April 11, 2021

Drs. Ghosh and Tarnawski

Editors-in-Chief, World Journal of Gastroenterology

Re: Editorial Revisions for Manuscript entitled "Neoadjuvant Therapy for Pancreatic Ductal Adenocarcinoma: Opportunities for Personalized Cancer Care"

Dear Drs. Ghosh and Tarnawski,

Thank you for reviewing our manuscript. We believe that the reviewer's comments and the corresponding responses will serve only to strengthen the manuscript. As requested, we have provided a point-by-point response to the reviewer comments below with changes to the manuscript highlighted in yellow. Please do not hesitate to contact us if any additional questions or concerns remain.

Reviewer #1:

Well written review that highlights the potential benefits of neoadjuvant therapy for pancreatic ductal adenocarcinoma also in the light of personalized medicine. The manuscript demonstrates a logical flow and is easy to follow. The authors give an interesting overview about current neoadjuvant therapy approaches, showing novel opportunities for personalized cancer care. However, unfortunately the review overall appears a bit one-sided, as the authors didn´t really address potential risks of NT, that might have to be taken into account. The authors should at least shortly state their opinion about frequently raised concerns like potential toxicity, that might affect perioperative morbidity and even mortality.

We appreciate the reviewer's favorable comments regarding our manuscript and agree that a review on neoadjuvant therapy is not complete without a discussion of disadvantages or challenges. In response, we have added a new paragraph on potential disadvantages which we believe leads to a stronger more balanced manuscript.

These advantages must be carefully weighed against the potential disadvantages of pursuing NT. First, unlike in a surgery-first approach, tissue diagnosis and biliary decompression are uniformly required. These procedures may delay the initiation of treatment and are associated with small, but non-zero, risks. Second, NT is inherently multi-disciplinary and require careful coordination among providers. Third, and most importantly, delivering aggressive chemotherapy and/or radiation prior to surgery can lead to severe toxicity that, in extreme cases, can preclude subsequent surgical resection. Indeed, a systematic review by the Dutch Pancreatic Cancer Group calculated a Grade III or higher toxicity rate of 64% among patients undergoing NT.[19] The recent SWOG S1505 trial of NT for resectable PDAC found that nearly 13% that started NT were

unable to undergo surgery because of performance status decline.[20] Finally, while distant progression while on NT is far more common, a small risk of local progression that leads to unresectability exists. These challenges highlight the importance not only of personalizing treatment decisions regarding NT, but also of emphasizing research that improves the delivery of NT for patients with localized PDAC.

Sincerely,

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