Stage I Nonsmall Cell Lung Cancer up to 3 cm in Diameter: Prognostic Factors

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OBJECTIVE: To assess the prognostic value of a series of clinicopathological variables in stage I nonsmall cell lung cancer, for tumors up to 3 cm in diameter.

PATIENTS AND METHOD: The study included 271 patients. Survival was analyzed with the Kaplan-Meier method. The Cox model was used for multivariate analysis.

RESULTS: Five- and ten-year survival were 78.63% and 67.59%, respectively. Survival did not significantly depend on sex, age, extent of resection, histology, visceral pleural invasion, level of bronchial invasion or T1 versus T2. The decade in which resection was performed did affect survival (*P*=.0037). Five-year survival was 58% for operations between 1970 and 1980, 77% for operations between 1981 and 1990, and 84% for operations between 1991 and 2000. Tumor size also affected survival (*P*=.0046), which was 86% for patients with tumors of less than or equal to 2 cm in diameter and 73% for those with tumors of more than 2 cm in diameter. In the multivariate analysis both variables entered into regression, remaining predictive of survival.

CONCLUSION: We found evidence for a prognostic stage migration (Will Rogers phenomenon) according to the decade in which resection was performed and that tumor size affected survival in our population. Finally, the current system of TNM staging fails in conforming groups of patients with a homogenous prognosis.

Key words: *Nonsmall cell lung cancer. Stage I. Surgery. Time trend. Tumor size.*

Carcinoma broncogénico no anaplásico de células pequeñas en estadio I y de diámetro máximo de 3 cm. Factores pronósticos

OBJETIVO: Valorar el papel pronóstico de una serie de variables clínico-patológicas en el carcinoma broncogénico no anaplásico de células pequeñas con un tamaño máximo de 3 cm y clasificado en estadio I.

PACIENTES Y MÉTODO: Se estudió a 271 pacientes. La supervivencia se analizó con el método de Kaplan-Meier. Para el análisis multivariante se utilizó el modelo de Cox.

RESULTADOS: La supervivencia fue del 78,63 y el 67,59% a los 5 y 10 años, respectivamente. El sexo, la edad, la amplitud de exéresis, la estirpe histológica, la invasión de la pleura visceral, el grado de invasión bronquial y T1-T2 no influyeron significativamente en la supervivencia. La década en que el paciente fue operado condicionó la supervivencia (p = 0,0037), que a los 5 años fue del 58% para los intervenidos entre 1970 y 1980, del 77% para los operados entre 1981 y 1990 y del 84% para los sometidos a la intervención entre 1991 y 2000. El tamaño tumoral también condicionó la supervivencia (p = 0,0046), que fue del 86% para los pacientes con tumores con un diámetro inferior o igual a 2 cm y del 73% para los que tenían tumores con diámetro de más de 2 cm. Ambas variables entraron en regresión cuando se utilizó el análisis multivariante.

CONCLUSIÓN: Hemos comprobado una migración pronóstica (fenómeno de Will Rogers) en relación con la década en que el paciente fue operado *(time trend)* y que el tamaño tumoral condicionó la supervivencia de nuestra serie. Por último, el sistema vigente de estadificación TNM es deficiente en la configuración de grupos de pacientes con un pronóstico homogéneo.

Palabras clave: *Carcinoma broncogénico. Estadio I. Cirugía. Tendencia temporal. Tamaño.*

Introduction

Interest in early diagnosis of bronchogenic carcinoma has been renewed recently because of the high prevalence of this type of cancer in the general population.[1-3]

Patz et al[4] have questioned the usefulness of early detection programs because tumor size did not affect survival in their extensive study population of patients who underwent surgical removal of stage IA nonsmall cell lung cancer (NSCLC). However, aspects of their study design[5] and the 18-year study period[6] have been criticized.

The effectiveness of programs for early detection of bronchogenic carcinoma remains unclear.[2,7] This debate notwithstanding, the objective of our study was to assess

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the affect of tumor size and the decade in which the operation was performed on the prognosis for stage I NSCLC up to 3 cm in diameter.

Patients and Method

From 1970 to 2000, 276 patients with stage I NSCLC up to 3 cm in diameter underwent complete resection. TNM classification followed the new guidelines proposed by the SEPAR.[8] Five patients (1.8%) died in the postoperative period and were excluded from the study. The remaining 271 patients underwent resection of all cancerous tissue, that is, there was no macro- or microscopic invasion at the resection borders. Our surgical procedure remained the same throughout the study. We removed only palpably enlarged or macroscopically visible lymph nodes. Patients who were classified as N0 therefore had no evidence of involved lymph nodes during the operation or, if lymph nodes with possible involvement were removed, the histological study showed they were not invaded. Surgery was the only treatment that patients received.

The sex, age, date of resection (decade), extent of pulmonary exeresis performed, histology, tumor diameter, visceral pleural invasion, degree of bronchial invasion, and tumoral invasion (T category) were the variables selected retrospectively for the survival analysis.

The Kaplan-Meier method was used to calculate survival. Survival curves were compared with the log rank test and the trend test, when necessary. The cut-off points for continuous variables (60 years for age, and 1 and 2 cm for tumor size) were arbitrarily selected. The Cox proportional hazards model was used for multivariate analysis of variables showing significance at $P<.05$ in the univariate analysis.

Results

Overall survival in our population was 78.63% after 5 years and 67.59% after 10 years (Figure). At the time of the study, 49 patients had died due to NSCLC, 18 due to a second lung tumor, 2 due to unknown causes, 63 due to causes other than NSCLC, and 10 were lost to follow up. Thus 129 patients were confirmed to be still alive.

Of the patients included, 250 (92%) were men and 21 (8%) were women. The mean age was 61.31 (SD 8.8) years (range, 36-81 years). Fifty patients (18%) required pneumonectomy and 221 (82%) partial lung resection (19 segmentectomies, 186 lobectomies, and 16 bilobectomies). The tumor removed was epidermoid in 172 (63%) patients and nonepidermoid in 99 (37%). Twenty-eight patients (10%) underwent surgery in the seventies, 97 (36%) in the eighties, and 146 (54%) in the nineties. The mean tumor size was 2.31 (SD 0.73) cm (range, 0.1-3 cm). In 41 tumors (15%), histological examination showed visceral pleural invasion. Endoscopy revealed a tumor proximal to a lobar bronchus but more than 2 cm from the carina in 72 patients (29%). There were 167 T1 tumors (62%) and 104 T2 tumors (38%).

Table 1 shows the variables and survival estimates according to the univariate analysis. We found significant differences in prognosis according to the decade when the operation was performed ($P=.0037$). Likewise, tumor size affected survival, such that prognosis was significantly worse with increasing tumor size ($P=.0194$ for tumors ≤1 cm and $P=.0046$ for tumors ≤2 cm). The remaining variables did not significantly affect survival (Table 2).

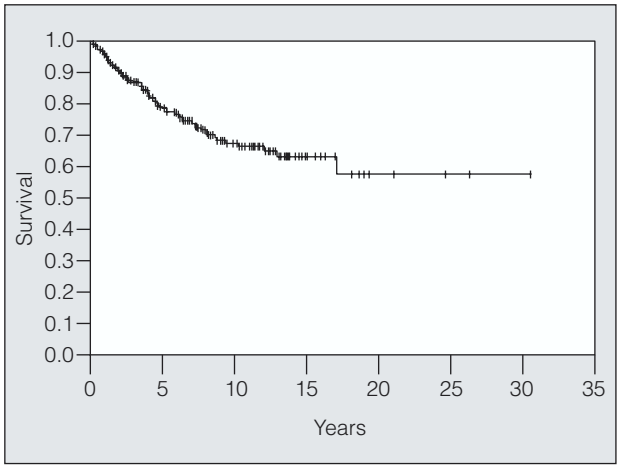

Figure. Overall Survival of the Population.

TABLE 1
Variables and Survival. Univariate Analysis

Variable	No. patients	5-Year Survival	*P*
Sex			
Male	250	80%	
Female	21	60%	.2090
Age			
≤60 years	123	79%	
>60 years	148	78%	.7237
Period, decade			
1970-1980	28	58%	
1981-1990	97	77%	
1991-2000	146	84%	.0037
Exeresis			
Partial	221	77%	
Total	50	84%	.1086
Histology			
Squamous	172	82%	.1667
Nonsquamous	99	71%	
Tumor size			
0.1-1 cm	25	88%	.0194
1.1-2 cm	85	86%	
2.1-3 cm	161	73%	
Tumor diameter			
≤2 cm	110	86%	.0046
>2 cm	161	73%	
Visceral pleural invasion			
No	230	81%	.0836
Yes	41	64%	
Degree of bronchial invasion			
Distal	208	77%	.1413
Proximal	63	84%	
Tumoral invasion			
T1	167	79%	.8587
T2	104	77%	

TABLE 2
Multivariate Analysis

Variable	Coefficient of Regression	*P*
Period*	–0.4951	.0043
Size, cm	0.5029	.0105

Risk = Period × –0.4951 + Size × 0.5029.
*Period: 1970-80=1; 1981-90=2; 1991-2000=3.

Discussion

Surgery remains the treatment of choice for NSCLC. Prognosis is closely linked to tumor size. The survival rates presented correspond to a large patient population over a long period,[9-12] and an improvement over time is apparent.[13-15] Our findings can be described by the so-called "Will Rogers phenomenon." This term was coined by Feinstein[16] who observed a prognostic migration with a significant trend towards better results over time, perhaps because of technological advances. The systematic use of computed tomography for preoperative study in our hospital since 1981 has meant that clinical staging has come to approximate pathological staging more closely.

Despite regular reviews of the staging system for NSCLC, a tumor size of 3 cm remains the cut-off between T1 and T2 classification, though some authors have questioned this classification and preferred a cut-off of 2 cm. Survival studies in patients with tumors classified as T1N0M0 have rarely investigated the influence of tumor size on survival so the information available is limited and contradictory. Read et al[17] found that patients with a tumor size equal to or less than 2 cm had a better prognosis than patients with tumor sizes between 2.1 and 3 cm. They therefore suggested that a new category should be introduced for these patients, thus tumor sizes up to 2 cm would be T1/2 and tumor sizes between 2.1 and 3 cm would be T1. Other authors have reported similar findings.[18,19] In contrast, Patz et al[4] did not find any influence of tumor size on survival in stage IA though, as mentioned in the introduction, the study design has been questioned.[5,6] First, surprisingly few patients died—only 12% of a population of 510 patients classified as stage IA and enrolled in the study between 1981 and 1999. In our 30-year study, 52% of patients died, a figure that is closer to the findings of other authors such as Machiarini et al[20] (mortality of 32% in 95 patients who underwent surgery over 11 years). More importantly, Patz et al do not report cause of death, which must be defined if we wish to determine the usefulness of surgery in prolonging patient survival. Consistent with other studies,[21] we found that 23% of deaths were unrelated to NSCLC and 4% of patients were lost to follow up. These cases were treated as censored data for the purpose of the survival calculation.

Some authors have found that visceral pleural invasion significantly affects survival in stage I tumors,[22,23] though Martini et al[24] observed an effect only with large tumors. In a previous study, we found that visceral pleural invasion did not affect survival in 154 patients classified as stage I with a tumor diameter up to 3 cm.[25]

Any tumor proximal to a lobar bronchus at more than 2 cm from the carina or which causes atelectasis is classified as T2, regardless of tumor size. Few studies have investigated the effect of endobronchial site on prognosis. Naruke et al[26] and Watanabe et al[27] found that patients with small tumors in the main bronchus at less than 2 cm from the carina and with no lymph node involvement had a survival of 80% after 5 years. This calls into question the use of bronchial location in defining the T category; indeed we found no significant difference in survival according to endobronchial site in a previous study.[25]

We have confirmed our findings from earlier studies[25,28,29] that the TNM staging system is of little use for determining prognosis, given that visceral pleural invasion, the degree of bronchial invasion, and, therefore, the degree of tumoral invasion (T category) do not significantly affect survival.

To conclude, we found evidence for a prognostic stage migration (Will Rogers phenomenon) according to the decade in which resection was performed and that tumor size affected survival in our population. Finally, the current system of TNM staging fails in conforming groups of patients with a homogenous prognosis.

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