Peer Review File

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Reviewer A

It is an interesting paper to read and could provide further insights in multidisciplinary tumor board decision making for early stage lung cancer patients.

Please find my comments below per section.

General

C1. Please check for spelling errors and other errors in the free text.

R1. We appreciate your comments and fully understand your concerns. We re-checked the spelling errors, and the term "visceral pleural invitation" was used repeatedly, so we substituted it with the abbreviation VPI.

C2. The paper is well structured.

R2. Thank you for your comment.

C3. Why only investigate stage IB with pleural invasion? Beneficial to minimize confounding, but outcomes are not generalizable to other patients with early stage lung cancer.

R3. This is an excellent point, which we should have addressed more clearly in the original manuscript.

Adjuvant chemotherapy (ACT) serves as the standard treatment for patients presenting with large tumors and positive lymph nodes. Nevertheless, its influence on overall survival (OS) in cases of stage I lung cancer (0- to <4-cm tumors without lymph node involvement) exhibits variability. Recent research has stratified stage I patients based on risk factors, revealing improved survival among high-risk individuals, where visceral pleural invasion (VPI) is one of the contributing risk factors, upon receiving adjuvant chemotherapy.

Current international guideline advocate for ACT in stage IB lung cancer, encompassing even smaller T2a tumors, if they exhibit high-risk factors. These high-risk factors encompass not only VPI but also other indicators such as vascular invasion, poorly differentiated tumors, wedge resections, and indeterminate lymph node status. Previous research has highlighted the intricate interplay among these factors. However, prompting this study to concentrate on assessing the impact of VPI on prognosis and the role of ACT in patients with 1-4 cm (stage IB) NSCLC with VPI. This is why we investigate stage IB with VPI.

As reviewer concerned, we mentioned this in the limitations section that generalizing

these findings may be challenging.

C4. What factors determined the indication for adjuvant chemotherapy? Could there have been a significant selection bias, which had a major impact on the results?

R4. We appreciate your comments and fully understand your concerns.

This study aimed to closely mirror real-world clinical settings. When considering the application of adjuvant chemotherapy (ACT) for patients with early-stage lung cancer, we must consider a multitude of criteria, including age, performance status, and the presence of high-risk factors. In this manuscript, we specifically concentrated on one of the high-risk factors outlined in the NCCN guidelines, which is visceral pleural invasion (VPI). Consequently, we excluded patients with neuroendocrine tumors (n=5) and those with 1-4 cm (stage IB) NSCLC who exhibited other high-risk factors but lacked VPI (n=26).

We firmly believe that these exclusions did not introduce any significant bias into our study. Nevertheless, it is essential to acknowledge in the limitations section that the findings of this study may not be universally applicable, given that they were derived under specific conditions and based on selective criteria. Therefore, we already mentioned these in limitation section (*First, given its retrospective nature, the study is subject to selection bias.... Lastly, clinicians decided to administer adjuvant chemotherapy based on several factors, which may have introduced bias*.)

Abstract

C5. Background: Is the only aim to explore prognostic significance of adjuvant chemotherapy? Or are you also interested in clinical significance and possible recommendations for treatment decision making in these patients?

R5. We appreciate your comments and fully understand your concerns. Thus, we have tried to better explain the objects for our study, see the revised manuscript in the Background section of the Abstract.

Page 3, line 43

The aim of this study was to explore the ***clinical and*** prognostic significance of adjuvant chemotherapy for stage IB (1–4 cm) non-small cell lung cancer (NSCLC) with VPI.

C6. Conclusions: Change "Our study suggests that adjuvant therapy may be appropriate….". Your study "shows" that adjuvant therapy "is" appropriate in terms of recurrence free survival and overall survival.

In general a study always "shows" something, regardless of the result being positive, negative, significant of insignificant, a study does not "suggest".

R6. Thank you for your comment. Please see the revised manuscript in the Conclusions section of the Abstract.

Page 3, line 61-62

Conclusions: Our study ***shows*** that adjuvant chemotherapy ***is*** appropriate for patients with stage IB (1–4 cm) NSCLC with visceral pleural invasion, and even those with smaller tumors (1–3 cm).

Introduction

C7. In the first paragraph: do you mean that the current NCCN guidelines are not evidence based enough since the impact of the risk factors on clinical outcomes in stage IB NSCLC patients is not considered? Please rewrite the first paragraph so it is clear what risk factors are used now to consider adjuvant therapy and why you think other risk factors (like pleural invasion) should be considered. Why do you do this study precisely?

R7. We appreciate your comments and fully understand your concerns.

We wrote the Introduction to highlight high-risk factors that may be associated with poor prognosis, even in cases of low-stage disease, as suggested in the NCCN guidelines. However, there is a lack of evidence regarding their specific effects in only stage IB NSCLC patients. Additionally, due to the clinical significance of VPI (as referenced in Introduction paragraph 2), we wanted to know the impact of VPI alone on solely stage IB NSCLC patients. We also aimed to explore the differences that arise when other risk factors are added on VPI.

The risk factors (poorly differentiated tumors, vascular invasion, wedge resection, visceral pleural invasion, and incomplete lymph node sampling) presented in the NCCN guidelines have already been mentioned in the main text.

We have made some modifications to the description of the background section of our study, respecting the reviewer's recommendations.

Page 5, line 84-88

Before: However, the guidelines simply state these risk factors as considerations for adjuvant chemotherapy in stage IB NSCLC and do not consider the impact of these risk factors on clinical outcomes in patients with stage IB NSCLC treated with adjuvant chemotherapy. Therefore, the decision to administer adjuvant chemotherapy should be individualized based on specific high-risk factors.

After: *However, the guidelines briefly describe these risk factors as considerations for adjuvant chemotherapy for stage IB NSCLC, and it is not enough to know what kind of prognosis each risk factor shows in stage IB patients classified as relatively low stage. Additionally, the effects when various factors are combined are not well known.*

C8. Does this study then only investigate pleural invasion, or does it combine other risk

factors as well, and why? This is not very clear.

R8. Thank you for your comment. We have revised the manuscript to be clearer than before.

Page 5-6, line 95-99

The aim of this study *was to correlate adjuvant chemotherapy to recurrence free and overall survival* in patients with stage IB (1 – 4 cm) NSCLC with visceral pleural invasion, and to investigate the effectiveness of adjuvant chemotherapy ***when other risk factors are added in those patients with visceral pleural invasion.*** ~~*in patients with visceral pleural invasion and other risk factors.*~~

C9. Move the following sentence to the "Methods" section: "To analyze the individual contribution of visceral pleural invasion and evaluate the interaction of visceral pleural invasion with other risk factors, we selected patients with stage IB NSCLC with visceral pleural invasion from a previous study".

R9. Thank you for your comment. We moved that sentence in Methods section.

Introduction -> Methods Page 6, line 108-110

To analyze the individual contribution of visceral pleural invasion and evaluate the interaction of visceral pleural invasion with other risk factors, we selected patients with stage IB NSCLC with visceral pleural invasion from a previous study (13). ~~*Of the six high risk factors mentioned in the NCCN guidelines, we focused on visceral pleural invasion.*~~

C10. For clarity purposes: consider this for the last sentence of the introduction: "The aim of the study was to correlate adjuvant chemotherapy to recurrence free and overall survival in stage IB NSCLC patients with pleural invasion". Instead of stating the aim was to look into "prognostic significance" of adjuvant therapy.

R10. Thank you for your comments. We agree with your suggestions. As per the reviewer's recommendations, we revised the sentences in the Introduction Section as below.

Page 5-6, line 95-99

The aim~~s~~ of this study ~~*were*~~ ***was*** to correlate ~~*determine the prognostic significance of*~~ adjuvant chemotherapy ***to recurrence free and overall survival*** in patients with stage IB (1 – 4 cm) NSCLC with visceral pleural invasion, and to investigate the effectiveness of adjuvant chemotherapy when other risk factors are added in those patients with visceral pleural invasion.

Methods

C11. Study design and participants: Do not mention results in the methods section. Clearly state inclusion and exclusion criteria, but do not mention number of patients, follow-up time

etc. already, since that belongs in the results section.
R11. Thank you for your comments. We moved the number of patients and follow-up time in Result section as you recommended.

Page 6, line 102
We retrospectively examined the medical records of ~~*285*~~ patients with T2aN0M0 (stage IB) (≤ 4 cm) NSCLC with high-risk factors from four Korean hospitals.

Page 8, line 154-156
*Total 285 patients were analyzed. Patients with T1a (≤ 1 cm) (n=3) or neuroendocrine tumors (n = 5) were excluded. Additionally, patients with stage IB (1 – 4 cm) NSCLC with high-risk factors other than visceral pleural invasion (n = 26) were excluded (**Figure 1**).*

C12. Examination and Treatment modalities: Again, the first three sentences belong in the "results" section. If other types of surgery than lobectomy, R1/R2 resection or lymph node metastases are exclusion criteria, please mention it like that. Now it is written as a result.
R12. Thank you for your comments.

Page 8, line 158-161
All patients underwent lobectomy and complete lymph node dissection. None of the patients underwent pneumonectomy, bilobectomy, segmentectomy, or wedge resection. All patients underwent R0 resection. There was no evidence of cancer in the lymph nodes (N0).

C13. Please elaborate on the criteria that were used to either assign a patient to the observation group or the adjuvant chemotherapy group. It was not a randomized controlled trial, so how was this decision made?
R13. We recognized the lack of our explanation about assignment of study groups.
This study is a retrospective study. Each clinician used adjuvant chemotherapy according to the researcher's individual judgment, considering various clinical situations at the time of encountering patients and NCCN guidelines. Therefore, it was bound to cause bias or become a limitation in our study. In regards to your comments, we elaborated these limitations in Discussion.

Page 13, line 280-281
Lastly, clinicians decided to administer adjuvant chemotherapy based on several factors, which may have introduced bias.

C14. Why and how were the subgroups made and defined? Based on literature? Arbitrary? Interesting to add a subgroup without pleural invasion?
R14. Thank you for your comment.

We conducted a subgroup analysis, which separately analyzed tumors measuring 1-3 cm within stage IB to assess the size's impact, and also performed a subgroup analysis focusing solely on adenocarcinomas to examine the differences based on pathology. Furthermore, within each subgroup, we aimed to evaluate the effects of including other risk factors recommended in the NCCN guidelines alongside VPI. Therefore, during the subgroup analysis, we used categories such as "≥ 1 risk factor including VPI (overall)" and "≥ 2 risk factors including VPI".

Results

C15. Baseline characteristics: As mentioned before, please import the patient selection data mentioned in the Methods.

R15. Thank you for your comments. We moved some part of Methods section into Result section as you recommended. (*See **C11 & 12***)

C16. Recurrence-free survival and Overall survival in total patients: The paper reads more easily if you don't use "respectively". For example change: "Recurrence was observed in 24 (19.7%) of 122 and 34 (26.4%) of 129 patients in the adjuvant chemotherapy and control groups, respectively (p=0.209)" to: "Recurrence was observed in 24 (19.7%) of 122 patients in the chemotherapy group, and in 34 (26.4%) of 129 patients in the control group (P=0.209)". Please change this throughout the results section.

R16. Thank you for your comment. Please see the revised manuscript.

Page 9, line 176-177

Recurrence was observed in 24 (19.7%) of 122 ***patients in the chemotherapy group, and in 34 (26.4%) of 129 patients in the control group (p = 0.209)***.

C17. The values (CI and P-value) given in the text are not always consistent with table 2, please double check.

R17. Thank you for your comments. We revised and rechecked the value.

Page 9, line 188-190

In the multivariable analysis, the adjuvant chemotherapy group had a lower risk of recurrence than the control group (adjusted HR, 0.57 [95% confidence interval (CI): 0.33–0.9***6***]; p=0.03***6***).

Discussion

C18. Again, please do not use sentences with "respectively" since this is harder to read and understand.

R18. We removed "respectively".

Page 11, line 226-229

Park et *al*. (2) and Zhang et *al*. (3) suggested that patients with stage IB NSCLC with visceral pleural invasion did not benefit from adjuvant chemotherapy. However, these single-center retrospective studies had relatively small sample sizes, with 27 and 22 patients with stage IB NSCLC with visceral pleural invasion receiving adjuvant chemotherapy~~, *respectively*~~(9,17).

Page 12, line 244-247

A ***United States*** study using the National Cancer Database(4) showed that, for all tumor sizes combined, patients with visceral pleural invasion who received adjuvant chemotherapy had a significantly better 5-year OS rate than those who did not receive adjuvant chemotherapy (65.5% vs. 58.8%~~, *respectively*~~; $p < 0.001$).

C19. Please write out "US" fully, it is not mentioned as an abbreviation in the manuscript before.

R18. We rewrote "US" as "United states".

Page 12, line 244

A ***United States*** study using the National Cancer Database(4) showed that, for all tumor sizes combined, patients with visceral pleural invasion who received adjuvant chemotherapy had a significantly better 5-year OS rate than those who did not receive adjuvant chemotherapy (65.5% vs. 58.8%; $p < 0.001$).

C20. Your compare your study with a lot of other studies in your discussion session, could you elaborate on why you think some of the results are different in you study when compared to other studies you mention?

R20. Thank you for your comment.

We presume that the variations in study outcomes are attributable to disparities in the stages and sizes encompassed in each study and the characteristics (age, sex, and race) of the study populations. Indeed, many studies did not exclusively focus on stage IB patients. Studies that included only stage IB had a small number of studies and the study population size included in the study was also small.

Our study investigated whether adjuvant chemotherapy was administered to a total of 251 Asian patients with VPI who underwent lobectomy alone. While our study is retrospective and has several limitations, it contributes additional evidence regarding the impact of adjuvant therapy in stage IB, particularly in cases involving VPI or various additional risk factors alongside VPI.

The differences between each study have already been explained in the Discussion section, and the fact that differences in conditions between each study may have led to differences in

results is also described in the Discussion as below.

Page 11, line 225-226
The stages and sample sizes in each study were different, and this may have affected the reporting of results.

Page 11, line 228-229
Park et al. (9) and Zhang et al. (17) suggested that patients with *stage IB NSCLC with visceral pleural invasion* did not benefit from adjuvant chemotherapy. *However, these single-center retrospective studies had relatively small sample sizes, with 27 and 22 patients* with stage IB NSCLC with visceral pleural invasion receiving adjuvant chemotherapy.

C21. Is it possible to still include PL1 and PL2 in your analysis since it shows significant survival differences? Or is this not available for your patient group?
R21. Thank you for your comment. We already mentioned this limitation in Discussion section (***In this study, we could not evaluate RFS and OS according to PL1 or PL2.***).

C22. In the conclusion you could state that adjuvant chemotherapy is effective in the population that you studied, but that further prospective studies, including research into toxicity and PL1-PL2 status etc. should be done before these outcomes can be further implemented into treatment decision making.
R22. We agree with your suggestions. We have revised the sentences in regard to reviewer's recommendation.

Page 13, line 286- page 14, line 292
In conclusion, adjuvant chemotherapy ***appeared to provide better*** RFS and OS in patients with stage IB NSCLC with visceral pleural invasion ***compared to the control group***. Adjuvant chemotherapy also ***provided better*** RFS and OS of patients with tumor size 1–3 cm and visceral pleural invasion compared to the control group. ***We suggest that*** adjuvant chemotherapy ~~may be effective in~~ ***offered to*** patients with stage IB NSCLC with visceral pleural invasion regardless of tumor size (>1 cm). ***To support our findings, additional prospective studies, including information on toxicity and PL1-PL2 status, should be conducted in the future.***

Reviewer B

This is a timely and important piece of work, conducted in a straightforward and well-designed manner.

C1. I have only one minor revision to suggest. I think that the discussion states the causal link between chemotherapy and outcome slightly too strongly for a retrospective study- please do not say that adjuvant treatment 'improved' outcomes or had beneficial 'effects'- these must remain associations until prospectively tested.

R1. Thank you for your comment. We revised the wording of what the reviewer said in the discussion section, and we toned down the expression in presenting our research results.

Page 13, line 286- page 14, line 292

In conclusion, adjuvant chemotherapy ***appeared to provide better*** RFS and OS in patients with stage IB NSCLC with visceral pleural invasion ***compared to the control group***. Adjuvant chemotherapy also ***provided better*** RFS and OS of patients with tumor size 1–3 cm and visceral pleural invasion compared to the control group. ***We suggest that*** adjuvant chemotherapy ~~may be effective in~~ ***offered to*** patients with stage IB NSCLC with visceral pleural invasion regardless of tumor size (>1 cm). ***To support our findings, additional prospective studies, including information on toxicity and PL1-PL2 status, should be conducted in the future.***

Reviewer C

In their retrospective multicentre study, the authors have analysed the impact of adjuvant therapy in stage IB NSCLC surgically treated patients with visceral pleural invasion. After investigating 251 patients (122 received adjuvant chemo) the authors concluded that adjuvant chemotherapy had a beneficial effect on RFS and OS in patients with stage IB NSCLC with visceral pleural invasion. Moreover, they stated that adjuvant chemo may be effective in patients with stage IB NSCLC with visceral pleural invasion regardless of tumour size (>1 cm).

I have read with particular interest this paper, especially because treatment of the stage IB because of its heterogeneity, is still a matter of debate.

• Abstract: please insert the time frame also in the abstract, in the method paragraph

R. Thank you for your comment. We added the time frame in the abstract.

Page 3, line 46-47

This retrospective study included 251 patients ***admitted between January 2008 and May 2018*** from four hospitals who underwent complete resection for TNM 8th edition stage IB NSCLC with visceral pleural invasion.

• Introduction: offers a precise and concise overview on the issue.
• Methods: well-articulated and accurate
• Results: accurate and detailed presentation
• Discussion: clear and comprehensive
• Tables: interesting and not redundant.

C1. However, I have a big concern: in the present study the mutational status of the resected patients hasn't been analysed. In my opinion this factor is important, especially since the ADAURA study showed a clear benefit of Osimertinib in EGFR mutated Stage IB resected NSCLC patients.

A comment on this aspect should be added, if mutational status has not been collected, a paragraph in the "limitation" section should be included.

R1. Thank you for your comment. We added this limitation in Discussion section.

Page 13, line 278-280

Additionally, our study did not investigate information on the mutation status of cancer-related genes, such as EGFR and ALK. Therefore, we were unable to provide additional information on this aspect.

Reviewer D

The authors should be complimented on their work. They have retrospectively reviewed patients from 4 hospitals with visceral pleural invasion and tumors of sizes ranging from 1-4cm. Their findings show that those patients receiving adjuvant chemotherapy, have improved OS and RFS.

C1. Can the authors comment on why none of the patients, with tumors ranging from 1-4cm, underwent segmentectomy? How many patients had to be excluded for non-platinum based adjuvant chemotherapy? Figure 1 seems to show that no patients had to be excluded for any reasons mentioned in the methods (like wedge resection, unknown lymph node status, non-platinum based adjuvant chemo, neoadjuvant chemo, or radiotherapy)

R1. Thank you for your comment.

This study is based on previously published studies that outlined detailed exclusion criteria based on reviewer comments. For clarity and better understanding of the reader, this article only mentioned details of patients who were additionally excluded for the purpose of this study.

Patients excluded as follows: (1)

6 Death within 30 days of surgery
89 Stage IA
186 Stage IIA to IIIB
39 Surgical margin positive
39 Lost to follow-up
138 No high-risk factors
19 Neoadjuvant therapy or radiotherapy
2 Non-platinum-based chemotherapy
3 Not completed 4 cycles

In our previous study, only patients who underwent lobectomy, the standard treatment, were selected to exclude bias from the extent of surgical resection, so there were no patients who had surgical resection other than lobectomy. We additionally mentioned this in the methods section.

Page 6, line 119-120

Our previously published study and this study included only patients who underwent lobectomy.

Reference

1. Choi J, Oh JY, Lee YS, et al. Clinical efficacy of adjuvant chemotherapy in stage IB (< 4

cm) non-small cell lung cancer patients with high-risk factors. Korean J Intern Med 2022;37:127-36.