Editorial Commentary

The role of extended lymphadenectomy in left-sided non-small cell lung cancer surgery

Camilla Vanni[1,2], **Mohsen Ibrahim**[2]

[1]Department of General and Specialized Surgery "Paride Stefanini", Sapienza University of Rome, Rome, Italy; [2]Department of Thoracic Surgery, Sant'Andrea Hospital, Sapienza University of Rome, Rome, Italy

Correspondence to: Mohsen Ibrahim, MD. Department of Thoracic Surgery, Sant'Andrea Hospital, Sapienza University of Rome, Via di Grottarossa 1035, 00189 Rome, Italy. Email: mohsen.ibrahim@uniroma1.it.

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Thanks to the advancements in diagnostic screening and imaging technologies, nowadays lung tumors can be identified at an ever earlier clinical stage than in the past. Surgical resection still represents the best curative choice in this setting.

The standard of lymph node dissection during the operation may potentially improve the prognosis of patients undergoing surgery for localized non-small cell lung cancer (NSCLC), due to the better local control of the disease and its more precise staging (1). This aspect was effectively highlighted in a recent paper by Wang and colleagues, who retrospectively compared outcomes of patients receiving or not 4L lymph nodes removal during the resective procedure for left-sided NSCLC (2). The 4L dissected group showed significantly increased 5-year overall survival (OS) and disease-free survival (DFS) compared to the 4L non-dissected group (OS: 58.9% *vs.* 47.2%, P=0.02; DFS: 54.8% *vs.* 42.7%, P=0.0376); improvement in OS (P<0.001) and DFS (P=0.0014) in 4L dissected patients were further confirmed by the use of propensity score weighting, applied to minimize observed confounders.

The pN status has been historically observed as one of the most powerful factors affecting survival after lung cancer surgery (1,3). It's the present authors opinion that a finding of underestimated lymph node metastases, the number of nodal stations involved and their location can provide valuable information in selecting the best postoperative strategy of care. In this respect, data arising from large-scale randomized trials have shown that adjuvant chemotherapy can increase survival after surgical resection (4).

Nevertheless, among the surgeons there is a lack of homogeneity in the intraoperative approaches currently employed to assess the lymphatic spread. General surgical practice ranges from visual inspection and biopsy of suspicious nodes to extended mediastinal dissection. In 2001, the American College of Surgeons carried out a patient care investigation of 729 hospitals to get information about the surgical treatment of patients with NSCLC (5): this study revealed that only 57.8% of more than 11,000 patients had mediastinal lymph nodes either sampled or removed during surgery.

Moreover, there remains a general confusion due to the subjective interpretations of the terms used to define different methods of lymphadenectomy, so that the same technique can also change from one center to another and among countries. This factor has to be considered when comparing results from several experiences. In order to standardize the intraoperative lymph node assessment and improve pathologic staging, the European Society of Thoracic Surgeons (ESTS) set out five definitions of intraoperative lymphadenectomy (6): selected lymph node biopsy, systematic sampling, lobe-specific lymph node dissection (L-SND), systematic dissection (SND), and extended node dissection.

Although an isolated randomized trial from the American College of Surgery Oncology Group (7) has shown no significant difference in postoperative recurrence and survival in favor of SND when compared with systematic sampling, the international surgical guidelines as well as the vast majority of authors, the currents included, recommend

to always perform the complete dissection of mediastinal stations, in order to obtain a more precise staging and improve survival through the removal of underestimated metastases (6,8-11). The reason is that the previously referred trial (7) included only patients with negative lymphatic metastasis assessed through intraoperative frozen section analysis on an initial mediastinal and hilar nodal sampling. Furthermore, differences in the total count of resected lymph nodes and the amount of surrounding adipose tissue between the two groups were hazy; these determinants might explain the lack of differences in postoperative results. The authors themselves suggested that SND should be performed in any case of resectable NSCLC, because the procedure does not increase mortality or morbidity relative to systematic sampling.

The value of the SND method for the proper assessment of lymph node spread in operable lung cancer is broadly accepted, but the effect of node dissection on long-term survival and recurrence rate is unclear as well as its optimal extent. A meta-analysis by Wright and colleagues (12). compared survival and recurrence rate of patients undergoing pulmonary resection for resectable stage I to IIIA lung tumors associated with either SND or sampling. In a pooled analysis of three trials (13-15), 4-year survival was superior in patients who underwent resection and complete mediastinal lymph node dissection in comparison with those undergoing resection and nodal sampling (HR 0.78, 95% CI: 0.69–0.89, P=0.005). In a more recent meta-analysis enlisting over 1,900 patients from 5 randomized trials, the relative mortality risk reduction and 5-year risk of death in the mediastinal sampling group resulted in absolute mortality risk reduction of 7.6% in favor of SND (16). Otherwise, pooled local recurrence does not significantly differ after SND than after sampling (55/900; 6.1% *vs.* 75/878; 8.5%, P=0.12); similarly, the difference in distant recurrence rate between the SND and the sampling groups was non-statistically significant (191/900; 21.2% *vs.* 219/878; 24.9%, P=0.07). Results from the paper by Wang *et al.* are in accordance with the literature, showing that the implementation of 4L lymph nodes selective dissection was an independent factor for DFS (HR 1.502; 95% CI: 1.159–1.947; P=0.002) and OS (HR 1.585; 95% CI: 1.222–2.057; P=0.001), together with histology, pT and pN stage (2).

The Bronchogenic Carcinoma Cooperative Group of the Spanish Society of Pneumology and Thoracic Surgery advocate a minimal dissection of at least stations 5, 6 and 7 for left upper lobe tumors and stations 7, 8 and 9 for the lower lobe (10). Similarly, the International Association for the Study of Lung Cancer (IASLC) suggest that systematic nodal dissection should provide for the excision of as a minimum three mediastinal nodal stations, including the subcarinal nodes, without strict requirement for superior mediastinal dissection in patients with left-sided NSCLC (11). Instead, other influential experiences recommend to always include the removal of stations 4L and, as suggested mostly by Japanese investigators, 2L in SND for neoplasm of the left lung (8,9,17). Nevertheless, the anatomical course of the left laryngeal nerve as well as the close proximity of the supra-aortic (left carotid and sublcavian) trunks and thoracic duct, and the eventual need to mobilize the aortic arch by dividing the arterial ligament, can make dissection of the left paratracheal stations perilous. Thus, superior mediastinal lymph node metastases from left lung tumors are rarely investigated in common surgical practice (17). In a report by Watanabe *et al.*, survival rate of patients with pN2 right-sided NSCLC was higher of those affected by left pulmonary malignancies, which can be attributed to the insufficient extent of lymphatic dissection due to the anatomic restrictions mentioned above (8). Nevertheless, in the paper by Wang and colleagues (2), the lower paratracheal station was the most frequent mediastinal site of metastatic involvement (29/139; 20.9%), the equal of aortopulmonary window lymph nodes. Furthermore, metastasis of station 4L was more likely to occur in patients with upper lobe tumors, although this evidence doesn't reach a statistical significance.

The primary localization of the pulmonary neoplasm is supposed to have an impact on the pathological pattern of lymph node metastatization, but a standardized scheme by lobe-dependent mediastinal drainage is still far from being specific. Regarding the left lung, a lesion in the upper lobe tends commonly to drain toward the aortopulmonary window (station 5) and the para-aortic (station 6) lymph nodes, the previous stations being the most likely to become the first metastatic site (18); nonetheless, left upper lobe tumors can further metastasize to the subcarinal nodes (station 7) and even to the lower mediastinal nodes (station 4L), with a higher incidence than for right-sided lesions (19). Tumors of the left lower lobe drain most frequently to the subcarinal lymph nodes (18-20), which is seen in patients with single-station mediastinal disease, while in multistation N2 disease the aortopulmonary window nodes are not infrequently involved too; the lower mediastinal nodes have been found to be the next more often affected mediastinal zone (20). According to these findings, Okada *et al.* showed the effectiveness of selective mediastinal lymphadenectomy

performed on the basis of the primary tumor site in clinical stage I NSCLC (21). These results have prompted frequent performance of L-SND in elderly patients or patients with no preoperative apparent nodal metastases. Available results from retrospective studies which compared postoperative outcomes and staging accuracy of L-SND and SND are still vague. This is partly the result of potential biases on recruitment (such as early stages, elders and patients with a poor performance status) when considering patients eligible for L-SND. To eliminate those confounding factors, a recent paper by Adachi *et al.* examined the potentiality of L-SND in surgically resected NSCLC with the use of the propensity score matching method (22). Although the overall detection rate of pN2 after SND was significantly higher (13.1%) than after nodal sampling (3.3%) and L-SND (9.0%), by applying the propensity score matching method the authors showed no relevant difference between L-SND and SND in terms of pN2 diagnosis (8.2% in both groups; P=0.779) and 5-year overall survival (L-SND, 73.5% *vs.* SND, 75.3%; P=0.977); indeed, long-term oncologic results were significantly lower in patients who undergone nodal sampling.

In a recent paper Liang *et al.* studied the incidence and lobe-specific distribution of mediastinal lymph node metastases in 4,511 NSCLC operable patients (23). The most common sites of mediastinal metastasis were station 5 for the left upper lobe (22.2%; 224/1,008) and station 7 for the left lower lobe (21.7%; 136/628). However, when N2 only positive patients were considered (404 cases; 9.0%), each mediastinal lymph node station can be involved with metastasis to a high proportion (>5%). When analyzing data from the study of Wang and colleagues (2), the presence of 4L lymph node disease was significantly correlated with most other positive pN stations (station 5, P<0.001; station 6, P<0.001; station 7, P=0.005; station 9, P=0.019; station 10, P<0.001); however, only station 10 metastasis confirmed its independent effect on 4L involvement at the multivariate analysis, which can be explained anatomically by the thin limit between station 4L and station 10 at the tracheobronchial angle. Results from multivariate analysis of the previous mentioned report by Liang *et al.* (23) also showed that adenocarcinoma histology, poor cell differentiation, large size of the tumor, central location and younger age were all independent factors favoring mediastinal metastasization, thus suggesting the opportunity to carry out a more aggressive method of staging in these subset of patients.

In recent years, video-assisted thoracic surgery (VATS) has emerged as the approach of choice for the treatment of patients with early clinical stage lung cancer. An analysis of the prospective database of the Society of Thoracic Surgeons revealed that up to one-third of all the lobectomies performed for NSCLC in 2006 were VATS approached, with an increasing trend over the years (24). Even though the encouraging results, the appropriateness of VATS lymph node dissection is currently under debate (25). The introduction of new technologies such as HD and 3D lens cameras as well as several types of surgical devices are allowing a real improve in this setting. Wang and colleagues suggest a potential benefit on visualization and careful assessment of some anatomically difficult regions such as the left paratracheal station (2). However, the same authors omit data on the rate of VATS-performed 4L lymph nodes dissection and related morbidity. Based on available data, more randomized controlled trials are needed to formulate a specific definition of radical lymphadenectomy and establish the best standard protocol of treatment in operable NSCLC, in order to get the most benefit for the patients without increasing the baseline risk.

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