

State of the art in surgery for early stage NSCLC—does the number of resected lymph nodes matter?

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Abstract: Surgery is the treatment of choice in patients with early stage NSCLC. However, the results remain poor in these patients. Lymph node involvement is the main prognostic factor in patients with NSCLC, but there is still no clear definition of the number of nodes required to consider a lymphadenectomy as complete. Although there is no defined minimum number of lymph nodes required for a complete lymphadenectomy, there are some recommendations to perform this procedure, published by different scientific societies. Current practice in thoracic surgery regarding lymphadenectomy, differs on some points from the guidelines recommendations, with data regarding patients with no mediastinal assessment between 30-45% according to some of the published data. Different studies have probed the fact that the probability of finding a positive node increases with the number of lymph nodes analyzed. Therefore, a complete lymphadenectomy provides proper staging, which helps to identify the patient's real prognosis. Several nonrandomized studies and retrospective series have shown that survival increases in the group of patients with a higher number of lymph nodes removed. There is no contraindication to performing a complete lymphadenectomy. The increase in survival in patients with a complete lymphadenectomy may be due to more accurate staging. Therefore, complete lymphadenectomy should be mandatory even in early stage patients.

Keywords: Early stage lung cancer; number of lymph nodes; lymphadenectomy; survival

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Introduction

Surgery is the treatment of choice in patients with early stage NSCLC. However, results remain poor in these patients, with 5-year survival rates ranging from 84% in stage I to 39% in stage IIIA, according to different studies (1).

The heterogeneity of patients in different stages and errors in staging may be related to these differences in survival.

Lymph node involvement is the main prognostic factor in patients with NSCLC, but there is still no clear definition of the number of nodes required to consider a lymphadenectomy as complete.

The objective of this article is to review the published

literature presented at the 10th Congress on Lung Cancer of the Spanish Lung Cancer Group, in Barcelona, November 2013.

Lymph node involvement

Mediastinal lymph node involvement is the main prognostic factor in patients with NSCLC, and therefore one of the goals of surgical treatment is to diagnose such involvement and establish accurate staging to provide the patient with proper treatment. One of the aims of lymph node dissection, both hilar and mediastinal, is to achieve an intraoperative staging as accurate as possible, and to obtain local control of the disease (2).

There is an ongoing debate about the extent to which a lymphadenectomy procedure can be performed in patients with stage I lung cancer. During the procedure, the surgeon can choose between different procedures: from not removing any nodes, to performing a non-systematic sampling or carrying out a bilateral complete mediastinal dissection, as is done by some Japanese teams (3,4). Only the pathologist can say what nodes are affected and detect the presence of micrometastases. The characteristics of the nodes, whether they are calcified for example, can determine the surgeon's attitude regarding what technique to choose, but, as Gaer and Goldstraw (5) proved, it is not possible to predict intraoperatively which lymph node will be affected based on its appearance. In 68% of patients in the series published by Takizawa, the surgeon was not able to determine whether the mediastinal nodes were involved or not because their macroscopic appearance was normal (6). In the series of Riquet, 20% of the positive nodes were perceived as possible negative by the surgeon, proving that ocular assessment is inexact (7). It is proved that non-systematic sampling is not reliable for proper staging (8,9).

Minimum number of lymph nodes

Unlike in lung cancer, in other tumors there does exist a defined number of nodes required to consider a lymphadenectomy as complete. In the case of colorectal cancer, survival has a direct relationship between the number of lymph nodes examined (10). Several authors have shown that twelve is the minimum number of lymph nodes needed to stage a patient as N0 (11,12). The American Society of Clinical Oncology (ASCO) recommends treatment with adjuvant chemotherapy for all patients staged as N0 with less than 12 lymph nodes resected, since they are at high risk of recurrence (13).

In lung cancer, the minimum number of lymph nodes necessary to consider a lymphadenectomy as complete is not clearly defined. Some authors have tried to state this in several studies. Doddoli considered a lymphadenectomy as complete when more than ten lymph nodes from at least two different mediastinal levels were removed (14). Wu *et al.* considered a lymphadenectomy as inadequate for proper staging and local control of the disease if less than 15 lymph nodes had been resected (15).

Guidelines recommendations

Although there is no defined minimum number of lymph

nodes for a complete lymphadenectomy, there are some recommendations for performing this procedure published by different scientific societies. Thus, the European Society of Thoracic Surgeons (ESTS) recommends systematic nodal dissection in all cases (16). Ideally, this should be done as an en bloc resection of the upper mediastinal nodes on the right side stations (2R and 4R), any visible nodes stations 3a and 3p, and the lower mediastinum, (stations 7, 8, and 9). On the left side, removal of stations 5 and 6, and inferior paratracheal (4L) lymph nodes is minimally required. For a complete nodal dissection of the left upper mediastinum, it is recommended to perform a division of the ligamentum arteriosus allowing mobilization of the aortic arch. In addition, it is important that the highest mediastinal node removed should be identified, in order to assess whether the resection is complete (16).

For peripheral squamous T1 patients, a lobe-specific systematic nodal dissection is acceptable, if the hilar and interlobar lymph nodes are negative, because it has been shown that the probability of unforeseen N2 disease is very low (<5%) in such patients. In this case, it is necessary to remove three mediastinal stations, always including station 7, and at least six lymph nodes must be excised (16).

Common practice in thoracic surgery

Current practice in thoracic surgery regarding lymphadenectomy differs on some points to the guideline recommendations. A survey of surgeons in the UK revealed that 45% of them did not perform sampling if mediastinal nodes had a normal macroscopic appearance, and only 23% of them performed routine complete lymphadenectomy (17).

In another survey conducted in 2001 to examine patterns of treatment of 11,000 patients with NSCLC, the authors observed that 42.2% of the patients did not undergo any type of lymph node dissection (18).

Analysis of the Society of Thoracic Surgeons' database also showed similar data, with no mediastinal lymph node evaluation in 35% of patients (19).

More recently, two papers continue to show similar practices. The review of the SEER database confirmed that 48% of patients had no assessment of mediastinal lymph nodes (20), and a retrospective cohort study in the Netherlands in 216 patients, demonstrated that no lymphadenectomy was performed in 21 patients with suspicious mediastinum by CT scan or PET-CT (21). This series also showed that only eight patients met ESTS criteria (21).

Table 1 Percentage of positive and negative lymph nodes according to the number of lymph nodes resected (27)

Resected lymph nodes	Negative lymph nodes	Positive lymph nodes
<10 (N=227)	166 (50.61%)	61 (38.85%)
≥10 (N=258)	162 (49.39%)	96 (61.14%)
Chi-square 5.89 (P<0.025).		

Table 2 Hazard ratio of disease-free survival and overall survival of patients with more than ten lymph nodes resected (27)

Multivariate analysis	HR	CI 95%	P
Disease free survival	0.97	0.96-0.99	0.004
Overall survival	0.97	0.95-0.99	0.001

The more lymph nodes resected, the more positive lymph nodes identified

It seems obvious, from a logical point of view, to think that the probability of finding a positive node increases with the number of lymph nodes analyzed. This was proved in the Izbicki series, in which a complete lymphadenectomy increased the percentage of patients in whom positive mediastinal lymph nodes were detected (22).

Comparing complete lymphadenectomy to sampling, Bollen *et al.* showed that more positive lymph nodes can be diagnosed with complete lymphadenectomy (35%) than with sampling (13%), concluding that sampling is inadequate for accurate staging (23). Similar data were found by Keller *et al.* (24).

In the papers published by Naruke *et al.* (25) and Yoshino *et al.* (26), the results are similar: sampling detected between 9% and 17% of positive nodes, and complete lymphadenectomy obtained between 22% and 32% positive lymph nodes.

In a review of patients operated on in our department in Vall d'Hebron University Hospital, Barcelona, similar data were found, with a greater number of positive nodes in the group of patients with more than ten lymph nodes resected (27) (Table 1).

Therefore, a complete lymphadenectomy provides proper staging which helps to identify patients' real prognosis. Hence, professionals are able to offer appropriate treatment according to the patient's stage.

The more lymph nodes resected, the better the survival

Several nonrandomized studies and retrospective series have

shown that survival increases in the group of patients with a higher number of lymph nodes removed.

Wu *et al.* published a series of 471 patients with stage I-IIIa NSCLC, comparing complete lymphadenectomy to systematic sampling. They observed that 5-year survival in the sampling group was 36.98%, compared to 48.37% in the lymphadenectomy group (statistically significant difference) (28).

In our data, the results were similar, identifying the number of nodes as a protective factor in the multivariate analysis (27) (Table 2).

In two articles published by Lardinois *et al.* (29) and Sakurai *et al.* (30), no significant difference in overall survival was observed between lymphadenectomy and sampling, but there was an increase in disease-free survival and in local recurrences if patients underwent complete lymphadenectomy.

A recent meta-analysis of three studies observed a benefit in survival in stage I, II and IIIa patients if lymphadenectomy was complete, and that this procedure reduced the risk of death in early stages (31).

Complete lymphadenectomy in stage I NSCLC patients

The improvement in survival in early stages is also seen in the series published by Wu *et al.*, with 5-year survival of 57.49% in the sample group compared to 82.16% if complete lymphadenectomy was performed (27).

In another study published in 2003 in which 321 stage I patients were analyzed, 5-year survival was significantly higher in the group with more than 15 lymph nodes resected (57.1% *vs.* 54.5%), concluding that the number of lymph resected could explain the differences in survival in stage I patients (15).

In a review of 442 stage I patients, those in whom less than six nodes were resected through lymphadenectomy showed higher recurrence and mortality rates than the group with complete lymphadenectomy (32).

Similar data were observed in a paper published by Ou *et al.*, analyzing stage IA patients. They found a 5-year

survival rate of 75.9% in the group with more than 15 resected lymph nodes, compared to 57.9% in the group with less than 6 resected lymph nodes (33).

Xu *et al.* recently published a series of 203 stage IA patients with 5-year overall survival of 62%. They divided the series into three groups according to the number of lymph nodes resected (<10 nodes, 10 to 20, and >20). The analysis of disease-free survival showed statistically significant differences between the groups: 20.26%, 58.8% and 75% respectively. The differences remain significant in the analysis of the number of resected stations, and the data are very striking when analyzing the mediastinal stations resected (9.1% when less than three mediastinal stations were resected *vs.* 65.1% when more than 3) (34). The authors point out that if an adequate lymphadenectomy is not performed, the true N stage remains unknown, which can result in misclassification of stage IA (33).

In a randomized study comparing sampling *vs.* complete lymphadenectomy in patients with T1 and T2 N0 or N1 with no hilar involvement, the authors found no differences in long-term survival rate of local or regional recurrence (35). This study did not include patients with nodal involvement of station 10, so the possibility of mediastinal stations may be low, which could explain the results. The authors, however, conclude that a complete lymphadenectomy provides the most accurate staging. They also point out that current preoperative staging cannot accurately identify patients with mediastinal lymph node involvement. Another reason for this procedure is that patients with known hilar or N2 disease, or with T3/T4 tumors, may benefit from mediastinal lymph node dissection. Therefore, the authors still recommend that all patients with resectable NSCLC undergo mediastinal lymph node dissection because the procedure does not increase mortality or morbidity (34).

Conclusions

There is no contraindication for performing a complete lymphadenectomy. The increase in survival in patients with complete lymphadenectomy may be due to more accurate staging. Therefore, complete lymphadenectomy should be mandatory, even in early stage patients.

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