

Peer Review File

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**Review Comment**

I thank the author and AMJ for the opportunity to review this manuscript. Authors present a literature review of lymphatic drainage of lung cancer, precisising anatomical lymphatic drainage pathways and variations in drainage patterns. They also reviewed preoperative and intraoperative staging/mapping strategies.

Per se, the content of this article adds no new data to the literature but summarize the recent evidence on lymphatic drainage in lung cancer that may be of interest for the reader.

My comments are below:

**Comment 1:** English is ok. Proofreading is required as they are some typos (2nd paragraph of the introduction for example).

**Reply 1:** Thank you for all the very helpful and insightful comments on this manuscript. With regards to this first comment, I have thoroughly proofread it and have corrected any typos or grammatical errors.

**Comment 2:** Regarding lymphadenectomy, authors share the results from Darling et al (ref #4), concluding in the absence of difference between sampling and systematic lymph node dissection. This study was published in 2011. I suggest the author to also report the results from more recent studies, highlighting the benefice of a systematic lymph node dissection in lung cancer surgery. Please consider adding these studies in your review and comment on that.

H Zheng et al. Radical mediastinal nodal removal improves disease-free survival for pulmonary low-grade malignant tumors. *Lung Cancer*. 2012 Mar;75(3):342-7. doi: 10.1016/j.lungcan.2011.07.016

S Mokhles et al. Systematic lymphadenectomy versus sampling of ipsilateral mediastinal lymph-nodes during lobectomy for non-small-cell lung cancer: a systematic review of randomized trials and a meta-analysis. *Eur J Cardiothorac Surg*. 2017 Jun 1;51(6):1149-1156. doi: 10.1093/ejcts/ezw439.

MA Ray et al. Survival After Mediastinal Node Dissection, Systematic Sampling, or Neither for Early Stage NSCLC. *J Thorac Oncol.* 2020 Oct;15(10):1670-1681. doi: 10.1016/j.jtho.2020.06.009. Epub 2020 Jun 20.

**Reply 2:** Thank you very much for these suggestions. It appears that the papers mentioned here by Zheng et al. and Ray et al. also support a similar conclusion in that there is no improvement in overall survival associated with radical lymph node dissection compared to nodal sampling. As the Mokhles et al. paper reviews studies published prior to 2007 which predate the routine use of PET/CT scanning and also do not mention adjuvant chemotherapy, I have not incorporated it into this review.

**Comment 3:** Other factors may impact the metastasis spread through lymphatic vessels and lymph nodes such as tumor size (HY Deng et al. Surgical Choice for Clinical Stage IA Non-Small Cell Lung Cancer: View From Regional Lymph Node Metastasis. *Ann Thorac Surg.* 2020 Apr;109(4):1079-1085. doi: 10.1016/j.athoracsur.2019.10.056. Epub 2019 Dec 14.) and should be pointed out in the literature review. Please consider adding this study in your review and comment on that.

**Reply 3:** Thank you very much for pointing out this aspect. This focus of this review was to highlight the lymphatic system itself, and as such I chose to omit additional factors which may contribute to lymphatic spread, such as tumor characteristics and microenvironments to better limit the scope of this review.

**Comment 4:** Preoperative strategies and intraoperative strategies have been reported in this reviewed (mainly EBUS and SLN). Surgical assessment of lymph nodes using intraoperative frozen section of lymph nodes is also a useful strategy, that may lead intraoperative change of plan. (W Li et al. Intraoperative frozen sections of the regional lymph nodes contribute to surgical decision-making in non-small cell lung cancer patients. *J Thorac Dis.* 2016 Aug;8(8):1974-80. doi: 10.21037/jtd.2016.06.49.). Please consider adding this study in your review and comment on that.

**Reply 4:** As the focus of this review was the highlight the structure of the lymphatic system itself, I chose to limit discussion regarding the pathology, markers, and microenvironments of the nodes themselves.

**Comment 5:** As a current hot topic, extent of surgical resection (lobar vs. sublobar) should be discussed, as it has an impact on lymphadenectomy.

**Reply 5:** I wholeheartedly agree that the extent of surgical resection is a hot topic. In an attempt to limit the scope of this article, I chose to defer discussion of surgical

resection to focus more on the mapping of lymphatic pathways, which will certainly down the road be applicable to discussion regarding resection.

**Comment 6:** Patterns of lung lymphatic drainage are well described. An illustration should be of interest for the readers unfamiliar with pulmonary anatomy, especially lymphatic drainage and lymph nodes.

**Reply 6:** Please see the schematic now included, Figure 1.

**Comment 7:** Same comment regarding the SLN strategies. Adequate illustration(s) should be of interest for the reader.

**Reply 7:** Multiple drafts of diagrams for SLN mapping strategies were attempted, and unfortunately it was felt that it was too difficult to accurately present these in detailed enough schematic form to support the article with overwhelming the main point.