

Non-small Cell Lung Cancer in Stage IA: Mortality Patterns After Surgery

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OBJECTIVE: To determine the causes of death in patients treated surgically for nonsmall cell lung cancer (NSCLC) in stage IA and to evaluate the impact on survival of not performing systematic lymph node dissection and of the number of nodes resected.

PATIENTS AND METHODS: The study sample consisted of 156 patients operated on for NSCLC and classified in stage IA according to TNM staging. Only palpable or visible lymph nodes were dissected. Kaplan-Meier survival curves were compared using a log-rank test.

RESULTS: At the end of the study, 85 (54.5%) patients had died, 67 (42.9%) were alive, and 4 (2.5%) were lost to follow up. Twenty-three (14.7%) died from a recurrence of NSCLC: 2 with local tumors (1.2%), 2 with mediastinal node involvement (1.2%), and 19 (12.1%) with distant metastasis. The cause of death was unrelated to NSCLC in 62 (39.7%) cases: 33 (21.1%) had a new tumor, 18 of which were bronchogenic, and 29 (18.5%) had nonmalignant disease. The 5-year survival rate was 81.4%. The rate was 88.9% among patients from whom no lymph nodes were excised and 79.9% among those with node excision, although the difference was not statistically significant ($P=0.4073$).

CONCLUSIONS: Our experience suggests that neither the fact of not performing systematic lymph node dissection nor the number of nodes resected has an impact on survival. A substantial number of patients died of causes unrelated to the NSCLC for which they had been treated.

Key words: Bronchogenic carcinoma. Stage IA. Surgery. Lymph node excision. Mortality.

Carcinoma broncogénico no anaplásico de células pequeñas en estadio IA. Cirugía y patrones de mortalidad

OBJETIVO: Determinar las causas de mortalidad en los pacientes operados de un carcinoma broncogénico no anaplásico de células pequeñas (CBNACP) en estadio IA y el impacto que tiene en la supervivencia el hecho de no realizar una disección ganglionar sistemática, así como el número de ganglios resecaados.

PACIENTES Y MÉTODOS: Se estudió a 156 pacientes operados de un CBNACP y clasificados en el estadio IA de acuerdo con el sistema tumor, nódulo, metástasis 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: Al finalizar el estudio, 85 (54,5%) pacientes habían fallecido, 67 (42,9%) estaban vivos y 4 (2,5%) se habían perdido en el seguimiento. Veintitrés (14,7%) pacientes fallecieron por recidiva del CBNACP: 2 por recidiva local (1,2%), otros 2 en el ganglio mediastínico (1,2%) y 19 (12,1%) por metástasis a distancia. En 62 (39,7%) de los casos la causa de la muerte no estuvo relacionada con el CBNACP: 33 (21,1%) fallecieron por aparición de un nuevo cáncer, 18 de los cuales fueron broncogénicos, y 29 (18,5%) por enfermedades no tumorales. La supervivencia a los 5 años fue del 81,4%. Cuando no se extirpó ningún ganglio, la supervivencia fue del 88,9%, mientras que cuando se extirparon fue del 79,9%, aunque la diferencia no fue significativa ($p = 0,4073$).

CONCLUSIONES: En nuestra experiencia, ni el hecho de no realizar disección ganglionar sistemática ni el número de ganglios extirpados han tenido una influencia en la supervivencia a los 5 años. Un número considerable de pacientes falleció de una causa distinta del CBNACP del que se les había operado.

Palabras clave: Carcinoma broncogénico. Estadio IA. Cirugía. Disección ganglionar. Patrón de mortalidad.

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Introduction

Surgery continues to be the treatment of choice for certain patients diagnosed with non-small cell lung cancer (NSCLC), for whom a 5-year survival rate of about 80% is achieved for tumors classified in stage IA.¹⁻³

However, that promising expectation of survival can be conditioned by concomitant disease, mainly caused by smoking,^{4,5} or the development of a second lung cancer.^{1,6} Some authors have arrived at the conclusion—based on retrospective analysis—that systematic lymph node excision may be not be necessary in certain circumstances,⁷⁻¹¹ while recent studies have suggested that the number of lymph nodes excised significantly affects prognosis in stage I disease.^{12,13}

The objective of our study, undertaken in a clinical context in which the expectation of survival is high, was to determine the causes of death in patients treated surgically for NSCLC in stage IA and to evaluate the impact on survival of not performing systematic lymph node dissection and of the number of nodes resected.

Patients and Methods

From 1981 through 2001, we resected tumors from 158 patients with NSCLC classified in stage IA by TNM staging following the guidelines of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR).¹⁴ Two (1.2%) patients who died during the postoperative period were excluded. Full resection, defined as excision with negative margins demonstrated macro- and microscopically, was performed on all the remaining 156 patients. The same surgical approach was maintained throughout the study period, such that we did not perform lymph node excision systematically. Nodes were only removed if they were palpable or visible; therefore, a classification of N0 meant that no lymph nodes were seen or felt during surgery or if they were seen and felt, and therefore removed, histology demonstrated no invasion by the tumor. No patient received adjuvant therapy.

Sex, age, extent of lung exeresis performed, histologic diagnosis, tumor diameter, number of lymph nodes removed, and cause of death were the variables chosen for study. When a tumor appeared again in the same lung or bronchial stump, local recurrence was diagnosed. Locoregional recurrence was defined as involvement of the mediastinum or supraclavicular lymph nodes, and distant metastasis was diagnosed if a tumor developed in the contralateral lung or another organ.¹ The appearance of a second bronchogenic carcinoma was diagnosed if the histologic diagnosis was different or, if identical, when at least 2 years had elapsed between the 2 tumor presentations or when the second tumor was located in a different lobe or lung without common lymphatic involvement or metastasis at the time of diagnosis.¹⁵

Kaplan-Meier survival analysis was applied and log-rank tests were used to compare curves. Data collection ended on January 1, 2004.

Results

Seven patients were women and 149 were men. The mean (SD) age was 61.6 (8.8) years (range, 36-81 years). Eighty-three tumors were found fortuitously, whereas 73 patients presented with symptoms. The tumor was found in the right lung of 93 patients and in the left lung of 63. A lobectomy was performed in 133 cases, a double lobectomy in 9, and a segmentectomy in 14. The histologic type was squamous cell carcinoma in

TABLE 1
Deaths From Non-Small Cell Lung Cancer and Location of the Recurrence

Location	No. of Patients
Local recurrence	2
Locoregional recurrence	2
Remote recurrence	19
Disseminated	5
Bone	6
Central nervous system	4
Liver	1
Adrenal gland	1
Lung	1
Undetermined	1
Total	23

TABLE 2
Deaths From Causes Unrelated to Non-Small Cell Lung Cancer*

Cause	No. of Patients
MIA	9
COPD	6
Stroke	4
Pneumonia	4
Other	6
Neoplastic disease	33
Second pulmonary carcinoma	18
Bladder	4
Esophagus	3
Larynx	3
Liver	3
Colon	1
Prostate	1
Total	62

*AMI indicates acute myocardial infarction; COPD, chronic obstructive pulmonary disease.

92 cases, adenocarcinoma in 56, and large-cell carcinoma in 8. The mean diameter was 2.2 (0.8) cm (range, 0.1-3 cm). Lymph nodes were removed from 124 patients; none were removed from 32. The mean number of lymph nodes excised was 3.7 (3.4) (range, 0-18). At the time data collection ended, 85 patients (54.4%) had died, 4 (2.5%) had been lost to follow up, and 67 (42.9%) were alive.

Table 1 shows causes of death from recurrence of NSCLC. Two (1.2%) patients developed a local recurrence: an ipsilateral generalization of bronchioloalveolar carcinoma in 1 case 15 months after surgery and a squamous cell carcinoma in the main right bronchus 7 months after a right lower lobectomy in the second case. Another 2 (1.2%) patients experienced locoregional recurrence. In the first patient, recurrence was in the region surrounding lymph nodes between the aorta and the lung 18 months after a left lower lobectomy in which the lobar hilum was negative for squamous cell carcinoma. In the second, the right paratracheal lymph node became involved 45 months after right lower lobectomy to treat adenocarcinoma with a negative hilum. Nineteen (12.1%) patients died from distant metastasis. The mean time elapsed

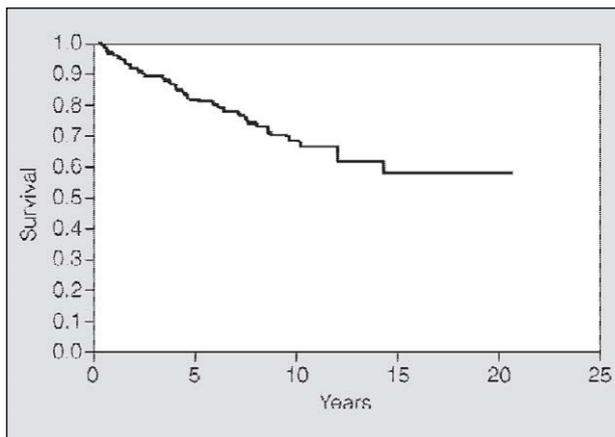


Figure 1. Overall survival for the patient series.

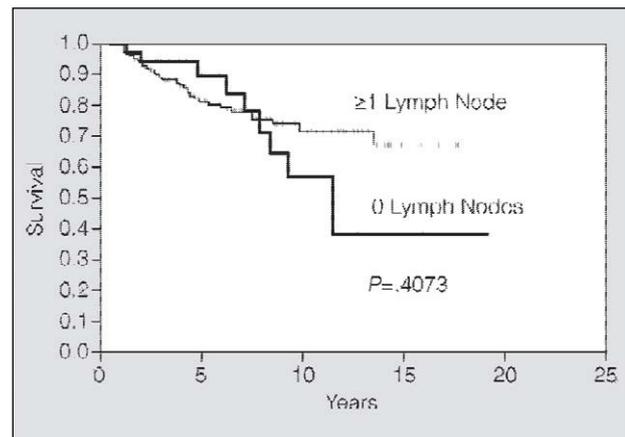


Figure 2. Survival, by number of lymph nodes excised.

between surgery and recurrence was 2.7 years (median, 1.2 years; range, 0.3-16.2 years). Metastasis appeared after 5 years in 3 patients. The cause of death was unrelated to the NSCLC for which they had been treated for 62 (39.7%) patients (Table 2): 29 (15.6%) died from nontumoral causes and 33 (21.1%) from a second cancer, 18 of which were bronchogenic (11.5%). The mean time until death from a cause unrelated to NSCLC was 7.5 years (median, 6.8 years; range, 0.2-16.9 years). The mean time until appearance of a second bronchogenic carcinoma was 5.7 years (median, 4.7 years; range, 0.7-13 years).

At the time the data was analyzed, 67 patients (42.9%) were alive and free of disease. Two patients survived 4 years after resection of a single metastasis to the brain and adjuvant radiotherapy. Six patients developed a second bronchogenic carcinoma and another 3 had malignant tumors at another site. The mean time of survival was 8.4 years (median, 6.9 years; range, 2.2-20.7 years).

Survival at 5 and 10 years was 81.4% and 68%, respectively (Figure 1). Survival at 5 years was 88.9% for patients from whom no lymph nodes were removed and 79.9% for those in whom excisions were performed (Figure 2), but the difference was not significant ($P=.4073$).

Discussion

Because the long-term prognosis is good for patients who undergo surgery for NSCLC in stage IA, it is possible to evaluate patterns of mortality. At present there is interest in studying the role of comorbidity in the prognosis of patients with NSCLC, and some authors include indicators of comorbidity when they analyze factors that affect survival.^{4,5} We certainly saw that a large number of patients who underwent surgery for NSCLC die of other causes, consistent with reports from other authors^{4,5,16}; in our series, that was the case for 39.7%.

As has been described elsewhere,^{1,6} we found that mortality due to NSCLC followed 2 patterns. The first was characterized by the development of metastasis that manifests soon after surgery, usually at a remote site; this occurred a mean 2.7 years later in our series. The second is marked by the appearance of a second carcinoma, which usually manifests late, a mean 5.7 years after surgery in our series.

One of the most important concerns, in our judgment, is the assessment of patterns of tumor recurrence in patients from whom lymph nodes are or are not systematically excised. Aside from the morbidity that can arise from lymphadenectomy,¹⁷ potential benefits can be derived in 2 ways: in the form of correct staging or an impact on survival. The various staging procedures applied range from no sampling at all to extended lymph node dissection.^{18,19} It seems logical to assume that the more extensive the lymphadenectomy, the greater the likelihood of accurate staging.²⁰ Nevertheless, there is controversy over this point. Some authors have been unable to demonstrate that the percentage of N1 or N2 found by systematic lymph node dissection is significantly different from the yield for nodal sampling of certain hilar or mediastinal stations.^{8,20,21} Therefore, some groups have proposed that sampling some minimum number of lymph nodes²² or certain preestablished stations depending on tumor location²³ would provide adequate information. Others, however, maintain that systematic lymph node excision is essential for correct staging.^{1,24,25} Systematic dissection, defended mainly by practitioners at the National Cancer Center Hospital in Tokyo,²⁶ is the most widely accepted approach. Their technique involves excision of all pulmonary lymph nodes and removal en bloc of all diseased ipsilateral mediastinal lymph nodes along with mediastinal fat.

There seems to be a tendency to believe that systematic lymph node dissection can be avoided in certain circumstances—in function of tumor size, location, or type—if intraoperative sampling of hilar nodes yields negative findings. That position is not

shared by others who base their views on retrospective analyses, mainly from the Japanese school,^{8,9,10,27} including from the National Cancer Center Hospital of Tokyo.^{7,11,28} There, systematic dissection is considered necessary in all patients because intraoperative sampling of hilar nodes does not guarantee that mediastinal nodes are uninvolved regardless of tumor location, size, or type.^{24,25}

As mentioned, we performed lymphadenectomy "on demand," based on assessment of clinical situation, such that there was a possibility that certain patients staged as N0 were in fact in stage N1 or N2. Tumor recurrence was located in mediastinal lymph nodes in only 2 cases (1.2%) in our series, 18 and 45 months after surgery. However, systematic lymph node excision does not guarantee that disease will not recur in that location.^{1,29}

The impact of systematic lymph node resection on survival of patients in stage I is uncertain according to results from randomized controlled trials. Izbicki et al³⁰ and Sugi et al⁸ found no difference in survival, although Wu et al,³¹ reported that survival was significantly better for patients who underwent systematic lymph node dissection in comparison with those who underwent only node sampling in a study of 321 patients in stage I. Funatsu et al,³² however, observed that the 70% 5-year survival rate for a group of 61 patients in clinical stage IA who underwent systematic lymph node dissection was significantly worse than the 90% survival rate for patients who did not have nodes routinely excised. The 81.4% survival rate at 5 years for the patients in our series was similar to rates reported by other groups practicing systematic lymph node excision.¹⁻³

Recently, it has been suggested that the number of lymph nodes excised has a significant effect on the prognosis of patients in pathologic stage IA. In studies in which the 5-year survival rate was around 70%, prognosis was found to be significantly better when more nodes were resected.^{12,13} In our study, however, the number of excised nodes had no influence on survival, which was somewhat higher than the rate reported in the studies cited here.

In conclusion, a large number of patients with early stage NSCLC die from unrelated causes and it is therefore advisable to include variables reflecting comorbidity in studies of prognosis.^{4,5} Moreover, the role of lymph node removal in oncologic surgery continues to be disputed³³ and can not be separated from issues related to NSCLC itself.¹⁹ We can hope that the results of a randomized controlled trial recently closed by the American College of Surgeons Oncology Group³⁴ will shed light on this controversial topic.

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