Editorial Commentary

Increasing T stage is associated with the need for more extensive lymph node assessment in clinical stage I non-small cell lung cancer

Andrew Brownlee[1], **Seth B. Krantz**[1,2]

[1]University of Chicago Pritzker School of Medicine, Division of Thoracic Surgery, Chicago, IL, USA; [2]NorthShore University Health System, Division of Thoracic Surgery, Evanston, IL, USA

Correspondence to: Seth B. Krantz, MD. NorthShore University Healthy System, 2650 Ridge Road, Walgreen Suite 3507, Evanston, IL 60201, USA. Email: skrantz@northshore.org.

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Lymph node assessment is an important determinant of stage in non-small cell lung cancer (NSCLC); the optimal number of nodes needed in a lymphadenectomy during pulmonary resection, however, remains unclear. Several recent papers, utilizing both the National Cancer Database (NCDB) and the Surveillance, Epidemiology, and End Results Database (SEER), have shown that increased lymph node assessment is associated with improved survival in patients with clinical early stage lung cancer. In the paper "Optimal Lymph Node Examination and Adjuvant Chemotherapy for Stage I Lung Cancer", Dai *et al.* expanded upon this work using the NCDB to identify patients between 2006 and 2014 who were either clinical or pathological stage I and treated with surgical resection (1). An important part in this paper, is that they stratified their clinical stage I patients by T stage, allowing the authors to provide a more granular assessment of what lymph node threshold should be considered depending on T stage. As in other similar papers, they defined nodal upstaging as patients who were clinical N0 and became pathologic N1/N2 after resection. Overall, they identified 65,438 pathologic and 117,112 clinical stage I NSCLCs. The median number of nodes examined in each group was 7. Multivariate analysis showed that optimal lymph node threshold was dependent on T stage. They identified optimal cutoffs of 8, 9, 10, and 11 lymph nodes for stage T1a, T1b, T1c, and T2a tumors, respectively. Reaching the respective lymph node threshold for each T stage was associated with a significant reduction in mortality compared to evaluating fewer nodes.

The authors then further validated lymph node cutoffs by looking at nodal upstaging. They identified 11,835 patients (10.1%) who were cN0 and pN1/N2, which is in line with prior studies (2-4). They then stratified patients into different lymph node assessment groups and found retrieving between 8 to 11 nodes as the ideal cutoff with respect to identification of node positive disease in a cN0 population. This number is somewhat lower than prior studies referenced above with optimal values of greater than 14 nodes. As a quality metric, the commission on cancer recommends assessment of at least 10 lymph nodes for resected lung cancer.

Lastly, after defining the optimum lymph node thresholds, the authors compared under-assessed and adequately assessed patients, broken down by T stage, and with respect to whether or not they received adjuvant chemotherapy (AChT). The rationale behind this being that the under-assessed group will have a higher percentage of "understaged" patients (i.e., actual pathologic stage II and higher patients who are counted as pathologic stage I due to inadequate lymphadenectomy) and that this population may benefit from adjuvant therapy. They identified 44,428

pathologic stage I patients who were under-assessed with 4.8% receiving AChT. The majority of these patients were T2a. After stratifying by T stage, they performed a propensity match comparing patients who did and did not receive AChT and found that in under-assessed T2a patients only, AChT was associated with improved survival compared to no AChT. Within the population of T2a patients with adequate lymph node assessment, there was no survival benefit to AChT.

The recommendations from the literature on the minimum number of lymph nodes required in thoracic lymphadenectomy for NSCLC have been reported as 4–20, with this number varying by stage (4-7). This study is an important addition to the field as it is a very large dataset, stratified by T-stage and suggests a possible survival benefit to adjuvant chemotherapy in patients with pathologic T2a NSCLC with less than 8 lymph nodes retrieved.

Much of the current research has focused on median number of nodes examined and the effect of number of nodes examined on mortality. Osarogiagbon *et al.* showed in their retrospective review of over 24,000 pN0 patients in the SEER database that the optimal number of lymph nodes was 18–20 and that the median number of nodes actually examined was six (6). On the other hand, a study by Cao *et al.* looked at sublobar resection in 3,269 stage IA patients in the SEER database and found that dissection of greater than 4 lymph nodes was associated with better survival. Despite this, the pathologic upstaging related to lymph node assessment in stage I NSCLC appears to be relatively consistent and ranges from 10.0–12.6% (2-4).

This paper is not without limitations. It is retrospective in nature and based on a large national database. The NCDB lacks granularity and does not give information on single station *vs.* multi-station disease, bulky disease, clinical staging modality, lymphovascular invasion and visceral pleural invasion. In addition, the action point for clinicians aside from obtaining less than 8 lymph nodes during surgical lymphadenectomy is to consider AChT for under-assessed patients with pathologic T2a. The role of chemotherapy in these patients is interesting, but the clinical likelihood and utility of providing chemotherapy to these patients is unclear. The role of adjuvant chemotherapy in stage II and higher patients is derived largely from the several randomized trials of platinum-based therapy published from 2003–2006. A subsequent 2008 meta-analysis of these trials (LACE) demonstrated a 5.4% improvement in 5-year overall survival for adjuvant chemotherapy in stage II and IIIa, resected patients, compared to no chemotherapy (8) The data for stage I patients remains controversial at best. The LACE trial actually demonstrated worse survival for adjuvant platinum-based chemotherapy in stage IA patients. For Stage IB patients with tumors greater than 4 cm, chemotherapy is generally offered based on the results of the CALGB 9633 trial (9). While the overall trial results, which looked at the use of 4 cycles of carboplatin/paclitaxel in stage IB resected NSCLC, showed no survival benefit, unplanned subgroup analysis showed a statistically significant improvement in overall survival in patients with tumors greater than 4 cm (T2b based on 8th edition AJCC staging guidelines).

In the current paper, only 4.8% of stage I patients with inadequate lymph node assessment received adjuvant therapy. For T2a patients who were understaged, the authors showed a benefit for AChT, with a HR of 0.84 compared to a similar population who did not receive AChT. Although the data achieved statistical significance, the percent of these patients is very low (in this study it accounted for 0.98% of stage I cancers), thus limiting the clinical applicability. The only patients who would receive a benefit are those with true stage II or higher disease that were grouped as stage I. With the 70% reduction in understaging the authors predict would occur with adequate lymph node assessment, the absolute number of patients this represents would become even smaller. Given only a 5% benefit even in large meta-analyses of stage II patients, it seems unlikely that the subgroup of inadequately staged T2a patients in the current paper is large enough to be adequately powered to show a meaningful difference. Despite propensity matching, the very small percentage that received adjuvant therapy in the group, and the fact that guidelines do not recommend it, imply a significant amount of selection bias that is unlikely to be truly mitigated by propensity matching. In addition, the true solution to this is to perform a more adequate lymphadenectomy rather than address this issue postoperatively after final pathologic staging.

Regardless of these limitations, this is an important contribution to the literature. It further solidifies the data on the value of lymph node assessment with regard to both survival and upstaging and provides additional perspective on how T stage contributes to this. Furthermore, while it is unlikely to lead the delivery of adjuvant chemotherapy to an understaged population, the fact that understaging had such a negative prognostic affect as to seemingly make chemotherapy beneficial, should be serve and glaring reminder about the importance of adequate nodal

assessment in lung cancer surgery.

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Footnote

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

Ethical Statement: The authors confirm that they are accountable for all aspects of the work and have ensured that any questions related to the accuracy or integrity of any part of the work have been appropriately investigated and resolved.

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