

Peer Review File

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Reviewer A

Comment 1: What I am concerned about in this article is that the authors seem to only list the pivotal studies without analyzing the clinical implication and limitations of the studies. For example, what they should have discussed in the section “Systematic lymph node dissection versus lymph node sampling (LNS)” could be addressed as follows.

Reply 1: As you instructed, we added sentences.

Changes in the text. Lines 5-20 on Page 8 were added.

Comment 2: In addition to these limitations, they should have also discussed a bit more about the reason why we need intraoperative LN assessment, predictors of occult LN metastasis, the optimal number of LN harvested, and the recently proposed R factor classification issue.

Reply 2: As you instructed, we added sentences.

Changes in the text. Lines 11-20 on Page 10 were added.

Reviewer B

Comment 1: Minor language issues - please polish the language by using language editing or software (e.g. grammarly).

Reply 1: We had a native check of our manuscript before submitting.

Comment 2: In my opinion, there are too many historical and well-studied aspects (with numerous existing narrative reviews). I would personally focus on the newest things. Especially your section about basic immunological science aspects of lymph nodes.

Reply 2: We added sentences as follow. “We have demonstrated that CTL that recognizes p53 mutation and attack lung cancer cells cannot be detected in peripheral blood, but is present in regional lymph node and tumor, and induces anti-tumor immunity in a lung cancer case”.

Changes in the text. Lines 20-23 in Page 12 were added.

Comment 3: Lymphadenectomy in segmentectomies is also such a topic. What about lymphadenectomy in very small tumours (i.e section about Low Dose Computed Tomography detected tumours).

Reply 3: We added sentences as follows. "Schlachtenberger et al. reported that 16.5% of patients with NSCLC ≤ 2 cm had lymph node upstage after surgery. It was emphasized that lymph node dissection and proper staging are important for her NSCLC patients, regardless of tumor size or surgical approach."

Changes in the text. Lines 10-13 in Page 11 were added.

Comment 4: Maybe because of lower immunological activity due to lymphadenectomy, immunotherapy could be better for neoadjuvant rather than adjuvant therapy. Besides that - tumor = more antigens for immune response. You could elaborate on that topic I think.

Reply 4: Unfortunately, the answer is still unknown. Validation research is currently being conducted around the world, including ours.

Reviewer C

Comment 1: Line 28-33: The intention of this sentence is unclear, also N2alpha and N3gamma are not international designation.

Reply 1: We added the following additional explanation.

N3alpha: Contralateral mediastinal lymph node

N3gamma: Ipsilateral or contralateral supraclavicular/scalene muscle lymph node

Changes in the text. Lines 14-15 on Page 6 were added.

Comment 2: In the Abstract the methods are described as: "We compared five randomized prospective comparative studies on systematic lymph node dissection (SLND) and lymph node sampling (LNS) in lung cancer surgery"

In the main text, a description of the method is missing. Furthermore, L-SLND was included in the main text as well as retrospective analyses such as Adachi et al.

Reply 2: We added a description of the method

Changes in the text. Lines 16-23 in Page 5 were added.

Comment 3: The caption "segmentectomy" does not fit, as the paper is about lymphadenectomy. Maybe a change to "Special aspects of lymphadenectomy in segmentectomy" would be reasonable.

Reply 3: We changed it according to the instruction.
Changes in the text. Line 22 on Page 10 was added.

Comment 4: Page 5, Line 22-29: what is the valid information of these two sentences? I do not understand.

Reply 4: We added sentences. For more details, please refer to the reference
Changes in the text. Line 24 on Page 10 and Lines 1-4 on Page 11 were added.

Comment 5: Page 5, line 33: "lenient" seems to be a wrong word. Did you mean careless? negligent?

Reply 5: We changed to "negligent".

Comment 6: page 6, line 22-26: This message is highly speculative and not helpful. ICIs are currently not indicated after curative NSCLC resection without lymph node metastases so ICI treatment cannot be justification to leave LN insitu. Furthermore, SLND uncover N1 or N2 disease leading to adjuvant ICI treatment. So do not tell the readers to leave regional lymph nodes unless you have better arguments.

Reply 6: Certainly, we also want to avoid being understood as leaving lymph nodes without showing any evidence. So we added the sentence.

Changes in the text. Lines 5-6 on Page 13 were added.

Comment 7: page 5, line 6: Do you mean "effect" instead of "affect"?

Reply 7: We changed it according to the instruction.

Comment 8: The references 27-32 are case reports and not suitable to underline general assumptions

Reply 8: Our studies are not just case reports. We take pride in conducting a basic and detailed analysis of cancer immunity and deriving universal results. They are considered sufficient for references.

Comment 9: page 5, line 15: LSD is not defined in the text...

Reply 9: We changed it according to the instruction.

Comment 10: 5 RCTs with different results concerning DFS and OS, but no discussion and comparison. Altogether I have the impression, that the intention of this paper is not clear. What is the message, and what are the arguments for it... Please think about it again and ask a native speaker for spelling corrections.

Reply 10: We added sentences related to 5 RCTs. We had a native check of our manuscript before submission.

Changes in the text. Lines 5-20 on Page 8 were added.