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Typical and atypical carcinoid tumours: analysis of the experience of the Spanish Multi-centric Study of Neuroendocrine Tumours of the Lung

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Abstract

Background: This study examines the experience of the Spanish Multi-centric Study of Neuroendocrine Tumours of the Lung with patients treated surgically for typical and atypical carcinoid tumours. **Methods:** From 1980 to 2002, 661 patients were treated surgically for 569 typical carcinoid tumours and 92 atypical carcinoid tumours. Three hundred and four cases were studied retrospectively from 1980 to 1997 (261 typical carcinoid and 43 atypical carcinoid tumours); the other 357 new cases (308 typical carcinoid and 49 atypical carcinoid tumours) were collected prospectively from 1998 to 2002. Tumours were classified according the 1999 classification from the WHO and the International Association for the Study of Lung Cancer (IASLC). Several variables were reviewed in all patients. Univariate and multivariate statistical analyses were performed in order to determine whether clinical characteristics were associated with significant differences in survival. **Results:** In the total of the patients, 5-year survival for different tumours was as follows: typical carcinoid: overall survival 97%; with nodal involvement 100%; atypical carcinoid: overall 78%; with nodal involvement 60%. A significant difference in survival was found between patients in the retrospective and prospective groups with atypical carcinoid and nodal involvement. The comparative analysis of several factors in typical and atypical carcinoid tumours showed a significant difference for mean age, tumour size, nodal involvement and distant metastases. **Conclusion:** Nodal involvement and histological sub-type appear as the most important factors influencing the prognosis. Adequate lung resection and systematic radical mediastinal lymphadenectomy should always be performed. Sleeve resection could be performed in central typical and atypical carcinoid tumours, avoiding pneumonectomy.

Keywords: Typical carcinoid tumours; Atypical carcinoid tumours; Neuroendocrine lung tumours

1. Introduction

In neuroendocrine lung tumours, histologic characteristics and clinical behaviour define the neoplasms belonging to this spectrum: at one end are the typical carcinoid tumours and at the other end small-cell neuroendocrine carcinomas. Intermediate degrees of differentiation and behaviour define the other neoplasms in this spectrum, atypical carcinoid tumours and large cell neuroendocrine carcinomas.

The distinction between typical and atypical carcinoid tumours was first described by Engelbreth-Holm [1]; the histologic criteria for this distinction were later established by Arrigoni et al. [2]. The initial classification of these tumours produced by the World Health Organization (WHO) [3] in 1982 has been amended various times. As a result of clinical and prognostic disputes, new histological criteria proposed by Travis et al. to separate typical and atypical carcinoid tumours [4] have recently been considered and accepted by the WHO and IASLC in the 1999 classification of lung tumours [5]. At present, the investigation of these pathological processes centres on the causes of their specific differentiation, behaviour and therapeutic possibilities.

The data compiled by the Multi-centric Study of Neuroendocrine Tumours of the Lung for the Spanish Society of Pneumology and Thoracic Surgery (EMETNE-SEPAR), on patients

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treated for typical and atypical carcinoid tumours, allow us to provide this paper with our experience in these tumours.

2. Material and methods

We have reviewed the data of 661 patients collected by EMETNE-SEPAR from 1980 to 2002 and treated surgically for 569 typical carcinoid tumours and 92 atypical carcinoid tumours. These patients were the result of the addition to our first 304 cases studied retrospectively from 1980 to 1997 (261 typical carcinoid and 43 atypical carcinoid) of 357 new cases collected prospectively from 1998 to 2002 (308 typical carcinoid and 49 atypical carcinoid). The pathologists reviewed all the samples and the tumours were classified according to the new 1999 WHO and IASLC classification, including Travis's new criteria for atypical carcinoid tumours and their distinction from typical carcinoid tumours. An adequate and complete surgical resection of the tumour was performed in all cases. In contrast to the mediastinal nodal sampling procedure carried out in our first 304 cases, systematic radical mediastinal lymphadenectomy, including all mediastinal nodal groups, was performed in the last 357 cases collected.

In these types of tumours, we have analyzed the behaviour of several prognostic factors, recurrence and survival. The clinical variables considered in the comparative analysis were: gender, age (mean and range), presence of endocrine syndromes (Cushing's, acromegaly, carcinoid), location (central – main, lobar or segmentary bronchus – or peripheral), tumour size (maximum diameter in millimetres measured by pathologist), surgical procedure, nodal involvement and staging (N0, N1 or N2) and pathologic stage of tumour disease using the TNM classification of the International Union Against Cancer (UICC) staging system [6]. Survival data were obtained from the case notes for the various check-ups of patients at each hospital. The incidence and percentage of metastases and local recurrence, as well as the cause of death for those who died during follow-up, were also determined.

The statistical analysis was performed with the SPSS programme (Statistical Package for Social Sciences), version 12.0. Correlation of categorical versus categorical and numerical variables between different groups was assessed using, respectively, chi-squared and Student's *t*-test, or the Mann–Whitney *U*-test as appropriate. Comparison of a numerical variable with other categorical variables of more than two categories was assessed using ANOVA for one factor; when the result of this test was significant, the post hoc comparisons were performed using Duncan's test. Cumulative survival probabilities were estimated by the Kaplan–Meier method. Log-rank and Breslow tests were used for comparing survival functions. To determine the prognostic factors with the greatest influence on survival, a multivariate analysis using linear regression was performed. A p value <0.05 was considered significant.

3. Results

Of our patients, 569 suffered from a *typical carcinoid tumour*. The demographic details, incidence of endocrine syndromes, location and size of the tumours are given in Table 1. The surgical procedures performed in these patients were: 374 lobectomies or bilobectomies (65.73%); 66 broncoplastic procedures (11.60%): 9 bronchial sleeve resection, 57 sleeve lobectomy or bilobectomy; 63 pneumonectomies (11.07%) and 66 wedge or segmental resections (11.60%). Lymph node metastases were found in 52 patients (9.1%), of which 32 were N1 and 20 N2. The distribution of cases by stages according to the 1997 TNM classification is shown in Table 2.

Table 1
Demographic and tumoural characteristics of patients with typical and atypical carcinoid tumours

	Typical carcinoid	Atypical carcinoid
Sex (%)		
Men	44	44
Women	56	56
Mean age (years)	47	53
Range	4–81	21–76
Endocrine syndromes	16 (2.81%)	4 (4.32)
Cushing	8	2
Acromegaly	3	1
Carcinoid	5	1
Location (%)		
Central	68	56
Peripheral	32	44
Mean tumour size (mm)	25.3	34
Range	9–94	9–99

The analysis of mortality during follow-up shows that 11 patients died of an independent cause (functional in 2 cases, and in the other 9 by other causes not related with the tumour). Nine patients (1.58%), eight of them in stage I (four in stage Ia and four in stage Ib) and the other in stage IIIa, presented recurrence at distant sites after 11, 12, 23, 24, 36, 56, 59, 98 and 212 months following operation. Chemotherapy treatment was performed in all of them. Four of the patients in stage I and another in stage IIIa are alive after 18, 30, 73, 79 and 115 months, and the other four died because of metastatic recurrence at 42, 103, 108 and 120 months. Five patients (0.88%), three in stage Ia, one in stage IIa and another in stage IIb, had local recurrence; all of them were treated with mediastinal radiotherapy. One of them died after 69 months and other died because of local recurrence 40 months later. The other three were patients are alive after 18, 19 and 106 months.

Table 2
Distribution of tumours by stages in patients with typical and atypical carcinoid

	Typical carcinoid	Atypical carcinoid
Ia	209 (36.73%)	16 (17.39%)
Ib	288 (50.62%)	37 (40.21%)
IIa	9 (1.58%)	2 (2.17%)
IIb	38 (6.68%)	14 (15.22%)
T3N0M0	15 (central)	3 (central 2)
IIIa	20 (3.51%)	15 (16.30%)
IIIb	3 (0.53%)	3 (3.26%)
IV	2 (0.35%)	5 (5.43%)
	(Separate tumours in 2 lobes)	Hepatic 1 Lung 4

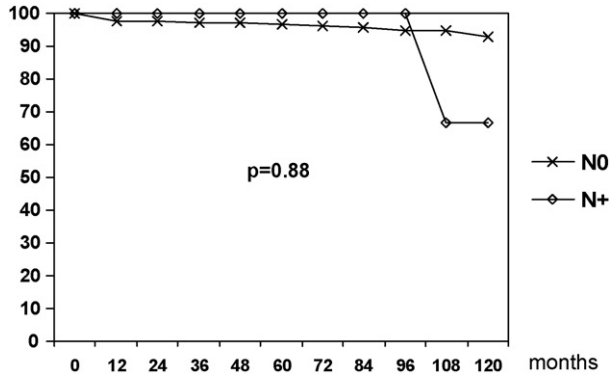

Fig. 1. Kaplan–Meier survival and statistical comparative analysis for patients with typical carcinoid without nodal involvement and those with typical carcinoid and nodal involvement.

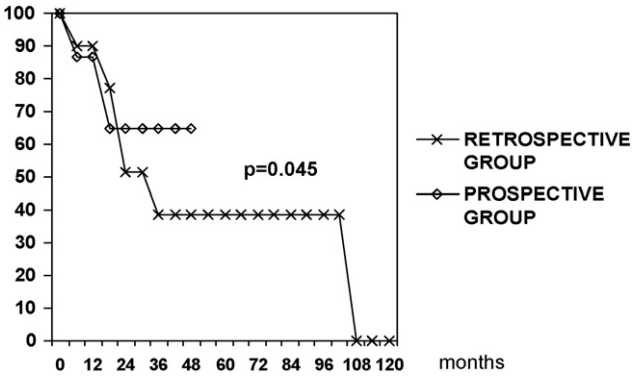

Fig. 3. Kaplan–Meier survival and statistical comparative analysis for patients with atypical carcinoid tumours in retrospective and prospective groups.

The overall survival after 5 and 10 years was found to be 97% and 92%, respectively. In relation to nodal involvement, the overall survival of N0 status was 97% and 92%, and 100% and 66% when nodal involvement was present (N1: 100% and 71%; N2: 100% at 60 and 90 months; $p = 0.88$) (Fig. 1). When the overall 5-year survival in the retrospective group of patients with nodal involvement was compared with that of patients in the prospective study group with this condition (following systematic mediastinal lymphadenectomy), no statistically significant difference was observed ($p = 0.19$). As for the surgical procedure, no difference in survival was observed between patients receiving a lobectomy or pneumonectomy and those in whom sleeve lung resection was performed ($p = 0.098$).

Ninety-two patients had *atypical carcinoid tumours*. The demographic details, incidence of endocrine syndromes, location and size of the tumours are given in Table 1. The surgical procedures performed were: 62 lobectomies or bilobectomies (67.39%); 4 broncoplastic procedures (4.35%): 2 bronchial sleeve resection, 2 sleeve lobectomy, 19 pneumonectomies (20.65%) and 7 (7.61%) wedge or segmental resections. Nodal involvement was present in a total of 33 of the 92 patients (35.87%), of whom 14 were N1 and 19 N2. The distribution of the cases by stages is shown in Table 2. After definitive staging, all patients at N2 were treated with post-operative mediastinal irradiation.

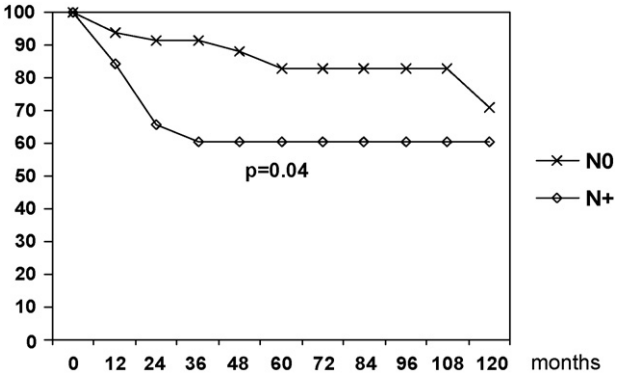

Fig. 2. Kaplan–Meier survival and statistical comparative analysis for patients with atypical carcinoid tumours without nodal involvement and those with atypical carcinoid tumours and nodal involvement.

During the follow up, four patients died due to causes not related with the tumour. Fifteen patients (16.3%) (five in stage Ib, three in stage IIa, three in stage IIIa, three in stage IIIb and another in stage IV) presented recurrence at distant sites. Twelve (80%) of the 15 patients presenting metastases died of this cause and the other three (2 in stage IIIb and 1 in stage IV) are alive after 45, 72 and 54 months. Among the prospective patients, three (3.26%) (one in stage I, one in stage IIb and one in stage IIIa) presented local recurrence. Following treatment, two of them are alive at 79 and 101 months and the other died of a local recurrence.

The overall survival at 5 and 10 years was 78% and 67%, respectively. A significant statistical difference in survival was found between patients without nodal involvement (83% and 70%) and those in whom nodal involvement was seen (60% and 60%, N1: 61% and 60%; N2: 60% and 60%) ($p = 0.04$) (Fig. 2). In addition, when the overall survival at 5 years of the retrospective group of patients with nodal involvement was compared with that of similar patients in the prospective group (following systematic mediastinal lymphadenectomy), a statistically significant difference was seen ($p = 0.045$) (Fig. 3). A statistically significant difference was also found in the analysis of survival by stages. The probability of survival after 5 years by subsets of patients in stage I was also different (100% for T1N0 and 83% for T2N0; $p = 0.03$). No difference in survival was observed between patients receiving lobectomy or pneumonectomy and those in whom sleeve resection was performed ($p = 0.50$).

Statistical comparisons were also performed for a number of variables for all the patients with typical and atypical carcinoid tumours (mean age, sex, presence of endocrine

Table 3
Statistical comparisons of several variables for all patients with typical and atypical carcinoid tumours

	Typical/atypical carcinoid	*p*
Female (%)	56/56	0.097
Mean age	47/53	<0.001
Endocrine syndromes (%)	2.81/4.32	0.978
Peripheral (%)	32/44	0.008
Tumour size (mm)	25.3/34	<0.001
Nodal involvement (%)	9.1/35.87	<0.001
Metastases (%)	1.58/16.3	<0.001
Local recurrence (%)	0.88/3.26	0.002

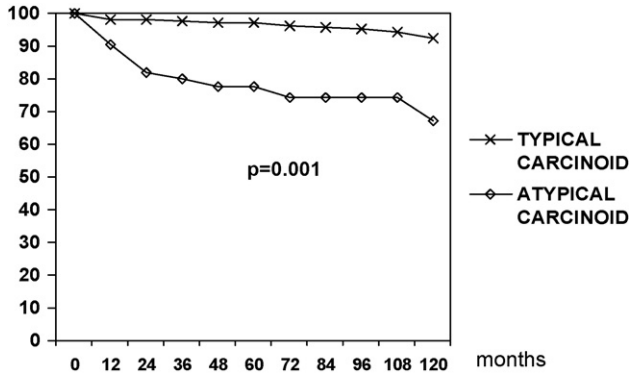

Fig. 4. Kaplan–Meier survival and statistical comparative analysis for patients with typical and atypical carcinoid tumours.

syndromes, location of the tumour, mean tumour size, lymph node involvement, metastases at distant sites and local recurrence); a significant statistical difference was found for mean age, tumour location, tumour size, lymph node involvement, metastases at distant sites and local recurrence (Table 3).

When overall survival in typical and atypical carcinoid tumours was compared, the survival of patients affected by an atypical carcinoid was significantly lower than that of those affected by a typical carcinoid tumour ($p < 0.001$) (Fig. 4). No difference in survival was observed between patients with typical and atypical carcinoid in stage Ia ($p = 0.79$), but a difference was found between patients in stage Ib ($p = 0.05$).

Finally, in order to determine the most significant prognostic factors influencing survival, a multivariate analysis was carried out. The histological tumour type ($p = 0.02$) and the presence of nodal involvement ($p < 0.001$) were shown to be the most significant factors influencing survival.

4. Discussion

Bronchial carcinoid tumours were in the past defined as bronchial adenomas and considered benign, with good clinical prognosis. In 1944, bearing in mind the more aggressive behaviour of some of these tumours, a distinction was established [1] between two different entities, typical and atypical carcinoid tumours. Later, in 1972, based on the different histological features observed, Arrigoni et al. [2] proposed histological criteria to separate typical and atypical carcinoid tumours.

Their histologic nature, characterized by cellular organization in nests or bands, and the rich fibrovascular stroma allow recognition of their neuroendocrine phenotype through routine microscopic techniques. In addition to morphology, the possibility of demonstrating the cells' neurosecretory capacity contributes to a strengthening of neuroendocrine differentiation in these tumours. On the basis of these facts, typical and atypical carcinoid tumours are nowadays included in the spectrum of neuroendocrine neoplasms of the lung and the gradual de-structuring of this pattern marks the histologic differences between them. Recently, based on the correlation between histologic differences and clinical prognosis of the patients, the 1999 WHO classification [5] has accepted the criteria proposed by Travis [4] for separating typical and atypical carcinoid tumours. A reduction in the lower limit of the number of mitoses observed from 5 to 2 per 10 HPF or the presence of necrosis define a new histological concept of atypical carcinoid tumours. The acceptance of these classification criteria allows us better to clarify patients' prognosis.

The number of patients analyzed allows us to affirm with confidence the relationship between the increase in mean age and histologic degradation. In fact and in line with the observations of other authors [6,7], the difference in mean age between our patients with typical and atypical carcinoid tumours is 6 years. In our experience, the incidence of these tumours also differs between the sexes and is significantly lower among females to atypical carcinoid tumours. The coincidence of this finding with the observations of others [8–10] merely confirms the link between an increased incidence in males and a higher degree of malignancy.

In our experience the percentage of tumours in peripheral location is significantly higher in atypical carcinoid tumours, potentially allowing us to correlate peripheral tumour localization with a worse prognosis. However, the influence of this factor on prognosis should not be linked solely with the potential evolution derived from histologic characteristics but also with the possibility of the tumour's prolonged evolution before discovery due to its location. A significant difference in size was found in our study between typical and atypical carcinoid tumours. The correlation of this finding with the observations of other authors [9,10] reaffirms the relation existing between increased tumour size and the advanced histologic deterioration.

In lung cancer, tumour size and the involvement of lymph nodes are the local anatomic factors with the greatest influence on prognosis; their classification in different degrees and the establishment of stages [6] provide an adequate understanding of the behaviour of the tumour and our possibilities of treating them. The classification of carcinoid lung tumours in this way has allowed us to state the incidence of the different stages and its variability in the two different histologic types. Staging of these tumours demonstrates that the number of patients affected by tumours in stage I gradually decreases from typical carcinoid (87.35%) to atypical carcinoid (57.6%). On the other hand, the number of patients classified in stages II and III of typical carcinoid tumours (8.26% and 4.04%) notably increases in the case of atypical carcinoid tumours (17.39% and 19.56%). This fact indirectly reflects the importance of histologic aggressiveness as a determining factor in tumour size and nodal involvement in these tumours.

The results of a previous paper [11] indicated the prognostic value of nodal involvement and the marked influence of histologic classification on its incidence. The analysis of this prognostic factor in a larger number of patients has reaffirmed this finding: 9.1% (52 of 569: 32 N1, and 20 N2) in typical carcinoid patients and 35.87% (33 of 92: 14 N1 and 19 N2) in the atypical carcinoid group; in addition, the ratio of N2/N1 in patients with atypical carcinoid tumours (1.36) turned out to be significantly higher than that encountered in the group with typical carcinoid tumours (0.63). Not only is the incidence of nodal involvement different, but so is its influence on the prognosis. Most of the patients with typical carcinoid tumour presenting metastasis

(88.9%) or local recurrence (60%) during follow-up were in stage I, and more than 55% are alive after treatment of the tumour's recurrence. However, among patients with atypical carcinoid tumours presenting metastasis or local recurrence (66.6% of those with nodal involvement detected in the operation), 80% of them died after treatment because of the recurrence. In agreement with other authors [12—16], an analysis of the results allows us to confirm that nodal invasion does not show an obvious influence on the prognosis for typical carcinoid tumours but only for atypical carcinoid tumours. Awareness of the new histologic limits between these two types of tumour [4] contributes to a better appraisal of the proportional significance of nodal involvement and histological type for prognosis.

There are few studies that have analyzed in depth the significance of lymph node involvement in bronchial carcinoid tumours [14,16]. Perhaps, as Cardillo et al. has said, this is why most authors do not systematically perform radical mediastinal lymphadenectomy. We did not routinely use this procedure either in our first 304 patients (261 typical carcinoid tumours and 43 atypical carcinoid tumours); however, nodal involvement was, in our experience, a factor with a high prognostic value. In contrast, we have systematically associated conventional lung resection to radical mediastinal lymphadenectomy in the last 357 patients (308 typical carcinoid tumours and 49 atypical carcinoid tumours) recruited prospectively. The comparison of survival in both groups of patients with nodal involvement showed a significant improvement in survival among those with an atypical carcinoid tumour when radical mediastinal lymphadenectomy was performed. The suitability of this indication is confirmed by the verification, in our experience and in that of others [14], of the significance of nodal involvement and histological sub-type on prognosis.

Additionally, we have analyzed the repercussion of tumour size on survival when nodal involvement was not present. We have been able to confirm that, in stage I typical carcinoid tumour patients, a tumour size of more or less than three centimetres does not have a significant influence on survival. The rate of survival were clearly different when, under the same conditions, the influence of tumour size on survival was analyzed in patients suffering from an atypical carcinoid tumour. Based on these facts and in line with other authors [14,17], the systematic performance of lung resection and mediastinal nodal dissection is decisive for the correct assessment of the co-responsibility of T and N factors in the prognosis for these tumours. This procedure has allowed us to individualize better the cases with a worse prognosis, perform more complete surgery, rationalize the possibilities of adjuvant oncology treatment and increase survival rates. Always complying with these norms, and in the light of our results, we feel, along with other authors [10,18,19], that sleeve resection could be performed in selected cases of typical and atypical carcinoid central tumours, thus avoiding pneumonectomy.

References

[1] Engelbreth-Holm J. Benign bronchial adenomas. Acta Chir Scand 1944;90:383—409.
[2] Arrigoni MG, Woolner LB, Bernatz PE. Atypical carcinoid tumor of the lung. Thorac Cardiovasc Surg 1972;64:413—21.
[3] The World Health Organization histological typing of lung tumors. Second edition. Am J Clin Pathol 1982;77:123—36.
[4] Travis WD, Rush W, Flieder DB, Falk R, Fleming M, Gal A, Koss M. 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.
[5] Travis WD, Sobin LH. Histologic typing of lung and pleural tumours; international histologic classification of tumours (No. 1). New York, NY: Springer-Verlag; 1999.
[6] Mountain CF. Revisions in the international system for staging lung cancer. Chest 1997;111:1710—7.
[7] Lequaglie C, Patriarca C, Cataldo I, Muscolino G, Preda F, Ravasi G. Prognosis of resected well-differentiated neuroendocrine carcinoma of the lung. Chest 1991;100:1053—6.
[8] Warren HW, Gould VE. Neuroendocrine tumors of the bronchopulmonary tract. A reappraisal of their classification. Surg Clin N Am 2002;82: 525—40.
[9] Marty-Ané CH, Costes V, Pujol JL, Aluzen M, Baldet P, Mary H. Carcinoid tumors of the lung: do atypical features require aggressive management? Ann Thorac Surg 1995;59:78—83.
[10] Chughtai T, Morin J, Sheiner N, Wilson J, Mulder D. Bronchial carcinoid. Twenty years' experience defines a selective surgical approach. Surgery 1997;122:801—8.
[11] García-Yuste M, Matilla JM, Alvarez Gago T, Duque JL, Heras F, Cerezal LJ, Ramos G, 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.
[12] Thunnissen FB, Van Eijk J, Baak JP, Schipper NW, Uyterlinde AM, Breederveld RS, Meijer S. Bronchopulmonary carcinoids and regional lymph node metastases. A quantitative pathologic investigation. Am J Pathol 1988;132:119—22.
[13] Martini N, Zaman M, Bains M, Burt M, McCormack P, Rusch V, Ginsberg G. Treatment and prognosis in bronchial carcinoid involving regional lymph nodes. J Thorac Cardiovasc Surg 1994;107:1—7.
[14] Cardillo G, Sera F, Di Martino M, Graziano P, Giunti R, Carbone L, Facciolo F, Martelli M. Bronchial carcinoid tumors: nodal status and long-term survival after resection. Ann Thorac Surg 2004;77:1781—5.
[15] Mezzetti M, Raveglia F, Panigalli T, Giuliani L, Lo Giudice F, Meda S, Conforti S. Assessment of outcomes in typical and atypical carcinoids according to latest WHO classification. Ann Thorac Surg 2003;76: 1838—42.
[16] Thomas CHF, Tazelaar HD, Jett JR. Typical and atypical carcinoids. Outcome in patients presenting with regional lymph node involvement. Chest 2001;119:1143—50.
[17] Filosso PL, Rena O, Donati G, Casadio C, Ruffini E, Papalia E, Oliaro A, Maggi G. Bronchial carcinoid tumors: surgical management and long-term outcome. J Thorac Cardiovasc Surg 2002;123:303—9.
[18] El Jamal M, Nicholson AG, Goldstraw P. The feasibility of conservative resection for carcinoid tumors: is pneumonectomy ever necessary for uncomplicated cases? Eur J Cardiothorac Surg 2000;18:301—6.
[19] Ferguson MK, Landreneau RJ, Hazelrigg SR, Altorky NK, Naunheim KS, Zwischenberger JB, Kent M, Yim AP. Long-term outcome after resection for bronchial carcinoid tumors. Eur J Cardiothorac Surg 2000;18:156—61.

Appendix A. The Spanish Multi-centric Study of Neuroendocrine Tumours of the Lung of the Spanish Society of Pneumonology and Thoracic Surgery (EMETNE-SEPAR)

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