ELSEVIER

European Journal of Cardio-thoracic Surgery 23 (2003) 818–823

EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY

www.elsevier.com/locate/ejcts

Bronchioloalveolar lung cancer: occurrence, surgical treatment and survival☆

József Furák[a,*], Imre Troján[a], Tamás Szőke[a], László Tiszlavicz[b], Zita Morvay[c], József Eller[d], Ádám Balogh[a]

[a]*Department of Surgery, University of Szeged, Szeged, Hungary*
[b]*Department of Pathology, University of Szeged, Szeged, Hungary*
[c]*Department of Radiology, University of Szeged, Szeged, Hungary*
[d]*Department of Medical Informatics, University of Szeged, Szeged, Hungary*

Received 22 September 2002; received in revised form 26 January 2003; accepted 3 February 2003

Abstract

Objective: The prevalence of pulmonary adenocarcinoma has risen worldwide. Bronchioloalveolar carcinoma (BAC) was studied with regard to whether it exhibits a similar tendency, and its typical features were analysed. **Methods**: Between 1992 and 2001, 278 lung resections were carried out for adenocarcinoma. Of these, 67 (24.1%) proved to involve BAC. Whereas BAC accounted for 6.9% of the cases in 1992, in 2001 the proportion was 46.9%. There were 37 men (55.2%) and 30 women (44.7%); the average age was 60.5 years. 58.2% of them had no complaints. Of the 26 non-smokers, 69.2% were women; of the 41 smokers, 29.2% were women. In consequence of the tumour, 49 lobectomies, three bilobectomies, six pneumonectomies and nine wedge resections were performed. **Results**: The surgical mortality was 1.6%. The pathology revealed that 26 (38.8%) tumours were in stage I/A. In 15 cases (22.4%), tuberculosis (TB) could be revealed besides the BAC: by skin tests in four cases, by CT in three cases, by case history in four cases, and by pathology in four cases. For the overall group of 67 patients, the 5-year survival rate was 61.9%, and the mean survival time was 75.7 months. The 5-year survival rate among the women (74%) was significantly better than that among the men (37%) ($P = 0.030$). There was no significant difference in survival with regard to the multiple BAC (85%). The 5-year survival rate was significantly worse in the mixed BAC group (20%) than in the non-mucinous (62.7%) and in mucinous (59%) group. The overall 5-year survival rate among the smokers and TB patients was 61 and 79%, respectively, which is higher than that among the non-smokers (47%) and non-TB patients (56%). The survival rate for the wedge resection cases was 37%, which was lower than that for the cases involving major resections (60%) ($P = 0.939$). **Conclusion**: BAC has a favourable survival, particularly in women. In spite of this, resection smaller than lobectomy is recommended only as a compromise. A multiple appearance does not imply a worse survival. The best survival rate was found in the non-mucinous BAC among the histological groups. TB seems to be frequent among BAC patients.

Keywords: Bronchioloalveolar carcinoma; Survival; Scar-carcinoma; Smokers

1. Introduction

The occurrence and importance of bronchioloalveolar carcinoma (BAC) have increased in recent years. Whereas in the 1950s, only 5% of all lung cancers were BAC, in the 1990s, the rate had increased to 24% [1].

BAC is mentioned as the lung cancer of non-smoking, middle-aged women. Its mass or nodular type appears as a small peripheral tumour, and it is subjected to surgery in an early stage. While only 15–25% of all lung cancer cases are in stage I, the proportion of stage I cases in BAC is 68% [2,3]. BAC spreads by the aerogenous route in 50–94% of the cases, but a lymphatic spread is not typical for this tumour. The N disease accounts for about 10% of these cases [2,4]. In 64% of the advanced cases, bilateral or multiple forms of BAC can be found [5]. 92% of BAC patients display intrathoracic recurrence, and 29% extrathoracic recurrence [6]. Non-BAC lung cancers frequently give brain metastases (20%), but in BAC cases this type of metastasis is seen in

☆ Presented at the 16th Annual Meeting of the European Association for Cardio-thoracic Surgery, Monte Carlo, Monaco, September 22–25, 2002.

* Corresponding author. Tel.: +36-30-99-55-815; fax: +36-62-545-701.
E-mail address: fj@surg.szote.u-szeged.hu (J. Furák).

1010-7940/03/$ - see front matter © 2003 Elsevier Science B.V. All rights reserved.
doi:10.1016/S1010-7940(03)00084-8

only about 8% [5]. It is generally observed that the overall 5-year survival rate after surgery for BAC (48–69%) is better than for other lung cancer cases (17–47%) [5–7].

The increasing number of BAC cases suggests a change in the aetiology factors of lung cancer. Naturally, that smoking remains a very important factor, but the scar-cancer theory postulates that BAC can develop in a previously scarred area of the lung parenchyma, such a previous inflammation therefore also being an aetiology factor for lung cancer. Tuberculosis (TB) was a very common disease in the not too distant past, and the scar of this inflammation could well be the bed of BAC [1]. We set out to evaluate the clinicopathology of BAC, and the types of surgery performed on it.

2. Materials and methods

In this retrospective analysis, the data of patient charts were studied. The survival data were obtained by means of phone call information.

2.1. Patients

Between 1992 and 2001, 278 lung resections were performed for adenocarcinoma, in the Division of Thoracic Surgery at the University of Szeged. Of these 278 adenocarcinoma cases, the final pathology indicated that 67 involved BAC. The yearly distributions of the adenocarcinomas and BAC are shown in Table 1.

The sex distribution of the 67 patients with BAC was as follows: 37 men + 30 women. Their mean age was 60.5 years (41–79). The tumour was detected on the basis of the complaints in 28 cases (41.8%); 39 patients (58.2%) were symptom-free and the tumour was found on routine chest X-ray examination.

Forty-one patients (61%) were smokers and 26 (39%) were non-smokers before the surgery: 70.7% of the smokers and 30.8% of the non-smokers were men, and 29.3% of the smokers and 69.2% of the non-smokers were women.

Table 1
Distributions of adenocarcinomas and BAC by year

Year	Adenocarcinoma	BAC	BAC (%)
1992	27	2	6.9
1993	17	2	10.5
1994	28	3	9.7
1995	28	5	15.2
1996	22	7	24.1
1997	12	6	33.0
1998	18	6	25.0
1999	18	4	18.2
2000	24	17	41.5
2001	17	15	46.9
Total	211	67	24.0

BAC: bronchioloalveolar carcinoma.

2.2. Tumour status

Of the tumours, 59.7% (40) were located on the right side, and 40.3% (27) on the left side. The distribution of the lobe involvement was as follows: 59.7% upper lobes (40), 35.8% lower lobes (24), and 4.4% middle lobe (3). The tumours were verified by fine-needle biopsy or bronchoscopic cytology. In 41.8% of the cases (28 cases), the preoperative investigation verified BAC; in 25.4% (17 cases) some other type of malignant tumour was proved; in 32.8% (22 cases) no identification was achieved.

2.3. Radiology

On the basis of its radiological appearance, BAC may be divided into three groups [1]: (1) the "mass-type", which is a well-circumscribed, single peripheral nodule; (2) the infiltrative tumour, which furnishes a pneumonitis-like picture (not circumscribed) and (3) their multiple forms. The preoperative computed tomographic (CT) examinations revealed 45 (67.2%) single mass lesions, 10 (14.9%) single infiltrative lesions and 12 (17.9%) multiple tumours (nine mass and three infiltrative). Only two of the 12 multiple tumours were bilateral.

2.4. Surgery

One patient, with bilateral multiple tumours, received neoadjuvant chemotherapy; in the other cases, there was no preoperative chemotherapy. Lung resection was performed through a standard posterolateral thoracotomy. For the 55 single mass or infiltrative tumours, 42 lobectomies, three bilobectomies, four pneumonectomies and six wedge resections were performed. For the 10 ipsilateral multiple lesions, four lobectomies, one right upper lobectomy with lower lobe wedge resection, three multiple wedge resections and two pneumonectomies were carried out. For one of the two bilateral, multiple tumours, after neoadjuvant chemotherapy, two-stage surgery was performed: first a right upper lobectomy, and 6 weeks later a left upper lobe wedge resection. For the other bilateral, multiple tumour, we performed the same surgery without neoadjuvant che-

Table 2
Surgery for BAC on the basis of preoperative CT findings

Type of surgery	Solitary tumour	Multiple tumour	Total
Lobectomy	42	4	46
Bilobectomy	3	0	3
Lobectomy + wedge	0	1	1
Lobectomy + other side wedge	0	2	2
Wedge resection	6	3	9
Pneumonectomy	4	2	6
Total	55[a]	12[b]	67

CT: computed tomography.
[a] Pathology verified three lesions as multiple.
[b] Pathology verified five lesions as multiple.

motherapy. The distribution of the surgery is shown in Table 2.

2.5. Pathology

The diagnosis of BAC was based on the current literature guidelines [8,9]. We accepted the adenocarcinoma as BAC if: (1) more than 50% of the adenocarcinoma was a BAC component, (2) the tumour grew along pre-existing lung structures without invasion or destruction of the lung parenchyma and (3) there was no pleural or vascular infiltration. The BAC was divided into three types: (1) non-mucinous, (2) mucinous and (3) mixed mucinous and non-mucinous or undetermined.

Atypical alveolar hyperplasia (AAH) is a preinvasive lesion, and only rare cases have been documented where AAH was identified and there was subsequent progression to invasive carcinoma. The tumours were staged in accordance with the international standards (TNM) [10,11]. The pathological investigation was performed by one pathologist.

The diagnosis of TB was based on the recommendations of the European Respiratory Society, the World Health Organization and the International Union against Tuberculosis and Lung Disease [12]: (1) "infection with Mycobacterium tuberculosis" is defined as infection with Mycobacterium tuberculosis manifested by a significant tuberculin skin test reaction without any sign of clinically and/or radiologically active disease, (2) "tuberculosis" refers to the clinically, bacteriologically, histologically and/or radiologically active disease. We classified case as TB if the patient gave a positive tuberculin skin test, if the patient had been treated for TB in the past (medicine or surgery), if a residual TB shadow was found on CT, or if the pathology revealed the disease.

2.6. Statistics

Survival curves were constructed according to the Kaplan–Meier method and the Cox regression test, by means of the SPSS9 computer program.

3. Results

One patient after pneumonectomy died in the post-operative period, from an acute myocardial infarction, yielding a mortality rate of 1.6%. One reoperation was necessary for haematoma evacuation after pneumonectomy.

3.1. Tumour characteristics and stages

The mean diameter of the tumours was 3.7 cm (0.9–17). Forty-two (62.8%) non-mucinous, 15 (22.4%) mucinous and 10 (14.9%) mixed tumours were found. In 46 cases (68.7%), scar or fibrosis was revealed in the tumour. 86.7% of the tumours from the TB patients and 63.5% of the tumours from the non-TB patients contained fibrosis or scar tissue. On the other hand, 83.3% of the non-mucinous, 26.7% of the mucinous, and 70% of the mixed cancers contained fibrosis or scar tissue.

As far as BAC was concerned, 58.2% were in stage I (26 IA and 13 IB). There were 13 stage II tumour (three IIA and 10 IIB), and seven stage IIIA tumours. Eight patients had multiple lesions: five of them were in the same lobe (stage IIIB), while three patients had intrapulmonary metastasis to another lobe (stage IV). The staging distribution of the tumours is shown in Table 3.

Of the 12 multiple BAC cases suggested by the preoperative CT, only six were verified as multiple BAC by the final pathology by light microscopic criteria. In the remaining six cases, the satellite lesions were found to be pseudotumours, intrapulmonary lymph nodes and other types of malignant lung cancers (second primary lung cancer). The preoperative CT investigations indicated 55 solitary nodules or infiltrative tumours, but in three cases the intraoperative findings were multiple lesions. These data revealed that the sensitivity of CT for the multiple BAC was 66.7%, and the specificity was 90.1%.

The characteristics of the tumours of the smokers and the non-smokers are summarized in Table 4. The incidence of non-mucinous BAC in the smoking groups was significant ($P = 0.019$). There was no significant difference in the incidence of mucinous and mixed BAC between the smokers and non-smokers, and the appearance of the mass and infiltrative forms of BAC was not significantly different between the two groups either.

In four cases, the pathology revealed TB besides the BAC. In the remaining 11 of the 15 TB patients, the diagnosis of TB was based on the skin tests (four patients), CT results (three patients) and case history (one patient was operated on for TB: wedge resection and three patients had been treated with antituberculotics). The appearance of the non-mucinous BAC among the TB cases was significantly higher (86.7%) than the mucinous and mixed BAC (13.3%) ($P = 0.036$). In the non-TB group, the incidence of non-

Table 3
TNM distribution of the BACs

Tumour stage	Total number	% distribution
IA	26	38.8
IB	13	19.4
IIA	3	4.5
IIB	10	14.9
IIIA	7	10.4
IIIB	5	7.5
IV	3	4.5

TNM: primary tumour (T), lymph node (N), distant metastasis (M), staging system.

Table 4
Tumour characteristics in smokers and non-smokers

	Non-smokers ($n = 26$)	Smokers ($n = 41$)	P
Non-mucinous (pathology)	12	31	0.019
Mucinous	9	6	0.074
Mixed tumour	5	4	0.294
Mass type (radiology)	22	32	0.752
Infiltrative	4	9	0.752

mucinous BAC was 55.7%, while that of mucinous and mixed BAC was 44.3%.

3.2. Survival

The overall 5-year survival rate was 61.9%, and the mean survival time was 75.6 months. There was a significant difference in 5-year survival rate between the males and females. For the women it was 74% (90.8 months), and for the men it was 37% (47.9 months). The P-value was 0.03, i.e. significant. The survival curve is shown in Fig. 1.

There was a borderline, non-significant survival difference between the patients with or without complaints: the 5-year survival rate for the patients with preoperative symptoms and complaints was 45.6% (58.4 months), and that for the patients without complaints was 65% (83.2 months). The P-value was 0.213, i.e. non-significant.

There were significant differences as concerns the histological type of BAC. The 5-year survival rate for patients with mixed type BAC was 20% (37.4 months), which is significantly worse than that for the non-mucinous (62.7%) and mucinous (59%) cases ($P = 0.016$).

A multivariate analysis was performed with the gender, symptoms and non-mucinous BAC to support the results of the univariate analysis. Cox regression test confirmed that the survival for female is significantly better than that for male ($P = 0.0269$), with 3.91 odds ratio. A borderline, but non-significant survival rate for non-mucinous BAC ($P = 0.0835$) confirms the better prognosis of this type of BAC (odds ratio was 0.41), and for the symptoms the result was non-significant ($P = 0.2936$) with 0.57 odds ratio.

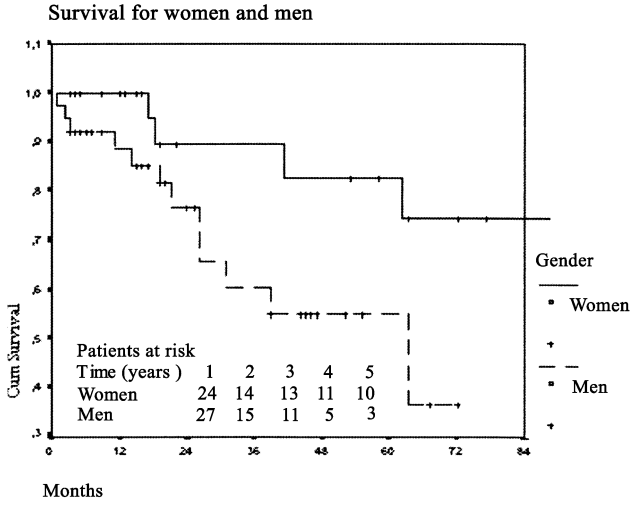

Fig. 1. Five-year survival rate for women and men.

In the multiple (!) tumour cases, the 5-year survival rate was 82% (83.3 months), while in the non-multiple tumour cases, it was 59% (74 months). The difference was not significant ($P = 0.636$).

As concerns the survival rate after the different types of surgery, we compared the minimal resections (wedge resection) with the major resections (lobectomy, lobectomy + wedge resection or pneumonectomy). The 5-year survival rate after the major resections was 60%, whereas after simple wedge resections it was only 37%. The difference was not significant ($P = 0.939$), but it is noteworthy.

We found an interesting situation as regards the survival data for smokers and non-smokers. The 5-year survival rate in the non-smoker group was 47%, while in the smoker group it was 61%. This difference was not significant ($P = 0.926$). The reason for this difference is suspected to be the higher proportion of non-mucinous BAC among smokers (Table 4).

The 5-year survival rate was 79% among TB patients and 56% among non-TB patients ($P = 0.177$). The better survival can be attributed to the frequent appearance of non-mucinous BAC among TB patients.

3.3. Recurrence

Eight recurrences were found in the follow-up period: four intrathoracic (three lung parenchyma and one chest wall) and four extrathoracic (three brain and one bilateral suprarenal gland) metastases developed.

4. Discussion

BAC accounts for an increasing proportion of the adenocarcinomas [1]. The sex distribution of the patients is also changing. The participation of women among BAC cases has been reported to be 42%, which was very close to that in adenocarcinoma, but much more frequent than that in squamous cell cancer (14%) [7]. In another study, the participation of women in BAC was only 14.4% [4]. In our practice, in 2001, 46.9% of the adenocarcinomas were BAC, and the involvement of women was 44.7%. This tendency points to a hormonal or genetic aetiology of BAC.

Although the incidence of BAC is increasing, the survival rate is markedly better than in other lung cancer cases [6,7]. Frequently (68–73%), BAC is operated on in stage I [2,4]. Stage I appearance in non-BAC cancers is only 15–25% [3], so the growth of BAC is slower. A lymphatic spread is not typical for BAC, and lymph node metastasis

occurred in about 10% in one study [2], with an aerogenous spread in 94% of the cases. On the other hand, one report [4] did not find a favourable survival in BAC, as compared with the international standard [11]. The 5-year survival rates were as follows: stage I, 65%; stage II, 16% and stage III, 19%. Others found a favourable survival in stage I (83%) [6]. In our cases, the 5-year survival rates were similar: stage I/A, 71%; stage I/B, 77%; stage II/A, 24%; stage II/B, 19% and stage III/A, 9%. From these data, we can conclude that the survival really is better in stage I than that in the non-BAC group [11], but in the N disease the survival is shorter. To reveal the cause of these data, we analysed the histological and radiological appearance of BAC. In stage I (A + B), the proportion of the non-mucinous BAC with a favourable survival is significantly higher 74.5% ($P = 0.024$), than in the more advanced stages II–IV. On the other hand, the proportion of the mass type tumour with an unfavourable survival curve in our study was 84.6%. Although, the survival in the mass or nodule type cases in our study was 58%, while in the infiltrative group it was 78%. It is well known in the literature that the nodule or mass type BAC has a favourable survival [4]. From these data, it can be concluded that the better survival duration in stage I can be attributed to the frequent appearance of non-mucinous and mass type lesions.

The overall survival rate in the literature is 48–69% [2,4]; in our study, it was 61.9%. In women, the 5-year survival rate (74%) is much better than the above-mentioned 61.9%, but it is only 37% in men. Thus, BAC is a frequent tumour in women, and the survival rate in females is better.

In our study, 58.2% of the tumours were in stage I, which is a little lower than in the literature. Our patients had more advanced cancer. We cannot confirm the statement that BAC rarely gives lymph node metastases. We found N disease in 29.8% of the cases, i.e. three times more frequent than in the literature (10%) [2]. In our work, of the 20 N disease cases, 10 N1 and 10 N2 metastases were verified, but we did not observe an aerogenous spread. A mucinous histological type [13], lymph node metastasis [2], multiple lesions [1] and an aerogenous spread [4] have been mentioned as unfavourable prognostic markers in BAC. Our study revealed better, but not significantly survival in infiltrative cases and in multiple lesions. This can be concluded as being due to the low number of cases.

In one study, the most frequent multiple lesions were observed in adenocarcinoma cases, 69% of them being BAC [14]. It is very interesting in that study that the 5-year survival rate for the multiple adenocarcinomas involving predominantly BAC cases was 46%, which was much better than that in stage III/B or IV. In our study, the 5-year survival rate for the multiple BAC cases was 85%. The various data allow the conclusion that the predicted survival rate based on the current staging for the multiple BAC lesion is not adequate, and that despite the stage III/B or IV active surgery should be performed.

The standard treatment for BAC is not really different from that for the other lung cancers. The most frequent forms of resection are lobectomy and pneumonectomy. Palliative pneumonectomy sometimes performed for bilateral multiple BAC with a serious shunt effect [15]. In our practice, the most frequent resection type was lobectomy. In multiple cases, the main tumour was removed by lobectomy, while the satellite lesions were excised by multiple wedge resections. 83.3% of the multiple lesions were situated ipsilaterally, so the management was not difficult. The contralateral side was rarely involved in the BAC spread.

Recurrence is mentioned as a typical feature of BAC. 92% of the recurrences after stage I and 56% of the recurrences after stage III–IV tumours develop in the thorax [5,6]. Others have stated that BAC gives rise to metastases more frequently than do squamous or pure adenocarcinoma [7]. In our practice, intra- and extrathoracic metastases appeared at equal rates.

For study of the scar-carcinoma theory [1], we considered the presence of scar tissue or fibrosis in the BAC. 68.6% of the tumours contained scar tissue or fibrosis, which may be an indication of some kind of inflammation and consequent fibrosis in the past. Table 4 reveals that non-mucinous BAC is the most frequent cancer type in the smoking group, and more than 80% of the cases of this type of the BAC contain scar tissue. These data suggest that, during smoking, not only the released carcinogen, but also the scars caused by the smoking inflammation can be a risk factor for carcinogenesis.

5. Conclusions

1. BAC is a typical lung cancer type, with a favourable survival rate in women.
2. A multiple appearance is not characteristic, but in multilocal cases the survival is reasonably good.
3. In multiple cases, active surgery is recommended, because the satellite lesions are frequently seen ipsilaterally.
4. In limited resection cases, the survival rate was somewhat lower, so resection smaller than lobectomy is recommended only as a compromise.
5. Among smoker patients, non-mucinous BAC is the most frequent subtype, with a favourable survival curve.
6. TB seems to be frequent among BAC patients.

References

[1] Barkley JE, Green MR. Bronchioloalveolar carcinoma. J Clin Oncol 1996;14:2377–86.
[2] Okubo K, Mark EJ, Flieder D, Wain JC, Wright CD, Moncure AC, Grillo HC, Mathisen DJ. Bronchoalveolar carcinoma: clinical, radiologic and pathologic factors and survival. J Thorac Cardiovasc Surg 1999;118:702–9.
[3] Kwiatkowski DJ, Harpole DH, Godleski J, Herndon II JE, Shieh D-B,

Richard W, Blanco R, Xu H-J, Strauss GM, Sugarbaker DJ. Molecular pathologic substaging in 244 stage I non-small-cell lung cancer patients: clinical implication. J Clin Oncol 1998;16:2468–77.

[4] Dumont P, Gasser B, Rougé C, Massard G, Wihlm J-M. Bronchoalveolar carcinoma. Histopathologic study of evolution in a series of 105 surgically treated patients. Chest 1998;113:391–5.

[5] Breathnach OS, Ishibe N, Williams J, Linnoila RI, Caporaso N, Johnson BE. Clinical features of patients with stage IIIB and IV bronchioloalveolar carcinoma of the lung. Cancer 1999;86:1165–73.

[6] Breathnach OS, Kwiatkowski DJ, Finkelstein DM, Godleski J, Sugarbaker DJ, Johnson BE, Mentzer S. Bronchioloalveolar carcinoma of the lung: recurrence and survival in patients with stage I disease. J Thorac Cardiovasc Surg 2001;121:42–7.

[7] the Lung Cancer Study Group, 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.

[8] Travis WD, Colby TV, Corrin B, Shimosato Y, Brambilla E. Histological typing of lung and pleural tumours. In: World Health Organization Pathology Panel, editor. World Health Organization. International histological classification of tumours. Berlin: Springer, 1995. p. 5.

[9] Castro CY, Coffey DM, Mederios LJ, Cagle PT. Prognostic significance of percentage of bronchioloalveolar pattern in adenocarcinomas of the lung. Ann Diagn Pathol 2001;5:274–84.

[10] Mountain CF, Dresler CM. Regional lymph node classification for lung cancer staging. Chest 1997;111:1718–23.

[11] Mountain CF. Revision in the international system for staging lung cancer. Chest 1997;111:1710–7.

[12] Migliori GB, Raviglione MC, Schaberg T, Davies PDO, Zellweger JP, Gremska M, Mihaescu T, Clancy L, Casali L. Tuberculosis management in Europe. Eur Respir J 1999;14:978–92.

[13] Carretta A, Canneto B, Calori G, Ceresoli GL, Campagnoli E, Arrigoni G, Vagani A, Zannini P. Evaluation of radiological and pathological prognostic factors in surgically-treated patients with bronchoalveolar carcinoma. Eur J Cardiothorac Surg 2001;20: 3667–71.

[14] Nakajima J, Furuse A, Oka T, Kohno T, Ohtsuka T. Excellent survival in a subgroup of patients with intrapulmonary metastasis of lung cancer. Ann Thorac Surg 1996;61:158–63.

[15] Barlesi F, Doddoli C, Thomas P, Kleisbauer JP, Giudicelli R, Fuentes P. Bilateral bronchioloalveolar lung carcinoma: is there a place for palliative pneumonectomy? Eur J Cardiothorac Surg 2000;20: 1113–6.