

T2N1M0 Non-Small Cell Lung Cancer: Surgery and Prognostic Factors

J. Padilla, V. Calvo, J.C. Peñalver, C. Jordá, J. Escrivá, J. Cerón, A. García Zarza, J. Pastor, and E. Blasco

Servicio de Cirugía Torácica, Hospital Universitario La Fe, Valencia, Spain.

OBJECTIVE: To determine the prognostic factors for the survival in a group of patients operated on for a non-small cell lung cancer classified as T2N1M0.

PATIENTS AND METHODS: Two hundred sixteen patients treated exclusively with surgery were studied. Kaplan-Meier survival and Cox multivariable regression analyses were used.

RESULTS: The overall survival rate was 39.8% at 5 years and 29.9% at 10 years. Sex, age, presence or absence of symptoms, type of resection, and number and location of affected lymph nodes had no effect on survival. Tumor size ($P=0.04$) and histologic type ($P=0.03$) did significantly affect prognosis. Both variables entered into the Cox multivariable regression model.

CONCLUSIONS: Patients operated on for non-small cell lung cancer classified as T2N1M0 have an overall probability of 5-year survival of approximately 40%. However, the prognosis for this group of patients is heterogeneous: in our study it was affected by the histologic type (45.5% for squamous cell and 25% for non-squamous cell cancers) and tumor size (53% for tumors with a diameter of ≤ 3 cm, 45% for tumors between 3.1 and 5 cm, and 29% for a tumor diameter >5 cm).

Key words: Carcinoma bronchogenic. Stage IIb. T2N1M0. Surgery. Prognosis.

Carcinoma broncogénico no anaplásico de células pequeñas T2N1M0. Cirugía y factores pronósticos

OBJETIVO: Determinar los factores pronósticos de supervivencia de un grupo de pacientes operados de un carcinoma broncogénico no anaplásico de células pequeñas y clasificados como T2N1M0.

PACIENTES Y MÉTODOS: Se estudió a 216 pacientes tratados exclusivamente con cirugía. La supervivencia se analizó con el método de Kaplan-Meier y se utilizó el modelo de Cox para el análisis multivariante.

RESULTADOS: La supervivencia global fue del 39,8% a los 5 años y del 29,9% a los 10 años. El sexo, la edad, la presencia o ausencia de síntomas, la amplitud de la exéresis, el número de ganglios afectados y su localización no influyeron en la supervivencia. El tamaño tumoral ($p = 0,04$) y la estirpe histológica ($p = 0,03$) sí condicionaron significativamente el pronóstico. Ambas variables entraron en regresión cuando se utilizó el análisis multivariante.

CONCLUSIONES: Los pacientes operados de un carcinoma broncogénico no anaplásico de células pequeñas clasificado como T2N1M0 tienen una probabilidad de supervivencia global a los 5 años en torno al 40%. Sin embargo, no es un grupo de pacientes con un pronóstico homogéneo, ya que en nuestro estudio estuvo condicionado por la estirpe histológica (un 45,5% para los epidermoides y un 25% para los no epidermoides) y el tamaño tumoral (un 53% en los tumores con un diámetro ≤ 3 cm, un 45% entre 3,1-5 cm y un 29% en > 5 cm).

Palabras clave: Carcinoma broncogénico. Estadio IIb. T2N1M0. Cirugía. Factores pronósticos.

Introduction

Stage II of the non-small cell lung cancer (NSCLC) classification system has undergone more change than any other stage during revisions. In the current system, stage IIb groups potentially resectable tumors that

invade extrapulmonary structures and do not affect the lymph nodes (T3N0M0) together with tumors confined exclusively to the lung parenchyma, but with non-mediastinal lymph node involvement (T2N1M0).¹

Several series of patients treated surgically for NSCLC classified as T2N1M0 showed the 5-year survival rate to be between 38% and 43.8%.²⁻⁶ Although studies on the impact of non-mediastinal lymph node involvement on survival do exist, they are few, and those focusing exclusively on tumors classified as T2N1M0 are even fewer.⁷

Correspondence: Dr. J. Padilla.
Servicio de Cirugía Torácica. Hospital Universitario La Fe.
Avda. de Campanar, 21. 46009 Valencia. España.
E-mail: jpadilla@comv.es

Manuscript received August 24, 2004. Accepted for publication November 16, 2004.

The objective of our study was to examine survival and the factors which affect it in a group of patients operated on for an NSCLC classified as T2N1M0.

Patients and Methods

Between 1970 and 2001, 222 patients with NSCLC classified as T2N1M0, according to the TNM staging following the guidelines proposed by the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR),¹ underwent surgery in the thoracic surgery department of La Fe University Hospital in Valencia. Six patients (2.7%) died in the postoperative period and were excluded from the study. The remaining 216 patients underwent complete resection; ie there was no micro or macroscopic evidence of marginal invasion. Our surgical protocol did not change throughout the study. That is, we did not perform systematic mediastinal lymph node resection and only removed palpable or visible lymph nodes. The lymph node map of Naruke et al⁸ was used to classify the level of node involvement. No patients received adjuvant treatment.

The variables chosen, retrospectively, for the survival study were sex, age, presence or absence of symptoms, extent of the lung resection performed, histologic type, tumor size, and number and location of affected lymph nodes.

Statistical Analysis

The Kaplan-Meier method was used to calculate survival and the curves were compared using the log-rank test and a test for trend when necessary. The cut point for the continuous variables (age, tumor size, and number of affected lymph nodes) was established arbitrarily on the basis of other, previous studies. The Cox proportional hazards model was used for the multivariable analysis and only variables with a significance of $P \leq .10$ in the univariate analysis were included.

Results

The survival rate for the series was 39.8% at 5 years and 29.9% at 10 years (Figure 1).

The group of patients studied consisted of 211 men and 5 women. The mean (SD) age was 61.7 (9.1) years

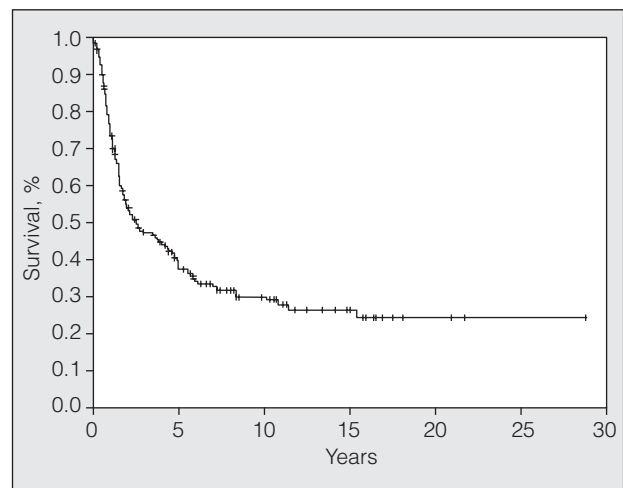


Figure 1. Overall survival in the series.

(range, 26-79). On 48 occasions the tumor was discovered by chance, whereas 168 patients presented with symptoms. A pneumonectomy was necessary in 91 patients and 125 required partial lung resection. Tumors were squamous cell on 153 occasions and non-squamous cell on 63. The average tumor size was 5.3 (2.1) cm (range, 0.6-15). The affected lymph nodes were hilar (station 10) in 87 cases, interlobar (station 11) in 12 cases, lobar (station 12) in 110 cases, and segmental (station 13) in 7 cases. In 101 patients, only 1 lymph node was affected and more than 1 was affected in 115 patients.

Table 1 shows the variables and the estimated survival using the univariate method. We saw that tumor size affected survival since the prognosis was significantly worse for larger tumor sizes ($P = .04$) (Figure 2). Similarly, squamous cell histologic type was related to a significantly better prognosis ($P = .03$) (Figure 3). These 2 variables were the only ones to enter the regression model in the multivariable analysis (Table 2).

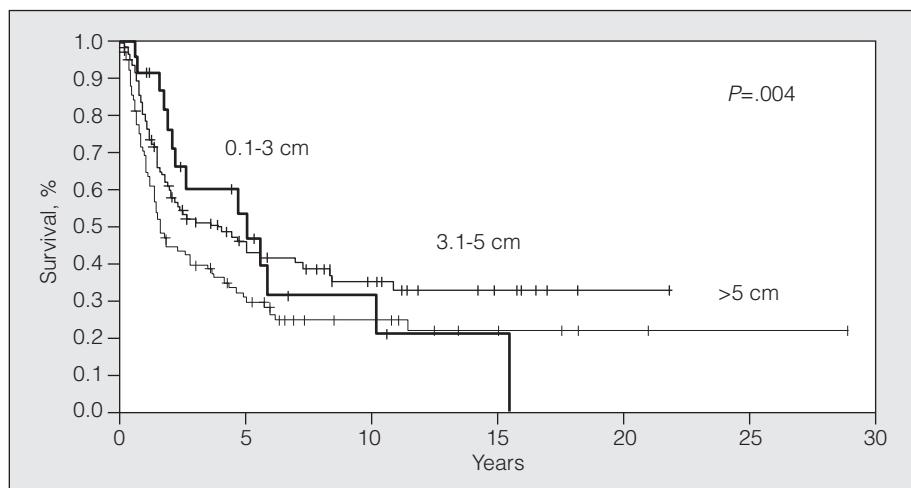


Figure 2. Survival and tumor size.

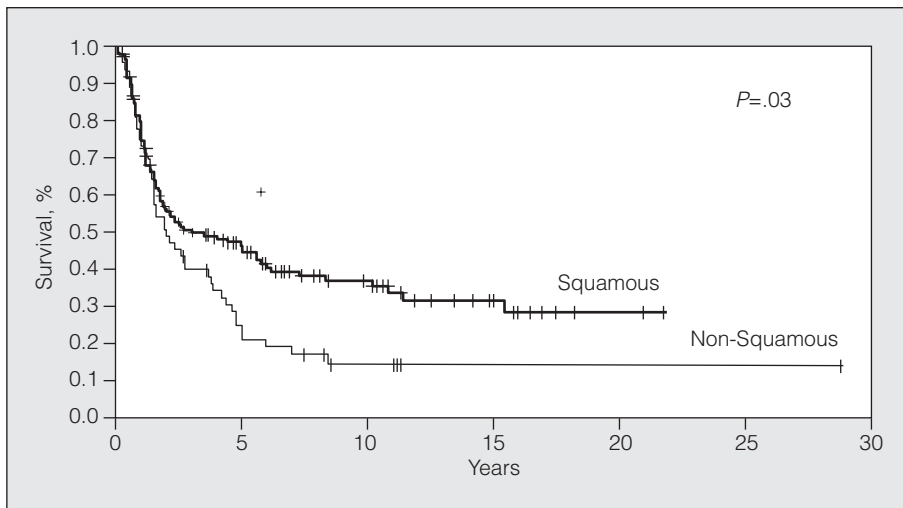


Figure 3. Survival and histologic type.

Discussion

In the current staging system, stage IIb covers a widely varying group of patients with one thing in common—surgery is still the treatment of choice for

them. In our study, the overall 5-year survival of patients with tumors classified as T2N1M0 was 39.85%, comparable to survival reported for other surgical series.²⁻⁷

As mentioned, most studies which assess the impact of non-mediastinal lymph node involvement on survival do so from the overall perspective of N1, independently of the degree of tumor invasion (T). Some authors agree that invasion of the pulmonary hilar (station 10) or interlobar (station 11) lymph nodes worsens prognosis in comparison with invasion of lobar (stations 12 and 13) nodes.⁹⁻¹¹

As a general rule, factors considered to indicate a poor prognosis are invasion of more than 1 lymph node, non-squamous cell type, and large tumor size.^{2,6,12,13} In an article exclusively on NSCLC cases classified as T2N1M0, van Velzen et al⁷ found using multivariate analysis that age over 60 years, lymph node involvement at station 10, and non-squamous cell type was associated with a worse prognosis. In our study, histologic type and tumor size influenced survival. Although invasion of more than a single lymph node was associated with a lower survival rate than when only one was affected, the difference was not significant.

Recently, Osaki et al¹² observed that if non-mediastinal lymph node involvement is detected before or during surgery (macroscopically), survival was equivalent to that of N2. However, when N1 was diagnosed by means of a postoperative histologic examination (microscopically), the prognosis was similar to that of N0.

For some authors, survival of patients with lymph node involvement at station 10 is closer to that of N2 and is significantly different from that of other stations that define N1.^{7,9-11} This has sometimes been considered to be the result of the existing limitations on anatomical classification of some lymph node stations, whereby mediastinal lymph nodes might be understaged as N1. Watanabe et al,¹⁴ in a recent study assessing interobserver variability, showed that a high percentage

TABLE 1
Variables and Survival. Univariate Analysis

Variable	No. of Patients	Survival at 5 Years, %	P
Sex			
Male	211	38	.69
Female	5	37.5	
Age, years			
≤60	90	45	.08
>60	126	36	
Symptoms			
Asymptomatic	48	31	.87
Symptomatic	168	39.5	
Resection			
Partial	125	37	.35
Pneumonectomy	91	45	
Histologic type			
Squamous	153	45.5	.03
Non-squamous	63	25	
Tumor diameter, cm			
0.1-3	23	53	.04
3.1-5	103	45	
>5	90	29	
No. of lymph nodes			
1	101	43	.28
>1	115	33.5	
Location of lymph nodes			
Hilar	129	39	.95
Non-hilar	87	39	

TABLE 2
Multivariable Analysis

Variable	Regression Coefficient	P
Histologic type	0.3958	.03
Size	0.0987	.02

Risk = histologic type × 0.3958 + size × 0.0987. Histologic type: squamous, 1; non-squamous, 2. Size in centimeters.

of patients (34.1%) classified as N1 by one observer were classified as N2 by another and vice versa. Station 10 was involved in all cases. Classic questions such as where the pulmonary hilum begins and the mediastinum ends remain unanswered.¹⁵ In our series, we found no difference in survival based on the location of the invaded lymph nodes.

There is no evidence that postoperative radiotherapy is of any benefit to these patients and, while it appears that the incidence of local recurrence can be reduced significantly, a meta-analysis has even shown that complementing surgery with radiotherapy had a significantly negative effect on survival.¹⁶ Similarly, adjuvant or neoadjuvant chemotherapy are not considered standard therapeutic practices and their use is reserved for patients enrolled in clinical trials.¹⁷⁻²⁰ As we have stated, none of our patients received treatment adjuvant to surgery.

To conclude, patients treated surgically for NSCLC classified as T2N1M0 have a 5-year survival probability of around 40%. This is not, however, a group of patients with a uniform prognosis as is shown in our series by the association between survival and tumor size and histologic type.

REFERENCES

- Grupo de Trabajo de la SEPAR. Normativa actualizada (1998) sobre diagnóstico y estadificación del carcinoma broncogénico. *Arch Bronconeumol.* 1998;34:437-52.
- Martini N, Burt M, Bains M, McCormack P, Rusch V, Ginsberg R. Survival after resection of stage II non-small cell lung cancer. *Ann Thorac Surg.* 1992;54:460-6.
- Mountain CF. Revision in the international staging system for lung cancer. *Chest.* 1997;111:1710-7.
- 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.
- 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.
- Calvo Medina V, Padilla Alarcón J, París Romeu F, Blasco Armengod E, Pastor Guillem J, García Zarza A. Supervivencia posquirúrgica en el estadio II del carcinoma broncogénico no anaplásico de células pequeñas. *Arch Bronconeumol.* 2001;37:19-26.
- van Velzen E, Snijder RJ, Brutel de la Rivière A, Elbers HJ, van den Bosch JM. Lymph node type as a prognostic factor for survival in T2N1M0 non-small cell lung carcinoma. *Ann Thorac Surg.* 1997;63:1436-40.
- 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.
- Yano T, Yokoyama H, Inoue T, Asoh H, Tayama K, Ichinose Y. Surgical results and prognostic factors of pathologic N1 disease in non-small-cell carcinoma. *J Thorac Cardiovasc Surg.* 1994;107:1398-402.
- Riquet M, Manac'h D, le Pimpec-Barthes F, Dujon A, Chehab A. Prognostic significance of surgical-pathologic N1 disease in non-small cell carcinoma of the lung. *Ann Thorac Surg.* 1999;67:1572-6.
- Marra A, Hillejan L, Zaboura G, Fujimoto T, Greschuchna D, Stamatis G. Pathologic N1 non-small cell lung cancer: correlation between pattern of lymphatic spread and prognosis. *J Thorac Cardiovasc Surg.* 2003;125:543-53.
- Osaki T, Nagashima A, Yoshimatsu T, Tashima Y, Yasumoto K. Survival and characteristics of lymph node involvement in patients with N1 non-small cell lung cancer. *Lung Cancer.* 2004;43:151-7.
- Sayar A, Turna A, Kilicgun A, Solak O, Urer N, Gurses A. Prognostic significance of surgical-pathologic multiple-station N1 disease in non-small cell carcinoma of the lung. *Eur J Cardiothorac Surg.* 2002;25:434-8.
- Watanabe S, Ladas G, Goldstraw P. Inter-observer variability in systematic nodal dissection: a comparison of European and Japanese nodal designation. *Ann Thorac Surg.* 2002;73:245-8.
- Asamura H, Suzuki K, Kondo H, Tsuchiya R. Where is the boundary between N1 and N2 stations in lung cancer? *Ann Thorac Surg.* 2000;70:1839-42.
- PORT Meta-analysis Trialists Group. Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials. *Lancet.* 1998;352:257-63.
- Non-small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. *BMJ.* 1995;311:899-909.
- The International Adjuvant Lung Cancer Trial Collaborative Group. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *N Engl J Med.* 2004;350:351-60.
- Pister KMW, Ginsberg RJ, Giroux DJ, Putnam JB, Kriss MG, Johnson DH, et al. Induction chemotherapy before surgery for early-stage lung cancer: a novel approach. *J Thorac Cardiovasc Surg.* 2000;119:423-39.
- Depierre A, Milleron B, Moro-Sibilot D, Chevret S, Quoix E, Lebeau B, et al. Preoperative chemotherapy followed by surgery compared with primary surgery in resectable stage I (except T1N0) II, and IIIa non-small cell lung cancer. *J Clin Oncol.* 2002;20:247-53.