Arch Bronconeumol. 2009;**45(2)**:87-91

ARCHIVOS DE BRONCONEUMOLOGIA

www.archbronconeumol.org

Original Article

Stage IB Non-Small Cell Lung Cancer: Impact of the Number of Lymph Nodes Examined on Survival

José Cerón,[a,*] Juan Carlos Peñalver,[a] Carlos Jordá,[b] and José Padilla[a]

[a] *Servicio de Cirugía Torácica, Hospital Universitario La Fe, Valencia, Spain*
[b] *Servicio de Cirugía Torácica, Hospital de la Ribera, Alzira, Valencia, Spain*

ARTICLE INFO

Article history:
Received December 18, 2007
Accepted May 26, 2008

Keywords:
Bronchogenic carcinoma
Stage IB
Surgery
Survival

ABSTRACT

Introduction and Objectives: To determine the causes of death in patients operated on for stage IB non-small cell lung cancer (NSCLC) and to assess the impact on survival of the number of lymph nodes removed.
Patients and Method: We studied 300 patients operated on for stage IB NSCLC. Only palpable or visible lymph nodes were excised. Kaplan-Meier survival estimates were calculated and the survival curves were compared using the log-rank test.
Results: The mean (SD) age of the patients was 62.9 (9.7) years; 280 were men, 20 were women. Pneumonectomy was performed in 84 patients, lobectomy in 186, double lobectomy in 23, and segmentectomy in 7. Squamous cell carcinoma was the most common histologic type. The mean number of lymph nodes excised was 5.05 (5.01). At the time of the study 201 patients (67%) had died, 63.2% from causes related to the NSCLC. Overall 5-year survival for the patient series was 51.9% (median, 5.50 years; 95% confidence interval [CI], 4.14-6.87 years), though the 5-year survival rate was 61.87% after non-NSCLC–related deaths were excluded (median, 11.05 years; 95% CI, 7.63-14.48 years). Tumor size and the number of lymph nodes examined significantly affected survival. In the multivariate analysis, these 2 variables were also significantly correlated with the risk of death from NSCLC (P<.0001), with relative risks of 1.158 (95% CI, 1.081-1.240) and 0.387 (95% CI, 0.254-0.591), respectively.
Conclusion: Besides being affected by stage and tumor size, survival in patients operated on for stage IB NSCLC is significantly influenced by the total number of lymph nodes examined. Therefore, surgical treatment of such patients should include the examination of as many lymph nodes as possible.

Carcinoma broncogénico no microcítico en estadio IB. Impacto del número de adenopatías analizadas en la supervivencia

Palabras clave:
Carcinoma broncogénico
Estadio IB
Cirugía
Supervivencia

RESUMEN

Introducción y objetivos: Determinar las causas de mortalidad en los pacientes operados de un carcinoma broncogénico no microcítico (CBNM) en estadio IB, así como el impacto que en la supervivencia tiene el número de adenopatías analizadas.
Pacientes y método: Se ha estudiado a 300 pacientes operados de CBNM en estadio IB patológico. Sólo se extirparon los ganglios palpables o visibles. La supervivencia se analizó con el método de Kaplan-Meier y las curvas se compararon mediante el test de rangos logarítmicos.
Resultados: La edad media (± desviación estándar) de los pacientes (280 varones) era de 62,9 ± 9,7 años. Se realizaron 84 neumonectomías, 186 lobectomías, 23 bilobectomías y 7 segmentectomías. La histología más

*Corresponding author.
E-mail address: ceronjs@yahoo.es (J. Cerón).

0300-2896/$ - see front matter

frecuente fue el carcinoma epidermoide. La media del número de ganglios extirpados fue 5,05 ± 5,01. En el momento del estudio, 201 pacientes (67%) habían fallecido, el 63,2% por causas relacionadas con el CBNM. La supervivencia global de la serie a los 5 años se estableció en el 51,9% (mediana: 5,50 años; intervalo de confianza [IC] del 95%, 4,14-6,87), mientras que la supervivencia a los 5 años relacionada con el CBNM se estableció en el 61,87% (mediana: 11,05 años; IC del 95%, 7,63-14,48). El tamaño tumoral y el número de adenopatías analizadas condicionaron significativamente la supervivencia. En el análisis multivariante mantuvieron la significación estadística (p < 0,0001) en su correlación con el riesgo de muerte por CBNM, con unos riesgos relativos de 1,158 (IC del 95%, 1,081-1,240) y 0,387 (IC del 95%, 0,254-0,591) respectivamente.

Conclusión: Además del estadio y del tamaño tumoral, el número de adenopatías analizadas en total condiciona de forma significativa la supervivencia en pacientes intervenidos de CBNM en estadio IB patológico, por lo que el tratamiento quirúrgico debe incluir el análisis del mayor número posible de adenopatías.

Introduction

Lung cancer is a major health problem around the world, with a growing incidence in developed countries due to the increase in smoking, especially among women. In Spain, too, the incidence of and mortality from lung cancer have increased in recent decades.[1]

In the early stages of non-small cell lung cancer (NSCLC), surgery is still the treatment of choice.[2-4] However, the extent of pulmonary resection and the need for and extent of mediastinal lymph node dissection are contentious issues. Some authors advocate systematic lymph node dissection,[4-7] while others propose a more selective approach.[8-10] Reflecting this controversy, attempts have been made to establish a consensus on the definition of complete surgery for the treatment of NSCLC.[11]

Looking beyond the debate over systematic versus selective lymphadenectomy, some authors have shown that in patients with stage I NSCLC, survival is significantly affected by the number of lymph nodes examined.[12-14] In a study by our group published in 2005[15] it was established that in stage IA disease neither the fact of not performing systematic lymph node dissection nor the number of lymph nodes examined significantly influenced survival.

The aim of the present study was to determine the causes of death in patients operated on for stage IB NSCLC and the impact of the number of lymph nodes examined on survival.

Patients and Method

We performed a retrospective, observational analysis of the patients who underwent surgery for NSCLC in Hospital Universitario La Fe between 1990 and 2000 and who were classified as having stage IB disease according to the staging rules proposed by the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR).[16] Complete tumor resection, defined as resection with macroscopically and microscopically negative margins, was achieved in all the patients. Patients who died in the early postoperative period (first 30 days) were excluded from the study.

Lymph node dissection was not performed systematically but rather selectively; that is, only lymph nodes that could be seen or touched in the surgical field following exploration of the various lymph-node stations were excised. Therefore, if a patient was classified as N0 it was either because no lymph nodes were seen or felt during surgery or because any that were removed were found to be histologically negative. No patient received adjuvant therapy.

The variables chosen for study were sex, age, form of presentation of the NSCLC, tumor site (central or peripheral), extent of surgery, histologic diagnosis, tumor size, number of lymph nodes examined, and causes of death.

Local recurrence was diagnosed when a tumor appeared in the same lung or in the bronchial stump; locoregional recurrence, when the mediastinum or supraclavicular lymph nodes were involved; and distant metastasis, when a tumor developed in the contralateral lung or another organ.[4] A second NSCLC was diagnosed in cases where the histologic diagnosis was different or, if identical, where at least 17 years had elapsed between the 2 tumor presentations, or where the second tumor was located in a different lobe or lung without common lymphatic involvement or metastasis at the time of diagnosis.[17]

Statistical Analysis

For the purpose of calculating survival, patients whose cause of death was the original NSCLC, a second NSCLC or unknown causes were considered to have died from cancer. Survival was analyzed with the Kaplan-Meier method and the curves were compared using a log-rank test. Multivariate analysis was performed using the Cox proportional hazard model and including only the variables that had been significant in the univariate analysis. Results were considered significant at $P<.05$. Data collection ended on January 1, 2007.

Results

A total of 300 patients were included in the study: 280 men and 20 women. The mean age was 62.9 (9.7) years (range, 35-87 years). In 102 cases the NSCLC diagnosis was the result of a chance finding, while in 198 cases the patient presented with symptoms. The most common complaints were productive cough with blood-tinged sputum (37.4%) and cold-like symptoms or respiratory infection (23.7%). The tumor was found in the right lung of 145 patients and in the left lung of 155. In 40% of the patients it was central and in 60%, peripheral.

Pneumonectomy was performed in 84 patients, lobectomy in 186, double lobectomy in 23 and segmentectomy in 7. Histologically, there were 204 squamous cell carcinomas, 62 adenocarcinomas, 7 bronchioloalveolar carcinomas, 24 large-cell carcinomas, 2 clear-cell carcinomas and 1 adenocarcinoma associated with mucin secretion.

Mean tumor size was 5.01 (2.28) cm (range, 0.1-15 cm). In 31 patients no lymph nodes were excised. The mean number of lymph nodes excised was 5.05 (5.01) (range, 0-42). Details of the distribution of the number of lymph nodes examined are given in Table 1. The patients were divided into quartiles based on the number and location of lymph nodes removed.

The median duration of follow-up in this series was 5.43 years. At the time of the study, 201 patients (67%) had died, 87 (29%) were alive and 12 (4%) had been lost to follow-up. Of those who had died,

Table 1
Distribution of Number of Lymph Nodes Examined by Location and by Quartiles[a]

Location, Mean (SD) (range)	
N1	3.14 (3.4) (0-32)
N2	1.94 (2.9) (0-21)
Total	5.05 (5.0) (0-42)
Quartiles,[a] No. of lymph nodes (%)	
0-2	106 (35.3)
3-4	68 (22.7)
5-6	68 (22.7)
≥7	55 (18.3)

Abbreviations: N1, number of lymph nodes examined in the hilar region or distal to it (station 10 or higher)[18]; N2, number of lymph nodes examined in the mediastinum (below station 10).[18]

[a] Quartiles of patients, divided on the basis of total number of lymph nodes sampled (N1 + N2).

126 (63.2%) had died from causes related to the NSCLC, 69 (34.3%) from causes other than the NSCLC and 6 (2.5%) from unknown causes. The causes of death related to the NSCLC are detailed in Table 2 and those unrelated to NSCLC, in Table 3.

The mean time until death due to NSCLC was 2.58 (2.40) years (range, 0.25-11.85 years) and the mean time until death from a cause other than NSCLC was 6.1 (4.1) years (range, 0.08-15.73 years). The mean time until death from a second NSCLC was 5.77 (3.50) years (range, 1.17-15.43 years). Five-year survival was 51.9% in the series as a whole, with a median survival of 5.50 years (95% confidence interval [CI], 4.14-6.87 years); the median 5-year survival was 61.87% among those who died from causes related to the NSCLC, with a median survival of 11.05 years (95% CI, 7.63-14.48 years).

In our analysis of the factors that might have influenced long-term survival among patients who died from causes related to the NSCLC, only tumor size in centimeters and the number of lymph nodes examined (Figures 1 and 2) were found to be significant (Table 4). In the multivariate analysis, tumor size and the number of lymph nodes examined (>5 or <5) once again showed a statistically significant correlation with the risk of death from NSCLC (P<.0001), with relative risks of 1.158 (95% CI, 1.081-1.240) and 0.387 (95% CI, 0.254-0.591), respectively.

Discussion

In our series, tumor size and the number of lymph nodes examined significantly affected survival in patients with stage IB NSCLC. Other factors that have been found to predict survival in such patients include smoking, sex, age and histologic type.[19-21] In our series, however, none of these variables was statistically significant (Table 4).

Table 2
Deaths From Non-Small Cell Lung Cancer (NSCLC) and Location of Recurrence

Cause of Death	No. of Patients (%)
Local recurrence	5 (4.0%)
Locoregional recurrence	13 (10.3%)
Distant recurrence	69 (54.7%)
Generalized	6 (4.7%)
Central nervous system	24 (19.1%)
Bone	16 (12.7%)
Lung	10 (7.9%)
Liver	6 (4.7%)
Adrenal gland	2 (1.6%)
Skin	2 (1.6%)
Pancreas	1 (0.8%)
Thoracic wall	1 (0.8%)
Muscle	1 (0.8%)
Unidentified cancer	15 (11.9%)
Second NSCLC	24 (19.1%)
Total	126 (100%)

Table 3
Deaths From Causes Other Than Non-Small Cell Lung Cancer

Cause of Death	No. of Patients (%)
Acute myocardial infarction	12 (17.4%)
Cerebrovascular accident	9 (13.1%)
Chronic obstructive pulmonary disease	5 (7.4%)
Pneumonia	4 (5.9%)
Head trauma	2 (2.9%)
Cardiovascular diseases	
Aortic aneurysm	2 (2.9%)
Cor pulmonale	2 (2.9%)
Heart failure	2 (2.9%)
Sudden death	2 (2.9%)
Intestinal ischemia	1 (1.4%)
Neoplastic diseases	
Bladder	3 (4.4%)
Prostate	2 (2.9%)
Trachea	1 (1.4%)
Rectum	4 (5.9%)
Larynx	1 (1.4%)
Melanoma	1 (1.4%)
Lymphoma	1 (1.4%)
Stomach	1 (1.4%)
Central nervous system	1 (1.4%)
Complications from other surgery	3 (4.4%)
Multiple diseases	2 (2.9%)
Bleeding ulcer	2 (2.9%)
Hepatic insufficiency	2 (2.9%)
Parenteral drug addiction	1 (1.4%)
Alzheimer's disease	1 (1.4%)
Gender-based violence	1 (1.4%)
Parkinson disease	1 (1.4%)
Total	69 (100%)

That tumor size affects survival in NSCLC is accepted by most authors; disagreement remains about the best cut-off point for identifying different prognostic groupings. In our series, tumor size was a first-order prognostic factor, as it was the first variable to enter the regression equation, with a relative risk of 1.158 (95% CI, 1.081-1.240).

Although surgery is still the treatment of choice in early-stage NSCLC, the type of surgery and, above all, the extent of mediastinal lymphadenectomy are contentious issue s.[22,23] In our experience, contrary to the findings reported by other authors,[13,14] the number of lymph nodes examined did not influence survival in patients classified as stage IA.[15,24] In patients classified as stage IB, by contrast, we found that the number of lymph nodes examined did significantly affect survival (P=.0001): patients who had 5 or more lymph nodes excised during surgery survived longer (5-year survival rate, 74.46%) than those from whom fewer than 5 were removed (5-year survival rate, 55.08%).

Firm advocates of systematic mediastinal lymph node dissection, such as Naruke et al,[25-27] maintain that the systematic approach gives better results in terms of survival. Similarly, Martini el al[4] argue that systematic dissection is necessary for correct staging of NSCLC, as it had a very clear impact on survival in their series: overall 5-year survival was 75%, compared to 59% in patients in whom none were dissected. More recently, however, a number of authors from the Japanese medical community[8-10,28] have demonstrated in various series that there were no significant differences in survival between patient groups in which systematic mediastinal lymph node dissection was performed and those undergoing to less extensive dissection. In a prospective, randomized trial in which tumors were less than 2 cm in diameter, Sugi et al[8] found no significant differences between their radical systematic dissection group and their group assigned to lymph-node sampling: 5-year survival was 81% and 84%, respectively. Okada et al[9] also described

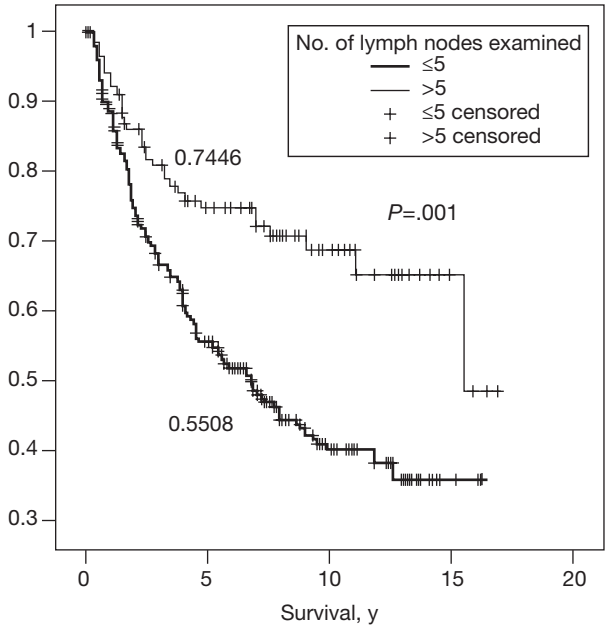

Figure 1. Survival in non-small cell lung cancer by number of lymph nodes examined

a series of 377 stage I patients in which they found no significant differences in survival between groups undergoing complete resection or sampling of nodes (*P*=.376 for disease-free survival).

Further fueling the controversy, Gajra et al[13] and Wu et al[14] established that not only the extent of lymphadenectomy but also the number of lymph nodes examined is important, as it significantly affects survival in patients with stage I NSCLC. Gajra et al retrospectively analyzed 442 stage I patients who were treated with surgical resection and some form of lymph node sampling. Their results showed significant differences in survival (*P*<.0001) depending

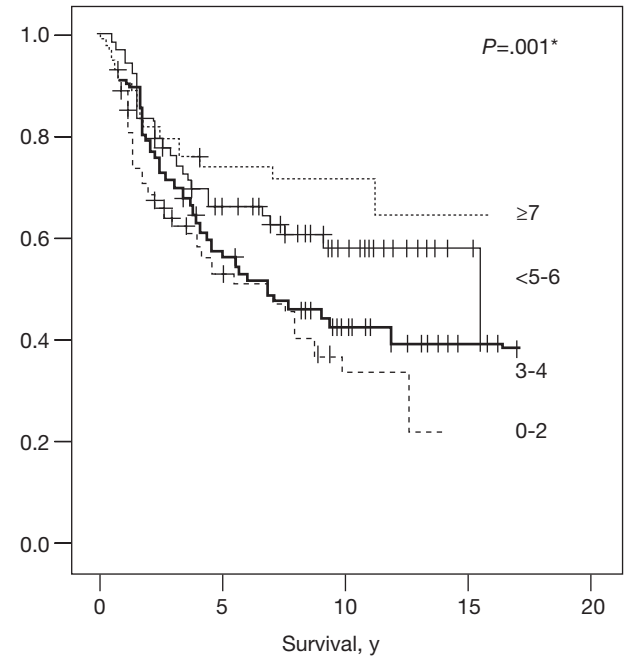

Figure 2. Survival in non-small cell lung cancer by number of lymph nodes examined (quartiles).
[a] Only significant when comparing quartiles 2 and 3, 1 and 4, and 2 and 4.

Table 4
Univariate Analysis of Survival of Patients Who Died From Causes Related to Non-Small Cell Lung Cancer

Variable	5-Year Survival (%)	P
Sex		
Male	62.83	NS
Female	47.41	
Age, years		
>60	60.93	NS
<60	62.40	
Symptoms		
Yes	60.93	NS
No	58.09	
Resection		
Pneumonectomy	65.38	NS
Without pneumonectomy	60.51	
Histology		
Squamous cell carcinoma	63.93	NS
Non-squamous cell carcinoma	67.52	
Tumor size, cm		
<3	75.44	.01
>3	58.58	
<5	68.82	.0003
>5	47.91	
Location		
Central	66.35	NS
Peripheral	58.76	
Lymph nodes examined		
>5	74.46	.0001
=5	55.08	
Lymph nodes examined (quartiles)[a]		
0-2	56.74	
3-4	53.20	.001[b]
5-6	66.39	
≥7	74.25	

Abbreviation: NS, not significant.
[a] Quartiles of patients, divided on the basis of total number of lymph nodes sampled (N1 + N2).
[b] Only significant when comparing quartiles 2 and 3, 1 and 4, and 2 and 4.

on the type of dissection carried out (random, selective, or complete mediastinal lymph-node sampling). Also, dividing the patients into quartiles according to the number of lymph nodes assessed (<4; 4-6; 7-9; and >9) and setting the cutoff at the mean (6 lymph nodes), again these authors observed significant differences in survival. Their finding that at least 6 lymph nodes must be assessed in order to accurately stage the N factor is close to our own results. Wu et al,[14] who retrospectively analyzed 321 stage I patients who underwent surgical treatment, set the cutoff at 15 lymph nodes examined and consider the number of lymph nodes examined a measure of the quality of lymphadenectomy.

On analyzing the specific causes of mortality from NSCLC in our series, we observed that the most frequent cause was distant metastasis, above all to the central nervous system and bones. These findings coincide with those of other authors[15,26] and may be taken to indicate that NSCLC is a systemic disease, even when it is at an early stage, as in our study. Furthermore, the incidence of local, bronchial, or mediastinal recurrence was low (14.3%) and could have been affected by the performance of selective lymphadenectomy. However, neither systematic sampling nor systematic lymphadenectomy provides a guarantee against mediastinal recurrence.[29]

Failure to perform extensive lymph node dissection could lead to understaging of NSCLC patients. When more lymph nodes are examined, metastases are more likely to be detected. As a result, patients are more

likely to be classified in more advanced stages (the Will Rogers phenomenon[30]), most probably impacting on survival. This point is contested, however. Izbicki et al[31] found that lymphadenectomy had no influence on survival in patients with pN0 disease and that in patients with limited lymph node involvement (pN1 and pN2), lymphadenectomy did not prolong the period without recurrence. Nor have other authors[8-10] obtained better results in patients who underwent systematic lymphadenectomy. Wu et al,[19] on the other hand, did find that systematic lymphadenectomy had a beneficial impact on survival. Despite many years of debate, it seems we will have to wait for the results of the ACOSOG Z0030 randomized trial,[32] in which survival is being analyzed according to the type of lymphadenectomy performed, for more reliable evidence on which to base a decision as to the best surgical treatment for early-stage NSCLC.

In conclusion, failure to perform systematic lymph node dissection could lead to inaccurate staging of NSCLC. It would appear self-evident that the more extensive the lymphadenectomy, the greater the probability of accurate pathologic staging. Selective lymphadenectomy may result in understaging, which would impact on survival and be reflected in a high rate of locoregional recurrence. In our experience, the rate of locoregional recurrence was no higher than that reported by other authors who practice systematic dissection; nor was the survival rate any higher. In view of our results, however, and of the impact of the number of lymph nodes examined on survival, mediastinal lymph node dissection should be as extensive as possible.

References

1. Bronchogenic Carcinoma Cooperative Group of the Spanish Society of Pneumology and Thoracic Surgery (GCCB-S). Clinical tumour size and prognosis in lung cancer. Eur Respir J. 1999;14:812-6.
2. Inoue K, Sato M, Fujimura S, Sakurada A, Takahashi S, Usuda K, et al. Prognostic assessment of 1310 patients with non-small-cell lung cancer who underwent complete resection from 1980 to 1993. J Thorac Cardiovasc Surg. 1998;116:407-11.
3. Manser R, Wright G, Hart D, Byrnes G, Campbell DA. Surgery for early stage non-small cell lung cancer. Cochrane Database Syst Rev. 2005;(1):CD004699.
4. Martini N, Bains MS, Burt ME, Zakowski MF, McCormack P, Rusch VW, et al. Incidence of local recurrence and second primary tumors in resected stage I lung cancer. J Thorac Cardiovasc Surg. 1995;109:120-9.
5. Deslauriers J, Gregoire J. Surgical therapy of early non-small cell lung cancer. Chest. 2000;117 4 Suppl 1:104-9.
6. Nesbitt JC, Putnam JB Jr, Walsh GL, Roth JA, Mountain CF. Survival in early-stage non-small cell lung cancer. Ann Thorac Surg. 1995;60:466-72.
7. Oda M, Watanabe Y, Shimizu J, Murakami S, Ohta Y, Sekido N, et al. Extent of mediastinal node metastasis in clinical stage I non-small-cell lung cancer: the role of systematic nodal dissection. Lung Cancer. 1998;22:23-30.
8. Sugi K, Nawata K, Fujita N, Ueda K, Tanaka T, Matsuoka T, et al. Systematic lymph node dissection for clinically diagnosed peripheral non-small-cell lung cancer less than 2 cm in diameter. World J Surg. 1998;22:290-4.
9. Okada M, Sakamoto T, Yuki T, Mimura T, Miyoshi K, Tsubota N. Selective mediastinal lymphadenectomy for clinico-surgical stage I non-small cell lung cancer. Ann Thorac Surg. 2006;81:1028-32.
10. Funatsu T, Matsubara Y, Ikeda S, Hatakenaka R, Hanawa T, Ishida H. Preoperative mediastinoscopic assessment of N factors and the need for mediastinal lymph node dissection in T1 lung cancer. J Thorac Cardiovasc Surg. 1994;108:321-8.
11. Rami-Porta R, Wittekind C, Goldstraw P. Complete resection in lung cancer surgery: proposed definition. Lung Cancer. 2005;49:25-33.
12. Doddoli C, Aragon A, Barlesi F, Chetaille B, Robitail S, Giudicelli R, et al. Does the extent of lymph node dissection influence outcome in patients with stage I non-small-cell lung cancer? Eur J Cardiothorac Surg. 2005;27:680-5.
13. Gajra A, Newman N, Gamble GP, Kohman LJ, Graziano SL. Effect of number of lymph nodes sampled on outcome in patients with stage I non-small-cell lung cancer. J Clin Oncol. 2003;21:1029-34.
14. Wu Y, Huang ZF, Wang SY, Yang XN, Ou W. A randomized trial of systematic nodal dissection in resectable non-small cell lung cancer. Lung Cancer. 2002;36:1-6.
15. Padilla J, Peñalver JC, Jordá C, Calvo V, Escrivá J, Cerón J, et al. Carcinoma broncogénico no anaplásico de células pequeñas en estadio IA. Cirugía y patrones de mortalidad. Arch Bronconeumol. 2005;41:180-4.
16. Grupo de Trabajo de la SEPAR. Normativa actualizada (1998) sobre diagnóstico y estadificación del carcinoma broncogénico. Arch Bronconeumol. 1998;34:437-52.
17. Martini N, Melamed MR. Multiple primary lung cancers. J Thorac Cardiovasc Surg. 1975;70:606-12.
18. Mountain CF, Dresler CM. Regional lymph node classification for lung cancer staging. Chest. 1997;111:1718-23.
19. Wu YC, Lin CF, Hsu WH, Huang BS, Huang MH, Wang LS. Long-term results of pathological stage I non-small cell lung cancer: validation of using the number of totally removed lymph nodes as a staging control. Eur J Cardiothorac Surg. 2003;24:994-1001.
20. Goya T, Asamura H, Yoshimura H, Kato H, Shimokata K, Tsuchiya R, et al. Prognosis of 6644 resected non-small cell lung cancers in Japan: a Japanese lung cancer registry study. Lung Cancer. 2005;50:227-34.
21. Padilla J, Calvo V, Peñalver JC, Zarza AG, Pastor J, Blasco E, et al. Survival and risk model for stage IB non-small cell lung cancer. Lung Cancer. 2002;36:43-8.
22. Barnard J, Dunning J, Musleh G, Odom N. Is there a role for the use of radical lymph node dissection in the surgical management of resectable non-small cell lung cancer? Interac Cardiovasc Thorac Surg. 2004;3:294-9.
23. Keller SM. Complete mediastinal lymph node dissection – does it make a difference? Lung Cancer. 2002;36:7-8.
24. Padilla J, Calvo V, Peñalver JC, Jordá C, Escrivá J, García A, et al. Carcinoma broncogénico no anaplásico de células pequeñas en estadio I y de diámetro máximo de 3 cm. Factores pronósticos. Arch Bronconeumol. 2004;40:110-3.
25. Naruke T, Suemasu K, Ishikawa S. Lymph node mapping and curability at various levels of metastasis in resected lung cancer. J Thorac Cardiovasc Surg. 1978;76:832-9.
26. Naruke T, Tsuchiya R, Kondo H, Asamura H. Prognosis and survival after resection for bronchogenic carcinoma based on the 1997 TNM-staging classification: the Japanese experience. Ann Thorac Surg. 2001;71:1759-64.
27. Naruke T, Tsuchiya R, Kondo H, Nakayama H, Asamura H. Lymph node sampling in lung cancer: how should it be done? Eur J Cardiothorac Surg. 1999;16 Suppl 1:17-24.
28. Asamura H, Nakayama H, Kondo H, Tsuchiya R, Shimosato Y, Naruke T. Lymph node involvement, recurrence, and prognosis in resected small, peripheral, non-small-cell lung carcinomas: are these carcinomas candidates for video-assisted lobectomy? J Thorac Cardiovasc Surg. 1996; 111:1125-34.
29. Lardinois D, Suter H, Hakki H, Rousson V, Betticher D, Ris HB. Morbidity, survival, and site of recurrence after mediastinal lymph-node dissection versus systematic sampling after complete resection for non-small cell lung cancer. Ann Thorac Surg. 2005;80:268-74.
30. Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. N Engl J Med. 1985;312:1604-8.
31. Izbicki JR, Passlick B, Pantel K, Pichlmeier U, Hosch SB, Karg O, et al. Effectiveness of radical systematic mediastinal lymphadenectomy in patients with resectable non-small cell lung cancer: results of a prospective randomized trial. Ann Surg. 1998;227:138-44.
32. Allen MS, Darling GE, Pechet TT, Mitchell JD, Herndon JE II, Landreneau RJ, et al. Morbidity and mortality of major pulmonary resections in patients with early-stage lung cancer: initial results of the randomized, prospective ACOSOG Z0030 trial. Ann Thorac Surg. 2006;81:1013-9.