Peer Review File

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Reviewer A

This is a well-written, but small study of 9 patients with locally advanced pancreatic cancer given neoadjuvant chemotherapy with Erlotinib and gemcitabine, followed by proton therapy in 28 sessions if no metastases were identified. Unfortunately, only 1/3 of patients were then able to tolerate 4 cycles of capctabime and oxaliplatin.

This is essentially a proof of concept paper, and I agree that the findings are somewhat promising. I only have a few comments.

1. As this is a journal geared towards surgeons, could the authors briefly add why proton therapy may have advantages when compared to standard external beam radiation therapy.
Reply 1: We have added additional information on proton therapy on page 4, line 76, 77.
Changes in text: This is due to the Bragg peak of proton beam therapy which could allow reduced dose to nearby normal tissues.

2. Assuming the authors are pleased with their results, could they let the reader know what their next steps plan to be? Do they wish to do larger trials with this regimen? The term locally advanced pancreatic cancer includes unresectable and borderline resectable patients. Would it make sense to look at only borderline resectable patients in future studies? If not, what endpoints do you plan on studying, and why? I wonder if adding clearly unresectable patients will confound future results for surgeons.
Reply 2: We would wish to do larger trials with more current systemic therapy regimens while still utilizing proton beam radiation therapy as we believe this provides a worthy toxicity improvement in this patient population. We are currently enrolling resectable pancreatic cancer patients in an ongoing protocol and in the future hope to do more studies on locally advanced pancreatic cancer. And another valid point about combining unresectable and borderline resettable patients. We have added to the limitation section of the discussion page 15 lines 287-291.
Changes in text: This trial also combined both unresectable and borderline resectable patients which could potentially complicate the interpretation of the results. Future studies should aim to divide this heterogeneous group to help determine which patient group would be best fit for a particular treatment paradigm.

3. Seeing as only 1/3 of patients actually tolerated the Capox at the end, how do the authors hope to get better compliance? Do they plan on eliminating this part of the regimen altogether?
Reply 3: This is a very valid point and is why many regimens are now moving more of the therapy into the neoadjuvant setting as compared to the adjuvant. With newer systemic therapy options such as promising results shown with FOLFIRINOX, this more aggressive neoadjuvant approach has shown promise. Additional comments made on this thought on page 15 lines 279-

281.
Changes in text: Adjuvant CapOx was not as well tolerated in this study with only one third of patients tolerating the regimen which is why there is also a rationale to moving more of the systemic therapy into the neoadjuvant setting.

4. Are there any Personalized genomic tests being developed to better determine which patients with pancreatic cancer would benefit from Erlotinib? Like there is with lung cancer?
Reply 4: There was an interest in developing genomic tests to better determine which patients would benefit from Erlotinib however due to funding difficulties we were unable to perform this analysis. We have banked tissue and would like to perform this analysis in the future when we are able to obtain appropriate funding. Additional text added on page 12 lines 220-222.
Changes in text: Additionally with personalized genomic testing becoming more widely available, future studies will hopefully be able to determine the best patient groups who may benefit from the addition of targeted therapies.

https://www.fda.gov/news-events/press-announcements/fda-approves-first-blood-test-detect-gene-mutation-associated-non-small-cell-lung-cancer#:~:text=The%20U.S.%20Food%20and%20Drug,cancer%20drug%20Tarceva%20(erlotinib).

Reviewer B

This is a small prospective, single arm trial evaluating locally advanced pancreatic carcinoma treated with gemcitabine+erlotinib followed by proton radiotherapy with concurrent xeloda followed by XELOX. The study aimed to compare overall survival to a historical prospective study, RTOG 9812. Unfortunately, the study closed early due to poor accrual likely due to outcomes from larger trials indicating no benefit of erlotinib in this setting and improved chemotherapeutic agents becoming available. The study planned to enroll 39 patients however enrolled only 9 before closure. Among those 9, only 7 completed the full course of chemoRT. Ultimately, the value of this study is additional prospective data with proton radiation and chemotherapy for this patient population. However, due to the limited patient numbers, that endpoint is only minimally valuable. The authors should address the following to improve the text of the manuscript:

1) explain the rationale for selecting RTOG 9812 as the comparison cohort
Reply 1: RTOG 9812 was chosen as it showed promising results in unresetable pancreatic patients as compared to historical studies and was the basis for ongoing RTOG trials at the time of the trial onset, Details added on page 9 lines 163-165.
Changes in text: This comparison was chosen as this phase II study showed promising survival in unresectable pancreatic patients as compared to previous historical studies.

2) in materials and methods and throughout, change "Gy" to "GyRBE" or "CGE"
Reply 2: Gy was chosen throughout the manuscript for reader convenience. As many of the

readers of the journal are surgeons and oncologists, we determine that using GyRBE or CGE may complicate understanding of the radiation dosing scheme.
Changes in text: none

3) materials and methods, radiotherapy section- “There was no prophylactic elective nodal irradiation”…" the ter“s "prophylac”ic" a“d "elect”ve" are redundant
Reply 3: The word prophylactic was removed from the section.
Changes in text: page 7 line 135

4) please provide more details for radiation planning and delivery- e.g. beam arrangements, motion management techniques
Reply 4: Additional radiation planning details were added to page 7 lines 136-141.
Changes in text: Number of beams along with beam choice and motion management information was added.

5) materials and methods, toxicity related therapy adjustment section- this section appears to be pasted from the study protocol and is not very relevant nor is it written in the correct verb tense.
Reply 5: Verb tense was corrected and adjusted to be more concise.
Changes in text: Page 8 lines 156-158.

6) materials and methods, statistical analysis and end points- same as #5 above- the verb tense is pasted from the protocol and should be revised to match the tense of the manuscript
Reply 6: Verb tense corrected and adjusted to be more concise.
Changes in text: Page 8 lines 156-158, page 9 lines 176-180.

7) results- please explain what "not evaluable" means for the confidence interval for OS and PFS.
Reply 6: Term changed to not reached.
Changes in text: Page 10 lines 196-197.

8) results- why did only 2 of 3 patients who had resectable disease undergo surgery?
Reply 8: One patient declined post-RT systemic therapy and resection.
Changes in text: Page 10 line 199-200.

9) discussion- the reference to the GITSG trial appears to use the wrong reference..i believe it should be PMID 2898536
Reply 9: Refernce corrected
Changes in text: bibliography updated

10) discussion- in the section describing the LAP07 trial- you should discuss the findings of the role of erlotinib in this trial in the context of your own study
Reply 10: Lack of benefit of erlotinib in maintenance setting added to manuscript.

Change in text: Page 14, lines 273-276.

11) In the discussion section about "carefully selected group of patients..." (line 266), I would add a few lines about the numerous trials (resectable and unresectable disease) showing improved local control with the use of RT (e.g. RTOG 9704, LAP07, etc)
Reply 11: The LAP07 study is discussed earlier in the manuscript. Additionally, the benefit in R0 resection is written earlier in the paragraph regarding the Alliance study. Improved survival is also discussed earlier in the discussion with the GITSG trial. In an effort to keep the paragraph slightly more concise, we decided not to rediscuss these points in this paragraph.
Changes in text: none

Reviewer C

This is a well written paper describing the outcomes for a group of 9 patients with locally advanced pancreatic cancer treated with an innovative regimen of Gemcitabine and Erlotinib and proton therapy followed by capecitabine and oxaliplatin. No changes or edits to suggest.