Editorial

Adequacy of intra-operative nodal staging during lung cancer surgery: a poorly achieved minimum objective

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Adequate intra-operative lymph node sampling (LNS) is a fundamental part of non-small cell lung cancer (NSCLC) surgery but adherence to standards is still far from being commonly obtained. Edwards and coworkers (1) reviewed 1,301 surgical resections performed from 2011 to 2014 to identify factors that may be the cause of the LNS inadequacy. Their article disclosed four key topics on the mediastinal lymph node (MLN) surgical management of NSCLC that deserve to be addressed: (I) guidelines concerning LNS and their consideration by surgeons; (II) impact of specialisation and effect of patients volume on the surgery results; (III) incidence of tumor size, type of surgery and MLN station anatomy on LNS quality; (IV) indisputability of long-term survival improvement after complete MLN dissection (MLND) by comparison with random LNS.

Guidelines concerning LNS and their consideration

The adequacy of intraoperative LNS was assessed by referring to the recommendations of the International Association for the Study of Lung Cancer (IASLC) reported by Goldstraw (2). These recommendations are commonly refered to (2,3), and include LNS or MLND of mediastinal LN-stations 2R, 4R, 7 for right-sided tumors, and LN-stations 5, 6, 7 for left-sided tumors; LN-station 9 is evaluated in case of lower lobe tumors. LN-stations are labeled in accordance with the IASLC table of definitions (2). According to Darling and coworkers (4), adequate MLND should include stations 2R, 4R, 7, 8, and 9 for right-sided cancers and stations 4L, 5, 6, 7, 8, and 9 for left-sided cancers. The latter is a less restrictive and more relevant proposal when considering the anatomical drainage of the lymphatics of the lungs (5,6).

Patients randomised to complete MLND have little added postoperative morbidity compared with those undergoing random-LNS (7-9), and generally MLND does not increase length of stay (8). Thus, MLND or LNS are recommended (2,3,10). However, the adequacy of guidelines adherence concerning LNS is challenged by a lot of considerations. First, the accuracy of cancer staging may intentionally vary, from random-LNS through lobe-specific LNS to systematic MLND. In addition, LNS appears rarely performed (11,12). Osarogiagbon and coworkers (12) reported that 62% of pathologic N0 and N1 NSCLC resections in the US Surveillance, Epidemiology, and End Results database had no mediastinal LN examined. The same authors (13) found in one city-wide audit reviewing the pathology reports that only 8% of all resections met systematic LNS criteria, 50% had random-LNS, and 42% had no MLNs examined. A blinded independent audit of the surgeons' operation notes revealed that 29% of cases had described a MLND procedure. Poor practice of LN surgical examination or even the failure of LN collection occurred as one of the main sources explaining such a quality gap in pathological LN staging (12,13).

Impact of specialisation and effect of patients' volume on the surgery results

Edwards and coworkers (1) found that adequate LNS increased significantly from 14% in 2011 to 53% in 2014. All lung cancer resections had been performed by five dedicated thoracic surgeons. The number of patients also increasing over years, they remembered that centralizing care in high-volume specialized centers might improve the quality of surgical cancer care and that hospital volume and surgeon specialty are important determinants of outcome in NSCLC resections. Le Pimpec-Barthes and coworkers (14) reviewing the literature before 2006, identified a significant decrease in postoperative mortality in 5 out of 7 studies and improved long-term survival in 2 out of 3 studies in establishments undertaking large numbers of lung resections. The threshold for defining high volume groups varied from study to study (from 28 to 128 procedures per year). The same tendency was seen among the surgeons where specialisation in thoracic surgery led to higher levels of resectability and parenchymal preservation. However, there was no data concerning LNS. Krantz and coworkers (15) recently reported that LN assessment had improved since 2004 and was varying by facility type. They reviewed 51,358 patients with clinical stage I NSCLC who underwent segmentectomy or lobectomy that were stratified into three groups (≤5, 6 to 15, and >15) based on the number of LNs assessed. There was a significant decrease in the percentage of patients with 0 to 5 LNs assessed (41.1% versus 31.1%, P<0.001) and a significant increase in patients with more than 15 LNs assessed (10.1% versus 17.0%, P<0.001) over the study period. The patients at academic centers were less likely to have only 0 to 5 LNs assessed (27.2% versus 43.6% for community). Thus, the unruly behavior in surgical practice concerning LNS might be attributed to a lack of specialization. However, adequacy of LNS performed by thoracic surgeons surprisingly also improves with time, and still hardly exceeds the 50% (1).

Incidence of tumor size, type of surgery and MLN station anatomy on LNS quality

LN assessment might vary not only by facility type and specialization but also by other characteristics.

Incidence of tumor size, type of surgery

Edwards and coworkers (1) reported LNS inadequacy in patients with T1a (< 2 cm in size) or T4 tumours, and those undergoing sub-lobar resections. Of the 32 T4 tumours, 31 were satellite tumors in an ipsilateral lobe. Only 5 of the 31 (16.1%) satellite tumours were adequately sampled. Size is very likely to be a major factor in favor of less surgery, the latter further favoring a poor LN harvest. Thus, Pricopi and coworkers (16) reviewed patients who underwent wedge-resections (n=66, 10.9%), segmentectomies (n=32, 5.3%), lobectomies (n=507, 83.8%) for NSCLC: there was most often a pStage I carcinoma in lesser resection than in lobectomy. Lymphadenectomy was not performed in half the wedge-resections. Stiles and coworkers (8), identified 196 patients undergoing wedge-resection; 138 patients (70%) had LNs resected (median = 4 nodes), and 58 patients (30%) had none. Median pT size was 1.5 cm in each group.

Video assisted thoracic surgery (VATS) resections are also reported to be associated with less complete intraoperative LNS (1,17). Martin and coworkers (18) reviewed 2830 NSCLC, of whom 1964 had open thoracic (OT) procedure and 500 VATS resections. P-stage was 1a in 30.5% of OT procedures and 38.0% of VATS (P=0.0002) and the overall LN-upstaging rate for OT was 9.9% and 4.8% for VATS (P=0.002).

Other factors are often associated with the above factors and may lead to a preference for minimal or no LNS. Age was more advanced in wedge-resection and segmentectomy and respiratory function was worse (16). Concerning VATS, failure to perform anatomical resection was related to previous malignancy, high-predicted surgical risk by European Society Objective Score and in octogenarian (17).

Lymphadenectomy and lymphatics of the lungs

The patients with left-sided resections had significantly higher rate of inadequate LNS (1). The disparity between left and right concerned LN-stations 2, 4, and 7.

Station 2 was sampled in 0.4% on the left 2 and 40.0% on the right; Station 4: 4.5% on the left and 67.6% on the right. Left Station 2 is rarely observed in anatomical study, which is not the case of left Station 4: in 210 left lung studied in anatomy (5), the lymph drained towards the LNs of station 4 in 28.6% of cases (n=60). It was mentioned in another study (6) that direct lymphatics reached those LNs in 23.3% of cases (14/60), possibly explaining the existence of skipping metastasis at that level. When considering pN2 disease (5), station 4L was involved in 18.5% of cases (12/65). Station 4L is difficult to dissect and the recurrent nerve risks to be injured during the procedure which probably explains that reluctance to strive to remove 4L LNs. In order to safely access these LNs, the arterial ligament can be sectioned resulting in mobilization of the aortic arch and exposure of the lower paratracheal region.

LNs of Station 7 were sampled in 43.8% on the left and 72.1% on the right (1). The same technical difference between right and left lung surgery explains that the bronchial stump is usually longer than a right stump after a left pneumonectomy, the calculated mean length of the bronchial stump being 0.7 cm on the right side and 2.2 cm on the left side (19). In effect, full exposure of the subcarinal region is generally more difficult on the left side due to the fact that the left bronchus is under the aortic arch. It is necessary to retract posteriorly the aorta and esophagus, whereas the left main bronchus is retracted anteriorly to expose the carinal bifurcation. A good exposure permits complete LD dissection.

Indisputability of long-term survival improvement after complete MLND

Edwards and coworkers (1) found that there was no difference in survival between patients with adequate versus inadequate intra-operative LNS and when survival was stratified according to overall stage, a wide spread knowledge possibly favoring tendency to lessen LNS. However, they found better survival for pN2 patients with adequate sampling.

Results of non-randomized studies are perplexing. For instance, LN removal appeared to decrease locoregional recurrence and might be associated with a survival benefit compared to absence of LN removal after wedge-resection (8). Inversely, survival was improved after VATS resection compared with OT resection whereas the overall LN-upstaging rate for OT was better (18). Selection biases and other concealed factors may play a role in these differences.

Randomized trials are few and their results are confounding. Two of them did not demonstrate difference in 5-year disease-free survival concerning early stage NSCLC. In the first one (3), the patients underwent sampling of 2R, 4R, 7, and 10R for right-sided tumors and 5, 6, 7, and 10L for left-sided tumors and only the patients whose LNs were negative for malignancy after frozen section were randomized to no further mediastinal LNS or complete MLND. However, despite this highly selective mode of selection, occult N2 disease was found in 21 patients in the MLND group. In the second study (20), 115 patients with peripheral NSCLC smaller than 2 cm in diameter were randomly assigned into a lobectomy with LNS (n=56) or a lobectomy with radical systematic MLND (n=59). There was the same number of involved LNs in both groups. No significant difference in the recurrence rate or survival was demonstrated.

Three other randomized trials comparing systematic MLND with random LNS in patients with early and more advanced stages of NSCLC are available.

Izbicki and coworkers (21) reported that recurrences rates tended to be reduced in MLND, but not significantly; MLND appeared to prolong relapse-free survival (P=0.037) with a borderline effect on overall survival (P=0.058) in patients with limited LN involvement (pN1 disease or pN2 disease with involvement of only one LN station); in patients with pN0 disease, no survival benefit was observed. In a previous study (22), the same team observed that the percentage of patients with pathologic N1 or N2 disease was similar in both groups. However, in the LNS group only 4 of 23 patients (17.4%) with N2 disease were found to have more than one LN level involved, whereas MLND resulted in the detection of excessive N2 disease in 12 of 21 patients (57.2%; P=0.007). This was associated with a shorter distant metastases-free (P=0.021) and overall survival. MLND resulted in a more detailed pN2 staging, which was of prognostic significance.

In Wu and coworkers' study (23) randomizing 532 clinical Stage I–IIIA NSCLC patients, the median survival was 59 months in the MLND group and 34 months in the LNS (P=0.0000). There was significant difference in survival in Stage I (5-year survival 82.16% *vs.* 57.49%) and Stage IIIA (26.98% *vs.* 6.18%). In Stage II there was significant difference in 5-year survival by Breslow test (P=0.0284) but no significant yet marginal difference in 10-year survival by log rank test (P=0.0523). Thus, MLND improved survival.

Zhang and coworkers (9) randomized patients to complete MLND or LNS (called minimal MLND). More stations of LNs were harvested through complete MLND, than LNS (8.9 *vs.* 6.2, P<0.001). No significant difference was detected in pathological staging: the pN2 rates (27.1% *vs.* 24.2%), skip-mediastinal metastasis (9.3% *vs.* 7.4%), and multi-stational mediastinal involvement (15.0% *vs.* 16.8%) were similar. However, complete MLND had significantly better 5-year survival than LNS (55.7% *vs.* 37.7%), especially in patients with a tumor size >3 cm, pN1–N2, and stage II–III.

Thus, for patients with stage II–III, complete MLND might improve survival compared with minimal LNS which was partly confirmed by two meta-analyses essentially based on the few preceding papers.

Huang and coworkers (24) included four of them (3,20,21,23) to evaluate long term benefits. They estimated that results for overall survival and local recurrence rate were similar between MLND and LNS in early stage NSCLC patients. Whether or not MLND was superior to LNS for stage II–IIIA, which was strongly suggested, remained to be determined.

Mokhles and coworkers (25) added Zhang and coworkers' paper (9) to the same sources in their meta-analysis. They confirmed a tendency to better long-term survival with MLND compared with LNS. However, they found a high risk of bias in these trials and considered the overall conclusion insecure.

Those authors estimate (9) that because of multiple variables in patients, cancers and available treatments, large multicentre trials testing currently available strategies might be the best way to find out which ones are most effective, and that the number of NSCLC patients should facilitate their feasibility. However, the standard approach to LNS has been a matter of debate for several decades and only five randomized studies are available. Despite the large number of NSCLC patients, the implementation of randomized trials has proven to be an extreme challenge not so easy to undertake.

In any case, the patients with more LNS demonstrate more LN-upstaging (3,7,8,14,18) and have more chances of cure in case of LN involvement, which is encouraging complete MLND. Furthermore, surgery possibly misknowing involved LN is at risk of being palliative and does not permit to guarantee resections with curative intent. Inversely, it is easy to understand that survival of patients at an early stage of NSCLC might not be demonstrated to be improved by complete MLND. Preoperative work-up is more and more precise and clinical N0 is more likely to be pN0; the percentage of occult N2 involvement discovered by complete MLND is decreasing and becoming very small. To demonstrate a difference of 5% to 10% in survival, it would be necessary to randomize a particularly important cohort of patients in each group over too many years, rendering such trial an unbelievably difficult task. Thus, systematic complete MLND is the only guarantee of an optimal surgical quality.

To conclude, performing a complete MLND is relatively harmless and low risk and remains the best "sampling". This action feasible by any thoracic surgeon worthy of the name should allow avoiding the endless publications on the subject which enrich the volume of the literature without providing answers solving the problem usefully. Of course, being able to remove only the involved LNs would be ideal, but being sure not to leave LNs carrying micrometastases is still far from possible, micrometastases themselves being discovered by completeness of surgery with systematic complete MLND.

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Footnote

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

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