Peer Review File

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Reviewer A:

Comment 1: Were some cN2 patients undergoing neoadjuvant chemotherapy later disqualified from surgery or did some of them resign from surgery? If so, how many? Could it have an impact on results?

Reply 1: This is an important point, and unfortunately the NCDB does not provide this information. Granularity regarding type of chemotherapy received and completion of course is not included. Whether a patient was planned for neoadjuvant chemotherapy plus surgery and did not eventually receive surgery is also unknown.

Changes in Text: Additional line added to limitations (Page 13, Line 296-297).

Comment 2: What about institutions/wards without accreditation? I suspect you do not have the data. But any suspicion or hypothesis how it looks like in this kind of wards? We have a similar problem in our country as the units without accreditation do not take part in the database.

Reply 2: The NCDB only provides data on Commission on Cancer accredited institutions, so we unfortunately do not have any data on non-accredited centers. The NCDB does capture approximately 70% of all new cancer diagnoses in the United States however, as is mentioned in the methods section.

Changes in Text: None

Comment 3: Neoadjuvant = adjuvant is an interesting result from this or other studies. Also, it is controversial. However, as you noticed some of the cN staging was not adequate due to insufficient preoperative diagnostic (EBUS, Mediastinoscopy, etc.) pN staging may compensate it, but in my opinion not in all cases. Especially, when you consider Osarogiagbon et al. (2013)* study, where pNx is a significant number of patients. This author only considered 0 lymph nodes as pNx, not less than 6 (like e.g. in ESTS guidelines). In your study, 15.4% of the whole population had less than 6 lymph nodes retrieved.

Thus, have you considered evaluating your hypotheses as a function of the number of lymph nodes removed? I think it could be an interesting and meaningful addition to this study.

Reply 3: Thanks for this comment. While there were slight differences in the number of lymph nodes removed between the three categories (no systemic therapy, neoadjuvant, and adjuvant - seen in Table 3) median number of lymph nodes removed from the groups as a whole were similar and not statistically significant (median of 11 nodes for each group). While we agree that appropriate mediastinal nodal evaluation is important to make sure that final staging is accurate, the NCDB does not provide any information on invasive mediastinal staging with EBUS, mediastinoscopy, or other modalities. There is also debate about whether total number of nodes evaluated is more important that number of stations, another metric that the NCDB unfortunately doesn't provide.
Changes in Text: None

Comment 4: What is your hypothesis: why cN1 had the worst survival?
Reply 4: This is an important point, as our analysis did show a slightly lower survival in the cN1 group when compared individually against cN0 and cN2 separately (median 3.7 months versus 4.3 for cN2 and 4.2 for cN0, Table 2). It is important to note though that the survival analysis by clinical stage is unmatched, and there were higher rates of positive margins in the cN1 group compared to both cN0 and cN2.
Changes in Text: None

Comment 5: A typo: Line 140, page 7. – p-value: 0.05
Reply 5: This has been corrected
Changes in Text: Page 7, Line 155 corrected to "0.05"

Comment 6: Lines 169 -171. Page 8. Some of these percentages seem to be wrong in comparison to the table. Please check if it is ok.
Reply 6: Thank you for pointing this out. The percentages were correct, but the paragraph was not entirely clear as to what we were stating, and we do apologize. The 1.6% and 3.8% for 30 and 90 day mortality for patients getting "up front surgery" are the results when no-systemic therapy and adjuvant systemic therapy patients were combined. So the first part of this paragraph was just to show the perioperative mortality difference based on whether the patient had chemotherapy before surgery or not. The second part of the paragraph breaks the mortality rates down into the 3 groups (neoadjuvant, adjuvant, and no systemic therapy).

Changes in Text: Page 8, Line 186 – "regardless of systemic therapy" was added to better explain "upfront surgery."

Reviewer B:

Comment 1: Page 4 ll. 76-77: The authors are not describing what the NCCN guidelines are. Please provide some information to our readers from Europe and Asia. Because probably your guidelines differ from ours.

Reply 1: For patients with mediastinal lymph node involvement, the NCCN guidelines recommend systemic therapy and specifically against upfront surgical resection. We believe this paragraph is clear explaining that statement, but we have added some additional details per your recommendation.

Changes in Text: Page 4, Line 79 – "with the specific recommendation being for induction chemotherapy plus or minus radiation therapy in potential surgical candidates"

Comment 2: Page 7 ll. 148-149: The authors are affirming that patients with cN2 disease were more likely to have private insurance. At least I have no idea of the American insurance system therefore this information is misleading. I would suggest either leaving out this part or better explaining the given information.

Reply 2: We understand that there will be some confusion regarding the American insurance system for non-American readers of this manuscript. It is a commonly analyzed variable in the NCDB, and our American readers will understand the utility of including it. Overall though, the insurance aspect is not a major finding in this study, and we feel it does not need further explanation as it doesn't impact the remainder of the study.

Changes in Text: None

Comment 3: How was staging performed?
Did it change during the inclusion time of 10 years?
Does it differ between academic and non-academic hospitals?
Please provide some information.

Reply 3: Unfortunately the NCDB does not provide information regarding how clinical stage was determined. This is one of the major limitations of utilizing this dataset. This is already included in our limitations section (Page 12, line 255-257, and again lines 268 through 274). That said, the NCDB only includes centers who are accredited by the Commission on Cancer,

where standards are fairly rigorous for appropriate workup and staging of patients and are checked through annual auditing.
Changes in Text: None

Comment 4: I have some questions about the administered adjuvant- and neoadjuvant therapy.
What did the patients receive?
Did it change during the inclusion period of 10 years?
Does it differ between academic and non-academic hospitals?
Please provide some information.
Reply 4: Specific chemotherapy regiment is also not included in the NCDB, so we can not analyze what was specifically given and any trends over the time period. This is stated already on page 13, line 274, and also is an important part of our conclusion (line 289). As with staging, the NCDB only includes centers who are accredited by the Commission on Cancer and are following nationally accepted guidelines, so we would hope that most chemotherapy regimen being administered are standard.
Changes in Text: None

Comment 5: Page 10 ll. 209-215: I appreciate this section where you explain why cN2pN2 patients might not receive, guideline-recommended therapy. Because while reading your manuscript this question popped into my mind as well. Precisely because we have a suitable explanation for why patients did not receive therapy, I find it problematic here to include this in the further analysis. I would suggest keeping this explanation in your manuscript and excluding those patients from your analysis.
Reply 5: Thank you for this comment. One of the major findings in our study is the lack of guideline concordance (specifically that for cN2pN2 patients, only 56% received neoadjuvant therapy when this is a standard and clear guideline from the NCCN here in America). Further, one of our major analyses in the study was the affect of different treatment regimen on overall survival for cN2 patients (Table 5). Remove all patients who did not follow guidelines would not be appropriate for this study. Lines 209-212 were specifically included to account for centers that may be offering non-guideline therapy (upfront surgery) for single station N2 patients, but as stated, we did not feel that this reason could account for so many patients not undergoing neoadjuvant therapy.
Changes in Text: None

Comment 6: Page 7 ll. 217-222: (Part about guideline concordance). May the authors provide information on why so many patients are not treated contrary to guideline recommendations?
Reply 6: To be honest, we wish that there was a clear reason, but there isn't. While it is comforting to see guideline concordance increasing during the time period, 62.9% as a max is still not optimal. One would expect much higher rates of concordance as these are Commission on Cancer accredited centers.
Changes in Text: Page 11, Line 243-245 – "Overall, there is no obvious reason why guideline concordance is not higher, but it is reassuring to see the rates generally increasing."

Comment 7: The tables are quite overcrowded and the authors present data, which they are not addressing in the manuscript, and which are, at least in my opinion, partly irrelevant for international readers.
I would suggest that the authors omit the insurance status, distance to a facility in miles (because 90% of the rest of the world are using the metric system), and the race from the tables.
Reply 7: We understand your concern with the length of the tables. For NCDB studies, it is fairly standard to include the full demographic and tumor characteristic tables (tables 1 and 3). We also do not feel that by removing those 3 variables from the tables would substantially shorten them to warrant omitting the information. I definitely agree with your comment about distance to facility not being metric and wish that American would get with the rest of the world, but this is what we have to work with. Race specifically is important to include as disparities in care are well known throughout the United States and therefore should be evaluated.
Changes in Text: None

Reviewer C:
Comment 1: The first hypothesis focuses on the difference between occult N2 disease and pathological N2 disease. This is only briefly touched on in the results (lines 157-160) and a significant number of these patients did not undergo systemic treatment. While the reasons for no systemic treatment were outlined for cN2, it is not addressed in this cohort. Given the increased lack of systemic treatment and decreased survival in this cohort, and as this was one of the hypotheses of the paper, this would be worth exploring further.
Reply 1: Thank you for this comment. We opted to focus much of our analysis on the clinical N2 group, as the guidelines are much more clear and the data is more granular with the NCDB as we

don't have to make any assumptions about if the patient received appropriate preoperative mediastinal staging. As we responded to the other reviewers and mentioned several times in the manuscript, the NCDB does not include any actual data on type of procedures performed to obtain clinical staging. It is therefore a major limitation in trying to evaluate the cN0 or cN1 groups, as we do not know if they were staged appropriately (ie: EBUS, mediastinoscopy). As we mention in our conclusion, future studies that include specific data and analysis on the diagnostic modalities for mediastinal staging will be beneficial to answer any questions regarding occult and known N2 disease. Unfortunately the NCDB won't be the database to answer that question.
Changes in Text: None

Comment 2: Line 94: would have better outcomes *than* patients
Reply 2: Thank you for finding this mistake. It has been corrected.
Changes in Text: Line 104 – "than"

Comment 3: Clarifying the second hypothesis (Line 96): the results appears to focus on timing of systemic treatment in clinical N2 disease, while in the introduction it could be construed as continuing to compare occult and clinical N2 disease and the timing of treatment.
Reply 3: We focused on timing of treatment for cN2 specifically as the guidelines from the NCCN are much more clear for this cohort (neoadjuvant therapy if considering surgery). The introduction does try to touch on numerous topics regarding mediastinal staging. We have clarified the hypothesis statement.
Changes in Text: Line 106 – "cN2"

Comment 4: The first sentence of the results section (Line 144) is convoluted, and confusing. Clarification here and calling the readers attention back to Figure 1 would be helpful to understand the patient population included.
Reply 4: We agree, on retrospect it is convoluted and confusing. We do believe the information is important to include here as well as the figure, so we have broken the sentence down into two separate sentences that should be easier to comprehend.
Changes in Text: New sentence Lines 160-161

Comment 5: Line 121: Capitalize Figure.

Reply 5: Fixed.
Changes in Text: Line 132 – capitalized “Figure”

Reviewer D:

Comment 1: In the conclusion of Abstract, ‘Responsiveness to neoadjuvant therapy … may become a prognostic adjunct for determining which patients would benefit from additional systemic therapy.’ – this not the main topic of this manuscript, and in this study design, the evidence to support this conclusion on additional systemic therapy is not provided. It can discuss in the discussion section, not in the conclusion.

Reply 1: Thank you for this comment. We respectfully disagree however, as the major analysis of this paper (Table 5 and Figure 4) relates to responsiveness to neoadjuvant chemotherapy. While we can’t make any major conclusion or sweeping statement about the analysis as there are numerous limitations, we feel it is appropriate to say that tumor responsiveness is a predictor of survival, and may help guide treatment decisions in the future.

Changes in Text: None

Comment 2: In the Introduction, the authors suggested 2 main hypotheses, first, “We hypothesized that patients who were occult N2 (cN0/cN1, pN2) would have better outcomes that (->than) patients with clinically evident N2”. However, the main topic of this study is the subgroup of cN2 disease, not occult N2. So, the sequence, hypothesis – result – conclusion, is a little out of context, and facts irrelevant with the main topic are reported sporadically, and that’s why reading this manuscript is somewhat difficult. Maybe this is because the database is very big and there are many facts to be mentioned. And in the title, “national trends’ are mentioned in the title, however, in the manuscript, there are no trends except ‘NCCN guideline concordance trend’. The concordance rate is a meaningful finding, however, I think this is not so important to mention as a title. So, I humbly recommend changing the title.

Reply 2: As you note, it is difficult to summarize the numerous results obtained when using the NCDB (or similar large databases). We utilized a fairly standard format for NCDB interpretation, where the cohort selected from the dataset is described, followed by significant differences in demographic and tumor characteristics. We then present the advanced statistical analyses (in this case multivariable regression and survival analysis) which attempt to address

our hypotheses. We do agree regarding the title, as there is only one trend. The title has been changed to represent this.
Changes in Text: Title changed to "National Guideline Concordance and Outcomes for Pathologic N2 Disease in Non-Small Cell Lung Cancer"

Comment 3: The second hypothesis, "We also hypothesized that there would not be significant clinical differences between patients who underwent neoadjuvant chemotherapy, compared with those who underwent adjuvant treatment.", is very important and need to be solved question. If you agree with my opinion, table 3 is the most important data of this manuscript. "Table 3. Patients with neoadjuvant therapy were more likely to have an R0 resection than patients undergoing upfront surgery. 30-day and 90-day mortality rates were similar among patients receiving neoadjuvant therapy (2.3%, 4.9%) vs. patients undergoing upfront surgery (1.6%, 3.8%)". The 1.6% and 3.8% may be from the data of the patients of upfront surgery alone or who received adjuvant treatment. Please clarify from where the value of 1.6% and 3.8% originates.
Reply 3: Thank you for mentioning this. Reviewer A also brought this up in comment 6, and we realized those two percentages were not explained well. Upfront surgery included patients who had resection without any neoadjuvant therapy (a combination of both the no-systemic therapy group and the adjuvant therapy group. This data is not broken out in our table). The manuscript has been updated to clarify this.
Changes in Text: Page 8, Line 186 – "regardless of systemic therapy" was added to better explain "upfront surgery."

Comment 4: In my opinion, one of the main limitations of this manuscript is that the data of patients who received neoadjuvant treatment but failed to undergo surgery is not included. If the ratio who could not undergo surgery after neoadjuvant therapy is high and if their survival was lesser than the upfront surgery (+/- adjuvant therapy) group, the approach supporting upfront surgery without invasive mediastinal staging could advocate in operable single-station clinical N2 patients. If authors could check this rate (failure to receive surgery after neoadjuvant therapy), it would be terrific, however, I know it is a very difficult task, so if not possible, please comment as a limitation. And, please comment on the importance of maintaining patients in good condition after surgery, because there is a big difference in outcome depending on whether or not they received adjuvant therapy.

Reply 4: We really appreciate this comment, and going into this study we had really hoped to include that sub-cohort of patients (neoadjuvant who did not receive surgery). We agree with every statement you just made – this is an extremely important group to understand, and if there is a high percentage of patients that don't make it to surgery, then performing surgery first in certain groups of patients may be beneficial. Unfortunately, we learned that there is no appropriate way to pull this subset of patients out of the NCDB. We would have to make numerous assumptions, which would lead to a poor analysis. Specifically, we would have to take pull out any patient who received chemotherapy without sugery, and then make the assumption that this was because surgery was planned and never happened. We would not be able to tell if the plan had always been just for chemotherapy.
Changes in Text: Lines 296 – 299 – "and whether a patient was planned for resection but did not make it to the operation is not included. A high percentage of patients receiving neoadjuvant chemotherapy but not making it to surgical resection would have significant implications on treatment recommendations."

Comment 5: Please check out guidelines for authors, esp. about the REFERENCES.
Reply 5: Thank you for pointing this out. References in the manuscript have been modified from superscript to parentheses.
Changes in Text: All reference citations modified to parentheses