



The ongoing debate regarding the impact of examined lymph node count on staging and long-term survival of resected non-small cell lung cancer: an editorial review

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While lymph node (LN) status continues to be one of the most important predictors of prognosis and survival in patients with potentially resectable lung cancer, controversy still remains regarding what is the optimal technique to assess LNs: sampling versus dissection (1-3). Additionally, just how many LNs are required to generate an accurate prognosis has also been a clinical question without a true answer for some time. While emphasis on the number of requisite stations has been discussed in the literature (4-6), the minimum number of LNs required to correctly stage patients at risk for recurrent cancer has not in any significant depth. In the referenced article (7), the authors attempt to quantify the impact of examined LN (ELN) count on precise staging and long-term survival of resected non-small cell lung cancer (NSCLC) using the United States Surveillance, Epidemiology, and End Results (SEER) database and a Chinese Multi-Institutional Registry. Attempts to identify the optimal minimal threshold for ELN counts were then determined.

LN sampling and/or dissection play an important role in determining the extent of disease in lung cancer patients. It not only correctly stages patients and appropriates the need for adjuvant treatment; it portends the risk of disease recurrence and is one of the best predictors of overall survival (OS). The correlation between larger numbers of LNs studied and improved patient survival has been well documented with many other cancers (7), especially in breast and gastrointestinal cancer, and the respective National Comprehensive Cancer Network (NCCN) guidelines recommend the minimal number of LNs needed

by either sampling or dissection (8-10). Regarding lung cancer, recommendations regarding the optimal number of nodes remain less defined. Current NCCN guidelines for NSCLC recommend sampling of one or more LN from all mediastinal stations as described using the LN map from the International Association for the Study of Lung Cancer (7,11,12), and provide little guidance as to which method: sampling versus dissection, is best.

When employing LN sampling in lung cancer operations, most centers have followed the protocol described in ACOSOG Z0030 (13), which describes sampling for right lung cancers at stations 2R, 4R, 7, and 10R; and stations 5, 6, 7, and 10L for left lung cancers. Alternatively, LN dissection traditionally involves removal of the nodal packet from the above stations intra-operatively. While there has been much debate whether sampling versus dissection is best (14-16), in general, the overall consensus appears to agree there is no difference in LN sampling versus LN dissection in T1 and T2 tumors (17). However, for more advanced tumors, the recommendations have included performing a mediastinal lymphadenectomy to optimize staging and local control, and guide adjuvant therapy.

The lack of consistency within studies to use either sampling or formal dissection has led to an inability to establish specific guidelines, with the “default” recommendations mentioned above being the norm in most cohorts. Disparities within studies regarding differences in treatment practices and diversity in populations in regards to race, ethnicity, geographic locations and socioeconomic status, have also further limited the ability to transcend

results from most studies (even those with large cohorts) to the general population. Liang *et al.* (7) rightly chose two very large populations, comprised of more than 25 centers in diverse geographic areas that utilized LN dissection combining the surgical count procured by the surgeon with the count procured by the pathologists to create a total LN count. Exclusion of patients with advanced disease (stage IIIB and IV) was also thoughtful given surgery is not the standard of care within those populations. While none of the studies were prospective in nature, the sheer number of patients evaluated helped to overcome bias in charting practices and using data that is retrospective in nature.

Yet, beyond the decision-making process of whether LN sampling versus dissection is more superior, an equally controversial topic is whether mediastinal LN dissection improves survival. On the one hand, a recent meta-analysis of five studies demonstrated two studies that found better survival in patients receiving mediastinal LN dissection than those receiving sampling, while the other three did not (13). On the other hand, one cannot argue the demonstrated benefits of LN dissection presented by Liang *et al.* (7) demonstrating the proportional increase in N stage with increasing ELN count after adjusting for characteristics including operation performed, T stage, tumor location, and respective histology. Further demonstrating the benefit of LN dissection over sampling included the facts that, (I) the greater number of ELNs was associated with a greater number of positive LNs, especially in patients with node-positive disease, (II) a greater number of ELNs positively correlated with better OS among patients with both node-positive and node-negative disease, and (III) all-cause mortality of patients with at least 16 LNs harvested in node-negative NSCLC was significantly reduced.

Certainly, the stage migration effects appreciated in patients with large samples of LNs cannot be ignored. Still, while the authors attempt to establish a benchmark for LN dissection, there are important questions that remain unanswered. For example, how many of the 16 nodes need to come from each N station? Is there a difference between a majority of N1 nodes versus N2 nodes? Regarding N2 stations, while we know single station disease usually portends a better prognosis than multi-station disease (18,19), is one station more important than others? Specifically, given the suggestion that in other cancers such as breast, full dissection is not always warranted (20) even in the case of node-positive disease (21), is the discovery of one positive LN from a respective N station enough to stop

the dissection and appropriately stage and treat the disease? Moreover, do we always need 16 nodes?

To date, the majority of studies evaluating the impact of ELN on precise staging and long-term survival (22-24), still leave many questions. Certainly, the effects that LN sampling and dissection can have on staging and prognosis are well described. As with other cancers (25), the specific advantage of LN dissection to influence stage migration and appropriately guide adjuvant treatment options while providing a more accurate prognosis is immense. The fact that a greater number of ELNs correlated with a higher probability of stage migration is promising. While most studies have either only provided single center experience, with reviews not representing a large demographic; most reviews have faltered due to lack of consistency in LN technique, tumor stage, patient characteristics or pathology acquisition. As endobronchial ultrasound (EBUS) has quickly become the standard first-line technique for LN acquisition, by default, LN sampling has also become slightly more popular. Given this, though future studies with LN dissection may be harder to perform, prospective trails using equally large populations of LN sampling and dissection in populations with similar demographics to see if this results in the same increase in N stage and stage migration would be key to answering this question. Furthermore, maximizing the ability to detect node-positive disease, especially in patients that are thought to be negative, has endless benefits to improving treatment options for lung cancer patients and providing more objective and realistic prognosis estimates at the time of surgery.

In conclusion, it is obvious that further prospective, randomized controlled trials with diverse patient populations that are matched with unified LN sampling protocols are necessary to determine the evolving role of ELN counts in resected NSCLC.

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