

From anatomy to lung cancer: questioning lobe-specific mediastinal lymphadenectomy reliability

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The prognosis of non-small cell lung cancer (NSCLC) is improving (1-3). The standard treatment of early-stage, mainly lobectomy with systematic complete hilar and mediastinal lymphadenectomy (MLND) (4), is questioned nowadays. Minimal surgery or still less aggressive procedures are being advocated and gaining preference due to emergence and development of new technologies. In fact, diagnosis of NSCLC in early-stage is more frequent and clinical-staging more precise, with the risk of overlooking lymph node (LN) involvement and distant metastasis becoming regularly smaller. Thus, surgeons are attempting to define the minimal and suitable extents of lung resection and LN-dissection, a technique concerning the latter being recently revisited in the review (5).

LN-involvement is effectively the keystone of long-term prognosis, and the quality of LN-dissection has always been a matter of debate. Complete-MLND permits the most curative resection by minimizing the risk of leaving tumor-LN behind and provides the most accurate pathological-TNM, which is crucial in adapting the best adjuvant therapy. Thus, complete-MLND is the gold standard. The reason of its relevance is demonstrated by anatomy and pathology studies.

An anatomical study was conducted in adult cadavers to research whether lymphatic vessels (LV) directly draining into the mediastinal LN without crossing any intrapulmonary LN could explain skipping metastases (6). Direct LVs into the mediastinal LN were observed in 54 right and 60 left lungs. Those direct LVs existed more often from the right and left upper lobes (RUL n=24 and LUL n=41) and mainly went into the upper mediastinum. However, there were three direct LVs from the RULs (12.5%) into the trachea-bronchial LN [LN-

station 7 (7,8)] and one from the LULs (2.4%). Direct LVs were less frequent from the right and left lower lobes (RLL n=22 and LLL n=19) and mainly went into LN-station 7. However, nine from the RLL (41%) went into the right paratracheal LN [LN-station 2R, 3, 4R (7,8)] and eight from the LLL went into the superior mediastinum LN (42%): aortic LN [LN-station 5 (7,8)] n=1, phrenic LN [LN-station 6 (7,8)] n=1, and left superior bronchial LN [LN-station 4L (7,8)] n=6. Complete-MLND is therefore anatomically advisable in pN0-NSCLC surgery. Direct LVs were also observed into the upper lobar bronchi LN, six times from the RLLs and 13 times from the LLLs, rendering also advisable clearance of the upper lobar LN in case of lower lobe NSCLC.

Another anatomical study including all the lymphatic drainages into the mediastinum and not only the direct ones (9), demonstrated that the RULs (n=99) had 20 LVs (20%) draining into the LN-station 7 and that the RLLs (n=178) had 87 LVs (48.9%) draining into the LN-station 2R, 3, and 4R. The LULs (n=178) had 25 LVs (14%) draining into the LN-station 7 and two (1.1%) into the LNs of the pulmonary ligament [LN-station 9 (7,8)]. The LLLs (n=166) had 99 LVs (59.6%) draining into the LN-station 4L and eight (4.8%) into the LN-station 5. Because of the high frequency of the lymphatic drainage from one lobe towards non-“lobe-specific” LN-stations in the mediastinum, anatomy logically supports recommending complete-MLND for NSCLC.

In the same paper (9), the lymphatic drainage was compared with the tumoral involvement of the mediastinal LNs obtained by complete-MLND in 260 pN2-patients. The tumor was located in the RUL 70 times and the LN-station 7 involved in 22 patients (31.4%) and in the RLL

46 times and the LN station 2R, 3, and 4R involved in 15 (32.6%). The tumor was located in the LUL 68 times and the LN-station 7 involved in eight patients (11.8%) and the LN-station 9 in one (1.5%). The tumor was located in the LLL 41 times and the LN-station 4L involved in 10 (24.4%) and the LN-station 5 in four (9.8%). The comparison between anatomy and oncology lymph mode of spread showed that both were parallel in nature. Both kinds of study confirmed the predominance of the drainage into the “lobe-specific” mediastinum, but not exclusively. The highest frequency observed from the lower lobes into the upper mediastinum was explained by the normal ascending drainage of the LVs through LN at that level before they join the cervical venous system (10), whereas descending LVs were particularly infrequent, those from the upper lobes joining the LN-station 7 and those of the lower lobes intra-abdominal LNs (9). Whereas intra-abdominal lymphadenectomy would not be reasonable in the latter, it is reasonably advisable to perform LN-clearance of both mediastina whatever the NSCLC location.

Many other authors reported surgical series demonstrating that complete-MLND was the best way to accurately determine LN status and to achieve curative resection in NSCLC. Watanabe *et al.* (11) observed 29 pN2-patients (10.8%) among 267 with peripheral small-sized NSCLC. Two thirds showed multiple-level pN2, even in cN0 patients, supporting complete-MLND even for RUL tumors. Defranchi *et al.* (12), identified 968 cases of pT1 NSCLC, 59 with pN2 disease (6.1%): 36 had negative non-invasive mediastinal staging (3.7%) and were incidentally discovered. The rate of pN2 was relatively low and that of N2-disease not observed on noninvasive preoperative mediastinal staging still lower. Nevertheless, pN2 was discovered by complete-MLND. Saeteng *et al.* (13) reviewed 197 patients [including: RUL n=63 (31.98%), RLL n=30 (15.23%), LUL n=55 (27.92%), LLL n=16] and did not observe tumor location to be a precise predictor of the LN-metastasis pattern, rendering complete-MLND the only way to accurately determine LN status. Maniwa *et al.* (14) confirmed that both superior and inferior mediastina were most frequently involved in case of multi-station pN2, a situation that was rarely diagnosed during work-up and commonly discovered by surgery. The recurrence of mediastinal LN cancer was significantly greater in patients undergoing “lobe-specific” LN-dissection (LSLND) than in those undergoing complete-MLND (14). They suggested that systematic complete-MLND was not only the option to accurately determine

LN status but also a way to decrease the rate of mediastinal recurrence.

Despite the anatomical and surgical works showing that lobe-specific lymphatic drainage is preponderant but not exclusive, many authors reporting specific and particular studies question the necessity of systematic complete-MLND in selective cases. Thus, Miyoshi *et al.* (15) in a sentinel LN study found that mediastinal sentinel LN were 2R, 3 or 4R in RUL; 3, 7 or 8 in RLL; 4L, 5 or 7 in LUL and 4L, 7 or 8 in LLL cancers. Asamura *et al.* (16) reporting 166 pN2 patients noticed that LN-station 7 resection was not always necessary in case of upper lobes NSCLC. Kotoulas *et al.* (17) observed that RUL tumors were mainly metastasizing to 4R, RML to 4R and 7, RLL to 7; LUL tumors to 5 and LLL to 7 and 9. However, they did not estimate it sufficient to rule out complete-MLND. Shapiro *et al.* (18) reported that N2 metastases follow predictable lobe-specific patterns in patients with negative preoperative CT scans and PET scans. In fact, the results are varying according to the lobe and the pathology stage. Normally, complete-MLND should be routinely performed even for c-stage I NSCLC to ensure a correct LN-status, but it might be omitted in some patients and not always necessary in upper lobes NSCLC. However, at which point and in which cases changing principles of oncology surgery might be justified, are still unanswered questions and further studies attempted to better define the limits.

Oda *et al.* (19), reviewed 524 c-stage-I NSCLC: 78% were pN0, 8% pN1, 13% pN2, and 0.8% pN3. Thirty-six patients had single-level and 35 multi-level pN2. Complete-MLND might be dispensable in case of peripheral squamous cell carcinoma (SCC) ≤ 20 mm in diameter, central SCC ≤ 30 mm, and adenocarcinoma ≤ 10 mm. Yoshimasu *et al.* (20), pathologically investigated one LN at previously defined sentinel LN levels (14) in 58 patients who underwent limited-MLND according to this strategy. Mediastinal LN recurrence was observed in only one patient. They suggested that limited-MLND might be applicable to patients whose regional mediastinal LNs were not metastatic. Aokage *et al.* (21), reviewed 1,099 patients with upper lobe NSCLC and found LN-station 7 metastases in 20. Two were free from superior mediastinal metastases but died of the disease at 1 month and of an unknown cause at 18 months, respectively. Seventeen developed multi-site recurrence. LN-station 7 metastases from upper lobe were rare and the authors estimated valid to omit subcarinal node dissection in upper lobe NSCLC patients, especially in cN0 SCC patients. Miyoshi *et al.* (22), evaluated 725 patients

with c-T2N1M0 or less extensive NSCLC, who underwent a complete-MLND. If pathological examinations were used during surgery, 599 pN0 and 39 pN1 patients diagnosed with no metastasis would have undergone a selective MLND, while 20 pN1 and 65 pN2 patients with a diagnosis of metastasis would have undergone a complete-MLND. An inappropriate selective MLND in two patients resulted in a 0.3% false negative rate. They suggested that intra-operative pathological examination techniques might lead to a selective or complete-MLND in patients with such c-staging. Haruki *et al.* (23) reviewed 876 patients with c-stage I NSCLC who underwent surgery. The incidence of pN2 was 9.1%. They suggested acceptable to perform selective-LND in patients with c-stage-I NSCLC with ground glass opacity-predominant tumor, but to be careful when applying selective-LND to patients with solid-predominant tumor, especially located in the lower lobe. Finally, Hishida *et al.* reported 5,392 patients with c-stage I-II NSCLC in a recent issue of the review (5). LSLND and complete-MLND were performed in 1,268 (23.5%) and 4,124 (76.5%) patients, respectively. The LSLND group included more upper-lobe and c-stage I tumors, and less pN2 than the MLND group. Extended pN2 outside LSLND area was found in 3.2% of the complete-MLND group. The study showed that LSLND did not have a negative prognostic impact, and instead was associated with favorable survival, the reason why being unexplained and questionable. The authors concluded that LSLND was an alternative to complete-MLND for selected c-stage I-II NSCLC patients. However, we have noticed that LSLND permitted to discover a pN2 population of 8.4% (106/1,268) and complete-MLND a pN2 population of 12.7% (524/4,124), a significant difference ($P=0.00025$) rather supporting an opposite conclusion.

Generally, the studies advocating LSLND involve clinical N0 or/and N1 patients whose risk of being pN2 in the “lobe-specific” mediastinum is low and, therefore, still lower in the non-“lobe-specific” one in single-level pN2. Thus, they don't have much power and more progress in technology is needed so that they do not underrate the anatomical realities. The tumor size and histology should also be more accurately considered. Although they are improving, conditions reliably ensuring the lobe-specific MLND indication are not yet fully guaranteed.

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