Localizador web
Artículo 141.832

Bronchioloalveolar Carcinoma in Spain: A Rare and Different Form of Lung Cancer

Ángel López Encuentra,[a] Francisco Pozo Rodríguez,[a] José Luis Martín de Nicolás,[b] Victoria Villena,[a] Javier Sayas Catalán,[a] and the Bronchogenic Carcinoma Cooperative Group of the Spanish Society of Pulmonology and Thoracic Surgery (GCCB-S)*

[a]Servicio de Neumología, Hospital Universitario 12 de Octubre, Madrid, Spain.
[b]Servicio de Cirugía Torácica, Hospital Universitario 12 de Octubre, Madrid, Spain.

OBJECTIVE: To describe a series of cases of bronchioloalveolar carcinoma (BAC) treated surgically between 1993 and 1997 in the 19 hospitals that make up the Bronchogenic Carcinoma Cooperative Group of the Spanish Society of Pulmonology and Thoracic Surgery (GCCB-S).

PATIENTS AND METHODS: From a total of 2944 cases of non-small cell lung cancer (NSCLC), 82 (3%) were BAC. The clinical characteristics and prognosis of patients with BAC were compared with those of the remaining 2862 patients with NSCLC.

RESULTS: The percentage of men was lower for BAC than for other types of NSCLC (64.6% compared with 93.5%; *P*<.001) and BAC was associated with less comorbidity (50% vs 62%; *P*<.05), particularly in terms of chronic obstructive pulmonary disease (33% vs 47.2%; *P*<.05). Other characteristics showing significant differences were the higher frequency of BAC as a chance finding and the lower likelihood of weight loss or reduced performance status at the time of diagnosis. Classification as stage cI was significantly more common in patients with BAC (87% vs 75%; *P*<.001), and this difference between groups was more pronounced for stage pI (68.5% vs 47%; *P*<.01). Only taking into account patients classified as stage pI with complete resection of NSCLC and following exclusion of operative mortality, patients with BAC presented an overall 5-year survival of 65% (95% confidence interval [CI], 51%-79%), compared with a significantly lower survival of 53% (95% CI, 50%-56%; *P*<.05) in patients with other forms of NSCLC.

CONCLUSIONS: In Spain, among cases of lung cancer treated by surgery, BAC is very rare (3%) and displays clinical characteristics that are different from other forms of NSCLC. Controlling for the most basic prognostic factors (stage pI and complete resection), survival is significantly higher for BAC.

Key words: *Lung cancer. Staging. Surgery. Bronchioloalveolar carcinoma.*

Carcinoma bronquioloalveolar en España. Un cáncer de pulmón infrecuente y diferente

OBJETIVO: Describir una serie de casos de carcinoma bronquioloalveolar (CBA) tratados quirúrgicamente por los 19 hospitales del Grupo Cooperativo de Carcinoma Broncogénico de la Sociedad Española de Neumología y Cirugía Torácica (GCCB-S) entre 1993 y 1997.

PACIENTES Y MÉTODOS: Del total de 2.944 casos de carcinoma broncogénico no microcítico (CBNM), 82 (3%) eran CBA. Se compararon las características clínicas y el pronóstico de los CBA con los de los restantes 2.862 CBNM.

RESULTADOS: Los CBA ocurren menos frecuentemente en varones (el 64,6 frente al 93,5%; p = 0,001), tienen menos comorbilidad en general (el 50 frente al 62%; p < 0,05) y enfermedad pulmonar obstructiva crónica en particular (el 33 frente al 47,2%; p < 0,05). Otras características con diferencias significativas son la mayor frecuencia de que el CBA sea un hallazgo casual y la menor probabilidad de que en el momento del diagnóstico exista historia de pérdida de peso o peor estado clínico. Por estadios clínicos, la clasificación Ic es significativamente más frecuente en los CBA (el 87 frente al 75%; p = 0,001), diferencia que se incrementa en la estadificación Ip (el 68,5 frente al 47%; p < 0,01). Considerando la población de CBNM con resección completa en estadio Ip, y una vez excluida la mortalidad operatoria, los CBA presentan una supervivencia global a los 5 años del 65% (intervalo de confianza [IC] del 95%, 51-79%), significativamente superior al resto de CBNM no CBA, en que es del 53% (IC del 95%, 50-56%) (p < 0,05).

CONCLUSIONES: En España, entre los casos de cáncer de pulmón operado, el CBA es muy infrecuente (3%) y presenta características clínicas diferentes del resto de los CBNM. Controlando con los factores pronósticos más básicos (estadio Ip y resección completa), la supervivencia del CBA es significativamente superior.

Palabras clave: *Cáncer de pulmón. Estadificación. Cirugía. Carcinoma bronquioloalveolar.*

This study was partially funded by grants FIS 97/0011, FEPAR-2002, RTIC-03/11-ISCIII-Red-Respira, and FIS 03/46, and support from the Autonomous Community of Castile and Leon and Fundación Menarini.

*A complete list of the members of GCCB-S is contained in the appendix.

Correspondence: Dr. A. López Encuentra.
Servicio de Neumología. Hospital Universitario 12 de Octubre.
Avda. Córdoba, 5. 28041 Madrid. España.
E-mail: lencuent@h12o.es

Manuscript received October 26, 2005. Accepted for publication January 17, 2006.

Introduction

Bronchioloalveolar carcinoma (BAC) is a histologic subtype of non-small cell lung cancer (NSCLC).[1] The International Consensus Conference on Bronchioloalveolar Carcinoma, held in New York in November 2004, considered evidence on the relative increase in diagnosis of the disease alongside a reduction in squamous cell lung cancer and the abundant information on clinical and radiologic forms, histologic classification (pure BAC or BAC mixed with adenocarcinoma) and the most selective treatments.[2,3]

The aim of this study was to describe a series of cases of BAC treated surgically between 1993 and 1997 in the 19 hospitals that make up the Bronchogenic Carcinoma Cooperative Group of the Spanish Society of Pulmonology and Thoracic Surgery (GCCB-S).

Patients and Methods

Patients

All patients who underwent thoracotomy for lung cancer in hospitals belonging to the GCCB-S[4] between 1993 and September 1997 were prospectively enrolled in the study. The cumulative number of cases treated annually corresponded to around 50% of the surgical cases treated in Spain. The participating hospitals perform a wide variety of activities and are representative in terms of the number of beds, teaching and research activities, private or public status, and the number of procedures performed annually. The sample was complete, since it was verified that all patients in whom surgery was performed for this disease were included in the registry; surgery included both complete resections and exploratory thoracotomies.

Operative mortality included all deaths directly related to surgery, irrespective of when (before or after 30 days) or where (in or outside hospital) they occurred. The initial number of cases included in the study was 2994. Following a repeat evaluation, 3 cases were withdrawn since assessment of pathology revealed that 1 was carcinosarcoma and the other 2 records corresponded to a single patient treated for different tumors in each lung in 1994 and 1996. Consequently, the final number of cases was 2991. Given that the operation on the last case in this series was performed on September 30, 1997, at the final follow-up (December 2004) an overall survival period of 7 to 11 years was considered.

For the purposes of this study, cases with diagnosis of BAC or NSCLC other than BAC in the excised tissue were selected for comparison of clinical characteristics and survival. Consequently, 47 patients with small cell lung cancer were excluded from the study.

Methods

Cases were classified according to the 1997 TNM system.[5] Clinical staging is defined as the classification obtained through any method, even surgically, prior to performing the definitive therapeutic procedure. Pathologic staging is defined as classification obtained through the signs observed during thoracotomy and using information collected following assessment of the excised tissue alongside information from the clinical stage. Similar criteria for functional operability of patients and tumor resectability were applied in all hospitals forming part of the GCCB-S.[6]

In the GCCB-S registry, each component of the cT, or clinical classification of the tumor component of TNM staging, was considered independently for each patient. Diagnostic techniques were recorded using a previously agreed code and the procedure that achieved the best resolution was identified in the prospective registry.

The degree of certainty of TNM staging depends on the diagnostic method used. According to some international organizations, autopsy carries the greatest degree of certainty and clinical data the least. By consensus between the members of the coordinating committee of the GCCB-S (2 thoracic surgeons and a pulmonologist), methods were defined to ensure the maximum degree of certainty of the classification for each component (maximum possible clinical certainty adjusted for each problem).[7] Node stages (N) were assessed using diagnostic criteria of differing certainty. The minimal requirement for confirmation of a cN0 classification was absence of enlarged lymph nodes or nodes of less than 1 cm in diameter in computed tomography scans of lymph node stations 4, 7, and 10.[8] In tumors of the left upper lobe or the main bronchus, the requirements for confirmation also included the absence of diseased lymph nodes in the aortopulmonary window or the prevascular nodes (stations 5 and 6). If those criteria were not met, a negative result was required either by mediastinoscopy, mediastinotomy, or fine needle aspiration. A cN1 classification was obtained based on cytologic or histologic evidence. The requirements for confirmation of a cN2 classification included cytologic or histologic evidence from mediastinoscopy, mediastinotomy, fine needle aspiration, video-assisted thorascopic biopsy, etc. Classification as pN0, based on pathologic assessment after thoracotomy, required systematic node dissection of the mediastinum or systematic sampling of at least 4 lymph node stations: 2 (only on the right side), 4, 7, and 10 ipsilateral to the tumor. In addition, if the tumor was localized to the left side (upper lobe or main bronchus) exploration of the anterior mediastinal area and the aortopulmonary window (lymph node stations 5 and 6) was necessary with the same degree of certainty. The value of systematic sampling was similar to that of systematic node dissection in the classification of presence or absence of mediastinal lymph node involvement in a randomized study.[9] These minimum requirements (systematic sampling or mediastinal lymph node dissection) are indispensable for classification as pN0, given the observation of prognostic differences compared with random sampling of a single lymph node.[10]

Internal and external audits were performed to assess the relationship between the number of patients treated surgically and the cases included in the registry (audit standard >95%) and the presence and validity of data collected for each case (audit standard >70%), including the consistency of tumor staging.[11,12] The criterion for validity of survival data was established as the existence of a known follow-up of at least 85% of the recorded cases in each hospital. In the hospitals that did not meet these conditions, cases corresponding to the period with problems were excluded. Finally, it was confirmed that the information contained in paper records was correctly transferred to the computerized databases in a central office for data management.

All of these procedures were designed to control for bias in the selection of surgical cases, cases recorded above the total number of surgical cases, sample size, hospital type, changes in prognosis over the course of the study due to a prolonged recruitment period, deficient classification or classifications with a low degree of certainty, contamination from incomplete data series or erroneous data, and loss to follow-up.

Given that this study is focused on lung cancer treated by surgery and that in our experience the agreement between

clinical and pathologic stages is very poor,[13] this article only reports the analyses in relation to pathologic stages.

Statistical Analysis

Prognostic data is shown as the probability of survival at 5 years with 95% confidence intervals (CI) and as the median in months. Kaplan-Meier survival analysis was used and events were defined as death by any cause. Time 0 was the date of surgery. The log-rank test was used to compare survival curves. Statistical significance was established at $P<.05$.

Results

Of the 2944 cases of NSCLC, 82 patients (3%) showed evidence of BAC in the excised tissue. When those cases were compared with the remaining 2862 cases of NSCLC, a significant difference was observed in relation to sex and the possibility that the disease was detected by chance (Table 1). Differences were also found in the degree of dyspnea, general clinical status (European Cooperative Oncology Group scale), significant weight loss (more than 10% of normal weight), and presence of comorbidities, in general or of chronic obstructive pulmonary disease (COPD) in particular (Table 1).

No differences in age were observed between the two groups (Table 2). Nevertheless, there were significant differences in smoking habit, size of the tumor by radiography, and hematologic parameters (Table 2). The percentage of active and former smokers was 90% in NSCLC other than BAC and 55% in the BAC group ($P<.001$).

A total of 87% of BAC were in stage cI, compared with 75% of NSCLC other than BAC ($P<.001$; Table 3). This 12% difference in relative frequency between the two groups was almost doubled (22%) when the comparison was performed for stage pI (69% vs 47%; Table 3).

In terms of surgical treatment, pneumonectomy was significantly more common for NSCLC other than BAC and complete resection was more common for BAC (Table 4). Mortality associated with surgery was 8% in the 2862 cases of NSCLC other than BAC and 4% in the 82 cases of BAC ($P=.2$, Fisher's exact test).

Tables 5 and 6 show the comparative survival data for the 2 populations (NSCLC other than BAC compared with BAC) overall and for stage pIR0 (R0 indicates complete resection), excluding operative mortality, respectively. In this study, 5-year survival associated with stage pIA in BAC was 79%.

Discussion

In this series of NSCLC treated surgically in Spain by the GCCB-S, a total of 82 cases of BAC (3%) were found. Some differences were observed in patient and tumor characteristics between BAC and other types of NSCLC. BAC was found more often as stage cI than other types of NSCLC (in 12% more cases) and the same was true for stage pI (22% more). Complete resection was more likely in BAC (93% vs 80%) and

TABLE 1
Bronchioloalveolar Carcinoma: Clinical and Biological Characteristics, Part I*

	Without BAC	BAC	*P*
Number of patients	2862	82 (3%)	
Male sex	2673 (94%)	53 (65%)	<.001
Chance finding	815 (29%)	48 (59%)	<.001
Mild or no dyspnea	1771 (62%)	64 (78%)	<.001
Clinical stage 0†	575 (20%)	35 (43%)	<.001
Recent weight loss‡	292 (10%)	4 (5%)	<.05
Comorbidity, any	1719 (62%)	39 (50%)	<.05
COPD	1322 (47%)	27 (33%)	<.05

*BAC indicates bronchioloalveolar carcinoma; COPD, chronic obstructive pulmonary disease. †Performance status (European Cooperative Oncology Group scale). ‡Greater than 10%.

TABLE 2
Bronchioloalveolar Carcinoma: Clinical and Biological Characteristics, Part II*

	Without BAC	BAC	*P*
Age, y	64 (9.6)	65 (8.7)	NS
Smoking habit, pack-years	50.3 (33.7)	27.3 (34)	.001
Tumor size by radiography, cm	4.5 (2)	3.7 (2.6) .02	
Hemoglobin, g/dL	13.7 (1.7)	14.4 (1.5)	.001
Polymorphonuclear leukocytes, %	64.4 (10.6)	60.7 (10)	.001

*Data are shown as mean (SD). BAC indicates bronchioloalveolar carcinoma; NS, not significant.

TABLE 3
Bronchioloalveolar Carcinoma: Clinical and Pathologic Stages*

	Without BAC	BAC	*P*
Clinical stage			
cIA	479 (19%)	30 (43%)	<.001
cIB	1403 (56%)	31 (44%)	
cIIB	364 (14.5%)	4 (5.5%)	<.01
Other stages	266 (10.5%)	5 (7.5%)	
Total	2512	70	
Pathologic stage			
pIA	262 (10%)	19 (26%)	<.001
pIB	958 (37%)	31 (42.5%)	
pIIB	432 (17%)	6 (8.2%)	NS
Total	952 (36%)	17 (23.3%)	
Total	2604	73	

*Data are shown as absolute frequencies and percentages of the total number of cases with an initial clinical (2512 non-BAC vs 70 BAC) or pathologic (2604 non-BAC vs 73 BAC) stage, and in whom follow-up of survival was undertaken. BAC indicates bronchioloalveolar carcinoma; NS, not significant.

TABLE 4
Bronchioloalveolar Carcinoma: Extent of Lung Resection and Surgical Mortality*

Resection	Without BAC	BAC	*P*
Pneumonectomy	848 (30%)	11 (13%)	<.001
Bilateral lobectomy	141 (5%)	3 (4%)	NS
Lobectomy	1270 (44%)	53 (65%)	<.001
Complete resection	2301 (80%)	76 (93%)	<.001
Surgical mortality	225 (8%)	3 (4%)	NS
Total	2862	82	

*Data are shown as absolute frequencies and percentages of the total number of cases in each tumor group. BAC indicates bronchioloalveolar carcinoma; NS, not significant.

TABLE 5
Overall Survival*

	Without BAC	BAC	*P*†
Number of patients	2862	82	
Median, months	29.4	49.3	
5-year survival (95% CI)	34% (32%-36%)	45% (34%-56%)	.007

*BAC indicates bronchioloalveolar carcinoma; CI, confidence interval.
†Log-rank test.

TABLE 6
Survival in Non-Small Cell Tumors in Stage pIA-B With Complete Resection (R0), Excluding Operative Mortality*

	Without BAC	BAC	*P*†
Number of patients	1107	48	
Median, months	>60	>60	
5-year survival (95% CI)	53% (50%-56%)	65% (51%-79%)	.05

*BAC indicates bronchioloalveolar carcinoma; CI, confidence interval.
†Log-rank test.

survival was higher at 5-year follow-up, even when only the most selected population (pIR0) was considered (65% vs 53%). The results of this study confirm the low frequency of BAC in Spain; it represented only 3% of lung cancers in this surgical population, meaning that for all NSCLC diagnosed it would represent around 1%. In addition, in this study, extended criteria were used for the diagnosis of BAC, which included adenocarcinomas with features of BAC.

Although some studies have reported a significant increase in the relative frequency of BAC within NSCLC,[3,14] other authors have not obtained similar results. In a study performed in 2004 in the United States of America that analyzed a database of cases recruited between 1979 and 1998, it was found that BAC accounted for less than 4% of all diagnosed NSCLC in any of the periods studied.[15] However, this is not the case on all continents. As analyzed in a recent conference on BAC held in New York, this type of NSCLC is much more common in Japan than in the USA and Europe.[2] This difference in the frequency of presentation between continents is difficult to explain, and as a consequence, various theories have been put forward, such as infection,[16,17] differences in screening policies for NSCLC by computed tomography in Japan, or the possibility that there are genetic or environmental differences.[2]

The clinical characteristics of patients with BAC in our study (greater number of women and nonsmokers) are consistent with other reports.[14] In our study, cases of BAC showed a lower frequency of comorbidity, in particular COPD (Table 1). Given that concomitant COPD can represent a negative prognostic factor, survival was calculated in highly selected populations on the basis of stage and radical nature of surgery (NSCLC-pIA-pIB-R0, Table 4), excluding cases of operative mortality and patients with associated COPD. The results for 5-year survival were not substantially different (53% for NSCLC other than BAC and 68% for BAC).

The higher relative frequency of earlier stages in BAC may partly explain the differences found in the distribution of stages in this study compared with the Japanese study.[18]

In our study, cases of BAC in stage pI represented 69% of the total, compared with 47% in other types of NSCLC, results that coincide with the frequency observed in the studies of Albertine et al[19] (70% in stage pI), Dumont al[20] (73%), and Daly et al[21] (72%) but that are lower than those reported by Okubo et al[22] (77%) and Grover and Piantadosi[23] (84%). However, some studies have reported even lower frequencies (53% in stage pI).[24]

In our study, survival in cases of BAC was significantly higher than in other types of NSCLC, both overall (Table 5) and only considering cases in initial stages (pI) and with complete resection (R0), and once operative mortality had been excluded (Table 6). In this last population, we found a 5-year survival of 65% (95% CI, 51%-79%), similar to that reported by Dumont et al[20] (65%) but different from the exceptionally high value reported by Ebright et al[25] (84%) and the low value reported by Regnard et al[24] (56%). In this study, 5-year survival for stage pIA BAC was 79%, higher than that reported by Grover and Piantadosi[23] (69%) and lower than that reported by Daly et al[21] (91%). In summary, survival in cases of BAC in our study corresponded to an intermediate prognosis when considered in relation to that observed in other studies.

This variability may be partly due to limitations of our study that may also exist in other studies. The first limitation concerns whether or not, according to the most recent guidelines, classification as BAC is correct.[1] It is clear that the majority of our cases were adenocarcinomas with features of BAC, as is commonplace outside of Japan.[2] The distinction between this entity and pure BAC is not always easy[14] and requires greater agreement between pathologists, clinicians, and researchers, as recently concluded by other authors.[2] This is an important limitation for the exchange of information among different hospitals, groups, and countries.

Significant prognostic differences appear to exist between subclasses of adenocarcinoma and BAC. In the classic staging performed in 1995 by Noguchi et al[26] in Japan, survival for pure BAC in a peripheral lymph node was 100%, in mixed adenocarcinoma with BAC it was 75%, and in invasive BAC it was 5%. However, in a different study performed outside of Japan no differences in survival were observed between pure BAC, adenocarcinoma with signs of BAC, and BAC with focal invasion.[25] The clinical, tumor, and prognostic features of BAC and the limitations of the studies performed may explain some of the differences in the results obtained in different studies of NSCLC and between countries. These considerations should be taken into account in the assessment of worldwide databases,[27] and a clear understanding of them may allow decisions to be made on specific adjuvant therapy following appropriate mutational studies.

Contributors

Bronchogenic Carcinoma Cooperative Group of the Spanish Society of Pulmonology and Thoracic Surgery (GCCB-S)

Study coordinators: José Luis Duque (Hospital Universitario, Valladolid); Ángel López Encuentra (Hospital Universitario 12 de Octubre, Madrid); Ramon Rami Porta (Hospital Mútua de Terrassa, Barcelona).

Local coordinators: Julio Astudillo and Pedro López de Castro (Hospital Germans Trias i Pujol, Badalona, Barcelona); Emilio Canalís (Hospital Clínic, Barcelona); Antonio Cantó and Antonio Arnau (Hospital General Universitario, Valencia); Juan Casanova (Hospital de Cruces, Baracaldo, Bilbao); Manuel Castanedo and Jorge Quiroga (Hospital Universitario, Valladolid); Antonio Fernández de Rota and Ricardo Arrabal (Hospital Carlos Haya, Málaga); Federico González Aragoneses and Nicolás Moreno (Hospital Gregorio Marañón, Madrid); Jorge Freixinet and Pedro Rodríguez (Hospital Nuestra Señora del Pino, Las Palmas); Nicolás Llobregat (Hospital Universitario del Aire, Madrid); Nuria Mañes and Helena Hernández (Fundación Jiménez Díaz, Madrid); Mireia Serra Mitjans and José Belda Sanchís (Hospital Mútua de Terrassa, Barcelona); José Luis Martín de Nicolás (Hospital Universitario 12 de Octubre, Madrid); Nuria Novoa (Complejo Hospitalario, Salamanca); Jesús Rodríguez (Complejo Hospitalario, Oviedo); Antonio José Torres García and Ana Gómez (Hospital Universitario San Carlos, Madrid); Mercedes de la Torre (Hospital Juan Canalejo, La Coruña); Abel Sánchez-Palencia and Javier Ruiz Zafra (Hospital Virgen de las Nieves, Granada); Andrés Varela Ugarte, María del Mar Córdoba (Clínica Puerta de Hierro, Madrid); Yat Wah Pun (Hospital de la Princesa, Madrid).

Data management: Agustín Gómez de la Cámara and Francisco Pozo Rodríguez (Unidad de Epidemiología Clínica, Hospital 12 de Octubre, Madrid).

REFERENCES

1. Colby TV, Noguchi M. Adenocarcinoma. In: Travis WD, Brambilla E, Müller-Hermelink HK, Harris CC, editors. Tumours of the lung, pleura, thymus and heart. Lyon: IARC Press; 2004. p. 35-44.
2. Travis WD, Garg K, Franklin WA, Wistuba II, Sabloff B, Noguchi M, et al. Evolving concepts in the pathology and computed tomography imaging of lung adenocarcinoma and bronchioloalveolar carcinoma. J Clin Oncol. 2005;23:3279-87.
3. Miller VA, Hirsch FR, Johnson DH. Systemic therapy of advanced bronchioloalveolar cell carcinoma: challenges and opportunities. J Clin Oncol. 2005;23:3288-93.
4. Grupo Cooperativo de Carcinoma Broncogénico de SEPAR (GCCB-S). Cirugía del carcinoma broncogénico en España. Estudio descriptivo. Arch Bronconeumol. 1995;31:303-9.
5. Sobin LH, Wittekind C. UICC International Union Against Cancer, TNM classification of malignant tumours. 5th ed. New York: Wiley-Liss; 1997. p. 91-7.
6. López Encuentra A, and the Bronchogenic Carcinoma Cooperative Group of the Spanish Society of Pneumology and Thoracic Surgery (GCCB-S). Criteria of functional and oncological operability in surgery for lung cancer. A multicenter study. Lung Cancer. 1998;20:161-8.
7. López Encuentra A, Gómez de la Cámara A, Varela de Ugarte A, Mañes N, Llobregat N y GCCB-S. El "fenómeno Will-Rogers". Migración de estadios en carcinoma broncogénico, tras aplicar criterios de certeza clasificatoria. Arch Bronconeumol. 2002;38: 166-71.
8. American Thoracic Society, Clinical staging primary lung cancer. Am Rev Respir Dis. 1983;127:659-64.
9. Izbicki JR, Passlick B, Karg O, Bloechle C, Pantel K, Knoefel WT, et al. Impact of radical systematic mediastinal lymphadenectomy on tumor staging in lung cancer. Ann Thorac Surg. 1995;59:209-14.
10. Gajra A, Newman N, Gamble GP, Kohman LJ, Graziano SL. Effect of number of lymph nodes sampled on outcome in patients with stage I non-small-cell lung cancer. J Clin Oncol. 2003;21: 1029-34.
11. López Encuentra A, Gómez de la Cámara A, for the Bronchogenic Carcinoma Cooperative Group of the Spanish Society of Pneumology and Thoracic Surgery (GCCB-S). Validation of a central review board of staging prior to surgery for non-small-cell lung cancer–impact on prognosis: a multicenter study. Respiration. 2002;69:16-24.
12. Grupo Cooperativo de Carcinoma Broncogénico de SEPAR (GCCB-S). Control de calidad en un registro multiinstitucional de carcinoma broncogénico. Arch Bronconeumol. 1996;32 Supl 2:70.
13. López-Encuentra A, García Luján R, Rivas JJ, Rodríguez-Rodríguez J, Torres-Lanza J, Varela Simó G. Bronchogenic Carcinoma Cooperative Group of the Spanish Society of Pneumology and Thoracic Surgery Comparison between clinical and pathologic staging in 2994 cases lung cancer. Ann Thorac Surg. 2005;79:974-9.
14. Detterbeck FC, Jones DR, Funkhouser WF. Bronchioloalveolar carcinoma. In: Detterbeck FC, Rivera MP, Socinski MA, Rosenman JG, editors. Diagnosis and treatment of lung cancer. An evidence-based guide for the practicing clinician. Philadelphia: WB Saunders; 2001. p. 394-407.
15. Read WL, Page NC, Tierney RM, Piccirillo JF, Govindan R. The epidemiology of bronchioloalveolar carcinoma over the past two decades: analysis of the SEER database. Lung Cancer. 2004;45: 137-42.
16. Wootton SK, Halbert CL, Miller AD. Sheep retrovirus structural protein induces lung tumours. Nature. 2005;434:904-7.
17. de las Heras M, Barsky SH, Hasleton P, Wagner M, Larson E, Egan J, et al. Evidence for a protein related immunologically to the jaagsiekte sheep retrovirus in some human lung tumours. Eur Respir J. 2000;16:330-2.
18. López-Encuentra A, Bulzebruck H, Feinstein AR, Motta G, Mountain CF, Naruke T, et al. Tumor staging and classification in lung cancer. Lung Cancer. 2000;29:79-83.
19. Albertine KH, Steiner RM, Radack DM, Golding DM, Peterson D, Cohn HE, et al. Analysis of cell type and radiographic presentation as predictors of the clinical course of patients with bronchioalveolar cell carcinoma. Chest. 1998;113:997-1006.
20. Dumont P, Gasser B, Rouge C, Massard G, Wihlm JM. Bronchoalveolar carcinoma: histopathologic study of evolution in a series of 105 surgically treated patients. Chest. 1998;113:391-5.
21. Daly RC, Trastek VF, Pairolero PC, Murtaugh PA, Huang MS, Allen MS, et al. Bronchoalveolar carcinoma: factors affecting survival. Ann Thorac Surg. 1991;51:368-76.
22. Okubo K, Mark EJ, Flieder D, Wain JC, Wright CD, Moncure AC, et al. Bronchoalveolar carcinoma: clinical, radiologic, and pathologic factors and survival. J Thorac Cardiovasc Surg. 1999; 118:702-9.
23. Grover FL, Piantadosi S. Recurrence and survival following resection of bronchioloalveolar carcinoma of the lung–The Lung Cancer Study Group experience. Ann Surg. 1989;209:779-90.
24. Regnard JF, Santelmo N, Romdhani N, Gharbi N, Bourcereau J, Dulmet E, et al. Bronchioloalveolar lung carcinoma: results of surgical treatment and prognostic factors. Chest. 1998;114:45-50.
25. Ebright MI, Zakowski MF, Martin J, Venkatraman ES, Miller VA, Bains MS, et al. Clinical pattern and pathologic stage but not histologic features predict outcome for bronchioloalveolar carcinoma. Ann Thorac Surg. 2002;74:1640-6.
26. Noguchi M, Morikawa A, Kawasaki M, Matsuno Y, Yamada T, Hirohashi S, et al. Small adenocarcinoma of the lung. Histologic characteristics and prognosis. Cancer. 1995;75:2844-52.
27. Goldstraw P. The International Staging Committee of the IASLC: its origins and purpose. Lung Cancer. 2002;37:345-8.