Peer Review File

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Reviewer A

The authors examined the effectiveness of opioids for dyspnea in lung cancer patients. This cohort study has larger sample size than previous studies, and they suggest the usefulness of opioids for dyspnea in real-world practice. In addition, lung cancer with ILD and pleural dissemination could be more sensitive to opioids. In contrast, efficacy seems to be poor in patients with a physician prognosis in days. The authors also discuss the limitation of the present study.
This paper is thought to be interesting and suggestive for oncologists, respiratory physicians, and trainees in addition to palliative care physicians, thus worthwhile publishing in 'Translational Lung Cancer Research'.
This paper is thought to be interesting and suggestive. However, it is considered to be desirable to refer to some concerns indicated below.

Comment to the authors:

1) Were there differences in changes in NRS and IPOS/STAS score of dyspnea according to various opioids (morphine, oxycodone, hydromorphone, or fentanyl)?

Reply 1:
We thank the reviewer for the important comment.
We also consider it to be a very important factor, but due to the small number of cases depending on the opioid used, we did not compare the effects of each opioid.

2) How did the physicians participating this study estimate the prognosis of each patient? Using palliative prognostic index?

Reply 2:
We thank the reviewer for the important comment.
As for the prognosis, it is based on the subjective prediction of the attending physician. No specific score was used.

3) Was the chest drainage excluded from this observational study? The drainage of pleural effusion could relief dyspnea. Thus, it causes a change in symptoms of dyspnea in a short period.

Reply 3:
We thank the reviewer for the important comment.
We excluded cases in which thoracic drainage was performed within 3 days.
Changes in the text:
We have added details of our exclusion criteria. (see Page 8, line 128)

4) I think that the changes in NRS and IPOS differ depending on the degree of retention of pleural effusion. For example, if there is a large amount of pleural effusion, dyspnea is severe, and opioid alone may not be effective to dyspnea. The same holds true for short-term retention of pleural effusion. Authors are encouraged to mention this query.

Reply 4:
We thank the reviewer for the important comment.
It is very important as you pointed out, but this study only evaluates the presence or absence of pleural effusions, not the volume.
Changes in the text:
We have added this to the Limitation section. (see Page 15, line 269)

5) According to the 'Procedure and measurements' section, the authors collected clinical data of concomitant use of benzodiazepine or corticosteroids. However, there is not this data in Table 1. I think that this concomitant intervention seems to be the factor of independent variable to analysis.

Reply 5:
We thank the reviewer for the important comment.
Since this is a very important factor, we have added it to Table 1.
Changes in the text:
We have added this to table 1. (see Page 21, line 373)

Reviewer B

I think this is an interesting subanalysis on a very relevant subject. However, I do have some comments on the manuscript, which I would like to see the authors to adress first.

Running title: lung cancer instead of LC

Reply 6:
We thank the reviewer for the important comment.
We have revised the text.
Changes in the text:
We have modified our text as advised. (see Page 3, line 42)

Abstract:
• Background: The background does not explain why it is specifically important to investigate safety of opioids in lung cancer patients

Reply 7:
We thank the reviewer for the important comment.

We have revised the text.
Changes in the text:
We have modified our text as advised. (see Page 4, line 54)

• Methods: Please also mention secondary outcomes

Reply 9:
We thank the reviewer for the important comment.
We have revised the text.
Changes in the text:
We have modified our text as advised. (see Page 4, line 66)

• Conclusion: Furthermore instead of further

Reply 9:
We thank the reviewer for the important comment.
We have revised the text.
Changes in the text:
We have modified our text as advised. (see Page 5, line 82)

Background:
• Line 82: Prefer dyspnea instead of dyspneic symptoms (which implies there are multiple symptoms)

Reply 10:
We thank the reviewer for the important comment.
We have revised the text.
Changes in the text:
We have modified our text as advised. (see Page 6, line 90)

• Line 84: Patients are not complicated with other diseases, but patients with lung cancer can have other lung diseases

Reply 11:
We thank the reviewer for the important comment.
We have revised the text.
Changes in the text:
We have modified our text as advised. (see Page 6, line 92)

• Line 88 and further: I feel that the authors could be more clear/elaborate more on why the response to opioids might differ between lung cancer and other forms of cancer. Additionally, it may be interesting to further elaborate on why investigating safety of opioids in lung cancer

may be especially important (i.e. risk of hypercapnia in case of concurrent COPD)

Reply 12:
We thank the reviewer for the important comment.
We have revised the text.
Changes in the text:
We have modified our text as advised. (see Page 6, line 97)

Methods:
• Patients: Is there a publication on the primary study or study design. If yes, please add as a reference here

Reply 13:
We thank the reviewer for the important comment.
We have not yet published on the main analysis.

• Patients: It says starting with opioids, but then mentions that a switch of addition of another opioid is also possible. Please describe this more clearly.

Reply 14:
We thank the reviewer for the important comment.
We have revised the text.
Changes in the text:
We have modified our text as advised. (see Page8, line 125)

• Line 112: and [an available] Integrated Pall..

Reply 15:
We thank the reviewer for the important comment.
We have revised the text.
Changes in the text:
We have modified our text. (see Page8, line 123)

• Please describe the possible scores for NRS and IPOS/STAS scores so anyone who is not used to these scores can still interpret the outcomes.

Reply 15:
We thank the reviewer for the important comment.
We have revised the text.
Changes in the text:
We have modified our text as advised. (see Page9, line 154)

Results:
• Line 162: How was the difference between pleural effusion and pleural dissemination made?

Reply 15:
We thank the reviewer for the important comment.
The presence or absence of pleural dissemination was determined by the presence or absence of nodules or other shadows on the pleura.

• Line 162: Lung tumor: Is this the primary tumor in the lung?

Reply 16:
We thank the reviewer for the important comment.
This refers to tumors within the lungs, whether primary or metastatic.

• Line 165: 30 mg morphine equivalent?

Reply 17
We thank the reviewer for the important comment.
Yes, it is morphine equivalent dose.
Changes in the text:
We have modified our text as advised. (see Page11, line 183)

• Line 174: Poor physicians prognosis of (instead of in) days

Reply 18:
We thank the reviewer for the important comment.
We have revised the text.
Changes in the text:
We have modified our text as advised. (see Page11, line 193)

• Line 174: The 95% CI doesn't include the odds ratio of 0.93

Reply 19:
We thank the reviewer for the important comment.
We have revised the text.
Changes in the text:
We have modified our text as advised. (see Page12, line 193)

• Line 182: Please add percentages

Reply 20:
We thank the reviewer for the important comment.
We have revised the text.
Changes in the text:
We have modified our text as advised. (see Page12, line 201)

Discussion:
• Does the IPOS/STAS provide additional information on dyspnea than the NRS? Maybe it is nice to elaborate on this some more

Reply 21:
We thank the reviewer for the important comment.
Patients who could not respond to the NRS alone, which is a patient-reported outcome, would have been excluded. We believe that the IPOS/STAS was also valid in that it is a peer-reported outcome that can include such patients.

• Some participants where already on opioids and some where not. Please elaborate in the discussion if this makes a difference for the expected effect and outcome of the analyses

Reply 22:
We thank the reviewer for the important comment.
Due to the small number of cases, no comparison was made between patients already receiving opioids and those not receiving opioids. We have added to Limitation.
Changes in the text:
We have modified our text as advised. (see Page16, line 270)

• I'm having some trouble interpretating the safety data, since it appears a lot of patients died during the follow up. I can imagine this is a consequence of the disease and most likely not of the opioids, but this is a challenge for the study design. I would suggest the authors elaborate on this, and add in the results the survival/number of patients that died during follow up.

Reply 23:
We thank the reviewer for the important comment.
We agree that it is important to include deaths, and we have added this information.
We have modified our text as advised. (see Page12, line 203)

• Line 189: Of days instead of in days

Reply 24:
We thank the reviewer for the important comment.
We have revised the text.
Changes in the text:
We have modified our text as advised. (see Page12, line 209)

• Line 191: Have reported

Reply 25:
We thank the reviewer for the important comment.
We have revised the text.

Changes in the text:
We have modified our text as advised. (see Page12, line 211)

• Line 193: Is the number of participants in this study 80? It is not easy to distinguish from the references

Reply 26:
We thank the reviewer for the important comment.
We have revised the text.
Changes in the text:
We have modified our text as advised. (see Page13, line 213)

• Line 202: 'It is controversial on the effectiveness of opioids on dyspnea in ILDs' I don't understand this sentence.

Reply 27
We thank the reviewer for the important comment.
We have revised the text.
Changes in the text:
We have modified our text as advised. (see Page13, line 222)

• Line 204: They have (not had) reported

Reply 28:
We thank the reviewer for the important comment.
We have revised the text.
Changes in the text:
We have modified our text as advised. (see Page13, line 226)

• Line 208: More difficult to treat?

Reply 29:
We thank the reviewer for the important comment.
We have revised the text.
Changes in the text:
We have modified our text as advised. (see Page13, line 229)

Table 1:
• Instead of noting yes/no, consider only the number of patients who are 'yes' with a percentage of the total number of patients in parenthesis.

Reply 30:
We thank the reviewer for the important comment.
We have revised the text.

Changes in the text:
We have modified our text as advised. (see Page21, line 373)

• Is there any information on brain metastasis and bone metastasis?

Reply 31:
We thank the reviewer for the important comment.
We did not examine for the presence of those metastases.

• The BMI may be more informative than just the weight without height

Reply 32:
We thank the reviewer for the important comment.
We did not collect height data.

Table 4: Why is a p value of <0.10 indicated with **, since this is not statistically significant?

Reply 32:
We thank the reviewer for the important comment.
There were no significant differences, however we thought we recognized a trend.

Table 5: Please explain the grades

Reply 33:
We thank the reviewer for the important comment.
CTCAE was used for Grade. (see Page9, line 144)

I think this is an interesting subanalysis on a very relevant subject. However, I do have some comments on the manuscript, which I would like to see the authors to adress first.