

# Examined lymph node count in non-small-cell lung cancer: will it be a decision making approach in treatment of NSCLC?

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Surgical therapy, which accurate staging and pathological diagnosis relay on, is still irreplaceable in the treatment strategy of lung cancer, especially for the early stage non-small-cell lung cancer (NSCLC) (1). Besides resection of tumors, many prognostic factors, including nodal status, histology, and tumor size, can be provided through surgical procedure. Nodal status, as one of the most important factors in the staging definition and adjuvant chemotherapy selection, has always been playing a significant role in the health care of lung cancer patients (2). However, differing from gastrointestinal and breast cancer, the recommendation of lymph node (LN) dissection or examinations from NCCN is in the qualitative level and the studies focus on the examined lymph nodes (ELNs) is still insufficient in lung cancer (1,3,4). Thus, Liang *et al.* investigated the effect of ELNs in the staging and prognosis of NSCLC in a real-world retrospective analysis, which tried to provide a reliable evidence of LN management in the quantitative level for NSCLC patients (5).

The investigation was performed according to Chinese registry and the SEER database, which were from multicenter and real-world data sets. The tremendous number of cases made this study more reliable. The authors chose the patients from stage I to IIIA, which aimed to emphasize the LN in the staging and treatment strategy selection. The patients of advanced local lung cancer such

as IIIB were excluded since the radical resection was not the standard care for these patients. They also excluded the patients of SCLC as this more aggressive histology may not be suitable for surgical treatment and therefore underrate the importance of LN in the prognosis prediction and treatment selection (6). The results were encouraging in that ELNs counts were strongly associated with the positive LNs in any N stage after the adjustment with other factors. The number of ELNs and overall survival (OS) were positively correlated in N0 stage and the cut off of 16 for ELNs counts were founded and confirmed according to this article. The result indicated that the pursuit of maximal LN resection may provide a better long-term survival in NSCLC patients and the count of 16 ELNs might be considered as a minimal number.

Two sets of database recruited different racial people worldwide. Asian patients may present different genetic and histological characteristics in contrast with Caucasians, but there was no significant difference on the relation of ELNs count and staging migrations and OS between both races (7). Different types of histology may present diverse clinical features, treatment strategy and long-term survival results. Therefore, the authors examined the difference of histological subgroups via stratification analysis, which tried to find out the more details of the correlation between ELNs and OS. The result demonstrated that there were no

subgroup differences in ENLs and OS correlation on the basis of histology. This might emphasize the importance of LN examinations or dissections for all the types of histology.

However, as a retrospective analysis, the bias is inevitable for this study. Firstly, as a multi-central database, different surgical skill may lead to the various prognosis. The radical LN dissection leads to a precise staging and a better long-term survival (8). Thus, the uniform and standard surgical treatment may improve the accuracy of this investigation. In addition, the diagnosis of LN metastasis and ELNs counting were depended much on the individual effort of surgeons and pathologists. The definition of ELNs count may be obscured by the fragmented LN. En bloc resection of LN is the ideal condition but requires good surgical skills. In some hospitals of western countries, mediastinoscopy is routinely performed for the diagnosis and resection of N2 LN before the surgery, which would increase the possibility of fragmented LN. In the Liang's study, they conservatively suggested that only complete LNs were counted if LN fragmentation existed in their retrospective analysis. However, fragmented LNs have to be counted manually by the pathologists, which is unavoidable in the real world. A more uniform counting method of LNs has to be designed and exploited in the further investigations. Moreover, the patients recruited in the study present different characteristics, which might influence the conclusion as well. For example, more epidermal growth factor receptor (*EGFR*) mutations were found in the Asian female non-smokers with adenocarcinoma, and therefore Chinese registry group may contain more patients with *EGFR* positive mutations (7). Targeted therapy contributes to a better OS for *EGFR* positive patients compared to *EGFR* negative patients. Thus, the somatic mutation such as *EGFR* or *ALK* mutation among the patients should be adjusted in this study. Similarly, the adjuvant chemotherapy regimen, dose of radiotherapy and other therapies involved have to be considered as the adjusting factors as well, which could further highlight the status of ELNs count in the OS of NSCLC.

Furthermore, the authors mentioned that ELN counts were positively related with the staging of NSCLC. However, the number of LN station is still controversial in the mediastinal lymphadenectomy. Basically, the systemic mediastinal lymphadenectomy covers the regions including intrapulmonary, hilar and mediastinum (9). However, a recent study suggests that the systematic mediastinal lymphadenectomy could be replaced by lobe-specific nodal

dissection (LSD) for selected patients of clinical stage I or II NSCLC. For example, the inferior mediastinal nodes were not necessary to be dissected for upper lobe NSCLC patients because no obvious benefit was observed for the 5-year OS but side effects and risks may increase by this procedure (10). Therefore, the recommendation of minimal 16 nodal dissections may not be appropriate for these selected patients.

As far as I am concerned, one of the merits of Liang *et al.*'s study is to determine that more LN examinations presented the better OS in NSCLC patients with N0 staging. The potential LN metastasis might be discovered and dissected via sufficient nodal examination that leads to a better long-term survival. Since it is hard to identify the micrometastasis precisely by the current techniques, performing LN dissection as much as possible may be considered as the most feasible complementary strategy (11). Besides, more nodal dissections in N0 staging NSCLC patients may lead to a lower risk of tumor cells immigrations as the adjuvant chemo- or radiotherapy was not recommended in these patients with specific histology and T stages (8).

In conclusion, the minimum ELNs number has not been recommended according to current guidelines. In the current analysis from Liang *et al.*, they demonstrated the significance of ELNs in the treatment of NSCLC and provided the recommended ELNs counts in the quantitative level. This study contributes to shed the light on the effects of ELNs in the prognosis of NSCLC. Further research has to focus on this issue through more randomized controlled trials (RCT) to confirm the ELNs count and OS. Thoracic surgeons have to pay more attention to the clinical significance of intrapulmonary, hilar and mediastinal lymphadenectomy in surgical treatment of NSCLC patients during their surgical procedure. However, due to the great variety of different patients, the precise LNs number may not be overemphasized without further evidence of RCT data.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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