

## Peer Review File

Article information: <https://dx.doi.org/10.21037/jtd-23-835>

### Reviewer A

**Comment A1:** Firstly, I'm sorry I could not understand the LCDY score well. Why and how the dyspnoea scale linearly transformed 0 to 100 score? The authors indicated score preoperative, and 6-12 months were 12.6 and 17.9, respectively, however, I could not understand how much these score reflected the actual dyspnoea. In addition, I also could not understand LCDY-late score well. What did it mean "combined 12 and 6 months"? How did you calculate it? These should be described more detail.

**Reply 1:** Thank you so much for the point raised. The Dyspnoea score is part of The European Organization for Research and Treatment (EORTC) published the Lung Cancer specific Quality of Life Questionnaire (LC13) (LCDY).The EORTC Manual has clear instruction to score the items and symptoms scale which we followed during the analysis and interpretation of results. Following their guidelines, we linearly transformed the result 0-100.

The late score was an arbitrary decision to see the late effect as demonstrated in other studies, the Proms tend to recover after 3-6 months from the operation. This allows us to get more data available in that timeframe.<sup>1</sup>

**Changes in the text:** The format of the dyspnoea score is explained in the methods (line 150).

We have added some specific details about the late dyspnoea:

We decided to investigate the late effects of dyspnoea as demonstrated by other studies, PROMs after surgery tend to have a marked worsening immediately after surgery, to start recovering after 3-6 months afterwards.<sup>12</sup> (Line 255)

1. Pompili C, Absolom K, Velikova G, Backhus L. Patients reported outcomes in thoracic surgery. *Journal of Thoracic Disease*. 2018;10(2): 703–706. doi:10.21037/jtd.2018.01.140

**Comment A2:** 2. Please indicate why the authors set a 10% difference as significant in LCDY score.

**Reply 2:** We thank the reviewer for this important point. Early EORTC guidelines for minimally important differences (MIDs) for the EORTC QLQ questionnaire proposed  $\geq 10$  points change as clinically meaningful for all scales.<sup>2</sup>

**Changes in the text:** (We added the reference 14) (Line 164)

2. Musoro J, Coens C, Sprangers M, Brandberg Y, Groenvold M, Flechtner H, Bottomley A. Minimally important differences for interpreting EORTC QLQ-C30 Change scores over time: A synthesis across 21 clinical trials involving nine different cancer types. *European Journal of Cancer*. 2023; 188, 171–182. doi:10.1016/j.ejca.2023.04.027

**Comment A3:** In Table 2, the number of patients in 3 months postoperative was only 51. Why did patients decrease so much? I considered that it is serious missing data.

**Reply 3:** We thank the reviewer for highlighting this important point. We agree that this is a very critical attrition point. However, it is in line with other published reports on the same patients, especially when we are considering real world data and not part of clinical trials.<sup>3</sup>

**Changes in the text:** Although, we had some missing data during the postoperative follow up period these were in line with other published reports on the same patients whilst working with real world data as opposed to clinical trials<sup>24</sup>. (Line 324)

3. Pompili C, Rogers Z, Absolom K, Holch P, Clayton B, Callister M, Robson J, Brunelli A, Franks K, Velikova G. Quality of life after VATS lung resection and SABR for early-stage non-small cell lung cancer: A longitudinal study. *Lung Cancer*. 2021;162:71-78. doi: 10.1016/j.lungcan.2021.10.004. Epub 2021 Oct 23. PMID: 34741885.

**Comment A4:** In Table 2, the number of patients in 3 months postoperative was only 51. Why did patients decrease so much? I considered that it is serious missing data.

**Reply 4:** We thank the reviewer for an important point. This analysis was not a per-participants longitudinal analysis of evolution of patient-reported outcomes, so we were not able to assess the effect size of change for each participant.

**Changes in the text:** Although, we had some missing data during the postoperative follow up period these were in line with other published reports on the same patients whilst working with real world data as opposed to clinical trials<sup>24</sup>. The study relied on voluntary help of medical staff, hence this translated to impossibility to calculate any consent rate and also in a lack of possible reminder system for the patients. This has been a possible explanation of the higher attrition rate especially at 3 months. (Line 324)

**Comment A5:** In Figure 1, it just looks like a graph that goes bad after 3 months and returns to preoperative statement after 6 and 12 months. It seems to be dissociated from the conclusions. It should be fixed to make it easy to understand.

**Reply 5:** We thank the reviewer for this comments and we'll try to explain a very common pattern in PROMs. As mentioned before, the proms in thoracic surgery are typically shaped with the reported graph as immediately after surgery, patients are less likely to fill the questionnaires and we had in the past the major amount of missing collection. The real clinical reason is not well investigated, but it would be certainly be part of future studied. The important message is more about the confirmation from the patient perspective of the effect of our procedure, although with minimally invasive procedure, on patient daily lifestyle, up to one year after the treatment.<sup>4</sup>

**Changes in the text:** The study relied on voluntary help of medical staff, hence this translated to impossibility to calculate any consent rate and also in a lack of possible reminder system for the patients. This has been a possible explanation of the higher attrition rate especially at 3 months. (Line 326)

**Comment A6:** Although it may not necessarily be correlated, if the data is existed, the relationship between postoperative dyspnoea and postoperative respiratory functions should be analyzed.

In addition, we guess that the amount of resected lung volume and dyspnoea may be correlated. So, for example, is it possible to analyze the relationship between the number of resected segments or subsegments and dyspnoea?

**Reply 6:** We thank the reviewer for these 2 valid comments however we did not collect or analyze such data, but we have recognized the importance of its collection within our discussion.

**Changes in the text:** This study did not measure patient activity levels or results from objective respiratory tests... Correlating LCDY score to objective respiratory scores may have highlighted their inaccuracy consolidating the rationale for our study and potential identification of ideal candidates for this intervention. (Line 292, 295)

Objectively it remains unclear whether it is possible to predict the postoperative dyspnoea difference for lobectomy vs segmentectomy in terms of lung preservation as

we found only marginal association in our study. Furthermore, further data should be collected to investigate dyspnoea levels between different segmentectomies and lobectomies types too which could inform discussions at MDT's. (Line 281)

**Comment A7:** If patients who actually develop dyspnoea may find preoperatively, what kind of intervention would be possible? And then, what are the postoperative change of performing the intervention?

**Reply 7:** We thank the reviewer for this important point raised. Pre-habilitation has demonstrated good results in relationship with preoperative fitness and postoperative complications. However financial and practical-related factors have limited these interventions being implemented for lung cancer surgery. Nevertheless, perioperative dyspnoea assessment can be incorporated in future studies to assess possible effects of pre-habilitation programs, especially in the era of longer multimodality treatments plans.

**Changes in the text:** Nevertheless, perioperative dyspnoea assessment can be incorporated in future studies to assess possible effects of pre-habilitation programs, especially in the era of longer multimodality treatments plans. (Line 299)

## **Reviewer B**

**Comment B1:** 1. Given that this study was conducted at a single site and with a relatively small sample size, caution must be exercised when generalizing these results.

**Reply 1:** We thank the reviewer for this comment and this is something that we have now highlighted more clearly as a limitation in our study.

**Changes in the text:** All patients were recruited from a single centre however, this allowed care pathways to be standardised, so we did not observe the effect of confounders in our results. Non-consecutive recruitment may have increased sampling bias, making it more difficult to generalise from our findings as well as the relatively small sample size. (Line 312)

**Comment B2:** Since dyspnoea is primarily a subjective complaint from patients, we believe that objective data is also necessary. For example, it would be valuable to know the actual exercise tolerance of patients who reported dyspnoea. Did it correlate with objective data such as the six-minute walk test, shuttle walk test, or cardiopulmonary exercise testing (CPET)? Furthermore, is it difficult to predict postoperative dyspnoea

based on preoperative exercise tolerance?

**Reply 2:** We thank the reviewer for this comment, but this is something that we initially established during our literature review as we have outlined in our introduction. We did not collect data related objective respiratory tests but agree that correlating them to LCDY scores would have been informative and further consolidated the rationale behind the study.

**Changes in the text:** This study did not measure patient activity levels or results from objective respiratory tests... Correlating LCDY score to objective respiratory scores may have highlighted their inaccuracy consolidating the rationale for our study and potential identification of ideal candidates for this intervention. (Line 292, 295)

**Comment B3:** Postoperative cardiopulmonary complications are likely to naturally impact the perception of postoperative dyspnoea. Do you have any data on this aspect?

**Reply 3:** We thank the reviewer for this comment however we did not collect or analyse such data beyond pre-operatively diagnosed co-morbidities, but we have recognized this as a potential limitation.

**Changes in the text:** Lastly, cardiopulmonary complications could impact the perception of postoperative dyspnoea. Although we measured pre-operatively diagnosed co-morbidities, we did not collect any data on this aspect. (Line 332)

**Comment B4:** 4. It is conceivable that there might be differences in postoperative dyspnoea between lobectomy and segmentectomy in terms of lung function preservation. Are there any differences observed when comparing different lobes of resection, such as upper and lower lobectomy?

**Reply 4:** We thank the reviewer for this valid comment however we did not collect or analyse such data, but we have recognized the importance of its collection within our discussion.

**Changes in the text:** Objectively it remains unclear whether it is possible to predict the postoperative dyspnoea difference for lobectomy vs segmentectomy in terms of lung preservation as we found only marginal association in our study. Furthermore, further data should be collected to investigate dyspnoea levels between different segmentectomies and lobectomies types too which could inform discussions at MDT's. (Line 281)

**Comment B5:** 5. Could the patient's original personality and psychological state influence the perception of dyspnoea after surgery? For instance, would patients with advanced lung cancer experience a smaller or greater impact on their dyspnoea?

**Reply 5:** We thank the reviewer for their comment and highlighting the subjectivity in the perception of dyspnoea, we agree that exploring these hypotheses would be an interesting expansion to our study and have therefore discussed within our text.

**Changes in the text:** Patients personality traits or psychological state may also influence their subjective perception of dyspnoea such as those advanced lung cancer. It would be elucidating to perform analyses on such subgroups of patients to gain a deeper understanding of the factors that influence perception of dyspnoea. (Line 278)

### **Reviewer C**

**Comment C1:** Have the authors collected any information on patient smoking status, pain, the specific lobe removed, anxiety or anemia? The authors list the lack of information on level of activity/exercise tolerance. These other factors could also lead to reports of shortness of breath.

**Reply 1:** We thank the reviewer for this comment and highlighting other factors that can all affect shortness of breath in theory however evidence is currently lacking. Unfortunately, we did not measure hence analyse such data, but we hope that our exploratory research necessitates further investigation and correlation of these factors with post operative dyspnoea. We have elaborated on this valid point in the discussion.

**Changes in the text:** We did not find an association between co-morbidities measured such as diabetes, COPD and dyspnoea within our patient cohort. However, we hope that our exploratory research raises interest of other factors which can affect dyspnoea in theory so we can start building an evidence base from investigation in larger cohort studies. Such factors should not be limited to co morbidities such as anaemia and may include anxiety, smoking status and pain. (Line 235)