Peer Review File
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Reviewer A

The authors provide a manuscript detailing the prognostic impact of pathologically confirmed rib invasion in patient with lung cancer requiring chest wall resection. I have the following comments:
Reply: Thank you for your comments regarding our manuscript. We have revised our manuscript in accordance with your comments.

1) Excellent manuscript, very well written. The authors should be congratulated!
Reply 1: Thank you for your favorable comments.
Changes in the text: None.

2)How were the surgeries performed? All open thoracotomies, any minimally invasive approaches? (Robotic or thoracoscopic). These details should be added to the manuscript.
Reply 2: Thank you for your questions regarding the approaches to chest wall resection and the methods of chest wall reconstruction.
Changes in the text: We have added further details regarding the surgeries (lines 151–152 in the unmarked manuscript).

3)How were the chest wall reconstructed? No reconstruction, patches, grafts, muscle flaps? These details must be added to the manuscript.
Reply 3: Thank you for your questions regarding the approaches to chest wall resection and the methods of chest wall reconstruction.
Changes in the text: We have added further details regarding the surgeries (lines 157–159 in the unmarked manuscript).

4)The legend for Fig 1 must expand the abbreviation p-rib (-/+) c-rib (-/+)
Reply 4: Thank you for pointing out the abbreviations in Figure 1.
Changes in the text: We have defined “p-rib” in the legend for Figure 1 (line 264 in the unmarked manuscript).

Reviewer B

The authors performed a single institution retrospective study of 44 patients with T3 (chest wall invasion) who underwent upfront surgical resection or neoadjuvant therapy followed by surgical resection. The authors found that pathological rib

invasion was associated with a worse prognosis as compared with those without rib invasion.
Reply: Thank you for the instructive comments regarding our manuscript.
We have revised our original manuscript in accordance with these comments, and we hope that the revised version is now suitable for publication.

Major Comments:
1. You included patients with clinical T3 tumors (Figure 1) regardless of rib involvement. Clarify whether these all had pathological T3 tumors (with and without rib invasion) and not other stages. Based on the data in the Abstract, it seems that 5 patients did not have pathological T3 tumors.
Reply 1: Thank you for your questions regarding the patient selection process. During the study period, 54 patients underwent lung resection combined with chest wall resection. After surgery, 10 patients were diagnosed with pT4 disease, and 2 patients had N2 disease. Thus, 42 patients with NSCLC who underwent chest wall resection were included in the study. Because we evaluated the prognostic impact of pathologically confirmed rib invasion in patients with lung cancer requiring chest wall resection, the five patients whose preoperative CT revealed an apparent osteolytic sign were included.
Changes in the text: None.

2. The manuscript needs to be more focused. The described aim of the study was to assess the prognostic impact of T3 with rib invasion vs T3 without. This aim gets lost in other details related to clinical rib invasion or not, induction therapy vs none, the diagnostic ability of CT to detect rib involvement, etc.
Reply 2: Thank you for your comments regarding the aim of this study. As you noted, the original version seemed to lack a clear focus. We have therefore revised the original manuscript to facilitate a greater understanding of the aim of this study. Because the descriptions of clinical rib invasion and the diagnostic ability of CT to detect rib invasion were somewhat confusing, we have deleted this content.
Changes in the text: We have extensively revised the text according to your comments.

3. I would limit your cohort to T3N0-1. Based on NCCN guidelines, we usually don't offer surgery to patients with chest wall invasion and N2 disease given the poor prognosis. Such patients are typically treated with definitive chemoradiation therapy followed by durvalumab. The number of patients in your study with N2 disease was small; I would remove them from your study since N2 disease could confound your findings.
Reply 3: Thank you for the instructive comments regarding the selection criteria in this study. We agree that it would be better to limit our cohort to patients with T3N0-1 disease. We therefore omitted the two patients with N2 disease.
Changes in the text: We have changed our cohort to include only patients with T3N0-1 disease (lines 135–138 in the unmarked manuscript).

4. According to NCCN guidelines, upfront surgery is typically the preferred treatment for T3N0/1 disease. Why did you perform neoadjuvant therapy, especially for those without clinical evidence of rib invasion? Was the disease too extensive? Did patients refuse surgery?
Reply 4: Thank you for your questions regarding the treatment for T3N0/1 disease. As you noted, upfront surgery is typically considered the best treatment for T3N0/1 disease without apparent clinical evidence of chest wall invasion. We considered that rib invasion might be a prognostic factor for tumors with chest wall invasion, and tumors with apparent rib invasion tend to be treated by preoperative therapy followed by surgery. Although the decision to administer induction chemoradiotherapy was determined by the extension of chest wall invasion and tumor resectability, all patients agreed to undergo surgery and received intentional induction therapy.
Changes in the text: None.

5. The Results section is hard to follow. Limit repeating information provided in the tables and highlight the salient points of those tables in a clear and concise fashion. For instance, you might rewrite lines 138-140 as "As compared with those without it, rib invasion was associated with a significantly (p=0.023) higher rates of locoregional recurrence (22.2% vs. 7.7%) and distant recurrence (33.3% vs. 19.2%)."
Reply 5: Thank you for the instructive comments regarding the Results section. We have revised the Results section for greater clarity and conciseness.
Changes in the text: We have revised the above-mentioned text accordingly (lines 179–181 in the unmarked manuscript).

6. You stated in your limitations section of the Discussion that the prognostic impact of rib invasion needs to be studied prospectively. Such prospective collection of data is how the AJCC staging system is periodically revised. Based on your study, should T3 chest wall tumors be reclassified based on rib invasion? What do you recommend for the next edition?
Reply 6: Thank you for the instructive comments regarding future classification of T3 chest wall tumors. In our study, the prognosis of T3 tumors without pathological rib invasion was significantly better than that of T3 tumors with pathological rib invasion. Moreover, when compared with previous reports from our institution, the prognosis of T3 tumors with pathological rib invasion was similar to that of T4 disease (the 5-year overall survival rate was 56.3% in our institution) (Prognostic factors related to postoperative survival in the newly classified clinical T4 lung cancer. Eur J Cardiothorac Surg. 2020 Apr 1;57(4):754-761). Although this analysis had some limitations, pathological rib invasion may be reclassified as T4 disease; the same findings were reported by Zhao et al. (Proposal for rib invasion as an independent T descriptor for non-small cell lung cancer: A propensity-score matching analysis. Lung Cancer. 2021 Sep;159:27-33).
Changes in the text: We have revised the Discussion section (lines 210–213 in the unmarked manuscript).

Minor Comments:

1. The Abstract needs work. In particular, much of the details of in the Results section of the Abstract is distracting and unnecessary to meeting the objective detailed in the Background section. Focus on the prognostic impact of rib invasion (lines 41-47).

Reply 1: Thank you for your instructive comments regarding the abstract. We have revised the abstract in accordance with these comments.
Changes in the text: We have revised the abstract (lines 42–69 in the unmarked manuscript).

2. State your hypothesis at the end of the Introduction.

Reply 2: Thank you for your instructive comment regarding the hypothesis.
Changes in the text: We have added our hypothesis to the end of the Introduction (lines 97–98 in the unmarked manuscript).

3. Was the difference in complications with and without induction therapy significantly different (lines 130-136).

Reply 3: Thank you for your question regarding the postoperative complications. Clavien–Dindo grade >IIIa postoperative complications occurred in 7 (16.7%) of 42 patients. Among the 15 patients who underwent surgery without preoperative treatment, 1 patient developed chylothorax and another patient developed prolonged air leakage requiring pleurodesis. Three of 27 patients who underwent surgery following induction chemoradiotherapy developed persistent pleural effusion requiring repeat drainage, and 1 developed acute respiratory distress syndrome requiring intravenous steroids. The occurrence rate of Clavien–Dindo grade >IIIa postoperative complications was similar.
Changes in the text: We have added these findings to the manuscript (lines 171–173 in the unmarked manuscript).

4. In the Discussion, you stated that "the prognostic impact of rib invasion is unknown" (line 172). You studied this, so it's no longer unknown.

Reply 4: Thank you for your comments. As you noted, we concluded that rib invasion might be a prognostic impact factor. Therefore, we have revised the Discussion.
Changes in the manuscript: We have revised the Discussion (lines 198–202 in the unmarked manuscript).

5. Why do you think CT in your study performed better for diagnosing rib invasion compared with other studies (lines 176-178).

Reply 5: Thank you for your question regarding the diagnostic yield of CT for rib invasion. In our institution, we performed 0.5-mm thin-slice CT, which might be why CT could more precisely detect rib invasion than other modalities. However, because our original manuscript needed to focus on the prognostic factors of rib invasion, and because the descriptions regarding the diagnostic yield of CT were somewhat

confusing, we have omitted these descriptions.
Changes in the manuscript: We have deleted the descriptions regarding the diagnostic yield of CT for rib invasion by lung cancer.

Reviewer C

Authors submitted their manuscript entitled « Prognostic impact of pathologically confirmed rib invasion in patients with lung cancer requiring chest wall resection" to JTD.
They performed a retrospective study including 44 patients, emphasizing the comparison between patients with or without rib invasion, either clinical or pathological. They observed a negative prognostic impact of pathological rib invasion, and highlighted the importance of multimodal strategies.
I congratulate the author for this manuscript, but I have some comments:
1. English is ok.
2. 6 out of 44 patients (14%) underwent a sublobar resection extended to the chest wall. I am surprized by the choice to perform a sublobar resection in a locally advanced non-small cell lung cancer. Do you have the reasons of the decision to perform sublobar resection in those patients? Please comment on that.
Reply 2: As you commented, sublobar resection is not usually selected for locally advanced lung cancer. In this study, the lung resections comprised 36 lobectomies, 5 segmentectomies, and 1 wedge resection with resection of 2.5 ribs on average. Sublobar resection was selected in the patients without nodal metastasis to maximize operative tolerability based on assessment of the patients' preoperative cardiopulmonary function.
Changes in the manuscript: We have added the above information to the manuscript (lines 154–155 in the unmarked manuscript).

3. The cohort is heterogeneous regarding perioperative treatment modalities, and the number of cases is small and excluding the possibility of a matching procedure to enhance the comparison between the two groups (usually perform in retrospective study to reduce biases). This is a serious limitation.
Reply 3: We agree with your comment regarding this limitation.
Changes in the manuscript: We have added this limitation (lines 245–251 in the marked manuscript).

4. References are a bit out-dated in my opinion. More recent reports are available on the same topic. As an example, I strongly suggest to consider the following reference, on the same topic with a larger cohort: Zhao M et al. Proposal for Rib invasion as an independent T descriptor for non-small cell lung cancer: A propensity-score matching analysis. Lung Cancer. 2021 Sep;159:27-33.
Reply 4: As you recommended, we have cited the report by Zhao et al.
Changes in the manuscript: We have added the above-mentioned reference (line 208

in the marked manuscript).

5. Correlation between clinical (CT-scan) and pathological rib invasion (pathology) is of interest. Could the model be improved with radiomics? Please comment on that.
Reply 5: Thank you for the instructive comment regarding the correlation between CT findings and rib invasion. Radiomics would enhance the accuracy of diagnosis of rib invasion. However, because we focused on the prognostic impact factors of pathological rib invasion and omitted the diagnostic yield of CT, we would like to focus on this issue in a future study.
Changes in the manuscript: None

Reviewer D

The article by Yojiro Yutaka and his colleagues entitled " Prognostic impact of pathologically confirmed rib invasion in patients with lung cancer requiring chest wall resection " is an exciting study. This could be an excellent paper to help treat chest wall invasion lung cancer. I want to express my respect to the authors for their efforts. However, it will require some revisions to show the difference from existing papers.

Major revision
・Line 114 – 116 Nine patients suspected clinically to have N2 disease received induction chemoradiotherapy; preoperative PET-CT showed the disappearance of FDG uptake in the N2 lymph nodes.
Do these cases histologically prove N2? If they are chest wall invasion and N2, we must be cautious about the indication for surgery. Is there any need to mention this matter?
Reply: Thank you for your question regarding the optimal treatment of N2 disease. As Reviewer D pointed out, when persistent multiple N2 disease is suspected after preoperative treatment, we do not select surgery. Operative treatment is indicated for lung cancer with chest wall invasion without N2 disease, and we have added this information to the manuscript.
Changes in the manuscript: We have added the above-mentioned information to the manuscript (lines 149–151 in the unmarked manuscript).

・Line 116 – 118 Six cases received sublobar resection.
Does this mean that they were lobectomy intolerable cases? What is the extent of lymph node dissection in these cases?
Reply: Thank you for your questions regarding sublobar resection. Sublobar resection was performed in the patients who were unable to tolerate lobectomy. In these patients, lymph node dissection was conducted to the same extent as in the patients who underwent lobectomy.
Changes to the manuscript: We have added the above-mentioned information to the

manuscript (lines 154–157 in the unmarked manuscript).

・Table 2
Please explain the details of local recurrence.
Also, in cases of local recurrence, do you perform lobectomy or sublobar? What is the N2 status?
Reply: Thank you for your question regarding the details of local recurrence. Recurrence was suspected in the presence of a growing shadow in the chest wall around the surgical margin on CT. Among six patients who underwent sublobar resection, recurrence was confirmed in five patients, and all of them had distant metastases. None of the four patients with N1 disease developed recurrence.
Changes in the manuscript: We have added this information to the text and Table 2 (lines 177–179 in the unmarked manuscript).

・How about treatment after recurrence?
Reply: For patients with multiple recurrences, chemotherapy was selected; however, when recurrence was suspected in only one site, chemoradiotherapy was selected.
Changes to the manuscript: None.

Depending on the presence or absence of driver mutation and the status of TPS, the choice of adjuvant therapy after recurrence may change and affect the prognosis.
Reply: Thank you for your comment regarding immunotherapy. As you pointed out, immunotherapy might change the prognosis. However, our study included previous cases when immunotherapy was not included in the standard treatment regimen, and none of the patients had EGFR driver mutation (40 patients were smokers). Although the potential effect of adjuvant therapy including immunotherapy on the prognosis should be considered, the additional description regarding immunotherapy seems to have introduced confusion. Therefore, we have revised the limitations section accordingly.
Changes in the manuscript: We have revised the manuscript as noted above (lines 249-251 in the unmarked manuscript).

Line 174-178
Is CT the only modality used to diagnose chest wall invasion preoperatively? MRI and chest wall echography have been reported to be effective.
Reply: Thank you for your question regarding the diagnostic modalities for chest wall invasion. As you noted, MRI and echography have been reported to be effective. As the other reviewers pointed out, our manuscript should be focused on the prognostic impact of pathological rib invasion; therefore, we have omitted the descriptions regarding the diagnostic yield of CT.
Changes in the manuscript: We have omitted the descriptions regarding the diagnostic yield of CT.

・Table 3

I agree that N2 disease is essential to address, as is chest wall invasion, which the authors also mention, but why was pathological nodal status not a prognostic factor in the authors' analysis?
Reply: Thank you for your question regarding the pathological nodal status as a prognostic factor. The nodal status has been shown to be an important prognostic factor in other research; however, it was not revealed to be a prognostic factor in the current study. Although the current study focused on T3N0-1 disease, the small number of nodal-positive cases may be the main reason that the nodal status was not a prognostic factor.
Changes in the manuscript: None.

Reviewer E

Thank you for the submission of your article to our journal. I've just read your manuscript and felt many problems as follows;

Major point
You should describe how you pathologicaldy determined the total cancer cell kill in the ribs when no viable cancer cell residuals were observed in the ribs after preoperative chemoradiotherapy.
You should not exclude the five patients with pathological complete response.
Reply: Thank you for your comments regarding the patient selection process.
Changes in the manuscript: We have added 5 patients with a pathological complete response, resulting in a total of 42 patients in the current study.

Minor points
Line 87 You should not use the abbreviation of FDG-PET at its first appearance in the text.
Reply: Thank you for your comment regarding the abbreviation "FDG-PET."
Changes in the manuscript: We have removed this abbreviation because the term is used very few times throughout the text; we have instead left the term spelled out (lines 117-118 in the unmarked manuscript).

Line 90 How did you get IC from the deceased patients? And could you really obtain IC from all alive patients.
Reply: Thank you for your comments regarding IC in this study. At the time of surgery, we obtained informed consent for the future observational study that would be performed for analysis of prognostic factors. Moreover, in each study, we used an opt-out approach. Unless the patients provided their express desire to be excluded, we included the patients in the current study.
Changes in the manuscript: None.

Line 115 Do not abbreviate PET-CT and FDG at its first appearance.
Reply: Thank you for your comment regarding these abbreviations.
Changes in the manuscript: We have removed these abbreviation because the terms are used very few times throughout the text; we have instead left the terms spelled out (lines 117-118 in the unmarked manuscript).

Line 116-7 The sentence “The lung resections comprised 38 lobectomies, 5 segmentectomies, and 1 wedge resection were performed with resection of 2.5 ribs on average. “ is grammatically strange.
Reply: Thank you for your comment regarding the grammar of this sentence.
Changes in the text: We have revised the sentence accordingly (lines 117–118 in the unmarked manuscript).

122 You should describe “others in 5 (○ %)”.
Reply: Thank you for your advice.
Changes in the manuscript: We have accordingly revised the description (lines 158-160 in the unmarked manuscript).

Line 133 Is the expression “Clavien-Dindo classification above IIIa” is true?
Reply: Thank you for your question regarding the CD classification. Clavien–Dindo grade >IIIa postoperative complications occurred in 7 (16.7%) of 42 patients. Because the description regarding the CD classification is correct, we have not changed the description (we have only slightly modified it for clarity).
Changes in the text: None.