Peer Review File

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Reviewer A

This studies are of great significance in clarifying the clinical features of tuberculosis-positive lung cancer patients.

I have some comments below.

1. The proportion of TB surveillance among bronchoscopy

To indentify incidence of TB among lung cancer patients has clinically significant. In this study, 0.48% of Lung cancer patients had active TB. However, incidence could be influenced by The proportion of TB surveillance among bronchoscopy. If TB surveillance (Brush, lavage sent for PCR, culture). Was routinely performed in bronchoscopy among lung cancer patients, this incidence was accurate. On the other hand, if not, there has risk of underestimate. Please clarify this point in method section.

- Response : Thank you for your comment about the TB surveillance among bronchoscopy. We agree with your opinion. As we described in introduction section, the annual incidence of TB in South Korea was 46/100,000 people in 2018 (1), which was considered an intermediate incidence country. So we are routinely performing TB surveillance (bronchial washing fluid for TB-PCR and culture) in bronchoscopy among lung cancer patients. We added this point in method section (line 134-35)

- Changes in the text : Because of the high incidence of TB in Korea, we are conducting TB surveillance routinely in bronchoscopy among the lung cancer patients.

2. Incidence of EGFR mutation with TB patients

In introduction, the authors referred to a higher incidence of EGFR mutation with TB patients. This is very important point in lung cancer management.

In this study population, EGFR mutation was not higher among lung cancer and TB patients.

In discussion, unfortunately, the authors did not describe this point. The proportion of adenocarcinoma did not differ among two groups. Smoking status could greatly influence the incidence of EGFR mutation. Therefore, please clarify the difference of smoking status among two groups, and please mention this point in discussion section.

- Response : As your comment, we re-analyzed the differences of smoking status between Tb and non-TB groups. Percentage of ever-smoker (current + ex-smoker) was slightly higher in

non-TB group (78.1% vs. 64.6%, OR 1.84 (1.05-3.22), P= 0.05). In addition to the smoking history, we thought other factors could have attributed to this low EGFR status in our TB group. First, majority of the included patients had non-adenocarcinoma (squamous cell 50%, small cell 4.2%) cell types. Second, the included patients were diagnosed lung cancer from 2009 to 2017, we could not analyze EGFR mutation status to all of the included patients in that time period. As we described in table 1, half of the patients were unable to perform EGFR mutation test. This could be the limitation of retrospective chart review. As your comment, we mentioned this point in discussion section (line 272-276).

- Changes in the text : In addition, the proportion of EGFR mutated patients was not higher in TB group, which was not consistent with Luo YH's study(5). This result could be because of the higher ever-smokers in TB group (78.1% vs. 64,6%, *P* = 0.05, data not shown) and we could not perform EGFR mutation test to all of the included patients during the study period (2009 to 2017).

3. Conclusion

In LINE 55 "TB in lung cancer patients could improve patient outcomes." I felt this overstatement. "might possibly" will be better.

- **Response:** Thank you for your comment. We change the expression

- **Changes in the text :** Active investigation of and treatment for active pulmonary TB in lung cancer patients might possibly improve patient outcomes.

Reviewer B

Major points

#1 In a previous study, which was limited to patients with adenocarcinoma of the lung, a higher percentage of patients with scar cancer or old tuberculosis had EGFR gene mutations. In the present study, which compared the presence or absence of active tuberculosis complications among all lung cancers, this matter should be discussed and included in the text.

- **Response:** Thank you for your precious comment. We agree to your opinion. Reviewer A also commented about that point, so we re-analyzed the difference of smoking status between the Tb and non-TB group. Percentage of ever-smoker (current + ex-smoker) was slightly higher in non-TB group (78.1% vs. 64.6%, OR 1.84 (1.05-3.22), P= 0.05). Moreover, as you commented, the comparison of the patients according to the active TB or not would have made different results from previous research. We added this point in discussion section (line 272-279).

- **Changes in the text :** In addition, the proportion of EGFR mutated patients was not higher in TB group, which was not consistent with the study of Luo YH (5). This result could be due

to the higher ever-smokers in the TB group (78.1% vs. 64.6%, P = 0.05, data not shown) and EGFR mutation testing was unavailable for all of the included patients during the study period (2009 to 2017). Moreover, the comparison of the lung cancer patients according to the presence of active TB or not would have made different results from the previous research comparing the presence of old TB lesions with existing adenocarcinoma lung cancer patients.

#2 NSCLC and SCLC are two different diseases with different prognoses. This study does not distinguish between NSCLC and SCLC in the prognostic analysis. In fact, there is a significant difference between 79 cases (13.7%) of SCLC in the non-tuberculosis lung cancer population and 2 cases (4.2%) in the tuberculosis complicated lung cancer population. The high proportion of SCLC may be one of the reasons for the worse prognosis in the non-tuberculosis population. I think that the authors should explain this point to the readers in a convincing manner.

- **Response:** Thank you for your comment about the patients' survival. We definitely agree to your opinion about the effect of cell types for survival in lung cancer patients. However, as we had shown in table 3, the number of SCLC patient was too small (total 2 patients) to compare in TB group. Moreover, since there was no statistical difference in cell type between TB vs. non-TB group (P=0.07) in univariate analysis, we did not include the cell type for survival analysis. We also re-analyzed the differences of cell type with another way (SCLC or non-SCLC) between TB and non-TB population. However, there was no statistical differences between them according to whether SCLC or not (P= 0.07). We added this point in discussion section. (line 289-292)

- **Changes in the text :** This effect was significant after adjustment of TNM stages. Lung cancer cell types were not included in the Cox analysis because the number of SCLC patients in the TB group was too small (2 among 48 patients), and there was no statistical significance in univariate analysis.

#3 It is possible that genetic mutations will be examined for the first time at the time of recurrence after surgical resection or radical radiotherapy, and that driver mutations with effective therapeutic agents will be found. PD-L1 TPS is more than 50% and ICIs may be significantly effective. This study ignores factors that significantly affect prognosis in its prognostic analysis. The prognosis is not homogeneous and there is bias between groups, so it is questionable whether prognostic comparisons are meaningful. I believe that the authors should explain this point to the readers in a convincing manner.

- **Response:** Thank you for your comment. PD-L1 status and ICI use are important factors in lung cancer survival, however, PD-L1 analysis was not available in our study period (2009-2017). Unfortunately, we could not have any information about PD-L1 status in our study group. We are very sorry for this, and we are going to consider this point in further research.

#4 Patients with TB complications tended to have a more advanced stage of disease. I believe that this should also be discussed to the reader's convinced.

- Response: As we described in discussion section (line 262-264) and table 3, initial clinical stages appeared to be higher in TB patients. However, these stages were decided clinically, without pathological confirmation We were interested in this point because we hypothesized that active TB could affect the T or N stages of the CT images with new nodules or enlarged lymph nodes which are difficult to discriminate TB from cancer cells by imaging findings. And our hypothesis turned out to be true in our study results. We thought that the lower mortality in TB group might be because of active TB surveillance and immediate TB and cancer treatment of our study population. We wanted to emphasize the possibility of lower mortality despite advanced clinical TNM stages in patients with concurrent lung cancer with TB through active TB surveillance and treatment in Korea. This point was mentioned in discussion section, line 316-322.

Reviewer C

This study showed that active TB was significantly associated with low BMI and advanced stages at the time of diagnosis. In addition, low mortality was found in lung cancer patients with active TB. However, there are potential limitations in this study. First, the case number of active TB was small, and the results were not supported by statistical analysis.

Some things important to address in this paper by section, include:

Methods:

#1. Lines 135-138: As the author mentioned in the manuscript, PCR should not be used to diagnose active TB because of the possibility of cross contamination and false positive. The diagnosis of active TB should be based on culture of the bacilli.

- Response: Thank you for your precious comment about the diagnosis of pulmonary tuberculosis (TB) in our study population. We totally agree with your opinion that a diagnosis of active TB by the pathology or a positive PCR result cannot be sufficient evidences. So we tried to have thorough inclusion criteria in the diagnosis of active TB during the chart review. First we included all 35 patients with positive AFB culture results from sputum, bronchoscopic washing fluid, or pathological specimens- which are definite diagnoses of active TB. And we included 13 patients with positive PCR results had other clinical evidences suggesting active pulmonary TB, including granuloma of lung tissue, CT images suggesting active TB, and efficacy of anti-tuberculosis medication. Moreover, tissue TB-PCR could differentiate between *M.tuberculosis* (MTB) and non-tuberculosis mycobacterium. Among patients with tissue PCR results, only MTB positive patients were included.

However, since these clinical criteria in diagnosing active TB could be a limitation of our study, we included this point in discussion section. (line 338-342)

#2. Lines 152: How was the control group selected? The authors should explain the details.

- Response: As we described in method section (line 152-162), we chose the control group in our multicenter lung cancer registry. We were collecting information on the histories of TB and underlying diseases in lung cancer registry, which allowed us to include 575 non-TB patients from a total of 584 patients enrolled in the same hospitals during the same study period. We added this point in method section (line 160-161).

- Changes in the text : This lung cancer registry allowed us to include 575 non-TB patients from a total of 584 patients enrolled in the same four hospitals during the same study period.

#3. Lines 169-177: Have the authors checked the normal distribution? If not, statistical analysis should be performed non-parametrically. Also, there was no description of statistical methods for mortality.

- Response: Thank you for your comment, we checked the normal distribution of the variables. In table 1, age and body mass index followed normal distributions, and serum albumin followed a non-normal distribution. The mean and standard deviation were calculated for normally distributed variables, whereas the median and interquartile range (IQR: 25^{th} – 75^{th}) were used for non-normally distributed data. We added the description of statistical methods for mortality in method section. (line 178-180)

- Changes in the text : The survival curve according to the death was analyzed using the Kaplan-Meier method. Hazard ratios (HRs) and corresponding 95% CIs were calculated for predictors that were significant in multivariate Cox regression analysis.

Results:

#4. Lines 200-201: Were the rest of the TB patients not treated? Misleading statements should be avoided.

- Response: Thank you for your comment. Since all of the included TB patients were treated, we changed 13 to 48.

- Changes in the text : All these 48 patients were treated with anti-TB medication.

Reviewer D

Major points:

#1 Survival rate of small cell carcinoma in the non-tuberculosis group also needs to be discussed. Please provide the median and range of survival rates for small cell lung cancer patients in the non-tuberculosis group. Also, please describe the impact of the survival rate of small cell carcinoma in the non-tuberculosis group on this study.

- Response: Thank you for your comment. As your comment, we analyzed survival duration and rate of small cell lung cancer (SCLC) patients in non-TB group. There were 79 SCLC and

495 non-SCLC patients in non-TB group (1 missed survival data), 66 (83.5%) of SCLC and 258 (52.1%) of non-SCLC patients died during the follow up period. In Kaplan-Meier survival analysis, median survival duration was 751 days in SCLC and 760 days in non-SCLC. There was no statistical significance in survival duration between SCLC and non-SCLC patients ($p = 0.76$, by Log Rank (Mantel-Cox) test). We added this point in discussion section as below (line 294-296).

- Change in the text : In non-TB group, median survival duration was 751 days in SCLC and 760 days in non-SCLC, without statistical significance in Kaplan-Meier survival analysis ($P = 0.76$, data not shown).

#2 We believe that the presence of PD-L1 analysis and the use of ICIs should be mentioned in the text. Please consider including them in the text. We also believe that if they were used to some extent, a discussion of ICIs is necessary.

- Response: Thank you for your comment. We added this point in discussion section. (line 296-300)

- Change in the text : In addition, expression of programmed death ligand 1 (PD-L1), which is effective for immune check point inhibitors should have been considered in survival analysis. Unfortunately, we could not have any information about PD-L1 status in our study group because the analysis was not available in our stud period (2009-2017).

Minor points:

#1 We believe that data should generally be expressed in terms of median rather than mean. Please consider correcting the corresponding part.

- Response: Thank you for your comment. We expressed age and body mass index in terms of mean ± SD because these variables distributed normally (Kolmogorov-Smirnov $p = 0.2$ (age), $p = 0.2$ (BMI)), and total follow up days and albumin in terms of median (IQR) because they followed non-normal distribution (Kolmogorov-Smirnov $p < 0.001$ (total follow up days), $p = 0.026$ (albumin)).

#2 Lines 206-207 of the text read "During the 361.9 ± 431.8 days of follow up, 32 (66.7%) were survived." However, in Tables 1 and 3, the follow up period for the TB group is 66-493 days, with a median of 186 days. Because of the discrepancy in the follow up period, we believe that the data needs to be corrected.

- Response: Thank you for your comment. We corrected the description.