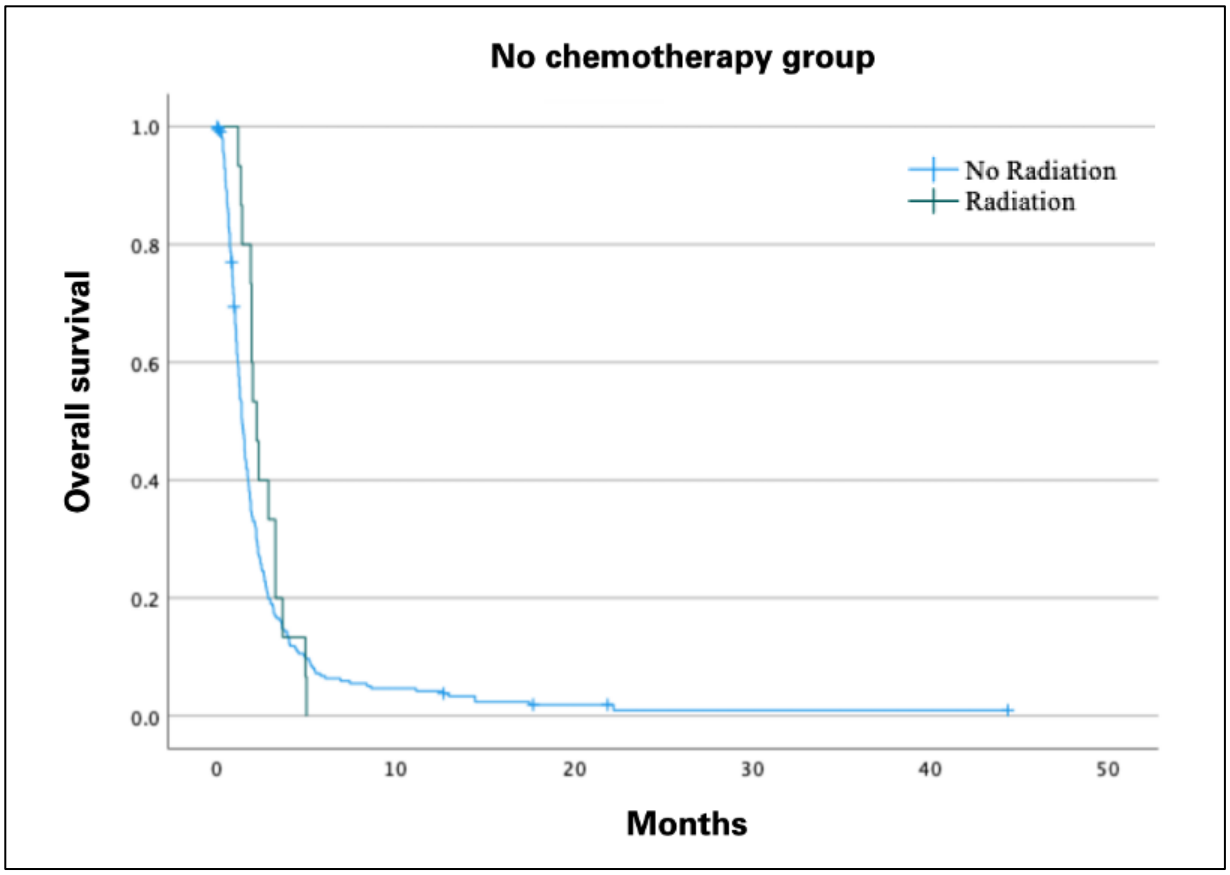
**Comment 2b: The manuscript also lacked important information including each imaging of PASC and metastasis lesion, the details of pathology, performance status, chemotherapy regimen details, and the presence or absence of radiation therapy. The manuscript fails to verify prognosis based on such information.**
Thank you for your response. As pancreatic adenosquamous carcinoma is a rare disease, a national data base was needed. However, there are certainly important drawbacks, as the reviewer recognized. Pathology was confirmed with the SEER histology validation list. We used both the Charlson Deyo Comorbidity Score and age as a proxy for performance status. While we recognize that a direct measurement of performance status would have been preferable, we do not have access to this information. Research by Dobbins and colleagues suggest that these measures are a reasonable surrogate for performance status. We have also added the lack of access to performance status to the limitations of the paper. (Dobbins, 2015, PMID: 26174550).

Changes to the text: We have added the following sentence: Lastly, other important pieces of information, such as patient performance status and specific pathological information, were also missing (page 11, lines 3-5).

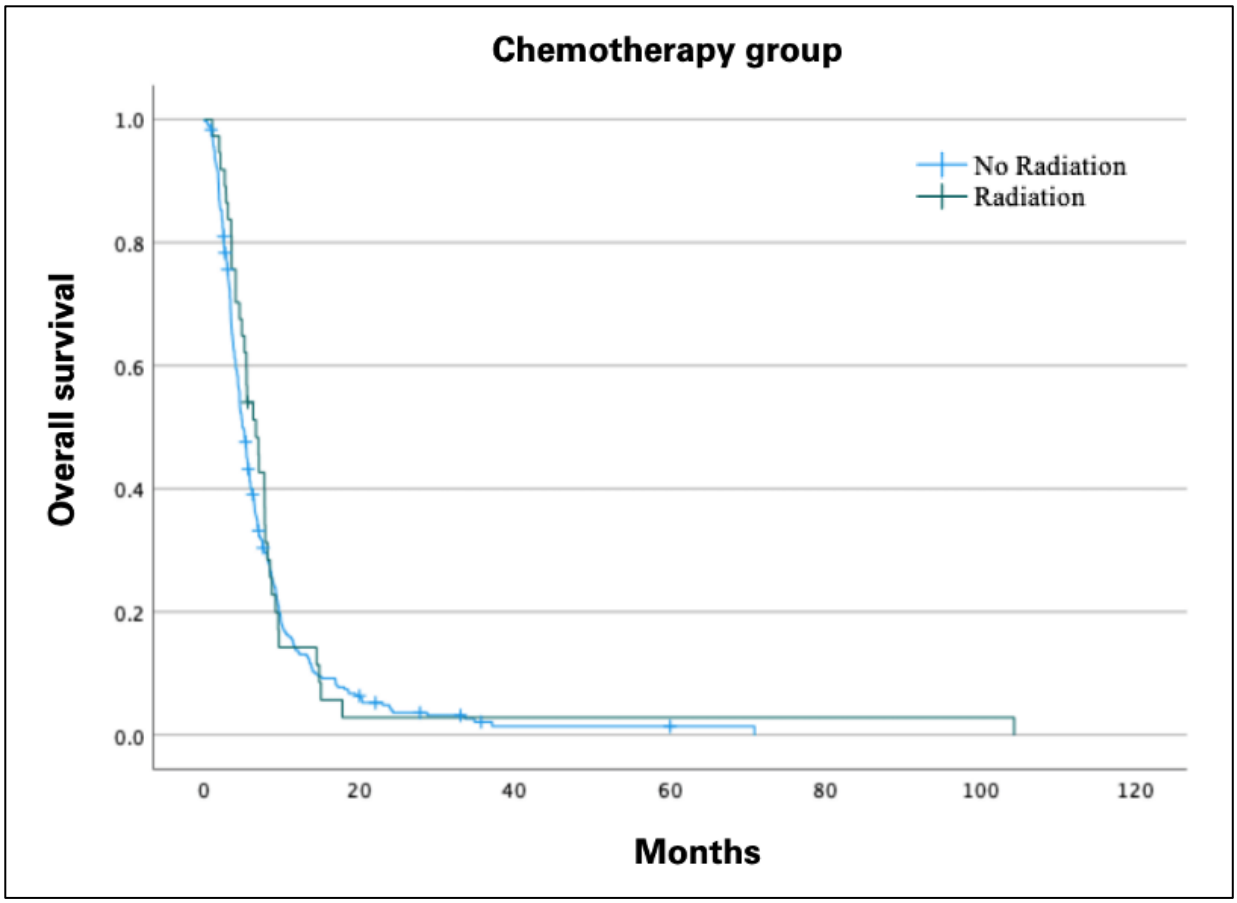
**Comment 2c: The manuscript also lacked important information including each imaging of PASC and metastasis lesion, the details of pathology, performance status, chemotherapy regimen details, and the presence or absence of radiation therapy. The manuscript fails to verify prognosis based on such information.**
We appreciate the reviewer's insight that radiation therapy was not provided. This information was available and was added to the manuscript. We initially did not consider this variable as we believe that radiation has no oncologic role in the treatment of metastatic pancreatic cancer. It could be used in palliation but is unlikely to change overall survival.
Since the reviewer is interested in showing this information, we reanalyzed the data and found that there was no association between radiation and overall survival. This was true for the entire cohort and on subgroup analysis for patients who did and did not receive chemotherapy.
Changes in text: Below is an abridged version of Table 1 with the added presence of absence of radiation.

| | Chemotherapy | | |
|---|---|---|---|
| Variable | Yes (n = 400) | No (n = 298) | p -value |
| Radiation | | | |
| Yes | 41 (10.3%) | 18 (6.0%) | 0.048 |
| No | 359 (89.8%) | 280 (94.0%) | |

We also added the following figures as supplements:




Supplementary figure 1. Kaplan-Meier curves for patients who did not receive chemotherapy and did receive radiation therapy (green) and patients who did not receive chemotherapy and did receive radiation (blue). There was no difference in overall survival between these groups ($p = 0.191$).



Supplementary figure 2. Kaplan-Meier curves for patients who received chemotherapy and did receive radiation therapy (green) and patients who received chemotherapy and did receive radiation (blue). There was no difference in overall survival between these groups (p = 0.595).

**Comment 3: Furthermore, although a menu of chemotherapy regimens is provided, details such as dosage and method of administration are not clear, and the paper has not yet reached the point where it can be used to inform clinical practice.**

Thank you for your comment. Based on your feedback, we reviewed the National Cancer Database and found that while we could not access chemotherapy details, we could access whether the regimen was single agent or multi agent. Changes to text: Whether chemotherapy was single agent or multi-agent was added to the results section. We state: "Among patients who received chemotherapy, 32.8% received a single agent regimen while 60.0% received a multi-agent regimen, 7.2% unknown" (page 7, lines 1-2).

We completely agree that the manuscript is not practice changing, but hypothesis generating. By design, this is a retrospective study on a relatively small dataset for a rare disease that could serve as a starting point for more research into pancreatic adenosquamous cancer rather than a definitive guide to treatment. That's why we were very purposeful in the title and the manuscript not to conclude that there is causal effect between receipt of chemotherapy and improved survival. We just confirmed there is an association after adjusting for potential confounders.

At this moment, clinicians have no good guide for whether chemotherapy is beneficial or not in pancreatic adenosquamous cancer due to lack of randomized trial specifically in this histology. Since this

is a rare disease, it is unlikely that there will be a trial specific to this pathology and as such the current study presents the largest analysis on the topic. With the noted limitations, we hope to convince the reviewer that this manuscript adds value to the literature and fills a gap in knowledge.