Peer Review File

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Reviewer 1

Comment 1: In page 7, Ca 19-9 should be corrected to CA 19-9 and long form is needed.

Reply 1: Thank you for the recommendation, we agree and have replaced Ca 19-9 with “Cancer Antigen 19-9”

2) It would be better to add long form in IMRT in page 8 and OAR in page 9, although OAR was explained in page 11.

Reply 2: Thank you for catching this. These have been replaced and fixed with IMRT added earlier in the text with long form, and the long form for OAR moved to page 9 only.

Reviewer 2

Borderline Resectable Pancreatic Cancer: A review of recent literature and clinical practice

By authors from the Department of Radiation Medicine

The authors attempt to provide a review of the literature for borderline resectable pancreatic cancer. Unfortunately, there are a number of significant errors in their definition and presentation starting with the abstract.

First, the authors attempt to define borderline resectable cancer as “contact” with vascular structures. This unfortunately is not correct there are well defined five different criteria that being either societal based, AJCC based, or European based very specific definitions of vascular involvement in which vascular involvement. Borderline resectable disease has never been defined by unfavorable tumor biology or even their “subclinical metastatic disease” this is a terminology that has never been linked to borderline resectable disease and they're utilizing it as a definition is wrong. Lastly borderline resectable disease has never been linked to a patient's poor performance status and thus again the authors are overreaching in their definition of what is borderline resectable. Also, within the abstract the data around chemo radiation therapy and stereotactic body radiation therapy for borderline resectable disease has not indeed been proven. There have been unfortunately numerous trials the most recent within the United States that was halted for futile resection percentages. Their abstract unfortunately is clearly bias and most importantly not clear and honest in regards to the recent literature over the last five to seven years in the management of borderline resectable disease. This manuscript unfortunately appears to be really a review of the radiation literature in the management of borderline resectable pancreatic cancer. If that is the true intent of the authors, then that is fine but they are ultimately misleading a reader with their title. Revision of the title and more importantly clearly stating the goals of the manuscript that this is

focused on radiation therapy is at a minimum way to clear this bias that is demonstrated within the abstract.

Reply to Reviewer 2: Thank you for your comments. This was meant to be a review of radiation therapy literature and the title has now been updated to reflect this better. Regarding the definition of BRPC, we have provided the reference from an international consensus definition published in 2018 and well cited 292 times since its publication. We agree that vascular involvement is well known and primarily used but the additional aspects of biology and tumor condition are important to highlight as they impact outcomes and patient tolerability to treatment approaches.

Reviewer 3 –
Comment 1: Clean-up the sentence on lines 76-79

Reply 1: Thank you for the recommendation. The text in these lines has been clarified.
Comment 2: Line 82-84: expand on the arms of RTOG 0848. There are results published- would mention those

Reply 2: Thank you for the recommendation, we have now expanded on the arms of the trial including the available published results.

Comment 3: Lines 87-88: put some data behind "margin positive resections have been associated with poorer outcomes"

Reply 3: Thank you, we have now added data from Generlich et al. and Fatima et al. on survival outcomes based on resection status in line 96-99.

Comment 4: Line 93-96: I would list of the guidelines in more detail- what vasculature involvement specifically etc

Reply 4: Thank you for the recommendation, specific information regarding arterial and venous involvement is now added in the text.

Comment 5: Lines 104: mention better adherence with neoadjuvant chemo vs adjuvant

Reply 5: Thank you for the recommendation, we do agree that a benefit of neoadjuvant therapy is better adherence to chemotherapy and this was noted as maximization of chemotherapy. To better highlight it, we have added the word adherence as well.

Comment 6: Line 105: Would say "neoadjuvant treatment provides a window for occult metastases to declare themselves"

Reply 6: Thank you, this change was done.

Comment 7: Line 107: move the references to the end of the sentence

Reply 7: Thank you, reference has been moved as recommended.

Comment 8: Line 128: what is the definition of persistent vascular involvement- any disease? What was the RT dose?

Reply 8: Thank you, we have added the additional information requested. Persistent vascular involvement was not defined specifically but clearly resectable patients that had no vascular involvement were given 25Gy in 5 fractions and the rest were given 50.4Gy in 28 fractions for persistent vascular involvement.

Comment 9: For the South Korean study, add chemotherapy adherence/compliance data, if available

Reply 9: Thank you for the suggestion, we have now added some numerical data from the study that highlights the adherence/ completion of therapy rates.

Comment 10: There is a new study available looking at dose to elective volume (PMID: 36119519)

Reply 10: Thank you for this additional data highlighting vasculature dose threshold using a specified vasculature clinical target volume. While we appreciate the findings and potential implications, the heterogeneity of the data presented using standard 7 different RT doses, and a mixture of chemotherapy use with only 12 local failures highlights data that needs further validation. It currently does not fit the elective volume definition for nodal coverage and as such we have for now chosen not to include it at this time.