Lymph node dissection after pulmonary resection for lung cancer: a mini review

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Abstract: An accurate staging of a malignant disease is imperative in order to plan pre- and post-operative therapy, define prognosis and compare studies. According to the European Society of Thoracic Surgeons (ESTS) guidelines a systematic lymph node (LN) dissection is recommended in all cases of pulmonary resection for non-small cell lung cancer (NSCLC). The current lung cancer staging system considers the lymphatic stations involved but not the number of LNs. Up to date, published scientific studies on hilar and mediastinal lymphadenectomy mainly have been regarded the type of LN dissection procedure after pulmonary resection (selected LN biopsy, LN sampling, systematic nodal dissection, lobe specific nodal dissection and extended LN dissection) focusing particularly on the comparison between mediastinal LN dissection (MLND) and mediastinal LN sampling (MLNS). Recently, further investigations have been concentrated on surgical approach (videothoracoscopic *vs.* thoracotomic approach) used to perform pulmonary resection and following LN dissection in order to achieve a complete mediastinal lymphadenectomy. This short synthesis aims to present the current experiences in this setting.

Keywords: Lymph node dissection; pulmonary resection; lung cancer

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Introduction

Non-small cell lung cancer (NSCLC) may be curable by surgical resection; however lymph node (LN) dissection may change the prognosis of the patient (1). Moreover, the required extent of LN removal and the real impact of mediastinal node dissection remain controversial. Removing a sufficient quantity of lymphatic tissue in order to guarantee an accurate pathologic nodal (pN) staging is mandatory. The pN status is a powerful prognostic factor. According to the last European Society of Thoracic Surgeons (ESTS) guidelines (1) the recommended types of node resection to describe intraoperative LN assessment are: (I) selected LN biopsy; (II) sampling; (III) systematic nodal dissection; (IV) lobe specific node dissection; and (V) extended LN dissection. The majority of the papers dealing with this topic handle two main issues: the comparison between systematic mediastinal LN dissection (MLND) and mediastinal LN sampling (MLNS); videothoracoscopic *vs*. thoracotomic mediastinal lymphadenectomy after pulmonary resection.

The need for precise evaluation of LN status was established in order to guide therapy, to estimate prognosis, to compare results from different institutions, and to conduct multi-institutional trials. A removal of at least six LNs from hilar and mediastinal stations is recommended to define nodal staging accurately and to determine eventual pN0 status (2). The number of LN stations involved and their anatomical location may be important prognostic factors (3).

However, the importance of the ratio between the numbers of sampled versus the number of involved nodes and has not been addressed in the current staging systems and LN dissection guidelines.

This review aims to identify all valuable and relevant evidences considering lymphadenectomy after pulmonary surgery for NSCLC.

MLND *vs.* MLNS

The main reason for performing lymphadenectomy in adjunction to pulmonary resection for lung cancer is to achieve a complete staging. Different studies analyze with a general agreement the exact number of nodes to dissect and the type of lymphadenectomy to perform, although no unanimous and standardized scheme about lobe specific drainage. Controversies still exists about the need of MLND or MLNS for the cure of early stage NSCLC. Riquet *et al*. (4) in their paper conclude that the lymphatic spread of NSCLC cannot be considered as lobe-specific. Therefore, systematic ipsilateral lymphadenectomy is the only option that accurately determines LNs status, and permits both complete resection of the LNs metastasis and interruption of the lymphatic pathways. In a more recent paper the same authors (5) deal with the exact number of nodes to be dissected and summarize that the number of intrapulmonary and mediastinal nodes is highly variable from a patient to another, with no relevant impact on overall survival. A theoretical cutoff, regarding the number of LNs, does not adequately guarantee the quality of NSCLC operations and may be misused, with two potential risks: underestimation of a satisfying lymphadenectomy in patients with a small number of LNs and overestimation of an unsatisfactory sampling in patients with a high number of LNs. Thus, any recommended cutoff number of LNs remains arbitrary. Concluding, they strongly recommend performing a complete hilar and mediastinal lymphadenectomy following established anatomical boundaries. On the other hand, the ESTS guidelines suggest a number of at least six nodes in order to guarantee a proper pathologic classification. Along the same line other studies are moving too. The ACOSOG Z0030 study group presented a randomized trial (6) comparing MLNS with complete lymphadenectomy in patients with N0 or N1 NSCLC. In this study the data of 1,023 patients (498 MLNS and 528 complete lymphadenectomy) have been analyzed in terms of overall survival, disease-free survival and recurrence (local, regional or distant). The authors found no statistically significant difference in the two groups for all the considered variables, concluding that these results are not generalizable to patients staged radiographically or those with higher stage tumors. The ACOSOG ZOO30 results should be interpreted with caution because the heterogeneity of the data was high, and higher heterogeneity implies greater variation in true effect sizes as a consequence of various confounding factors. In this clinical trial, all patients had rigorous systematic node sampling prior to randomization, so that the proportion of patients with N2 disease was reduced. Another source of heterogeneity is the methods of LN sampling leading to different rates of upstaging. When adequate LN sampling is not performed, the true pN stage would remain unrecognized because all the LNs are not dissected and pathologically examined, which may result in a spurious downstaging in MLNS groups. The study of Sugi *et al*. (7) also presented a low proportion of N2 disease. This is a randomized trial conducted in patients with clinical stage I small (<2 cm) T1 NSCLC. In this study, the node positive N2 rate was similar in both groups, and the proportion was 12% and 14% for MLND and MLNS groups, respectively. Darling *et al*. (6) pointed out that there was only 4% of patients appeared to be upstaged to pN2 by complete dissection in their ACOSOG Z0030 trial which had performed rigorous systematic node sampling prior to randomization. Because adjuvant chemotherapy is now the standard of care for patients with pN2, these increased node positive patients would result in additional survival at 5 years of 1–7% of participants as a result of appropriate administration of chemotherapy. As there was no systematic indication for adjuvant chemotherapy at the time of these trials, this study cannot evaluate the potential added survival benefit for patients upstaged by MLND compared to MLNS. On the other hand in a non-randomized retrospective study, Cerfolio *et al*. (8) demonstrate a higher rate of N2 disease in patients underwent pulmonary resection for NSCLC with MLND than in patients underwent MLNS. Authors are admitting several limitations of this study. It was neither prospective nor randomized. The control group was obtained from a national registry database and thus all of the inherent problems that come with national registry data plague the study.

In a paper published in 2000, Keller and colleagues (9) reported improved long-term survival in patients who had a MLND instead of a MLNS. However, it was a non-randomized study and the survival benefit was only found for patients with right-sided NSCLC tumors. Wu *et al*. (10) pointed out in their prospective randomized trial that the MLND group showed significantly better survival compared with the MLNS group. Similarly to Cerfolio, Wu evaluated the impact of MLND compared with MLNS in patients who undergone pre-operative invasive staging (doing mediastinoscopy, EBUS, and EUS in selected patients pre-resection and not sending multiple N2 and N1 LNs for frozen section at the time of resection).

In terms of local recurrence and distant metastasis, whether MLND might decrease the incidence of local recurrence and distant metastasis after complete resection for NSCLC is still a question that remains unanswered. In the ACOSOG Z0030 trial, the authors found that MLND does not affect the probability of local recurrence or distant metastasis. Izbicki *et al*. (11) on the other hand found that MLND was related with lower rates of recurrences, but without any statistically significant results. In a paper from Sugi *et al*. (7) the comparison between MLND and MLNS in patients with NSCLC, clinical stage I (<2 cm), reported no statistically significant differences in terms of local recurrence and distant metastasis.

Another issue to deal when comparing MLND and MLNS is the complications. Some authors (12) argue against MLND in terms of prolonging hospitalization and increasing mortality. However according to the meta-analysis of Huang *et al*. there was no statistical difference in complications rate comparing MLND and MLNS (13). These results were in accordance with the ACOSOG Z0030 trial (6). In this last trial Allen *et al*. reported a total complications rate of 37.9% and 38.6% for MLND and MLNS respectively, without any significant difference for any specific complication.

Mini-invasive *vs*. open

There are different studies that deals with the technique (mini-invasive *vs*. thoracotomy) used for the pulmonary resection and the following lymphadenectomy. In recent years, video-assisted thoracic surgery (VATS) lobectomy has emerged as the operation of choice at some centers for patients with early stage NSCLC. Many papers analyze the advantages of such a technique in terms of postoperative pain, morbidity, hospital stay comparing with the open procedures (14-16). An analysis of the prospective database of the Society of Thoracic Surgeons (9,033 pulmonary resections for lung cancer operated on between 1999 and 2006) revealed that about 20% of the lobectomies were VATS performed with an increasing number ranging from 21.6% in 2004 to 32% in 2006 (17). Despite the good results and satisfactory long-term survival (18), the feasibility and completeness of a true radical LN dissection by VATS remains controversial, many surgeons raising concerns about the adequacy of LND compared with open surgery. In a prospective randomized trial Sagawa *et al*. (19) compared LN dissection during VATS and thoracotomy. In this study, patients with clinical stage I lung cancer were operated on by VATS with a 7-cm utility incision and a standard thoracotomy was then performed by another surgeon to complete LN dissection. On the right side, the average numbers of resected LNs by VATS and remnant LNs were 40.3 and 1.2, respectively. On the left side, there were 37.1 and 1.2 LNs. No nodal involvement was observed in the remnant LNs. The authors concluded that LND by VATS was feasible and the LNs missed by VATS were 2–3%, which was acceptable for clinical stage I lung cancer. In a recent study Merritt *et al*. (20) found significantly greater mean number of LNs dissected during lobectomy by thoracotomy than during VATS lobectomy. In addition, the total mean numbers of N2 LNs dissected were significantly higher during lobectomy by thoracotomy; however, the mean number of N1 LNs was similar between the groups, with only a trend toward more N1 nodes being resected during open lobectomy. The overall pathologic upstaging from N0 to N1 or N2 was significantly higher in the open lobectomy group, apparently because of the increase in the number of nodes evaluated. The study of Denlinger and colleagues (21) reported results along the same lines in their retrospective study. Significantly more overall LNs were dissected in the open group (8.9±5.2 *vs*. 7.1±5.2 nodes; P<0.006) than in the VATS lobectomy group. Subset analyses demonstrated that significantly more N2 LNs were dissected in the open lobectomy group; however, the mean number of N1 nodes dissected was similar between the two groups. In the experience of Palade and colleagues (22), an average of 21–25 LNs were resected, 12–18 of them from mediastinal LN levels. Similar numbers have been published by other European and Northern American studies on lymphadenectomy. For example, in the ACOSOG Z0030 Study, the median number of additionally resected nodes after the systematic sampling was 18 for both sides (range, 1–72 for right-sided and 4–69 for left-sided tumors) (6). In contrast, in Japanese publications, the number of dissected LNs was significantly higher (19).

Complications such as bleeding, nerve damage, chylothorax and pleural effusion can occur eventually after mediastinal lymphadenectomy. In the study of Palade *et al*. (22) the difference was not statistically different in terms of complications between thoracotomy *vs*. VATS group. The patients in the VATS group had significantly less morbidity due to a reduced incidence of pneumonia and chronic respiratory failure. The only complication that was encountered significantly more frequently in the VATS group was a postoperative pneumothorax (lung collapse after successful chest tube removal).

Comments

MLND and MLNS presented no significant differences in terms of overall survival, local recurrence and distant metastasis. There was no evidence that MLND increased complications compared with MLNS.

Concerning the comparison between thoracoscopic and open mediastinal lymphadenectomy, even if the total number of nodes dissected seemed higher in the open procedures the overall survival was not influenced. There was a small evidence of a higher complications rate in the open procedures.

Clearly, newer systematic review and meta-analyses are required to resolve these differences, and definitive analyses can provide stronger rationales for the choice of a specific therapy.

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Footnote

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

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