

Peer review file

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Reviewer A

This is an interesting analysis on outcomes of patients with non-small cell lung cancer who have pleural dissemination. The investigators characterized factors associated with pleural dissemination in a single-institution cohort of patients with non-small cell lung cancer undergoing surgery. While the authors miss a chance to characterize the outcomes of this cohort, they do provide information on these patients that can help with patient prognostication and surgical selection. Several issues need to be addressed:

Abstract

Comment 1: Results: add the number of patients in the analysis.

Reply 1: I added.

Changes in the text: Page 3, line 36.

Comment 2: Clarify that 7 patients is the focus of the analysis who had pleural dissemination who were compared wo 137 patients without pleural dissemination.

Reply 2: I added the sentence.

Changes in the text: Page 3, line 41-42.

Comment 3: Conclusions: “might tend to disseminate to pleural cavity in early term” should be reworded to something like “are factors associated with early pleural cavity dissemination”.

Reply 3: I changed the sentence.

Changes in the text: Page 4, line 51-52.

Comment 4: Keywords: ‘young age’ would be more descriptive than just ‘young’.

Reply 4: I changed to young age.

Changes in the text: Page 2, line 28.

Introduction

Comment 1: At the end of the Introduction section, add the purpose of the present study, why it is a needed addition to the medical literature, and what the hypothesis of the

study is.

Reply 1: I added the sentence.

Changes in the text: Page 6, line 76-78.

Methods

Comment 1: Patients were not “enrolled,” as this is a retrospective study. Instead, 144 patients were the subject of the retrospective analysis.

Reply 1: I changed the sentence.

Changes in the text: Page 7, line 90-91.

Comment 2: Were the CT measurements based on the original diagnostic CT reports, or were they performed in a standardized fashion for this study, and if so were they completed by one or multiple radiologists and were the radiologists board certified thoracic radiologists? Same with PET.

Reply2 : I changed the sentence.

Changes in the text: Page 7, line 95-96, page 8, line 110-111.

Results

Comment 1: In the Patients’ characteristics paragraphs, list the histology breakdown for the 7 patients with pleural dissemination.

Reply1: I added the sentence.

Changes in the text: Page 10, line 142-144.

Comment 2: Similarly, list the grade for the 7 pleural dissemination patients.

Reply2): I added the sentence.

Changes in the text: Page 10, line 147-148.

Comment 3: In the manuscript text, make it more clear what predictive factors are for pleural dissemination. For example, do not just say ‘age’ and ‘differentiation’ but say young versus old age and well versus poorly differentiated (which needs to be defined) tumors are the ones more associated with pleural dissemination.

Reply 3: I changed the sentence.

Changes in the text: Page 12, line 174-175.

Comment 4: The rates of pleural control, ipsilateral hemithoracic tumor control, progression free survival and overall survival should be provided for the 7 patients with

pleural metastases and ideally compared to the other 137 patients.

Reply 4: There was not significant difference between patients with pleural dissemination and without pleural dissemination. Therefore, we only added the overall s
Changes in the text: Page 10, line 148-150.

Discussion

Comment 1: Fix line 174 that current states, "...it might be necessary to be careful that young patients with NSCLC cannot be deny that the possibility...".

Reply1: I changed the sentence.

Changes in the text: Page 13, line 197-198.

Comment 2: Actual data and quantitative discussion as opposed to brief generalizations on outcomes after resection for pleural metastases should be added.

Reply 2: I added the sentence.

Changes in the text: Page 15-15, line 224-229.

Comment 3: A discussion that it took 11 years to have 7 analyzable patients needs to be added as a limitation and bias.

Reply 3: I added the sentence.

Changes in the text: Page 15, line 232-236.

Figure 2

Comment 1: Correct the caption for "292 patients did not adjacent to visceral pleura". This likely should be "292 patients did not have a lesion adjacent to the visceral pleura."

Reply1: I changed the sentence in Figure 2.

Comment 2: Patients were not "enrolled" as this is a retrospective study. Change "enrolled in this study" to something like "included in this analysis". Similarly, change the word "enrollment" in the title of this figure.

Reply 2: I changed the sentence in Figure 2.

Table 1

Comment 1: Add 'years' after age [this should similarly be performed for tables 2-5 as well].

Reply 1: I added the 'years' in Table 1-5.

Comment 2: Stage 0 can be removed.

Reply 2: I removed the 'stage 0'.

Table 3-4

Comment 1: I am not sure that both tables are needed. Table 2 and 3 are similar and tables 3 and 4 are similar. While of course the populations are somewhat different between Tables 2 and 3, and Table 4 is a statistical analysis of the population in Table 3, this feels to the reader to be redundant.

Reply 1: Actually, Table 2 and 3 or Table 3 and 4 are similar. However, because squamous cell carcinoma was considered to tend not to show dissemination to the pleural cavity in the early term, the predictive factors related to pleural dissemination in non-squamous cell carcinoma patients were analyzed. Therefore, we did not change Table 2-4.

Reviewer B

I have a few minor questions/clarifications:

Comment 1: Can the authors explain why they excluded patients with tumors not located at visceral pleura or those invading the chest wall? Is there less risk of DPD with tumors without visceral pleural invasion and higher risk with invasion of chest wall? What's the justification? I am not entirely clear on the data on this after reading the paper.

Reply 1: Pleural dissemination was difficult if it was distant from the visceral pleura, and chest wall invasion was considered to be a more advanced condition, so it was excluded.

Comment 2: Figure 2 legend: "Flowchart for patient enrollment" is mis-worded. This is not a trial, and therefore there is no enrollment. Perhaps, this should be reworded to say "Flowchart of study design".

Reply 2: I changed the Figure 2 legend.

Changes in the text: Page 23, line 357-359.

Comment 3: Figure 2: can the authors correct the English in this diagram when they state "292 patients did not adjacent to visceral pleura".

Reply 3: I changed the sentence in Figure 2.

Comment 4: Given that the 7 patients with DPD had a Brinkman index of 0, was there a

higher risk of EGFR or any other genetic mutation?

Reply 4: 3 patients with Brinkman index of 0 had EGFR mutation. Although EGFR mutation might lead to pleural dissemination, EGFR mutation was not analyzed in all cases, therefore the relationship between EGFR mutation and pleural dissemination was unclear.

Comment 5: What is the "non-Ad" pathology as mentioned in Tables 3 and 4?

Reply 5: LCNEC or adeno-squamous cell carcinoma, pleomorphic carcinoma, and carcinoid were included in non-Ad pathology. 1 patient with pleural dissemination was LCNEC.

Comment 6: After reading this paper, I get the image that the patients discussed in the paper underwent radical surgery b/c of "missed DPD" and were declared M1a later in their clinical course. But then I also got confused at one point that the patients were found to have unsuspected M1a at the time of surgery. Is the goal of the study to identify those patients with unsuspected M1a prior to surgery so as to avoid bringing them to the OR and starting them on systemic therapy sooner? However, I am not sure if most surgeons and oncologists would just start systemic therapy until proven M1a disease, at least in the US.

Reply 6: The purpose of this study is clarification of the risk factor of pleural dissemination. If the risk factor of pleural dissemination is identified, it might be able to detect the patients with DPD.

Comment 7: Under Discussion, page 6, lines 172-175, can the authors clarify the following statement "it might be necessary to be careful that young patients with NSCLC cannot deny that the possibility of development pleural dissemination earlier than elderly patients"?

Reply 7: I changed the sentence.

Changes in the text: Page 13, line 197-198.

Comment 8: In most patients with a preoperative biopsy, the grade of the tumor is not clear or even reported until definitive surgery. I am not entirely clear what the authors are suggesting - how can we use the final grade of tumor to predict the risk of DPD?

Reply 8: We described the risk factors (non-squamous, young age, and poor differentiation) related to pleural dissemination in conclusion section. We can not say anything more at this time.

Comment 9: Under Discussion, lines 184-190, are the authors suggesting to proceed with tumor resection despite DPD because the survival is better for those patients who underwent resection? What extent - lobectomy, bilobectomy, or just a wedge? This would be a paradigm shift on how we currently practice.

Reply 9: I added the sentence.

Changes in the text: Page 15, line 234-236.

Reviewer C

In this manuscript the authors performed a retrospective analysis of non-small-cell lung cancer (NSCLC) patients in order to identify predictive factors related to pleural dissemination of the tumor. The authors conclude that such clinicopathological factors could include cases with non-squamous cell carcinoma, a young age, and poor differentiation. The manuscript is well written and comprehensive, with solid statistical analysis. However, the small sample size consists a major limitation of the study.

Other minor comments:

Comment 1: Figure 1 should become more comprehensive. The authors should include arrows etc to label organs on the figure and to indicate the presence of pleural dissemination so as readers not acquainted with computed tomography photographs can understand the figure.

Reply 1: I added the label and changed figure legends.

Comment 2: I did not see any data concerning the presence of malignant pleural effusion formation. Are all the cases of pleural dissemination dry?

Reply 2: All cases with pleural dissemination of this study did not detect pleural effusion on CT.