# Peer Review File

**Article Information:** https://dx.doi.org/10.21037/tcr-21-2633

**Reviewer A**

This paper was well written, and confirms prognostic factors of resected lung cancer, already known in the literature.

**Reply: We thank Reviewer A for compliment. Though several identified prognostic factors have been described in other studies, our study has demonstrated the distance of bronchial resection margin as a new prognostic factor which have implication on the importance of the adequacy of proximal resection margin. In addition, we demonstrated that EGFR mutation is not an independent prognostic factor in homogeneous population of early-stage lung cancer without lymph node involvement.**

**Changes in the text: No**

**Reviewer B**

1. Population of the patient seems to be different between non-recurrence and recurrence group. Obviously, more high Stage patients are included in the recurrence group. However, statistical significance would not be seen for Stage classification in Table 2 which means that the Staging system is not that useful in this cohort. How do you explain this discrepancy?

**Reply: We thank Reviewer B for constructive criticisms. Since we recruited only resected lung cancer without lymph node involvement, the T stage will be the only factor determining the prognosis from TNM staging. The discrepancy between higher recurrence rate in higher stage but staging system was not statistically significant by multivariate analysis may stem from relatively lower number of populations in stage II (N=27) and IIIA (N=5). However, the univariate analysis has shown the importance of this T stage in our study cohort. According to the second comment from Reviewer B, we decided to reanalyze the regression analysis by excluding the TNM staging. We still found the same result of four significant prognostic factors.**

**Changes in the text: We have modified the data in Table 4. (Original Table 2.) after excluding TNM staging from regression analysis. (See new Table 4.)**

2. Author pointed out that the tumor size more than 4 cm would be a significant prognostic factor. However, TNM classification states the T as the tumor size. More than 4 cm seems to be equal to T2b, but the number of staging and tumor size differs in Table 1. Since the N+ patients are excluded from this analysis, I assume that the staging and tumor size would be nearly equal and should not be calculated in the same regression analysis.

**Reply 1: In our study, we divided the tumor size into less than 4 cm or equal to or greater than 4 cm. Tumor less than 4 cm size included patients in Tis stage 0 5.4%, T1 stage IA 64.5% and T2a stage IB (excluding tumor size equal to 4 cm) 11.5%, total 81.4%. For**

**tumor size equal to or greater than 4 cm in our study included T2a stage IB (4 cm tumor), T2b stage IIA, T3 stage IIB, and T4 stage IIIA which were 4%, 7.3%, 5% and 2.3% respectively. The total number in the equal to or greater than 4 cm were 18.6%.**
**Changes in the text 1: No**
**Reply 2: We thank Reviewer B for this critical suggestion. We agreed that the staging and tumor size in this regard have overlapping populations and share very similar prognostic factor in N0 disease. To reduce this redundancy, we revise the analysis to include only tumor size in the regression analysis. After excluding the TNM staging and reanalyzing the regression analysis, the overall results remain the same with our original analysis which showed similar four significant prognostic factors.**
**Changes in the text 2: We removed the TNM staging from the regression analyses and moved the original table 2 to table 4. (See new Table 4.)**

3. What is the novelty of this manuscript? Analysis seems to be fairly done in some of the points, but all the results seems to be well known.
**Reply: Similarly with Reviewer A, we believe that our study has addressed a new prognostic factor, bronchial resection margin of 2 cm, and a more definitive result on prognostic value of EGFR mutation. Prior studies regarding the prognostic values of EGFR mutation in early-stage NSCLC had been described but the results were not consistent partly due to the heterogeneity of the studied population and variabilities of EGFR mutation testing which were lessen in our study.**
**Changes in the text: No**

**Reviewer C**

They reported of prognostic factors of pN0 lung adenocarcinoma based on the retrospective analysis of 220 cases from a single institution.

The results of the study showed four significant pathological factors including tumor size, VPI, necrosis and resection margin. However, most of them have been already reported in several previous studies. So, we cannot find ant novelty in the manuscript. The author should claim some kind of novelty. The author also should mention about usefulness of their results in clinical practice, for example, for determining the indication of adjuvant treatment or follow-up planning.

**Reply: We thank Reviewer C for the important suggestions to improve our manuscript. Again, we believe we have identified a new prognostic factor and the more decisive results regarding EGFR mutation was not a prognostic factor in our study population. We agree with Reviewer C in adding the usefulness of our results to clinical practice.**
**Changes in the text: We have modified our text "Mutation of EGFR is not a significant prognostic factor in this population so the adjuvant treatment should be considered for the patients who have sensitizing EGFR mutation after complete resection if they have any additional poor prognostic risks" (see Page3, line 54-57 and Page13, line 276-279).**

The study aim was to determine the value of EGFR mutation predicting recurrence. The author should also clarify differences in the clinicopathological factors, the recurrent cites and time to recurrence according to EGFR mutant status.

**Reply: We agreed with the Reviewer C suggestion. When compared the clinicopathological characteristics of the EGFR wild type and mutant groups, there were more poor prognostic factors in the EGFR wild type group i.e. tumor necrosis and larger tumor size. However, the sensitizing EGFR mutation was not a favorable factor when determine the risk of recurrence. The pattern of relapse and time to recurrence were not statistically different according to the EGFR status.**
**Changes in the text: We added Table 2 to describe the clinicopathological characteristics between EGFR wild type and mutated group and Table 3 to demonstrate pattern of relapse and time to recurrence according to EGFR status (see Page 8, line 174-175, Page 9, 181-182 and new Table 2. and 3.)**

Although DFS was not, OS was significantly different between EGFR mutant and wild type groups. Please, consider the gap of these results.
**Reply: Overall survival was significantly different between EGFR mutant and wild type groups because of interference from the subsequent treatment with an effective EGFR inhibitor. 21 of 31 recurrent EGFR mutated patients (68%) received EGFR TKI when tumor recurred.**
**Changes in the text: We added the data "Most of patients with EGFR mutation, 21 out of 31 patients (68%), received EGFR tyrosine kinase inhibitor upon recurrence which help improving the overall survival of these patients." (see Page 11, line 244-246).**

In Table 1, although this study included only adenocarcinoma cases, the case number with bronchial resection margin <2cm, 60 cases, was too many. Most of cases were treated by lobectomy. Does it mean that the tumor located within 2cm of lobar bronchial dissection line? Please, clarify the situation of these cases.
**Reply: The bronchial resection margin in our manuscript was defined as the distance from the proximal border of the tumor (not the center of the tumor) to the bronchial resection line evidenced from the gross appearance in surgical specimen. In our cohort, we found the bronchial resection margin of less than 2 cm in 60 of 220 cases (27.3%), compared to 53.8% of patients in the previous literature (Reference No. 29).**
**Changes in the text: We have modified our text "Tumor size was defined by maximal diameter. Bronchial resection margin was defined by the distance from the border of tumor to the bronchial resection line and number of removed lymph node were all determined from the gross appearance in surgical specimen." (see Page 6, line 118-120).**

In Table 2, the author included all 13 covariates in multivariate analysis. Statistically, in order to avoid overfitting, the number of covariates included in multivariate analysis should be less than 1/10 of the number of events. We suggest a statistical review of the analysis methods.
**Reply: We thank Reviewer C for your critical suggestion. We decreased the number of covariates and reanalyzed the data in multivariate analysis by excluding the TNM staging**

**that overlapped with tumor size and age group that did not reach a statistical significance in univariate analysis. In addition, we re-analyzed by including only seven pathological factors and EGFR status in multivariate analysis to avoid overfitting. However, the results from re-analyses showed similar results to the original analyses.**

**Changes in the text: We have modified the data in Table 4 (original Table 2) after excluding TNM staging and age group from multivariate analyses. (See new Table 4.)**