Peer Review File

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Reviewer Comments

Reviewer A

Herein the authors present a commentary regarding the article "Association of Adjuvant Chemotherapy in Patients With Resected Pancreatic Adenocarcinoma After Multiagent Neoadjuvant Chemotherapy". The original article is an NCDB study which performed a propensity score matched analysis comparing survival amongst PDAC patients that underwent neoadjuvant chemotherapy alone as compared to those who underwent neoadjuvant chemotherapy followed by adjuvant chemotherapy. Overall, the commentary is well written and the reviewer agrees with the general sentiment. I would offer the following as suggestions to improve the work:

Major comments:

Comment 1: In the final paragraph, the authors present their stance that the presented data, as well as other retrospective analyses in this space, are unable to effectively demonstrate that the addition of adjuvant chemotherapy improves survival over neoadjuvant therapy alone. They cite the selection bias inherent to retrospective studies wherein more fit and potentially more biologically favorable patients go on to receive (and tolerate) the adjuvant chemotherapy regimen. The reviewer would also posit that patients in this NCDB analysis who started adjuvant therapy have an immortal time bias equating to the time to recovery after surgery prior to receiving the first dose of adjuvant therapy. It is unlikely this can be controlled for using the NCDB data.

Reply 1: Thank you for raising this important point. We have amended the manuscript (see page 4, lines 103 – 105)

Changes in the text: "Additionally, there is potentially an immortal time bias for patients receiving adjuvant chemotherapy due to the recovery

period after surgery which would be difficult to control for."

Comment 2: Further, the lack of granular details regarding the regimen employed or the duration employed are quite problematic for an analysis such as this, especially within the context of the NCDB. "Multi-agent chemotherapy" can mean a wide variety of things in PDAC, therefore understanding confounders is difficult. Without an understanding of the duration of treatment, the "dose density" of chemotherapy between these 2 groups is also impossible to appreciate and may confound the findings. It is challenging, if not impossible, to understand why a difference in overall survival exists amongst the two.

Reply 2: Thank you for raising this important point. We have amended the manuscript (see page 4, lines 100 – 103)

Changes in the text: "Information about the specific chemotherapy regimens used was also not available, which introduces a further confounding variable. Future studies will need to control for the specific treatment regimens used, and the cumulative dosages used during a patient's treatment course"

-Minor comments:

Comment 3: Lines 49-50: The improvement in survival in PREOPANC was largely relegated to patients with borderline resectable disease. The subgroup analysis of resectable disease was underpowered and not statistically significant. Would favor diminishing the strength of this conclusion.

Reply 3: Thank you, this sentence has been amended (see page 2, lines 46 – 47)

Changes in the text: "analysis of long-term results suggest that neoadjuvant chemotherapy is beneficial in both resectable and borderline resectable subgroups"

Comment 4: Line 91: typo, should read "limited by"

Reply 4: Thank you, this has been addressed (page 4, line 92)

Changes in the text: “this conclusion is limited by the inherent biases..”

Reviewer B

Well written commentary summarizing current literature and ongoing studies on the benefits of neoadjuvant therapy in PDAC as well as the role of adjuvant chemotherapy in those who have already received neoadjuvant chemotherapy (NAC) as receipt of NAC is becoming common practice even in resectable cases rather than upfront surgery.

Comment 1: Authors properly mentioned the PREOPANC trial as an example to evaluate neoadjuvant chemotherapy in comparison to upfront surgery. I believe the authors made a typing mistake while explaining the PREOPANC trial in line 45 with upfront chemotherapy instead of upfront surgery.

Reply 1: Thank you for pointing out this error, this has been addressed (page 2, line 42)

Changes in the text: “..upfront surgery followed by adjuvant gemcitabine”

Comment 2: In the original article by Sugawara et al., absence of performance status in the NCDB was mentioned as one of the limitations as authors in this commentary also mentioned this as the most notable bias. However, this factor was moderated by including Charlson-Deyo comorbidity index score. One suggestion would be to include postoperative complication rates among those who received and did not receive adjuvant chemotherapy. This information is more readily available in databases such as NCDB and presence of these complications can prevent patients who are otherwise eligible/can benefit from (based on current studies) to receive adjuvant chemotherapy.

Reply 2: Thank you for raising this important point. We have amended the manuscript (page 4, lines 97 – 98).

Changes in the text: “It would be of interest to analyze post-operative complication rates in future studies, to identify any potential impacts on eligibility for adjuvant chemotherapy.”