**Author's response to reviews**

**Title:** Trimodal therapy for stage III-N2 non-small-cell lung carcinoma: a single center retrospective analysis

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**Author's response to reviews:** see over
Dear editors,

enclosed please find a revision of our paper entitled: "Trimodal therapy for stage III-N2 non-small-cell lung carcinoma: a single center retrospective analysis" which we would like to offer as an original article to BMC Cancer for possible publication.

All specific points and concerns raised by the reviewers have been revised.

Sincerely yours,

Vasileios Askoxylakis, MD
Reviewer's report

Reviewer 1:

**Major compulsory revisions**

1. The manuscript is lacking a research hypothesis
   Response:
   The research hypothesis and aim of our manuscript is to evaluate the results of a retrospective analysis of 71 patients with stage III-N2 NSCLC, who received trimodal treatment in our institution. The main hypothesis is that trimodal treatment is effective, with acceptable toxicity. This is stated in the introduction section of the manuscript (Page 7).

2. In the method section the time of N2-diagnosis is not specified: Was N2-disease confirmed during preoperative staging (thus representing IIIA3 disease)? If so, why did one-third of patients (n=23) receive chemotherapy in a neoadjuvant setting and two-third of patients (n=48) in an adjuvant setting?
   Response:
   The time of N2-diagnosis is added in the method section as suggested (Page 8). N2-disease was confirmed postoperative (pN2). Patients who received chemotherapy in the neoadjuvant setting had a cN2 stage during preoperative staging that was histologically confirmed postoperative.

3. The calculation of post-radiation loss of lung function with the post-operative lung function as baseline is problematic: Thoracic surgery results in a permanent (due to resection of lung parenchyma) and a temporary (due to reversible tissue changes in the remaining lung parenchyma) loss of lung function. Depending on the time interval between lung resection and determination of postoperative lung function the effect of radiation on lung function will be underestimated. The median time interval between surgery and adjuvant radiation was 4 weeks or 4 months respectively, depending on pre- or postoperative chemotherapy. However, the range was 1 to 12 months for the entire cohort.
   Response:
   This is a very important point raised by the reviewer. Indeed the time interval between surgery and radiotherapy might influence the ratios of the lung function. This is now included in the discussion (page 20-21). Since there are different medians for the neoadjuvant and the adjuvant setting we performed the analyses for the 2 settings separately. For patients receiving adjuvant chemotherapy (median time between surgery and RT 4 months) the post-to-pre radiotherapy ratio of FEV1 was 90%, whereas the same value for VC was 92%. For the group of patients receiving neoadjuvant chemotherapy (median time between surgery and RT 1 month) the respective values were 87% and 91%. Despite the differences in the time between surgery and radiotherapy between the 2 groups the differences in %FEV1 and VC were not statistically significant.
4. No consensus exists regarding the optimal treatment of patients with locally advanced NSCLC IIIA and IIIB and these patient cohorts are subject of numerous recent and ongoing clinical analyses. Above all, the effect of pre- or postoperative radiation therapy in a multimodal setting has been addressed by various groups. However, in the submitted manuscript 15 of 29 cited references are older than 5 years and it has to be questioned if the authors’ argumentation is based on most recent clinical findings.
Response:
More recent citations are included in the manuscript, as suggested. 11 additional clinical trials or large meta-analyses, published within the last 5 years, are included in the revised version of the manuscript.

5. The pneumonectomy rate in the presented cohort was 28% (n=20), which is rather high and similar to other studies that apply radiation therapy in the neoadjuvant setting. The authors should specify the amount of sleeve-resections in their cohort. Especially, since bilobectomy and pneumonectomy is associated with decreased patient survival.
Response:
4 patients from the lobectomy group received a sleeve resection. This is included in the manuscript (page 8).

Minor Essential Revisions

6. Chemotherapy is better tolerated in the neoadjuvant setting. Surprisingly, in the presented cohort more chemotherapy cycles were given in the adjuvant setting. The authors should specify the reasons for this unusual distribution.
Response:
Indeed chemotherapy can be better tolerated in the neoadjuvant setting. However, a recent systematic review and meta-analysis of large prospective trials by the NSCLC Meta-analysis collaborative group reveals that in large prospective studies patients received 2-3 cycles chemotherapy for preoperative and 2-6 cycles for postoperative treatment (cited in Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data. Lancet 2014, 383(9928):1561-1571). The data of the cohort presented in our study (treated between March 2001 and August 2008) is in concert with data from large prospective trials conducted at that time and, therefore, the distribution is not unusual.

7. The R0-resection rate in the presented cohort is 74.6%. The authors should discuss if a neoadjuvant radiation therapy that has been shown to increase the R0-resection rate could have resulted in an improved outcome.
Response:
A discussion on the role and the toxicity of neoadjuvant radiotherapy is included in page 16.
Reviewer 2:

**Major remarks**

1. Is this an analysis of all consecutive patients? If yes, state so. If not: how many were not included? How were they treated?
Response: This is not an analysis of all consecutive patients. We included only patients who consecutively received surgery, chemotherapy and radiotherapy at the University Hospital of Heidelberg. Patients who received one or more modalities outside the University Hospital were not included due to the lack of detailed data. This is included in the manuscript as suggested (page 8).

2. What were the reasons for using neoadjuvant vs adjuvant chemotherapy: was it part of a trial protocol or depending on tumor size?
Response: The decision on neoadjuvant or adjuvant chemotherapy was an individual decision, based on tumor characteristics, such as tumor size and resectability at diagnosis. This is included in the manuscript as suggested (page 8).

3. Similarly: what was the reason for using cisplatin vs carboplatin?
Response: The main criteria were performance status and co-morbidities, i.e. renal function. This is included in the revised version of the manuscript, as suggested (page 8). We also provide a discussion about how the difference in performance status and co-morbidities can lead to selection bias of the comparison between patients who received cisplatin and the ones that received non-cisplatin chemotherapy (page 18).

4. Since many treatment decisions are influenced by staging factors and patients' characteristics a multivariate analysis would help.
Response: A multivariate analysis was performed as suggested. This is included in the abstract (Page 3), the methods (Page 10) and the results section (Page 13). Furthermore, it is included in Table 3.

5. When was the data cut off? If it was recently, the median follow-up should be more than 30 months. In fact, looking at the survival curves it seems to be longer. Were patients that had an event perhaps counted for follow-up?
Response: Data cut off was defined as the date of the last follow up visit at the University Hospital of Heidelberg. This is included in the manuscript, as suggested (page 9). To have completed data for the overall survival analysis, further information on survival (patient alive or not, date of death) was thereafter collected from the treating physicians outside of the university hospital.

**Minor essential remarks**
1. Please describe how staging was done.
Response:
Patients included in this analysis were diagnosed with NSCLC between 2001 and 2008. Preoperative staging included for all patients CT-scans of the thorax, abdomen and brain, as well as a bone scan. This is included in page 8.

2. Shorten the description of patients characteristics in the text, all is shown in the table.
Response:
The description of patients’ characteristics is shortened, as suggested.

3. I suggest to pool lobectomy with bilobectomy and compare to pneumonectomy, this is how most reports show it.
Response:
Indeed most reports provide a comparison between lobectomy/bilobectomy versus pneumonectomy. Our goal was to compare patients with simple lobectomy, which was the majority of the cases, to patients with more extended surgical resections, such as bilobectomy or pneumonectomy. In the revised version of the manuscript we provide a comparison of lobectomy/bilobectomy versus pneumonectomy in the discussion (page 19).

4. Are there any data on secondary cancers?
Response:
We do not have any data on secondary cancers. The follow up periods are probably too short to obtain data on secondary malignancies.

5. Please rephrase the introduction and discussion: in all fairness, all randomized data show a lack of effect for radiotherapy in this situation, at least in terms of survival (IFCT and SAKK trial for preoperative RT, the Meta-analysis for PORT). Anita was a retrospective unplanned subgroup analysis and the SEER data is a cohort analysis.
Response:
The introduction (Page 6-7) and discussion (Page 15) were rephrased as suggested. We clearly state that data on the efficacy of postoperative radiotherapy remains controversial. Since our manuscript focuses on postoperative radiotherapy, we also focused in the introduction and discussion on studies and analyses of postoperative radiation treatment. We also included a more recent meta-analysis, indicating a survival benefit for modern, linear-accelerator given therapies (Billiet et al. 2014).

6. Similarly: all international guidelines state definitive chemoradiotherapy as standard treatment for stage III NSCLC: this should at least be mentioned as one other therapeutic option.
Response:
Definitive chemoradiotherapy is indeed the standard treatment of choice for not resectable/operable stage III NSCLC. Our manuscript focuses on
operable/resectable cases. The therapeutic option of definitive chemoradiotherapy in mentioned in the discussion as suggested (page 17).

Finally, we would like to thank the referees for the careful review of our manuscript.