Trends in Prognostic Factors for Neuroendocrine Lung Tumors

Mariano García-Yuste,[a] Laureano Molins,[b] José M. Matilla,[a] Federico González-Aragoneses,[c] Javier López-Pujol,[d] Guillermo Ramos,[a] Mercedes de la Torre,[e] and members of the Spanish Multicenter Study of Neuroendocrine Lung Tumors of the Spanish Society of Pulmonology and Thoracic Surgery (EMETNE-SEPAR)*

[a]Servicio de Cirugía Torácica, Hospital Clínico Universitario, Valladolid, Spain
[b]Servicio de Cirugía Torácica, Hospital Sagrado Corazón, Barcelona, Spain
[c]Servicio de Cirugía Torácica, Hospital Gregorio Marañón, Madrid, Spain
[d]Servicio de Cirugía Torácica, Hospital Reina Sofía, Córdoba, Spain
[e]Servicio de Cirugía Torácica, Hospital Juan Canalejo, A Coruña, Spain

OBJECTIVE: The aim of this study was to analyze trends in a variety of prognostic factors for neuroendocrine lung carcinomas through analysis of 2 groups of surgically treated patients.

PATIENTS AND METHODS: Group A contained the first 361 patients, treated between 1980 and 1997. That group was analyzed retrospectively and contained 261 patients with typical carcinoid tumors, 43 with atypical carcinoid tumors, 22 with large-cell neuroendocrine carcinoma, and 35 with small-cell neuroendocrine carcinoma. Group B contained 404 patients enrolled prospectively between 1998 and 2002: 308 with typical carcinoid tumors, 49 with atypical carcinoid tumors, 18 with large-cell neuroendocrine carcinoma, and 29 with small-cell neuroendocrine carcinoma. The following clinical variables were considered: sex, mean age, tumor site, tumor size, lymph node involvement, stage, metastasis, and local recurrence. The 1997 TNM classification was used for staging of lung cancer and survival analysis was performed along with assessment of factors influencing survival. Statistical analysis of the data involved univariate and multivariate analysis.

RESULTS: In both groups, significant differences were observed between patients with typical and atypical carcinoid tumors in terms of mean age, tumor size, node involvement, and recurrence. In group A, female sex, node involvement, and recurrence differed between patients with atypical carcinoid tumors and those with large-cell neuroendocrine carcinoma; the same was true for group B, with the exception of lymph node involvement. Node involvement differed between patients with small-cell versus large-cell neuroendocrine carcinoma in group A but not group B.

Both groups displayed significant differences in overall survival and survival of patients with lymph node involvement between patients with typical and atypical carcinoid tumors and between patients with atypical carcinoid tumors and those with large-cell neuroendocrine carcinoma; no differences were observed between patients with large-cell versus small-cell neuroendocrine carcinoma. Histological type and lymph node involvement had the greatest influence on prognosis in the multivariate analysis.

CONCLUSIONS: A well-defined trend is observed in prognostic factors for neuroendocrine lung tumors. Histological type and lymph node involvement show the greatest influence on survival.

Key words: *Neuroendocrine lung tumor. Staging. Mediastinal lymph node excision.*

Tendencias en los factores pronósticos de los tumores pulmonares neuroendocrinos

OBJETIVO: Este estudio tiene como objetivo determinar la tendencia de distintos factores pronósticos en carcinomas neuroendocrinos del pulmón a través del análisis de 2 grupos de pacientes tratados quirúrgicamente.

PACIENTES Y MÉTODOS: En el grupo A se incluyeron los primeros 361 casos, tratados entre 1980 y 1997 —261 carcinoides típicos (CT), 43 carcinoides atípicos (CA), 22 carcinomas neuroendocrinos de células grandes (CNECG) y 35 carcinomas neuroendocrinos de células pequeñas (CNECP)—, que se estudiaron retrospectivamente. El grupo B estuvo compuesto por 404 casos, recogidos desde 1998 a 2002 —308 CT, 49 CA, 18 CNECG y 29 CNECP—, que se estudiaron prospectivamente. Las variables clínicas consideradas fueron: sexo, edad media, localización tumoral, tamaño tumoral, afectación ganglionar, estadio, metástasis y recurrencia local. Se utilizó la clasificación TNM del carcinoma broncogénico de 1997 y se practicó un estudio de supervivencia y de factores que influyen en ella. Se realizó un análisis estadístico uni y multivariante con los datos obtenidos.

RESULTADOS: Por lo que se refiere al CT y al CA, se observaron diferencias significativas en los 2 grupos de pacientes en cuanto a la edad media, el tamaño tumoral, la afectación ganglionar y la recurrencia. Entre CA y CNECG, el sexo, la afectación ganglionar y la recurrencia difirieron en el grupo A; lo mismo ocurrió en el grupo B, con la excepción de la afectación ganglionar. Entre CNECG y CNECP, la diferencia en la afectación ganglionar observada en el grupo A no estuvo presente en los pacientes del grupo B. Respecto a la supervivencia, global y por afectación ganglionar, se observaron diferencias significativas en ambos grupos al comparar CT frente a CA y CA frente a CNECG; no se encontraron diferencias entre CNECG y CNECP. El tipo histológico y la afectación ganglionar mostraron la mayor influencia pronóstica en análisis multivariante.

CONCLUSIONES: En los carcinomas neuroendocrinos de pulmón se observa una tendencia definida en sus factores pronósticos. El tipo histológico y la detección de afectación ganglionar se muestran como los factores con mayor influencia en la supervivencia.

Palabras clave: *Tumor pulmonar neuroendocrino. Estadificación. Disección ganglionar mediastínica.*

*The names of the EMETNE-SEPAR members are provided at the end of the article.

Correspondence: Dr. M. García-Yuste. Servicio de Cirugía Torácica. Hospital Clínico Universitario. Ramón y Cajal, 3. 47005 Valladolid. España.
E-mail: mgyuste2@wanadoo.es

Manuscript received October 5, 2006. Accepted for publication November 22, 2006.

Introduction

In the last 5 years, various studies have been undertaken to analyze the results of treatment for neuroendocrine lung tumors.[1-4] In 2000, we published the results of a retrospective analysis of our experience with 361 cases treated surgically between 1980 and 1997.[5] Subsequently, the Spanish Multicenter Study of Neuroendocrine Lung Tumors of the Spanish Society of Pulmonology and Thoracic Surgery (EMETNE-SEPAR) prospectively analyzed 404 new cases between 1998 and 2002. The aim of this study was therefore to analyze trends in prognostic factors in these types of tumor by comparing data from the initial period with those from cases identified and treated during the second period.

Patients and Methods

Two groups of patients were established: group A, containing the first 361 cases—261 typical carcinoid tumors, 43 atypical carcinoid tumors, 22 large cell neuroendocrine carcinomas, and 35 small cell neuroendocrine carcinomas—obtained retrospectively between 1980 and 1997; and group B, containing 404 new cases—308 typical carcinoid tumors, 49 atypical carcinoid tumors, 18 large cell neuroendocrine carcinomas, and 29 small cell neuroendocrine carcinomas—collected prospectively between 1998 and 2002. The pathologists reviewed and classified all of the tumor samples according to the 1999 World Health Organization (WHO) classification, including the new criteria developed by Travis for the classification of atypical carcinoid tumors.[4] All patients were studied using the same protocol based on information from clinical follow-up and pathology reports. The mean follow-up was 93 months (range, 12-273 months) in group A and 39 months (range, 12-81 months) in group B. In addition, data were collected on survival and tumor recurrence in both groups.

In all cases appropriate complete surgical resection of the tumor was performed. The following variables were considered in analysis of the 2 groups: sex, mean age, tumor site (central or peripheral), tumor size, lymph node involvement, and pathological stage according to the TNM classification of the International Union Against Cancer (UICC).[6] Survival data were obtained from the clinical notes of the periodic follow-up of the patients in each hospital. The incidence and the percentage of metastasis and local recurrence were determined along with the cause of death in patients who died during follow-up.

TABLE 1
Distribution of Tumors According to Stages in 1980-1997 (Group A) and 1998-2002 (Group B)*

	Groups	TC	AC	LCNEC	SCNEC
No. of patients	A	261%	43	22	35
	B	308%	49	18	29
Stages					
Ia	A	23.7%	13.9%	13.6%	20.0%
	B	47.7%	20.4%	27.8%	20.7%
Ib	A	65.9%	48.8%	31.9%	34.3%
	B	37.7%	32.6%	27.8%	24.2%
IIa	A	0.4%	4.7%	4.5%	0.0%
	B	2.7%	0.0%	0.0%	0.0%
IIb	A	6.5%	16.3%	36.4%	25.7%
	B	6.8%	14.3%	5.6%	13.8%
IIIa	A	2.7%	9.3%	13.6%	17.1%
	B	4.2%	22.5%	33.2%	37.9%
IIIb	A	0.8%	4.7%	0.0%	2.9%
	B	0.3%	2.1%	5.6%	3.4%
IV	A	0.0%	2.3%	0.0%	0.0%
	B	0.6%	8.1%	0.0%	0.0%

*TC indicates typical carcinoid; AC, atypical carcinoid; LCNEC, large cell neuroendocrine carcinoma; SCNEC, small cell neuroendocrine carcinoma.

Statistical Analysis

Statistical analysis was performed using version 12.0 of the Statistical Package for Social Sciences. The Student *t* test or, where necessary, the Mann-Whitney U test were used for comparison of numeric variables with binary variables. Comparison of numeric variables with categorical variables of more than 2 categories was performed by 1-way analysis of variance (ANOVA); when the result of ANOVA was significant, subsequent comparisons were made using the Duncan test. The Kaplan-Meier method was used to analyze survival.

The log-rank test and Breslow test were used for comparison of survival curves according to the different factors. Multivariate analysis was performed by linear regression to identify the prognostic factors with the most significant influence on survival. A value of $P \leq .05$ was considered statistically significant.

Results

Typical Carcinoid Tumors

A typical carcinoid tumor was diagnosed in 261 patients (72.3%) from group A and 308 patients (76.3%) from group B. In both groups, 44% of the patients were men and 56% women. Likewise, the mean age was 47 years in both groups. The mean tumor size in group A was 26.6 mm, very similar to that observed in group B (24.9 mm). The site of the tumor was central in 73% and peripheral in 27% of patients from group A, whereas in group B the rates were 63% and 37%, respectively. Lymph node metastases were found in 11 patients (4.1%) from group A (10 N1 and 1 N2) and 41 (13.3%) from group B (22 N1 and 19 N2). Table 1 shows the distribution of stages in both groups according to the 1997 TNM classification.

In terms of analysis of mortality, 12 patients from group A and 5 from group B died as a result of causes unrelated to the tumor. Of all the patients studied, 9 (1.6%) had distant metastases: 5 in group A (4 in stage I—2 in stage Ia and 2 in stage Ib—and 1 in stage IIIa) and 4 in group B (3 in stage Ia and 1 in stage Ib) at 11, 12, 21, 23, 24, 36, 56, 59, and 98 months after surgery. Following chemotherapy, 5 were still alive 18, 30, 73, 79, and 115 months later and 4 died as a result of recurrence of metastasis. Of all the patients, 6 presented local recurrence: 2 patients in group A had recurrence at 23 and 60 months after surgery and died at 40 and 69 months, following radiation therapy; the other 4 patients, treated after 1997 (group B), are currently alive at 18, 19, 42, and 84 months.

Survival at 5-year and 10-year follow-up (Figure 1) was 96% and 93%, respectively, in group A, and 98% at 5 years in group B (patients in that group have not yet completed 10 years of follow-up).

Atypical Cazrcinoid Tumors

Atypical carcinoid tumors were diagnosed in 43 patients from group A (11.9%) and 49 from group B (12.1%). The

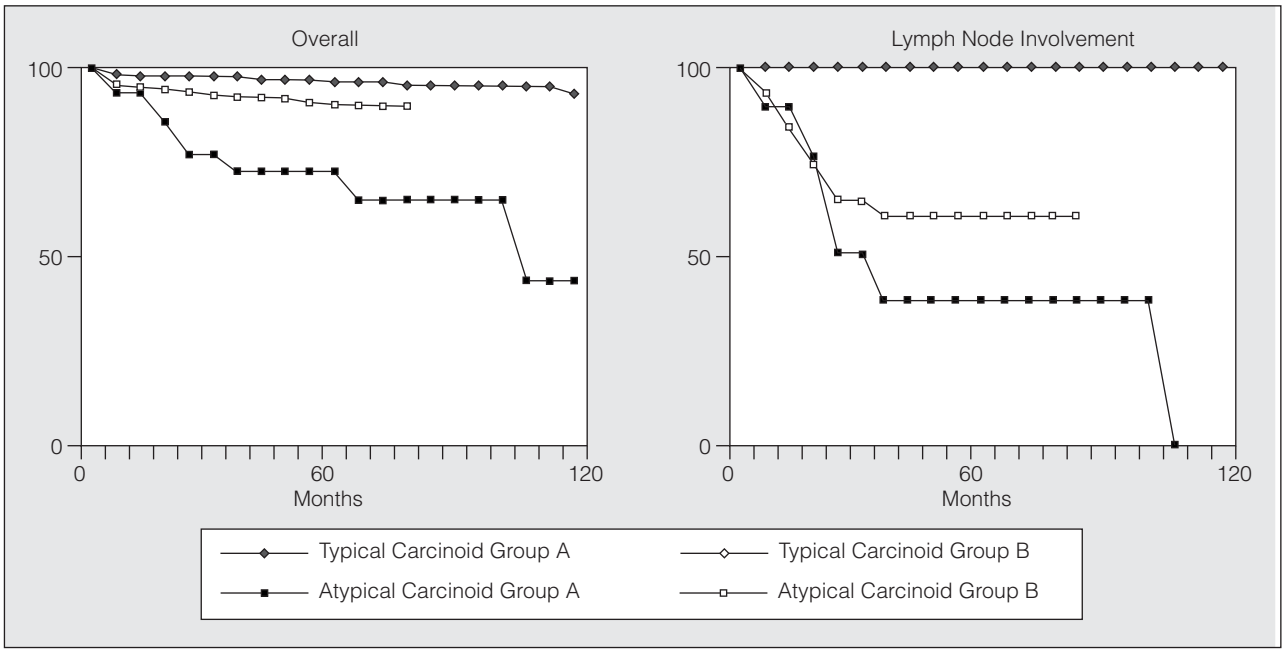

Figure 1. Kaplan–Meier analysis of overall survival and survival of patients with lymph node involvement for patients with either typical or atypical carcinoid tumors in groups A and B.

percentages of men and women in those groups were 47% and 53%, respectively, in group A, and 65% and 35%, respectively, in group B. The mean age was 56 years in group A and 53 years in group B. Central and peripheral tumors were observed in, respectively, 65% and 35% of patients in group A and 49% and 51% of patients in group B. The mean size of the tumor was 36.5 mm in group A and 33.1 mm in group B. Lymph node involvement was observed in 10 patients (23.3%) from group A (6 N1 and 4 N2) and 23 of the 49 patients from group B (46.9%; 8 N1 and 15 N2). Classification according to tumor stage in both groups is shown in Table 1. Following definitive staging, all patients with N2 lymph node involvement received adjuvant mediastinal radiotherapy following surgery.

During follow-up, 4 patients from group A died due to unknown causes. Distant metastasis was observed in 11 patients and local recurrence in 1. Nine of the patients with distant metastasis died as a result and 2 are currently alive after 48 and 72 months of follow-up; the patient with local recurrence is currently alive after radiotherapy at 101 months. Five patients from group B presented metastasis during follow-up. Three died as a result of the metastasis and the other 2 are currently alive at 45 and 54 months. Local recurrence following treatment was observed in 2 patients: the first is currently alive at 79 months and the other died as a result of the local recurrence.

Statistical comparisons of a number of variables were made between patients in groups A and B with typical and atypical carcinoid tumors (Table 2).

The probability of survival in group A was 72% and 43% at 5 and 10 years, respectively, and in group B it was 90% at 5 years (patients in that group have not yet completed 10 years of follow-up). Analysis of survival according to tumor stage revealed a significant difference between groups A and B. Comparison of the survival of patients with typical carcinoid tumors with that of patients with atypical carcinoid tumors showed that survival was significantly lower in patients with atypical tumors than in those with typical tumors in both groups ($P<.001$ and $P=.009$, respectively). Similar results were obtained for the probability of survival in patients with lymph node involvement ($P=.012$ and $P=.001$) (Figure 1).

Large Cell Neuroendocrine Carcinoma

Twenty-two patients (6.1%) from group A and 18 (4.4%) from group B were surgically treated for large cell neuroendocrine carcinomas. The percentages of men and women were, respectively, 77% and 23% in group A and 89% and 11% in group B. The mean age was 67 and 66 years in groups A and B, respectively. The mean size of the tumor was 38.4 mm in group A and 45.6 mm in group B. In both groups, 33% of the tumors were central and 67% peripheral.

The pathologic node stage for patients in group A was N0 in 13 cases (59.1%), N1 in 5 (22.7%), and N2 in 4 (18.2%), and for patients in group B it was N0 in 10 (55.6%), N1 in 2 (11.1%), and N2 in 6 (33.3%). Classification according to tumor stage is shown in Table 1. Postoperative adjuvant therapy was administered with chemotherapy, radiotherapy, or both in those patients with a pathological stage higher than Ib. During follow-up, 16 of the 40 patients presented metastasis and another 3 local recurrence. Twenty-one patients died during follow-up, 7 from other causes and 14 due to recurrence of the disease. Currently, 17 are alive, 3 with signs of local recurrence or distant metastasis; 2 patients were lost to follow-up.

Table 2 shows statistical analysis for comparison of different variables in atypical carcinoid tumors and large cell neuroendocrine carcinomas in patients from groups A and B.

TABLE 2.
Trends in Prognostic Factors for Neuroendocrine Lung Tumors in 1980-1997 (Group A, n=361) and 1998-2002 (Group B, n=404)*

	Group	TC	AC	*P* TC/AC	LCNEC	*P* AC/ LCNEC	SCNEC	*P* LCNEC/ SCNEC
No. of patients	A	261	43		22		35	
	B	308	49		18		29	
Mean age, y	A	47	56	.001	67	.3	63	.17
	B	47	53	.081	66	.001	60	.03
Women, %	A	56	53	.89	23	.02	3	.002
	B	56	35	.044	11	.036	10	.643
Mean tumor size, mm	A	26.6	36.5	.004	38.4	.8	36.5	.42
	B	24.9	33.1	.000	45.6	.024	38.1	.194
Lymph node involvement	A	11 (4.1%)	10 (23.3%)	<.001	9 (40.9%)	.02	7 (20.0%)	.002
	B	41(13.3%)	23 (46.9%)	.002	8 (44.5%)	.37	15 (51.7%)	.518
Metastasis	A	5 (1.5%)	9 (20.9%)	<.001	10 (45.5%)	.001	23 (65.7%)	.19
	B	4 (1.3%)	7 (14.3%)	.002	6 (33.3%)	.023	6 (20.7%)	.59
Local recurrence	A	2 (0.7%)	1 (2.3%)	.09	3 (13.6%)	.69	1 (2.9%)	.29
	B	4 (1.3%)	2 (4.1%)	.19	0 (0.0%)	.38	0 (0.0%)	–

*AC indicates atypical carcinoid; LCNEC, large cell neuroendocrine carcinoma; SCNEC, small cell neuroendocrine carcinoma; TC, typical carcinoma.

Five-year survival in patients from group A was 20.8%. Survival was 33% for patients in stage I, whereas no patients survived more than 18 months in stages II and IIIa. Survival at 3 years in group B was 38%. No patients in stages IIIa and IIIb survived beyond 33 months. Comparison of survival between patients with atypical carcinoid tumors and large cell neuroendocrine carcinomas revealed a statistically significant difference between the 2 types of tumor in both groups (*P*=.05 and *P*=.001). When survival of patients with lymph node involvement was compared for these types of tumor, a significant difference was observed for both study groups (*P*=.04 and *P*=.011) (Figure 2).

Small Cell Neuroendocrine Carcinoma

Thirty-five patients in group A (9.7%) and 29 in group B (7.2%) were treated surgically for small cell neuroendocrine carcinomas, most of them in stage I. The percentages of men and women were, respectively, 97% and 3% in group A and 90% and 10% in group B. The mean age was 63 years in group A and 60 years in group B. The mean size of the tumor was 36.5 mm in group A and 38.1 mm in group B. The tumors were central in 47% of patients from group A and 45% of patients from group B. In patients from group A with lymph node involvement, 1 was classified as N1 (2.9%) and 6 as N2 (17.1%); in group B, 4 were N1 (13.8%) and 11 N2 (37.9%). Classification according to tumor stage in both groups is shown in Table 1. All patients received postoperative radiotherapy and chemotherapy. During follow-up, out of a total of 64 patients, 30 displayed tumor recurrence; 25 died as a result of recurrence and 13 due to other causes.

A number of variables were compared between patients with small cell neuroendocrine carcinoma and those with large cell neuroendocrine carcinoma. The statistically significant differences in groups A and B are shown in Table 2.

The survival at 3 and 5 years in group A was 35% and 17%, respectively. Three-year survival in patients from group B was 39%. In patients with lymph node involvement, 3-year survival was 12% in group A and 14% in group B; none of those patients lived to 5 years. In both groups, no differences in survival were observed between patients with large cell neuroendocrine carcinoma and those with small cell neuroendocrine carcinoma (*P*=.93 and *P*=.81). Similar results were obtained when survival of patients with lymph node involvement was compared (*P*=.82 and *P*=.831) (Figure 3).

Finally, multivariate analysis was performed to identify the most significant prognostic factors that influenced survival in patients with neuroendocrine lung tumors. Histological type showed the most significant influence on survival in both groups (*P*=.006 for group A and *P*=.004 for group B). In addition, lymph node involvement was significant both in group B (*P*=.011) and groups A and B together (*P*<.001) (Table 3).

Discussion

Building on our earlier experience,[5] we considered this study to be warranted in order to analyze the same prognostic factors in both groups of patients (retrospective and prospective analysis), on the basis that there was sufficient homogeneity in terms of number and type of tumors in both groups, and since such an analysis would allow trends to be identified in different clinical and treatment-related factors along with their effect on prognosis.

Based on the recent study by Travis et al[1] addressing the correlation between histological type and clinical prognosis in carcinoid tumors, the WHO classification has accepted stricter criteria for histological classification of typical and atypical carcinoids.[7] The reduction in the lower limit for number of mitoses from 5 to 2 per 10 high-power

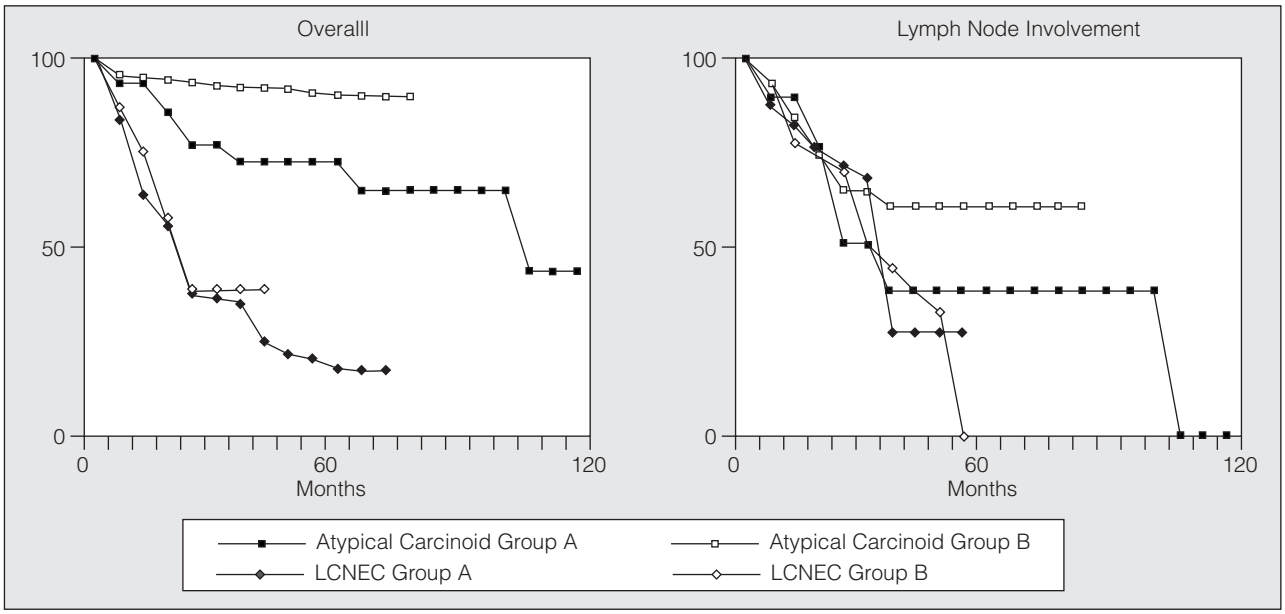

Figure 2. Kaplan–Meier analysis of overall survival and survival of patients with lymph node involvement for patients with atypical carcinoid tumors and large cell neuroendocrine carcinomas (LCNEC) in groups A and B.

TABLE 3
Influence of Prognostic Factors on Survival of Patients Diagnosed With Neuroendocrine Lung Tumors in 1980-1997 (Group A) and 1998-2002 (Group B): Multivariate Analysis by Multiple Regression

	Group		
	A	B	A and B
No. of patients	361	404	765
Size of the tumor	.640	.274	.501
Lymph node involvement	.507	.011	<.001
Histologic type	.006	.004	<.001

fields or the presence of necrosis define the new histological concept of atypical carcinoid tumors. In addition, based on the high incidence of metastasis and local recurrence following surgical resection, both large cell and small cell neuroendocrine carcinomas are now recognized as highly malignant tumors with a poor prognosis.[7,8] On this basis, we undertook a histological review of all of the cases included in the study, both retrospectively and prospectively, to determine their definitive histological classification and facilitate the analysis proposed in this study.

There were no significant differences between the groups in terms of the demographic characteristics of the patients.

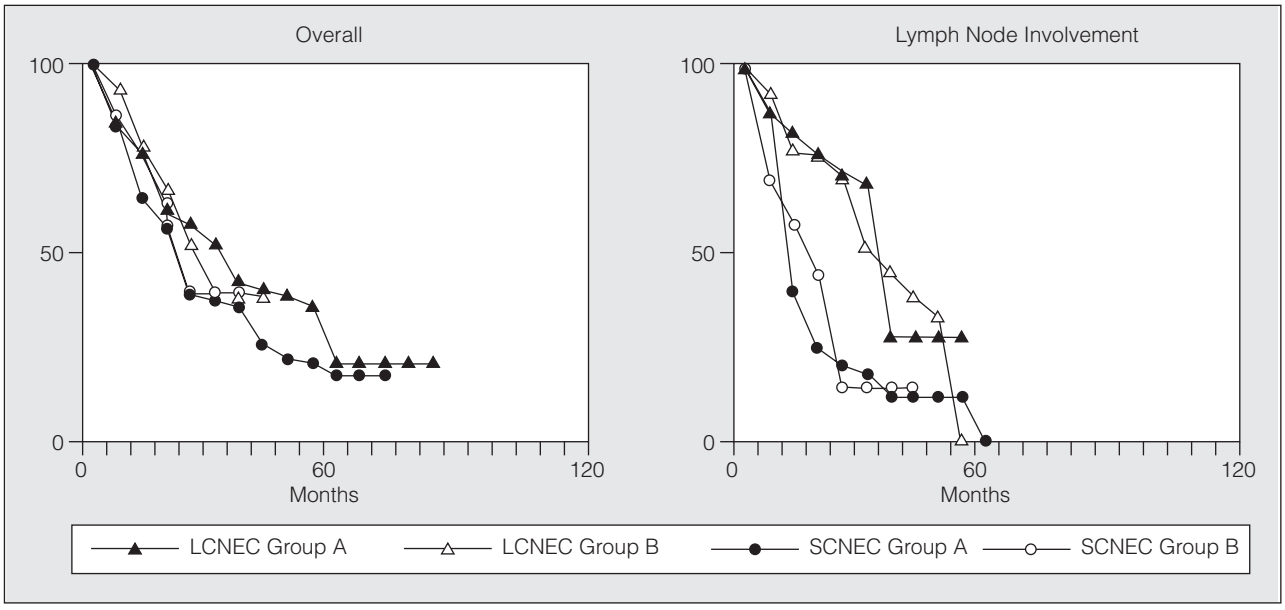

Figure 3. Kaplan–Meier analysis of overall survival and survival of patients with lymph node involvement for patients with large cell neuroendocrine carcinomas (LCNEC) and small cell neuroendocrine carcinomas (SCNEC) in groups A and B.

In terms of sex differences, the rate of typical carcinoid tumors in men and women remained constant, whereas there was an increase in the percentage of atypical carcinoid tumors in men, although this difference was not statistically significant. The number of women with large cell or small cell neuroendocrine carcinoma was significantly lower than the number with carcinoid tumors in both study groups. These findings confirm the relationship between malignancy and incidence in men for these types of tumor. In terms of age, the number of patients analyzed allowed clear confirmation of the relationship between increased age, histological deterioration, and aggressiveness of the tumor.

The number of patients included in the study sample also allowed us to confirm that the percentages of central and peripheral tumors remained constant. However, a significant increase was observed in the percentage of peripheral atypical carcinoid tumors in the patients studied prospectively, and this provided further confirmation of the difference in the tendency towards peripheral localization between typical and atypical carcinoids. The increase in the number of peripheral tumors with higher histological malignancy in large cell and small cell neuroendocrine carcinomas confirms the findings of other authors[4,6]; nevertheless, this tendency should be analyzed carefully when the patients considered have been treated surgically. In our opinion, the predominance of peripheral localization is related in part to the limited possibility of surgical treatment in central tumors, a limitation derived from the frequent association of mediastinal involvement; thus, the possibility of surgical benefit essentially corresponds to peripherally located tumors that are in an early stage.

In lung cancer, size of the tumor and involvement of lymph nodes represent anatomical factors with a notable influence on prognosis. The classification of these factors in different grades and the establishment of stages[9] facilitate better understanding of the behavior of the tumor and the therapeutic options available. In this way, classification of neuroendocrine lung tumors in 2 large groups has allowed us to confirm trends in the incidence of tumors in the different stages and the variability in the incidence rates for different histological types. The results of staging show that the number of patients with tumors in stage I reduces steadily from typical carcinoids to large cell and small cell neuroendocrine tumors, an observation which indirectly reflects the determining role played by tumor aggressiveness in the progression and size of the tumor and in lymph node involvement. In the 2 groups of patients studied, analysis of tumor size in each of the histological types showed that the mean and range remained essentially uniform in both and confirmed the trend in the correlation between size and progression of histological deterioration.

In our retrospective study, we confirmed the notable prognostic value of histological type of neuroendocrine tumors on the incidence of lymph node involvement.[5] Prospective analysis of this factor in another large group of patients confirmed that finding. However, comparison of the results in the 2 groups revealed some significant changes. In the prospectively studied patients, a notable increase was observed in the percentage of lymph node involvement in typical and atypical carcinoids; also, the ratio of N2 to N1 in those patients was significantly higher than that observed in the group of patients analyzed retrospectively. Analysis of the results also allows us to confirm that in both groups lymph node invasion in the typical carcinoid tumors did not display an obvious influence on prognosis, whereas in atypical carcinoids it did; the establishment of the new histological distinctions between typical and atypical carcinoids[7] undoubtedly allows a better assessment of the relative importance of lymph node involvement and histological type in the prognosis of both types of tumor.[10,11] As observed in those tumors, the percentage of lymph node involvement in large cell and small cell neuroendocrine carcinomas also increased significantly in the group of patients studied prospectively; furthermore, the ratio of N2 to N1 involvement in those patients increased significantly in both types of tumor.

The increase in the percentage of lymph node involvement in all histological types in the patients studied prospectively could be explained by the decision to perform appropriate lung resection along with systematic and complete mediastinal lymph node dissection. This procedure allowed us to better identify cases with worse prognosis, perform more complete surgical treatment, and in accordance with other studies,[11,12] rationalize the possibilities of adjuvant treatment and increase rates of survival. Consequently, we agree that mediastinal lymph node dissection should always be performed during surgical treatment of neuroendocrine lung tumors ranging from typical carcinoid tumors to small cell neuroendocrine carcinomas.[2,11-14]

The increase in the number of cases studied allowed us to analyze trends in the probability of survival and recurrence for the different types of tumor. Our study confirmed a discernible trend in the survival of patients with typical and atypical carcinoid tumors. In both, the prognostic value of lymph node involvement continued to be manifestly different; in the group of patients analyzed prospectively the improvement in survival of patients with atypical carcinoid tumors and lymph node involvement is explained by the systematic mediastinal lymph node dissection and use of adjuvant cancer therapy. In terms of the rate of local recurrence or distant metastasis, there continued to be a clear difference between the 2 types of tumor. However, not only was the rate of presentation different, but the probability of survival following recurrence also differed, a finding that is consistent with the results of other studies[2,4,10] and more clearly defines the influence of histological aggressiveness on prognosis.

Large cell neuroendocrine carcinoma currently represents a well-defined histological group. An increasing number of studies have been published on these tumors, although the numbers of patients in the samples continue to be limited.[9,15,16] In our experience, consistent with the findings of other authors, 75% of surgically treated patients in both groups were in stages I and II according to the final staging. Overall survival was 23% at 5 years in the patients from the retrospective group and 38% at 3 years

in the patients from the prospective group; no patient in stages IIIa or IIIb was alive at 3 years in either of the groups. These observations are consistent with reports that lymph node involvement clearly reduces the likelihood of long-term survival in these patients.[17,18] In our opinion, preoperative confirmation of the absence of lymph node involvement by mediastinoscopy or positron emission tomography is absolutely necessary. Mediastinal lymph node dissection should always be carried out.

In our experience, tumor recurrence occurs in 40% to 50% of patients. As in other studies, chemotherapy showed poor results in the treatment of recurrence. Surgical treatment can be accepted as appropriate in early stages, but the severity of the prognosis leads us to consider adjuvant therapy to be necessary following resection, even though the optimal treatment is not yet clearly defined. The significance of the prognostic factors and of recent genetic studies of growth factor inhibitors[19,20] may be important in specifying the indication.

Among patients surgically treated for small cell neuroendocrine carcinoma, 70% were in early stages, more than 50% were peripheral tumors, and the rates of survival and recurrence were similar to those observed for large cell neuroendocrine carcinoma. The question is whether these results justify surgery. Firstly, it should be accepted that surgery only plays a minor role in the treatment of these tumors, since disseminated disease is the most frequent presentation.[4] In addition, it is generally accepted that there is no possibility of survival in case of lymph node involvement. However, tumors can occur with no clinical evidence of extension beyond the lungs at the time of diagnosis. They are often found to be situated peripherally and would fit the concept of localized disease in the traditional classification of small cell neuroendocrine tumors, as well as in stages I and II of the TNM classification. In those cases, surgery is only indicated with the aim of obtaining acceptable survival.[6,13] Analysis of our experience reveals a discernible trend in the behavior of these tumors: in stages I and II their behavior is very similar to that of large cell neuroendocrine carcinomas, an observation which leads us to agree with those who consider surgery to be a reasonable option in early stages of small cell neuroendocrine carcinoma. Preoperative confirmation of the absence of lymph node involvement is always necessary and a combination of radiotherapy and chemotherapy should always be used.

In conclusion, analysis of the results of surgical treatment of neuroendocrine lung tumors in 2 large groups of patients—analyzed retrospectively and prospectively—allowed us to confirm the existence of a discernible trend in various prognostic factors. In carcinoid tumors, the application of general criteria for staging of lung cancer and the election of a therapeutic strategy facilitates improved understanding of treatment and prognosis. The experience obtained in the treatment of large cell and small cell neuroendocrine carcinomas confirmed the possibility of surgery in early stages, and adjuvant treatment should be provided in all cases. Molecular and genetic studies will help to improve our understanding of the significance of neuroendocrine differentiation in the prognosis of lung tumors.

Spanish Multicenter Study of Neuroendocrine Lung Tumors of the Spanish Society of Pulmonology and Thoracic Surgery (EMETNE-SEPAR).

Study Coordinator: Mariano García-Yuste (Hospital Clínico Universitario, Valladolid).

Members and Collaborators: José M. Matilla, Guillermo Ramos, Félix Heras, Jorge Quiroga, and Tomás Álvarez-Gago (Hospital Clínico Universitario, Valladolid); Ramón Pujol Rovira, Gerardo Ferrer, and Juan Moya (Hospital de Bellvitge, Barcelona); Juan Lago, David Saldaña, Ignacio Muguruza, and Pilar Garrido (Hospital Ramón y Cajal, Madrid); Javier López-Pujol, Francisco Cerezo and Javier Algar (Hospital Reina Sofía, Córdoba); Federico González-Aragoneses, Nicolás Moreno, Emilio Álvarez and María Cebollero (Hospital Gregorio Marañón, Madrid); José M. Rodríguez-Paniagua and José Galbis (Hospital Universitario, Alicante); Antonio Arnau and Antonio Cantó (Hospital General Universitario, Valencia); Luis López-Rivero, Santiago Quevedo and María del Carmen Camacho (Hospital Insular, Las Palmas); Julio Astudillo, and Ignacio Escobar (Hospital Germans Trias i Pujol, Barcelona); Laureano Molins (Hospital Sagrado Corazón, Barcelona);Antonio Cueto, Abel Sánchez Palencia, and Ángel Concha (Hospital Virgen de las Nieves, Granada); Jorge Freixinet, Pedro Rodríguez, and Teresa Romero (Hospital Dr. Negrín, Las Palmas); Juan Torres and Juan Bermejo (Hospital Virgen de la Arrixaca, Murcia); Ana Blanco (Hospital Virgen del Rocío, Sevilla); José M. Borro, Mercedes de la Torre and Ana Capdevila (Hospital Juan Canalejo, A Coruña); Ramón Moreno and Lorenzo Fernández Fau (Hospital la Princesa, Madrid); Mireia Serra and Ramón Rami (Mútua de Terrassa, Terrassa); Ricardo Arrabal, José L. Fernández-Bermúdez, and Antonio Benítez (Hospital Carlos Haya, Málaga); Andrés Varela and Mar Córdova (Hospital Puerta de Hierro, Madrid); Miguel A. Cañizares, Eva M. García Fontán, and Ana González Piñeiro (Hospital Xeral, Vigo).

Research Unit: Hospital Clínico Universitario, Valladolid (Ana Almaraz and María F. Muñoz).

International Members Invited by EMETNE-SEPAR: William D. Travis (Sloan Kettering Cancer Center, New York, USA); Richard Battafarano (Washington University, Saint Louis, Missouri, USA); Pierre Fuentes (Marseille University Hospital, Marseille, France).

REFERENCES

1. Travis WD, Rush W, Flieder DB, Falk R, Fleming M, Gal A, et al. Survival analysis of 200 pulmonary neuroendocrine tumors with clarification of criteria for atypical carcinoid and its separation from typical carcinoid. Am J Surg Pathol. 1998;22:934-44.
2. Filosso PL, Rena O, Donati G, Casadio C, Ruffini E, Papalia E, et al. Bronchial carcinoid tumors: surgical management and longterm outcome. J Thorac Cardiovasc Surg. 2002;123:303-9.
3. Mezzetti M, Raveglia F, Panigalli T, Giuliani L, lo Giudice F, Meda S, et al. Assessment of outcomes in typical and atypical carcinoids according to latest WHO classification. Ann Thorac Surg. 2003; 76:1838-42.
4. Warren WH, Gould VE. Neuroendocrine tumors of the bronchopulmonary tract. A reappraisal of their classification after 20 years. Surg Clin N Am. 2002:82:525-40.
5. García-Yuste M, Matilla JM, Álvarez Gago T, Duque JL, Heras F, Cerezal LJ, et al, and the Spanish Multicenter Study of Neuroendocrine Tumors of the Lung (EMETNE-SEPAR). Prognostic factors in neuroendocrine lung tumors: a Spanish multicenter study. Ann Thorac Surg. 2000;70:258-63.

6. Ginsberg RJ. Small cell lung cancer: how should be treated it? What is it? Ann Thorac Surg. 2000;70:1453-4.
7. Travis WD, Sobin LH. Histologic typing of lung and pleural tumours; International Histologic Classification of Tumours. New York: Springer-Verlag; 1999.
8. Dresler CM, Ritter JH, Patterson GA, Ross E, Biley MS, Wick MR. Clinical-pathologic analysis of 40 patients with large cell neuroendocrine carcinoma of the lung. Ann Thorac Surg. 1997;63: 180-5.
9. Mountain CF. Revisions in the international system for staging lung cancer. Chest. 1997;111:1710-7.
10. Thomas CHF, Tazelaar HD, Jett JR. Typical and atypical pulmonary carcinoids. Outcome in patients presenting with regional limph node involvement. Chest. 2001;119:1143-50.
11. Cardillo G, Sera F, Di Martino M, Graziano P, Giunti R, Carbone L, et al. Bronchial carcinoid tumors: nodal status and long-term survival after resection. Ann Thorac Surg. 2004;77:1781-5.
12. Dodoli CH, Barlesi F, Chetaille B, Garbe L, Thomas P, Giudicelli R, et al. Large cell neuroendocrine carcinoma of the lung: an aggressive disease potentially treatable with surgery. Ann Thorac Surg. 2004;77;1168-72.
13. Inoue M, Miyoshi S, Yasumitsu T, Mori T, Iuchi K, Maeda H, et al, and the Thoracic Surgery Study Group of Osaka. Surgical results for small cell lung cancer based on the new TNM staging system. Ann Thorac Surg. 2000;70:1615-9.
14. Zacharias J, Nicholson AG, Ladas GP, Goldstraw P. Large cell neuroendocrine carcinoma and large cell carcinomas with neuroendocrine morphology of the lung: prognosis after complete resection and systematic nodal dissection. Ann Thorac Surg. 2003; 75:348-52.
15. Mazières J, Daste GH, Molinier L, Berjaud J, Dahan M, Delsol M, et al. Large cell neuroendocrine carcinoma of the lung: pathological study and clinical outcome of 18 resected cases. Lung Cancer. 2002;37:287-92.
16. Paci M, Cavazza A, Annessi V, Putrino I, Ferrari G, de Franco S, et al. Large cell neuroendocrine carcinoma of the lung: a 10 year clinicopathologic retrospective study. Ann Thorac Surg. 2004;77: 1163-7.
17. Iyoda A, Hiroshima K, Baba M, Saitoh Y, Ohwada H, Fujisawa T. Pulmonary large cell carcinomas with neuroendocrine features are high-grade neuroendocrine tumors. Ann Thorac Surg. 2002;73: 1049-54.
18. Takei H, Asamura H, Maeshima A, Suzuki K, Kondo H, Niki T, et al. Large cell neuroendocrine carcinomas of the lung: a clinopathologic study of eighty-seven cases. J Thorac Cardiovasc Surg. 2002;124:285-92.
19. Casali CH, Stefani A, Rossi G, Migaldi M, Bettelli S, Parise A, et al. The prognostic role of C-kit protein expression in resected large cell neuroendocrine carcinoma. Ann Thorac Surg. 2004;77: 247-53.
20. Filosso PL, Ruffini E, Oliaro A, Rena O, Casadio C, Mancuso M, et al. Large-cell neuroendocrine carcinoma of the lung: a clinicopathologic study of eighteen cases and the efficacy of adjuvant treatment with octeotride. J Thorac Cardiovasc Surg. 2005;129: 819-24.