

Peer Review File

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Thank you for allowing me the opportunity to submit a revised manuscript titled “Assessing Patient Perception and Preferences for Outcomes in Lung Cancer Resection Surgery: A Cross-Sectional Study” to The Journal of Thoracic Disease (JTD). We appreciate the time and effort that you and the reviewers have dedicated to providing valuable feedback on our manuscript. We have been able to incorporate changes to reflect most of the suggestions provided by the reviewers, and have highlighted these changes within the manuscript.

Here is a point-by-point response to the reviewers’ comments as demonstrated below:

Comments from Reviewer A

- **Comment 1:**

One of the stated rationales for the study is the fact that patient perceptions have already been extensively assessed using certain questionnaires, including the EORTC-QLQ-Q-C30, but that a significant knowledge gap remains. Yet the authors use the EORTC-QLQ-Q-C30 questionnaire for their study. I think that the authors should explain why they chose to re-use this questionnaire.

Reply 1:

In our paper, we acknowledge the extensive use of various patient-reported outcome measures (PROMs), including the EORTC-QLQ-C30, MD Anderson Symptom Inventory, and Short Form-36, in previous studies to evaluate the impact of lung cancer resection on health-related quality of life (HRQOL). However, these are asking about patient reported health and wellbeing.. While these PROMs provide valuable insights into general HRQOL, they do not specifically address patients' perceptions of which outcomes hold genuine significance to them personally, the difference taking shortness of breath as an example quantified on the EORTC scale versus how important is shortness of breath to you?

As seen from Page 5 Lines 103-113, our study aims to address this gap by quantifying what outcomes in lung cancer surgery matters most to patients and “explore how baseline clinical, demographic factors and patient’s preoperative health-related quality of life may influence how groups of individuals place their importance on different post-operative outcomes measures.”

Regarding our use of the EORTC-QLQ-C30 questionnaire, we clarified that we employed it at a singular time point to assess preoperative HRQOL and its potential influence on patients' perceptions of outcome importance.

Changes in the text:

N/A

- **Comment 2:**

The authors also developed an original questionnaire. The way that they describe this questionnaire suggests a priori expectations on the part of the authors regarding certain specific outcomes and their effects on patients. Could the authors elaborate further on how and why they chose the specific outcomes that they did for inclusion in the questionnaire? In addition, I am not sure how an outcome such as « atelectasis » is meaningful to a patient. Were the terminology and clinical implications of these outcomes explained to patients?

Reply 2:

Firstly, we acknowledge your concerns regarding the selection of outcomes included in our questionnaire. We added more information regarding such issue in Page 6, Lines 134-138. We conducted a comprehensive literature review and engaged in discussions with our thoracic surgical and research team. These discussions helped us identify and prioritize outcomes that are commonly encountered in our clinical practice and discussed during the surgical consenting process in the context of patients undergoing lung cancer surgery. By drawing upon both existing literature and clinical expertise, we aimed to ensure that the questionnaire captured a comprehensive range of outcomes that are meaningful to patients.

In response to your query about the inclusion of technical terms such as "atelectasis" in the questionnaire, we took measures to ensure that the language used was accessible to patients. We utilized layman terms wherever possible and provided clear explanations of medical terminology. In the case of "atelectasis", we asked the patient about the importance of not having a "collapsed lung" as a complication after lung cancer surgery. Additionally, any potential misunderstandings regarding terminology or clinical implications were addressed by a member of our thoracic surgical team during the survey administration process. Our priority was to ensure that patients fully understood the implications of each complication or outcome included in the questionnaire, facilitating their informed decision-making process. We have attached the original survey as an supplementary file and we hope that would be clarify your query.

Changes in the text:

We have modified the text as advised in Page 6, Lines 134-138.

- **Comment 3:**

I would think that the preoperative discussion between the surgeon and patient is very important, and that the way that certain risks and outcomes are framed may have a significant impact on patients' subsequent perceptions and expectations. How was the content of such discussions taken into account by the authors? I think that for patients, understanding the implications of complications, conceptualizing the natural history of cancer, and the implications of a recurrence (local or distant) on treatment, morbidity, and longer term survival, may not be straightforward.

Reply 3:

Thank you for highlighting the importance of preoperative discussions between

surgeons and patients. We agree with the significance of these discussions in shaping patients' perceptions and expectations regarding their surgery and outcomes. In addressing your concern about the significance of preoperative discussions between surgeons and patients, we took into account the content of such discussions by ensuring that the questionnaire was reflective of the common information provided to patients during the preoperative consenting process. We carefully reviewed consent forms to understand the risks of surgery as quoted by surgeons, along with the associated complications and outcomes. By aligning the content of our questionnaire with the typical information conveyed during these discussions, we aimed to capture the outcomes that patients deemed important based on the information they receive from their healthcare providers. This approach allowed us to explore patients' perceptions of surgery outcomes within the context of the information provided to them during the decision-making process.

We acknowledge the complexity of these conversations and their potential impact on patients' perceptions. Moving forward, incorporating qualitative research methods or patient interviews could provide further insights into the nuances of preoperative discussions and their influence on patient perspectives.

Changes in the text:

The above is now explained on page 6 to 7, lines 134 to 141 of our revised manuscript.

• **Comment 4:**

One of the limitations of this study is the small number of patients. I am not sure how the inclusion of stage 4 patients is justified here, since these patients find themselves in a fundamentally different situations than patients undergoing curative resection. I would argue that even the inclusion of stage 3 patients is debatable, since they represent more advanced disease requiring a fundamentally different treatment approach than earlier stage cancers.

Reply 4:

Regarding the limited sample size, we acknowledge this constraint and its potential implications for the generalizability of our findings. Although a larger sample size would enhance the statistical robustness of our analysis, it's important to recognize that even with a small sample, we were able to discern significant trends in patient preferences for various outcomes following lung cancer surgery. These insights provide a valuable foundation for future research endeavours involving larger cohorts, which could further validate and expand upon our findings.

As for the inclusion of stage III and IV patients, we acknowledge that these individuals present with more advanced disease stages and may necessitate different treatment strategies compared to those with earlier stage cancers. However, we believe their participation in our study is justified by the evolving role of surgery in managing advanced-stage lung cancer, especially in light of advancements such as local consolidative therapy for oligometastatic disease. Understanding the preferences and priorities of patients with advanced disease is essential for

comprehending the role of surgery in this subgroup of patients and for optimizing treatment decisions and clinical trial designs.

Furthermore, by encompassing patients across diverse disease stages, we were able to discover specific trends in how individuals with more advanced lung cancer prioritize certain outcomes. As highlighted in lines , patients with more advanced stages were less inclined to prioritize factors such as the ability to return to work promptly and the likelihood of requiring reoperation. These findings underscore the significance of considering disease stage when interpreting patient preferences and tailoring treatment approaches accordingly.

Changes in text:

The above is now added on page 6, lines 116 to 118 of our revised manuscript.

- **Comment 5:**

I am curious about the collection of clinical and demographic data. In some ways, many of the results are intuitive, and, not surprisingly, oncologic outcomes are rated highly. I am curious about the association between clinical data and survey results. I think it is reasonable to assume, once again, that the authors had some a priori expectation or hypothesis regarding how demographic or clinical characteristics might influence patients' responses, that guided their data collection and statistical analysis. I think that making this explicit would be helpful to the reader to make sense of the results.

Reply 5:

Regarding the collection of clinical and demographic data, we appreciate your curiosity and interest in understanding the association between these factors and the survey results. It's important to clarify that our aim was indeed to investigate the potential influence of various clinical and demographic characteristics on patients' responses to the survey. However, we did not have specific a priori expectations or hypotheses regarding how these factors might impact patient perceptions.

It is worth noting that the selection of variables for data collection was determined during the protocol phase of the project, prior to the commencement of the study. This ensured that our investigation was guided by a predefined set of variables, and the inclusion of these variables was not influenced by post-hoc considerations or biases. We have added this to our study in Page 8, lines 169 to 175 to clarify such misunderstanding.

While certain results may seem intuitive, we were not only surprised by the heavy emphasis on oncologic outcomes as compared to survival by patients, but also how various patient factors demonstrated unexpected relationships with patient's perception in our ordinal logistic regression analysis, an example of such is the fact that patients' preoperative health-related quality of life did not have any significant association with whether they were more likely to rank an outcome or factor as more important.

Changes in text:

We have modified the text as advised in Page 8, Lines 175-181 in our manuscript.

- **Comment 6:**

I am not sure how lay patients would conceptualize « overall survival » vs « disease-free survival », and indeed how these would relate to « R0 » vs « non-R0 » resection, and perhaps even how they relate to possible outcomes following alternative treatments (e.g. radiotherapy). I would suspect that what patients would rate highest is « cure » but the very fact that such a concept does not even appear in the questionnaire serves to underscore just to what extent these concepts (OS, DFS, and « cure ») are moot even among experts. And so I don't really know what to make of the conclusions of the paragraph beginning 238. These are complex issues without a simple answer and this should be highlighted.

Reply 6:

You raised valid points about the potential ambiguity and differing interpretations of these terms among patients. However, we specially used simple terms that patients could understand such as complete removal of the cancer (R0) and recurrence (in lieu of disease free survival). We agree that these issues are multifaceted and do not have simple answers. Our intention in highlighting the importance of oncologic outcomes, particularly the observation that more patients rated outcomes such as R0 resection and cancer recurrence as important compared to overall survival, was to provoke critical discussion about the evolving landscape of outcome measurements in clinical trials concerning lung cancer.

In the paragraph you referenced, we aimed to underscore the shifting focus towards disease-free survival as a primary endpoint in major clinical trials, as evidenced by recent large scale thoracic surgical trials in immunotherapy. We are suggesting that considering disease-free survival as a co-primary outcome alongside overall survival in future studies could better align clinical research with both clinical significance and patients' needs.

Changes in text:

This is now elaborated on page 7, lines 147-148 of our revised manuscript.

- **Comment 7:**

The paragraph on line 252 also raises interesting issues. Once again, several of these can be said to be « philosophical » in nature, i.e. what does an increased risk of local recurrence mean, if survival is the same? This has bearing on how one conceptualizes cancer, cancer treatment, and treatment outcomes. These issues also have bearing on the previous discussion on the acceptance of mortality risk (paragraph line 172).

Reply 7:

Thank you. For clinician this concept is often interpreted as you describe. The results of our survey, however, suggest that recurrence is an important issue, despite the same overall survival. Recurrence has the additional burden of investigations, admission and impairment to quality of life. We have modified the text from Page 13,

Line 328 to 333, to address this philosophical issue on patient acceptance towards increased local recurrence risk while achieving better overall survival. We have also highlighted future directions in how to better quantify patient decision making through other complex decision-making analysis techniques

Changes in text:

We have modified the text in Page 13 to 14, Line 334 to 339 in our revised manuscript.

- **Comment 8:**

I am personally not convinced about the equal loss of lung function after lobectomy vs segmentectomy. I think that part of the problem is a misunderstanding concerning the term "lung function". In fact what is being measured, essentially, are lung volumes, not function per se. Since it is really counterintuitive to conclude that parenchymal sparing would not preserve function, I think that such a conclusion requires one to define lung function appropriately and precisely, and then to make a well-constructed argument as to how, exactly, lung function would be related to lung volumes or to a particular kind of resection. I have not yet seen any such arguments in the broader literature. In addition, I am also personally skeptical of the purported higher risk of complications with segmentectomy vs lobectomy. This has certainly not been our experience, and perhaps there were other factors at play in the studies cited. I think that patients should definitely be active participants in the surgical decision-making process, but I also think that there are many subtleties related to segmentectomies vs lobectomies that the discussion here does not capture.

Reply 8:

Thank you, but that is not within the scope of our study. We are merely quoting from JCOG0802 by Saji et al., which demonstrated that they “did not find the expected evidence of superiority in postoperative respiratory function in the segmentectomy group”. In terms of the higher risk of complications with segmentectomy, we are yet again quoting from the aforementioned trial, which indicated that “Multivariable analysis showed that predictors of pulmonary complications, including air leak and empyema (grade ≥ 2), were complex segmentectomy (vs lobectomy; odds ratio [OR] 2.07, 95% CI 1.11–3.88; $p=0.023$)”. Our discussion on segmentectomies and lobectomies stems from possible implications from the results of our patient survey, which suggested strong patient preference for better oncologic outcomes and surgery with less postoperative complications. We are highlighting concerns patient may have if presented data from this landmark study during the surgical consenting process. To address this, we have amended the text in Page 13, Line 328 to 333 about the possible questions on patient acceptance of segmentectomy versus lobectomy, and also point out certain directions for future research to be done on comparing patient acceptance for segmentectomy versus lobectomy.

Changes in text:

We have modified the text in Page 13 to 14, Line 334 to 339 in our revised manuscript.

Comment 9:

I would say that my main take-aways from this paper are the low importance given by patients to certain specific issues such as cosmesis and length of stay, compared to other outcomes. Although I think that these are important observations, I also think that the paper perhaps overreaches in attempts to make broader conclusions.

Reply 9:

Thank you for your comment. We have incorporate your aforementioned comments to make sure that the paper does not overreach in making any broad conclusions. We hope our clarifications in the replies above can also demonstrate that we intend to demonstrate the importance that patient places on various outcomes/complications and how that these findings relate to pertinent issues in the current thoracic surgery landscape and literature as highlighted in our discussion on oncological outcomes, extent of resection and ERAS from Page 12 to 14, Lines 303-385.

Changes in text:

N/A

Comments from Reviewer B

- **Comment 1:**

This is an original article about patient's desire before lung cancer surgery using quality of life questionnaire (EORTC QLQ-C30) prior to surgery.

Reply 1:

Thank you for your comment

- **Comment 2:**

As a result, oncologic outcomes as well as postoperative quality of life are most concern in those patients, and each tendency are also investigated in Tables.

Reply 2:

Thank you for your comment

- **Comment 3:**

We understand the study concept, however, the results are reasonable and acceptable in single institute with small numbers of patient.

Reply 3:

Thank you for your comment. We have noted this in our limitations.

- **Comment 4:**

We would like to suggest practical analysis ex) difference between elderly patient vs younger patient, difference between preoperative vs postoperative (not done), difference between lobectomy vs segmentectomy, etc.

Reply 4:

Regarding the difference between elderly and younger patient, difference between lobectomy vs segmentectomy, we have actually done the analysis via ordinal logistic regression as seen from Page 10, Lines 236 to 254. Age had no significant effect on outcomes that patients were more or less likely to rate as important as seen from Table 4.

As for the difference between preoperative and postoperative scores, one may find in the study title that this study is a cross-sectional study which examines one specific timepoint (preoperative).

- **Comment 5:**

Practical question for general thoracic surgeons should be investigated in such kinds of study; Study design is good.

Reply 5:

Thank you for your comment.