

## Peer review file

Article information: <http://dx.doi.org/10.21037/jtd-21-110>

### Reviewer A

Curative-intent surgery for non-small cell lung cancer (NSCLC) sometimes results in occult N2 or positive tumor margins. The authors compared the survival of patients who underwent lobectomy or more with two forms of these postoperative residual diseases to clarify the importance of guideline-concordant adjuvant therapy and, furthermore, the impact of these forms upon prognosis. They showed that guideline-concordant treatment in the setting of residual disease was associated with better survival compared with non-guideline concordant treatment. They also showed that pathologic N2 disease was associated with a lower survival rate than positive tumor margins, suggesting the systemic nature of pN2.

The purpose, methods, and results of their study were clear. Considering the current role of surgery for NSCLC, this report would be of great interest to the readers. Several concerns were raised in my mind, however, the authors correctly mentioned these in a limitation section.

My comments for the authors are as follows:

**Comment 1:** The authors defined 5-year OS as the interval from the date of diagnosis to the date of last contact or last vital status. Given every patient in this study underwent surgery, the first day would be preferred to be the date of operation.

**Reply 1:** We thank you for highlighting this important consideration. We have redefined our survival intervals using date of operation as the first day of the survival interval. The modified results have resulted in minor changes to the hazard ratios and p-values for the Kaplan-Meier survival curves and Cox proportional hazards model, though there was no change in which variables were independent predictors of mortality.

The amendments to the “Variables and Outcomes” section of the manuscript are as follows:

“The primary outcome of interest was 5-year overall survival, defined as the interval from the date of surgery to the date of last contact or last vital status.”

The modified results of the multivariable analysis are reflected in the “Results” section of our manuscript. The modified results to the overall survival are reflected in the survival curves for each cohort.

**Comment 2:** The following sentence ‘with positive margins after resection, which may represent local recurrence of disease’ on page 5, line 176 should be reconsidered.

**Reply 2:** We thank you for your highlighting this statement and have modified our text as advised.

The amendments to the “Conclusion” section of the manuscript are as follows:

“positive margins after resection, which may represent local extension of disease.”

#### **Reviewer B**

The authors should be congratulated on their work. The project appears to have merit with thoughtful analysis. I have a few comments.

**Comment 1:** What mechanism is used to ensure that the reason patients did not receive adjuvant therapy is the same reason they had higher associated risk or mortality aka post-operative complications, malnutrition or other factors that would otherwise preclude the receipt of chemotherapy.

**Reply 1:** We thank you for highlighting this excellent point – unfortunately, due to limitations with NCDB, we are unable to determine the rationale behind receipt of adjuvant chemotherapy. We have amended the limitations section of the manuscript to

reflect this.

The amendments to the “Conclusions” section of the manuscript are as follows:

“It is not known whether patients who did not receive adjuvant therapy may have had risk factors that both precluded receipt of chemotherapy and predisposed them to higher mortality.”

**Comment 2:** Please correct the use of 'multivariate' throughout the manuscript.

**Reply 2:** We thank for pointing out this error and have adjusted the text accordingly.

The amendments to the “Methods” section of the abstract are as follows:

“Multivariable analysis using Cox proportional hazards modeling identified factors that contributed to worse overall survival.”

**Comment 3:** How do the authors explain that having a both residual disease conditions are worse than having an N2 node which is historically the most significant driver of all mortality apart from metastatic disease?

**Reply 3:** We believe that having both an N2 node in addition to positive residual margins has a multiplicative effect on mortality, causing the “both” group to have the worst overall survival. An N2 node in isolation is a significant driver of mortality, but we believe that the addition of a positive margin further increases the burden of disease.

The amendments to the “Conclusions” section of the manuscript are as follows:

“While an N2 node in isolation is known to be a significant driver of mortality, the addition of a positive margin may further increase the burden of disease.”

**Comment 4:** Do you think a propensity match analysis would be helpful in this analysis?

**Reply 4:** We agree with you that a propensity matched analysis would be helpful for this analysis. Unfortunately, there is violation of the propensity score methods assumption, so propensity score matching is not possible. By definition, each patient is assigned to one of the three residual disease groups, and patients in one group have 0% chance to be in other group – this violates the propensity score matching assumption. We used a multivariable analysis model to identify independent predictors of mortality.

The amendments to the “Statistical Analysis” section of the manuscript are as follows:

“Propensity match analysis was not performed due to violations of the propensity score match assumption.”

**Comment 5:** Did you exclude 30 or 90 day mortalities to avoid immortal time bias?

**Reply 5:** Your observation is correct. We have added a statement to the manuscript to more explicitly state this reasoning.

The amendments to the “Variables and Outcomes” section of the manuscript are as follows:

“Landmark analysis of 30 day and 90 day mortality post-surgery were tested separately as sensitivity analysis to account for potential immortal time bias. Results were similar to main results. For simplicity, only the main results were reported.”

**Comment 6:** Why did you choose to include both surprise N2 and R+ disease in this

analysis? It appears to unnecessary and make the analysis and discussion clunky.

**Reply 6:** Prior studies have analyzed long-term survival for patients with surprise N2 disease or R+ disease individually, but no study has comparatively analyzed long-term survival for surprise N2 vs. R+ disease using the same cohort or looked at the combined effects of having both surprise N2 disease in addition to R+ disease. In this way, we felt that this study would help fill a gap in knowledge.

The amendments to the “Conclusions” section of the manuscript are as follows:

“Though prior studies have independently analyzed long-term survival of N2 disease or positive margins independently, no study has comparatively analyzed both forms of residual disease using the same cohort or looked at the combined effects of having both occult N2 disease and positive margins.”