

## Peer Review File

Article information: <https://dx.doi.org/10.21037/apm-23-526>

### Reviewer A

1. Line 80-87: the most recent NCCN guideline is from 03. 2023, which needs to be updated in the manuscript (2020 version). Also, the recommendation also included neoadjuvant chemotherapy and immunotherapy, which needs to be included.

Reply 1: The manuscript has been updated and corrected to the latest NCCN guideline version 2023.03 in accordance with the latest guideline. Additionally, neoadjuvant chemotherapy and immunotherapy were also added to the treatment options.

Page 6, lines 71 – 74: Systemic therapies, such as neoadjuvant/adjuvant chemotherapy and targeted immunotherapies, are recommended for patients with stage IIIB and stage IV NSCLC.

2. Line 143-147: the definition of Group B and C is somewhat confusing. Group B: “Patients failed to start adjuvant chemotherapy (less than 4 times for chemotherapy) or radiation therapy and stopped adjuvant treatment after standard surgery.” Was postop radiation also considered as adjuvant treatment in your study or just chemotherapy? “stopped adjuvant treatment after standard surgery”, does it mean the treatment was started before the surgery? Post-operative is reserved for only selected patients e.g., positive margins. Please clarify. Group C: “patients received limited resection”. Did the Group C patient have chemotherapy? The number of patients who received chemotherapy and/or RT should be listed in your results table.

Reply 2: In this study, for group B, both chemotherapy and radiation therapy were considered adjuvant treatments after surgery. Discontinuation of adjuvant treatment after standard surgery refers to stopping adjuvant treatment (chemotherapy or radiation therapy) after surgery. Radiotherapy was applied only to selected patients with positive margins.

Group C included patients who received either chemotherapy or radiation therapy after undergoing limited resection. Because the number of patients was small, the chemotherapy group and radiation therapy group were not classified separately, and the number of patients in group C was the same.

Page 9, lines 119 – 123: Group B included patients who were not provided adjuvant chemotherapy (less than 4 chemotherapy sessions) or radiation therapy after standard surgery. Group C included patients who underwent limited resection (wedge resection and segmentectomy) because of poor condition or refusal of standard surgery for any reason.

3. Line 178: please clarify why performance status is not included in the propensity score matching. If not included, it should be adjusted in your model.

Reply 3: Performance Status is included in propensity score matching. Due to the

presence of lots of data and variables, they were missed. The main text has now been modified to include performance status.

Page 11, lines 154 – 155: Covariates included in the propensity score matching were age, sex, BMI, performance status (PS), clinical stage, and pathological stage.

4. Line 201-204, please define all the abbreviations at first appearance, EBUS-TBNA, PCNA etc.

Reply 4: Abbreviations such as EBUS-TBNA, PCNA, etc. have been defined and added in the main text.

Page 13, lines 179 – 182: Preoperative diagnostic tools included bronchoscopy (32.5%), endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA, 13.0%), percutaneous needle aspirations (PCNA, 46.2%), surgical biopsy (95.1%), and Lymphnode biopsy (2.6%).

5. Line 277-281. This sentence is very confusing. Please rewrite.

Reply 5: It has been rewritten. “For patients with advanced lung cancer who cannot undergo surgery, targeted immunotherapy and stereotactic body radiation therapy (SBRT) may be another treatment option.” It was rewritten as.

6. Line 290-292: “However, it was not easy for the remaining patients to complete standard surgery or adjuvant chemotherapy due to death, cost, or other co-morbidities.” I don’t think I completely understand this sentence. The reasons why people undergo Group B and Group C were not presented in your results.

Reply 6: This is the meaning of “For patients with stage 2 or 3 lung cancer, lung cancer surgery or chemotherapy may not be completed due to various complex reasons such as the patient's physical ability, economic situation, or co-morbidity.”

7. Line 295: the 5-year relative survival rate of what disease is 32.4%?...

Reply 7: The total lung cancer survival rate was 34.7% in 2015-2019, and a numerical error was entered and corrected.

8. Line 297-304: you are repeating results here.

Reply 8: Thank you for pointing out. The presentation of repeated results has been deleted.

9. It would be helpful to list the insurance coverage, and drug costs in Korea, as many newer drugs such as neoadjuvant or adjuvant immunotherapy and TKIs (i.e. osimertinib in EGFR mutated lung cancer) have shown survival benefits. Your study will have merit only if you show that those drugs are extremely expensive and not covered by insurance. Is immunotherapy used in the metastatic lung cancer in Korea?

Reply 9: Thank you for pointing out. In Korea, immunotherapy using new drugs such as immunotherapy and TKI has begun to be used for metastatic lung cancer, but it was excluded from the study as it was not applicable at the time of the data of this study (2014-2016).

## Reviewer B

Please find our comments below per section.

### General

- Please get the paper checked by a native English speaker to correct grammatical errors, to improve vocabulary, and improve the structure of the sentences.

-Reply: The paper has been re-edited and the corrected grammatical errors have been corrected and the vocabulary and sentence structure have been improved.

A confirmation letter regarding the relevant information about English language editing is enclosed.

- Please use and incorporate all STROBE guidelines that should be included in all observational studies.

-Reply: The study was carried out according to STROBE guidelines.

### Abstract

- Please state the aim of your study more clearly: define “clinical impact”.

- Reply: The term “clinical impact” was defined and revised.

We would like to raise awareness about the importance of surgery and the benefits of surgical treatment for patients with stage 2 or 3 lung cancer who are unable to complete treatment for any reason.

With this study results, we can explain to patients that surgical treatment should be actively considered in those who are unable to complete surgical and adjuvant treatment.

- Group C, should be “neo-adjuvant therapy” followed by surgery.

Reply: Group C includes patient who received adjuvant therapy after limited surgery. There was an error during the translation process.

- Why don't you report the survival rate of group A?

Reply: The survival rate of Group A was calculated and group A was compared with groups B and C. As expected, it showed better results compared to groups B and C; however, this was omitted as it was considered that it did not meet the purpose of this study. Group A included patients who completed all standard treatments; therefore, it was unnecessary to compare with groups that received incomplete treatment. The purpose of this study is to emphasize the importance of surgery among patients who inevitably receive incomplete treatment for lung cancer.

### Introduction

- Please make the introduction shorter and focus only on the things you are studying in this article □ Stage II and III lung cancer.

Reply: The introduction was briefly summarized and revised to focus on the treatment

of stage 2 and 3 lung cancer.

- How do you define “failed therapy”?

Reply: Failed therapy means that the treatment provided by the guideline for each stage was not completed.

- The last sentence belongs in the methods section.

Reply: The last sentence was deleted.

#### Methods

- The number of patients belongs in the results section.

Reply: I have moved it to the results section.

- Group C is differently defined in your abstract, please rectify/elaborate.

Reply: It has been corrected.

- Why do you only compare Group B and C? Why do have group A then?

-Reply: The survival rate of Group A was calculated and group A was compared with groups B and C. As expected, group A had good results compared to groups B and C. Since this comparison did not meet the purpose of this study, the comparison results were omitted.

#### Results

- First describe the characteristics of the entire group and then of the subgroups, now you go back and forth between total group and subgroups.

Reply: The characteristics of the group have been revised and explained again.

- The significant difference between lobectomy/segmentectomy./wedge is inherent to your definition of group C, so you can leave this out.

Reply: The characteristics of the group have been revised and explained again.

- The last paragraph of “patient characteristics” is very hard to understand, please re-write this.

Reply: This paragraph refers to the proportion of patients who received chemotherapy and radiotherapy as initial treatment in the group that received non-surgical treatment. It has been rewritten.

- Please include a table/figure of the univariate and multivariate survival analysis and state how many independent variables you included in this analysis. (with a sample size of 39, the general rule is that you can include a maximum of 4 independent variables.)

-Reply: We have added the table.

#### Discussion

- Please shorten and write a more cohesive, structured discussion section. There is a lot of repetition of the introduction, methods, and results now, this does not belong in the

discussion.

-Reply: The Discussion section has been revised to be short and concise.

- Did you really find something new? Patients that undergo no/or limited surgery, will obviously have worse survival than patients that undergo complete resection. Again, emphasize on why you think this study is important

-Reply: This study aimed to compare which treatment will be most effective for patients who inevitably do not complete lung cancer treatment. Of course, as stated in the limitations of the study, the specificity of the study subjects was large-scale statistical data; therefore, individual circumstances and comorbidity could not be clearly known, and the specific reason why limited surgery had to be performed was unknown. In addition, it can be assumed that not receiving standard surgery means that the severity of the patient's lung cancer is higher than the stage, which is likely to have had a negative impact on mortality and prognosis. This is considered a limitation of the study, and although this selection bias occurred, there are advantages of surgery in these patients and the positive effects of surgery could be confirmed.

- What are the clinical implications of this study? Can you improve treatment in group C patients?

Reply: For high-risk patients or elderly patients who are unable to continue treatment due to socio-economic reasons, the effectiveness of surgery can be discussed and recommended once again.

#### Conclusion

- You cannot state that target therapy, SBRT or immunotherapy can be alternatives, since this is not what you investigated in your study.

Reply: We have revised the sentence to state that target therapy, SBRT, or immunotherapy can be considered.

- You suggest that complete resection should be performed, however, group C patients are not fit for complete resection, how do you propose to improve this?

Reply: We once again emphasize and recommend the effectiveness of surgery for patients with advanced lung cancer who cannot undergo surgery for reasons other than their systemic condition. A multidisciplinary approach is needed for patients with systemic conditions that make surgery impossible.

#### Reviewer C

The authors need to undergo English editing again. For example, the sentence "received adjuvant therapy followed by limited surgery" (p2, lines 46-47). Is this correct? If this is correct, it means that limited surgery was performed after adjuvant therapy.

Reply: The manuscript has been edited for English language and a certificate has been submitted for the same.

The sentence has been corrected appropriately.

Page 2, lines 40 – 41: In group C, the patients received adjuvant therapy after limited surgery.

- The authors simply "state stage II or III", but please clarify whether this refers to clinical stage or pathological stage. Depending on which stage you are referring to, the significance of the results of this study will vary greatly.

-Reply: The stages 2 and 3 refer to the pathological stage. This has been clarified in the manuscript.

- In Group C, why has pathology proven lymph node metastasis when only limited surgery has been performed? Usually, lymph node dissection is not feasible in limited surgery, especially in wedge resection. Also, why was adjuvant therapy administered to such a high-risk patient who could only undergo limited surgery? In other words, Group C is a very special population, and we must recognize that there is a large selection bias when comparing the prognosis of this group with other groups. The authors are attempting to remove that bias using PSM.

Reply: The patients included in group C underwent limited surgery; however, LN biopsy or mediastinal LND was also performed to determine the stage. Patients with unknown stage were excluded from the data.

In patients who could not undergo standard surgery due to physical conditions or other reasons, additional adjuvant treatment was administered only to those who were eligible. Thus, the study could only be applied to a small number of patients.

- Why don't the authors perform a prognostic analysis comparing the three groups A, B, and C?

Reply: A comparison of the prognosis of groups A, B, and C was performed; however, it was not written separately in the paper. As expected, the prognosis of group A was naturally better than that of groups B and C.

- The authors conclude from the results of the prognostic comparison of groups B and C after PSM that having limited surgery is a worse prognostic factor than having an inadequate Adj, but is this really the case? In Group C, where only limited surgery can be performed, isn't there a high probability that the patient will die from a disease other than lung cancer? Why not evaluate lung cancer-specific survival rates and postoperative recurrence-free rates?

Reply: As it is large-scale data, there are limitations in the information of individual patients, so it is believed that interpretation is possible because the prognosis results of groups B and C were compared, showing a worse prognosis. However, it is acknowledged that selection bias may be significant and there are limitations to the study due to the lack of detailed information.

Although it is impossible to confirm the possibility of death due to other diseases due to the lack of detailed information on individual patients as it is large-scale national data, I think there is a possibility and it would be a good way to evaluate lung cancer-

specific survival rates and postoperative recurrence-free rates. We will use this as a reference in further research.

- It would be desirable to add cStage for each group in Table 1.

Reply: I will create a table by adding cStage.