**Author’s response to reviews**

**Title:** Predictive risk factors for lymph node metastasis in patients with resected Non-small cell lung cancer: A case control study

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Dear Dr. V. Zamvar,

We would like to thank you for the very careful and thoughtful review of our manuscript, "predictive risk factors for lymph nodes metastasis in patients with resected Non-small cell lung cancer: A case control study". We appreciate the comments of the reviewers and would like to address these concerns as well as providing a revised manuscript. We believe that this revised version of the paper is improved, and will be of interest to the readers of Journal of Cardiothoracic Surgery JCTS. Please find our point-by-point response to the reviewer’s concerns.
Reply to editor

• Based on reviewer comments we revised our paper accordingly, changes are marked in RED.

Reviewer 1 – Critique

Thanks for the opportunity to review this manuscript. This study presents an interesting concept of developing perioperative standards in our thoracic department to predict a good strategy for diagnosis, staging and therapy, with the ultimate aim to predict and reduce the complications and the costs. I have a few comments and queries which are as follows:

1. The number of patients included in this study does not allow for relevant statistical analyses, particularly multivariate or subgroup analyses. Including a limited number of patients from a quite long period carries the risk of changing staging and treatment strategies. Particularly the availability and expertise in invasive mediastinal staging by bronchoscopy will be an issue.

We agree with the reviewer that the number of patients is limited. Therefore, we tried through our analysis to describe the predictive factors for all patients with lymph node metastasis (pN+) without other subgroups, especially in patients with small size tumors (T1 tumors). Invasive mediastinal staging was limited performed. It has been done only in patients with cN2-cN3 depending on the radiologic findings.

2. You describe a median number of dissected lymph nodes of 25 with a range of 6-69. It is very likely that this high number results from counting fragmented lymph nodes rather than complete lymph nodes. The number of dissected lymph nodes was detected as a predictive factor for lymph node metastasis in resected NSCLC, which may be influenced by this fact and of course by the completeness of mediastinal lymph node dissection.

Principally, we have dissected all lymph node stations systematically. The number of lymph nodes was taken from the histological reports. Once again, we agree with the Reviewer that this number of lymph nodes is high and may be counting fragmented lymph nodes. Unfortunately, the retrospective nature of this study does not allow the proof of this point. The number of lymph node metastases was only significant in the univariate analysis and wasn’t in the multivariate analysis. Therefore, the number of lymph node metastases can’t be detected in our study as a predictive factor of lymph node metastasis. Furthermore, as the reviewer said, we have detected high number of lymph nodes, this is why we can’t through our Analysis accept this factor. This factor has been deleted from the table of univariate analysis (Page 17, Table 2)
3. The role of tumour size and location as a predictor of nodal involvement has been extensively studied in the past and actually has resulted in the current TNM classification and international guidelines for staging and treatment. You have mentioned the ESTS guidelines on preop mediastinal staging and in your discussion you propose an algorithm which is already part of these guidelines. According to these guidelines you mention, that patients with tumours exceeding 3 cm or with a central location should undergo EBUS/EUS and even mediastinoscopy in patients with suspected mediastinal nodal involvement after negative EBUS. How many of your patients underwent invasive mediastinal staging over the whole period? Which patients did not undergo invasive preoperative mediastinal staging?

As mentioned in the study, the performance of invasive mediastinal staging was limited in our pulmonary department and has been done principally only on patients with cN2 and cN3 depending to the preoperative thorax-CT or PET/CT. The aim of our study is to change this strategy depending on our analysis, supported by the international Guidelines and the literature.

the invasive mediastinal staging has been eventually performed by 35 patients of our cohort (17.1%). Other patients without cN2 didn’t undergo EBUS/EUS preoperatively (Page 4, Line 72-75)

4. Describing your surgical strategy in systematic nodal dissection for left-sided tumours you include the removal of stations 2, 3 and 4 on the left side. Please explain your technique

Thank you again for your notice. The description of lymph node dissection in superior mediastinum on the left side has been included.

“Then, we proceeded to the dissection to the upper mediastinum (tracheobronchial lymph node stations 2&4), which located medial to the subaortic lymph nodes. These lymph nodes could be dissected after mobilization the aortic arch anteriorly (Ligament of Botalli could be divided) and by giving an extreme care of the left recurrent laryngeal nerve and left vagal nerve. the Lymph node stations in lower mediastinum (stations No. 7, 8 and 9) were dissected, similarly to the right side” (Material and patients, Page 4, Line 88-92)

Reviewer #2:

1. How was the preoperative mediastinal staging of these patients?

The preoperative staging in our clinic included mainly Thorax-CT, PET-CT, eventually Brain MRT (symptomatic patients) and Bronchoscopy. Furthermore, Thorax-CT with upper abdomen, eventually Brain-MRT, skeletal Scintigraphy, and Bronchoscopy were done in the cases, in
which when we couldn’t get a PET-CT regularly (Page, Line). Invasive mediastinal staging such EBUS/EUS was done only by patients with cN2, cN3 according to the radiological findings. Therefore, we tried through this analysis, depending on the literature, to reform our standards and perform the invasive mediastinal staging in patients with risk factors in spite of the preoperative lymph node status cN2 (Page 4, Line 72-75)

2. In which n2 lymph nodes were positively detected.

Thank you for your notice, actually we didn’t include the pattern of lymph node metastasis, because of limited number of patients with mediastinal lymph nodes metastasis. By the way, the most positive lymph node station on the right side was station 4 (n=19 from 28 patients with right sided tumors, 67.8%) and station 5-6 on the left side (n= 10 from 17 patients with left sided tumors, 58.8%). Overall, lymph node station 4 was the most positive station (n=20 from 45 patients 44.4%) (Page 6, Line 136-137)