Peer review file

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Reviewer A

This is a retrospective observational study summarizing clinical outcomes and associated factors in 32 patients treated with trimodality therapy for Pancoast tumors at provincial multi-center in British Columbia, Canada. It was suggested that complete resection of the tumor after chemoradiation therapy may be highly effective in some patients. However, univariate analysis showed that the presence of pathologic complete response after chemoradiotherapy was not significantly associated with overall survival and disease-free survival.

It is interesting that the authors reported better outcomes compared with previous reports in the treatment of Pancoast tumors, which are relatively rare and often difficult to treat. This study is considered to be a valuable case series because of the uniqueness that the efficacy of the treatment regimen was suggested in a cohort of patients underwent a homogeneous treatment approach. However, the report is not highly novel compared to similar reports in the past, and some additional data would be desirable.

There are some improvements that can be made to this study in order to make it a more informative report.

Comment 1:
The contribution of pathologic complete response to survival is extremely important information and will be an important topic in this study.
Although the presence or absence of pathologic complete response was not significantly associated with survival in univariate analysis, the authors attributed the cause to the small number of cases.
While statistical power is certainly dependent on sample size, I recommend adding data adjusted for confounders to clarify differences from previous studies.
I believe that the addition of this data will clearly differentiate the outcome from

previous studies and make your discussion of the importance of pathological response more convincing.
For example, I can propose to perform a multivariate analysis using the Cox proportional hazard model as follows.
The outcome is defined as the presence or absence of recurrence.
Since there are 14 recurrences for 32 cases, there are at most three explanatory variables that can be included in the Cox hazard model.
Since one of them is the presence or absence of pathological complete response for the primary endpoint, confounders that can be included in the Cox model are two factors.
Ideally, all confounders should be included in the model, but this is not possible due to the small number of cases.
Using a Cox model adjusted for two of the various confounders that may affect recurrence, we can evaluate the adjusted hazard ratio.
For example, the following Cox models are considered, Cox model adjusted for age and gender, and Cox model adjusted for clinical stage (I-II and III) and histologic types (adenocarcinoma and others).
I do not know if significant differences will be detected in these models, but the results remove the effect of confounders compared to univariate analysis.

Reply 1: Our statistician ran Cox proportional hazards models based on Reviewer A's suggestions using three variables per model (pathological response plus two potential confounding factors). We found that pathological response remained a non-significant predictor of survival even when accounting for age, gender, clinical stage, and histology.

Changes in the text: Statistical methods were described in the main text under the "Statistical analysis" Methods subsection (page 4, lines 20-24). We added our finding that pathological response remained non-significant to the "Pathological response" Results subsection (page 7, lines 14-15). We also presented the above data in full as a table (Table 5, page 18).

Comment 2: There is a description of the results that showed no significant

difference in 2-year, 5-year, and 10-year overall and disease-free survival between the pathologic incomplete response group and the complete response group.
These results are important in your study. Therefore, it is recommended that the results are presented as a table.

Reply 2: We have presented the differences in survival based on pathological response as a table as per above suggestion.

Changes in the text: We have moved the full description of the above results to the "Pathological response" Results subsection of the main text (page 7, lines 6-14) as well as presented it as a table (Table 4, page 17).

Comment 3: Although no significant difference has been shown, there seems to be a trend of higher overall and disease-free survival in the incomplete response group compared to the complete response group. It is recommended that the reasons for these relations are included in the discussion.

Reply 3: We completely agree with Reviewer A with regards to pointing out the opposite trend we see in our study. We have not been able to find convincing reasons behind this reversed trend, but we have attributed it mainly to the small sample size and loss of follow-up.

Changes in the text: We have included further explanation to why our study showed a higher overall and disease-free survival rate in patients with incomplete pathological response (page 10, lines 6-16).

Comment 4: Although you consider that your results are comparable to previous retrospective studies even with this small sample size, it is recommended to show in the discussion whether pathological complete response does not contribute to survival in previous studies as well.

Reply 4: We have reviewed the previous studies that did not show statistically significant prognostic value in pCR (namely SWOG 9416 trial, RTOG 0229 trial,

SWOG 0220 trial, Kwong *et al.* 2005, and Uchida *et al.* 2019). The RTOG 0229 trial only showed three patients that obtained pCR. The SWOG 0220 trial had a n=29 for patients who underwent trimodality therapy. Kwong *et al.* specifically cited low sample size as a reason for their low statistical power, while Uchida *et al.* cited limited length of follow-up time.

Changes in the text: We have included the above information in the main text (page 10, lines 2-4).

Reviewer B

This is well written and clearly reflects a lot of work. This is an interesting cohort of patients. Strengths of this paper are that the patients are from multiple cancer centres within a single provincial institution which hopefully implies consistency in therapeutic approach.

You have addressed your study aim of reporting clinical outcomes of trimodality approach to Pancoast tumours and they are rare so I accept that it is difficult to acquire larger numbers, despite this very long period of analysis of 15 years. However, I think this paper could be a lot more clinically relevant and interesting if some key questions are addressed and teased out of this patient cohort.

Comment 1: The majority of these patients do not have trimodality treatment so it would be very interesting to know more about the selection process behind this key decision step.
How many patients with Pancoast tumours were identified over this 15 year period in this province? Hence what percentage of patients with SSTs does this cohort represent?
HOW were they selected?
-is such information documented in patients' notes?
- More on tumour anatomical characteristics eg. proximity to spinal cord/ involvement of brachial plexus/ size- did these characteristics influence treatment decisions.

What percentage of those selected for trimodality treatment went on to actually have it? What happened to patients who had neoadj CRT but then did not go on to have surgery?
Was MRI thorax used to help identify potential surgical candidates? Was radiological down-staging demonstrated prior to surgery?
For patients deemed unsuitable for neoadjuvant CRT, what proportion were treated with primary CRT/ primary radiotherapy alone/ palliative radiotherapy.

Reply 1: In our study, we wanted to report the outcomes for only those patients who completed trimodality treatment. In order to gather this patient cohort, we screened 1373 patients with upper lobe tumours treated at the cancer centre during this time period. Out of these patients, 329 patients were identified as having primary tumours located in the superior sulcus, but they had various stages and presentations. Due to various reasons such as stage IV disease, poor performance status or comorbidities, 84 patients were recommended to have palliative approach during initial consultation and were excluded for the purpose of our study. 80 patients underwent definitive chemoradiation only, either due to being unfit for surgery or patient preference against surgical management, and they were excluded as well. 108 additional patients were excluded as they had upfront surgery with adjuvant therapy. 57 patients were selected for trimodality therapy with curative intent, but 25 (44%) were found to be surgically inoperable after induction chemoradiation; we did not collect data on what happened to this subset of patients. This left us with 32 patients who truly were treated with trimodality. Unfortunately, we did not collect data on tumor anatomical characteristics.

MRI thorax was not used routinely. We did not collect data on whether MRIs were used to help identify potential surgical candidates. Patients did have repeat imaging prior to surgery and surgeons assessed suitability for surgery, but we did not collect the details of whether they had down-staging effect.

Changes in the text: We added how we selected our 32 patients in the “Methods: Patient selection and staging” section (page 3, lines 11-17).

Comment 2: Reporting on dosimetry would be helpful given radiotherapy techniques have changed significantly over 15 years- do you think state-of-the-art radiotherapy techniques (photon or proton) that are now available impact treatment outcomes based on what you found in your study?
Most of the patients here treated with 3D conformal radiotherapy which no longer standard of care- did this impact target coverage? Would motion management strategies, image verification, adaptive strategies etc improve on this?
PTV size

Reply 2: IMRT or VMAT radiation technique is now commonly used for lung patients. This does improve conformality of the plan and reduce doses to the organs at risk. Most of our study patients were treated with 3D conformal radiotherapy during that time period. As our study focuses on the overall management and outcome, we did not collect detailed radiation treatment information. But all radiation treatment plans were reviewed and approved by the treating radiation oncologists, dosimetrists and physicists, per standard institutional protocol. Given the era of the treatment, I would assume these cases did not have 4D CT or daily cone beam CT for image verification, but wider PTV margins (1 cm – 1.5 cm) would have been applied. If you feel that these radiation specific details are crucial for the paper, then we will need to request more time to perform that additional chart review.

Changes in the text: As our study focuses on the overall management and outcome, we did not collect detailed radiation treatment information. We are unable to add additional information to the manuscript at this time without performing more chart review.

Comment 3: Patients with positive margins/ non- path CR- can this be related to their radiotherapy plans?
Margins in-field/ regional recurrence
Will MR linac/ PBS improve on this?

Reply 3: We apologize that we did not look into where the positive margins were to know whether these were related to their radiotherapy plans. For those without pCR,

it would be difficult to ascertain whether this is due to the biology of the tumor, or if it is related to their radiotherapy plan. The same goes for local regional recurrence.

We do not have MR Linac/PBS in our province, so we do not have enough knowledge to comment on this question. If there were tumor motion or anatomical variation during the treatment course, daily cone beam CT and adaptive treatment planning will definitely improve coverage and potentially outcomes. However, we did not utilize these during the time period.

Changes in the text: No changes were made to the manuscript regarding this comment for the reasons cited above.

Comment 4: Conflicting documentation: 31 (97%) completed full radiotherapy (line 134); line 190 “all” completed

Reply 4: This was an error on our part. Thank you for catching this.

Changes in the text: We have removed this conflicting documentation (page 8, lines 9-10).

Comment 5: Conclusions- How will your review of practice guide future treatment strategies? What can we learn from your review?- Do you think advances in imaging, radiotherapy and surgical techniques improve patient outcomes?

Reply 5: It provides reassurance that trimodality treatment works for this patient cohort. We learned that preoperative chemoradiotherapy, with a radiation dose of 45 Gy in 25 fractions, followed by surgery, can lead to good complete or partial pathological response rates, surgical resection with clear margin, and long term survival in some patients. There is always room for improvement. At our centre, with our surgeons’ agreement, we sometimes increase the preoperative radiation dose to 60 Gy in 30 fractions. This can avoid the scenario where the patient does not end up going to surgery and a boost of radiation is added with a delay, if one still wants to deliver a curative dose of radiation. This increase in dose may provide additional

tumour killing effect. Advances in imaging, radiotherapy and surgical techniques will improve patient outcomes. Immunotherapy following trimodality treatment has not been studied in lung cancer, but this might provide additional benefit.

Changes in the text: We added a final sentence in the Conclusion section (page 11, line 8).