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Surgical treatment of synchronous multiple lung cancer located in a different lobe or lung: high survival in node-negative subgroup☆

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Abstract

Background: The International Association for Study of Lung Cancer Staging Committee proposes for the next revision of TNM (tumour, nodes, metastases) classification that additional nodules in a different lobe of the ipsilateral lung moves from an M1 designation to T4, while additional nodule(s) in the contralateral lung should be classified as M1a, because of poorer survival. We analysed the survival after surgery of patients presenting with synchronous lung cancers located in a different lobe or lung. **Methods:** A database of 1551 patients operated on for non-small-cell lung cancer (NSCLC) between 1990 and 2007 was evaluated for unilateral (other lobe) (n = 15) and bilateral (n = 28) synchronous multiple lung cancers. The relationships among the location of tumours, histology, date of surgery (before and after 2000), lymph node metastasis, type of surgery, adjuvant therapy and survival were analysed. **Results:** The 5-year survival for all synchronous multiple lung cancers (n = 43) was 34%, with a median survival of 32 months. Postoperative mortality was 7%. On univariate analysis, only lymph node metastasis and surgery before the year 2000 affected the overall survival adversely, and both prognostic factors maintained a statistical significance on multivariate analysis. The 5-year survivals were 57% and 0% for patients without (n = 25) and with (n = 18) lymph node metastasis, respectively (p = 0.004), and were 43% and 18% for patients operated upon after (n = 27) and before (n = 16) the year 2000, respectively (p = 0.01), perhaps reflecting a better selection process related to the extensive use of positron emission tomography (PET) scanning. The 5-year survival was not different between bilateral (43%) and unilateral (27%) synchronous lung cancers (p = n.s.). **Conclusions:** Our data support complete surgical resection of synchronous multiple lung cancers in patients with node-negative NSCLC. Even patients with bilateral lung cancer should not be treated as metastatic disease. Provided there is no evidence of node and distant metastasis, after an extensive preoperative work-up, including PET scanning and mediastinoscopy, bilateral surgical resection should be performed in fit patients.

Keywords: Synchronous multiple lung cancer; Metastasis; Surgery; Multifocal; TNM classification; NSCLC

1. Background

With the recent advancement in diagnostic imaging techniques, such as multi-slice spiral computed tomography (CT) and positron emission tomography-computed tomography (PET-CT) scan, thoracic surgeons are increasingly facing the problem of synchronous multiple lung nodules, which can correspond to multiple primary lung cancers (MPLCs), or pulmonary metastasis from the index tumour.

This distinction can have important clinical and therapeutic implications, but the preoperative diagnosis is almost impossible and can remain difficult even after pathologic examination of the resected specimen, considering that an identical histology does not exclude two primaries with absolute certainty [1]. Immunostaining is an even more widely adopted tool to achieve a diagnosis, but its preoperative usefulness is impaired by the difficulty to obtain adequate specimens from all foci of tumours.

According to the last TNM (tumour, nodes, metastases) classification, revised in 1997, the presence of multiple tumour nodules located in a different lobe or lung is classified as M1 (stage IV) [2]; consequently, most patients are treated with chemotherapy or chemo/radiotherapy and are not offered surgical resection.

For instance, the proposal from the International Association for Study of Lung Cancer Staging Committee (IASLC) for the next upcoming revision of the TNM staging system to reclassify an additional nodule in the contralateral lung as M1a is based on data of 362 patients with synchronous bilateral lung cancer, of which only seven underwent bilateral surgery [3].

However, few selected patients with synchronous multiple lung cancer (MLC) can benefit from surgery [4—8], but the

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difficult diagnostic definition in the clinical setting makes the selection for surgery controversial.

It must be also emphasised that majority (57–86%) of the additional nodules seen radiographically in patients with clinical stage I–III NSCLC are benign lesions [9,10]. Therefore, a patient should not be denied a curative approach on the basis of a second pulmonary nodule without a definitive tissue diagnosis.

The additional nodules are often small and the only way to obtain tissue from the lesion is by thoracotomy, meaning that a decision has to be established on the basis of clinical criteria such as radiological characteristics.

Our policy has always consisted in offering the chance of surgery to patients with synchronous MLC if judged completely resectable and in absence of extrathoracic metastasis.

We reviewed our experience with synchronous MLCs discovered before surgery in order (1) to estimate the outcome after surgical resection and (2) to determine the clinical and pathological prognostic factors of long-term survival to improve our selection process of candidates to aggressive surgical treatment.

2. Matherials and methods

The lung cancer database of the Thoracic Surgery Unit at the University of Siena was reviewed to identify all patients operated on for non-small-cell lung cancer (NSCLC) from 1990 to 2007.

Patients with more than one physically distinct tumour, located in a different lobe or lung and discovered preoperatively, were selected and form the basis of the study.

These tumours were defined as MLCs irrespective of histology (same or different), location (different lobe or lung) and in the absence of extrathoracic disease.

All the patients with synchronous lesions within the same lobe as the primary tumour had been excluded from this study, since they are often discovered during or after surgery and no extra work-up nor a different surgical approach is required.

Patients with carcinoid tumours and bronchioloalveolar adenocarcinomas (BACs) showing pure ground-glass opacity at CT scan were excluded as well.

Assessment included history, physical examination, routine blood tests, electrocardiogram, echocardiography, blood gas analysis, spirometry and estimation of CO diffusion capacity of the lung.

Cardiac stress tests and coronary angiography were performed when indicated by history of angina pectoris or by significant ischaemic signs in the basal electrocardiogram; cardiorespiratory tests and/or lung perfusion scintigraphy were executed as second-level tests in case of predicted postoperative forced expiratory volume in 1 s (FEV1) lesser than 40%.

Clinical staging was based on broncoscopy, contrast-enhanced CT of the chest, upper abdomen and brain, as well as bone scintigraphy; mediastinoscopy was carried out selectively in case of enlarged mediastinal lymph nodes on CT (short axis >1 cm).

Since 2000, PET scan was performed in all patients with synchronous MLCs.

For bilateral lesions, our surgical policy favoured sequential lobectomies over sublobar resections if respiratory function allowed it, while in case of unilateral resection, whenever possible, we tried to perform lobectomy and wedge resection, avoiding pneumonectomy.

In case of anatomical resection (lobar resection, i.e., lobectomy, bilobectomy and pneumonectomy), a systematic mediastinal nodal dissection was performed.

Sublobar resections (e.g., segmentectomy and wedge resection) and lymph node sampling were preferred for small peripheral tumours (<2 cm) in patients with limited pulmonary function tests, especially after the first operation.

The second surgery was performed only when the patient had fully recovered, as demonstrated by a fresh spirometry and in the absence of progressive disease at re-staging with CT of the chest, brain and upper abdomen.

Tumour histology was classified according to the World Health Organization classification [11]; pathologic staging was based on the International System for Staging Lung Cancer [12].

The standard follow-up protocol included a total-body CT scan and serum markers every 6 months for the first 2 years, then a chest CT scan every 12 months until the 5th year. Follow-up information was obtained either during office visits or by telephone with patients, their relatives or physician, and follow-up was completed in all patients through January 2009.

Quantitative variables were expressed as mean $\pm$ standstandard deviation; range is reported where appropriate.

Survival was defined as the interval between the date of surgery and date of death or last follow-up, whereas disease-free survival was defined as the duration from pulmonary resection to the date of recurrence or non-cancer-related death.

The survival curves were computed according to the Kaplan–Meyer method and the differences between groups were determined by long-rank test.

A series of covariates were tested for their influence upon overall survival, including sex, age, location of tumours, presence of co-morbidity, date of surgery (before and after 2000), lymph node metastasis, adjuvant therapy and type of surgery (lobar vs sublobar).

Identification of the independent impact of covariates on long-term survival was made through Cox regression analysis.

The Fisher's exact and K2 tests were used to estimate the differences between synchronous MLC categories on clinical and pathological variables previously described. All statistical tests were two-sided: a p-value less or equal to 0.05 was accepted for statistical significance.

Perioperative mortality (defined as death occurring intraoperatively or in-hospital or within 30 days after operation) was included in calculation of survival.

The Statistical Package for the Social Sciences version 14.0 software (SPSS Inc., Chicago, IL, USA) was used for all analysis.

The University Hospital of Siena Ethic Board granted approval for this study, with no requirement for patient's consent considering that this was a retrospective study.

3. Results

During the study period (1990–2007), 50 patients were found to have unilateral (other lobe) ($n = 15$) or bilateral ($n = 35$) synchronous MLCs, representing 3.2% of all pulmonary resections ($n = 1551$) for NSCLC at the University of Siena.

We could surgically treat only one side of seven patients with bilateral lesions: the insufficient pulmonary reserve of three patients after the first resection prevented the contralateral resection. These patients were treated with radiotherapy.

Two patients in whom the first resection was incomplete and two other patients with a progressive disease on re-staging were treated with chemotherapy.

Those 28 patients with bilateral disease who underwent surgery on both sides and those 15 patients with unilateral MLCs were further analysed.

The main features of these 43 patients are listed in Table 1. Forty males and three females with the mean age of 66 (±6.9) years (range: 44–77 years) are enumerated in the list.

A total of 40 patients (93%) were smokers, and 18 patients (42%) were current smokers at the time of surgery.

Co-morbidity, mainly cardiopulmonary, was present in 14 patients (32%).

Five patients (12%) had a previous malignancy, with no evidence of active disease at the time of evaluation for their new primary lung tumour.

Two malignant tumours had been found in 37 patients while the remaining six (14%) had three or more.

Since 2000, all patients ($n = 27$; 60%) had PET scan, including 20 patients in the bilateral group and seven patients in the unilateral group. Fourteen patients (32%) underwent mediastinoscopy. All the 28 patients with bilateral lesions were treated sequentially, with a median interval of 67 days (range: 35–300 days).

Table 1
Main features of population (percentages reported within columns).

	Unilateral nodules in non-primary lobe ($n = 15$)	Contralateral additional nodules ($n = 28$)	Total ($n = 43$)	p
Age (mean ± SD)	66.9 ± 7.6	66.5 ± 6.7	66.7 ± 6.9	0.86
Sex				
Male	13 (86.7)	27 (96.4)	40 (93)	
Female	2 (13.3)	1 (3.6)	3 (7)	
Smokers				0.265
Yes	15 (100)	25 (89.3)	40 (93)	
No	0	3 (10.7)	3 (7)	
Co-morbidity				0.048
Yes	2 (13.3)	12 (42.9)	14 (32.6)	
No	13 (86.7)	16 (57.1)	29 (67.4)	
cTNM				0.145
100	1 (7.7)	7 (25)	8 (18.6)	
200	13 (86.6)	12 (42.9)	25 (58.1)	
210	1 (7.7)	2 (7.1)	3 (7)	
300	0	1 (3.6)	1 (2.3)	
400	0	5 (17.9)	5 (11.6)	
410	0	1 (3.5))	1 (2.3)	
Period				0.103
1990–1999	8 (53.3)	8 (28.6)	16 (37.2)	
2000–2007	7 (46.7)	20 (71.4)	27 (62.8)	

Table 2
Details of surgical procedures performed (percentages reported within columns).

Unilateral MPLC ($n = 15$)		Bilateral MPLC ($n = 28$)	
Lobectomy and sublobar resection	8 (53.3)	Bilateral sublobar resection	2 (7.1)
Sublobar resection	2 (13.3)	Lobectomy and sublobar resection	13 (46.4)
Bilobectomy	2 (13.3)	Bilateral lobectomy	10 (35.7)
Pneumonectomy	3 (20)	Pneumonectomy and sublobar resection	3 (10.7)

The details of surgical procedures are given in Table 2. Thirty-one lesions were resected by a sublobar resection in 28 patients (65%), including 12 segmentectomies and 19 wedge resections. Systematic nodal dissection was performed in 23 patients (53%) and lymph node sampling in 20 (47%).

One or more complications developed in 16 patients, giving an overall morbidity of 37%. The most frequent complication was prolonged air leak, which was observed in six cases, followed by supraventicular arrhythmia in two cases; pulmonary oedema in two cases; and pneumonia, haemothorax requiring re-thoracotomy, empyema and atelectasis requiring bronchoscopy in one case.

The operative mortality was 7% ($n = 3$). Acute respiratory distress syndrome (ARDS) was the cause of death in two patients and pulmonary embolism in one. Mean hospitalisation stay was 16 days for both two interventions.

Histology (Table 3) was identical in 27 patients (60%): adenocarcinoma and squamous cell carcinoma were the predominant histologic types, 65% and 25%, respectively. Two patients in the bilateral group had a bronchioloalveolar carcinoma in only one side. None of patients, including those with previous malignances, had metastases from extrapulmonary tumours, as confirmed by immunostaining on resected specimens.

At the final pathological examination, the highest pN factor was pN0 in 18 patients, pN1 in seven and pN2 in three patients in the bilateral group, and pN0 in seven patients, pN1 in two and pN2 in six patients in the unilateral group.

Eighteen patients received adjuvant treatment, consisting of chemotherapy in 14 cases, radiotherapy in two cases and sequential or combined chemo-radiotherapy in two other cases.

The intent-to-treat survival analysis of all 50 patients with synchronous MLCs showed a 3-year and 5-year survival of 40% and 31%, respectively, with a median survival of 30 months (95% confidence interval (CI): 20.5–39.5).

In the group of 43 patients who underwent planned resection of all lesions, median survival was 32 months (95% CI: 21.1–42.9), with an overall 3- and 5-year survival of 41% and 34% (Fig. 1).

Survival was not affected by age, sex, location (unilateral vs bilateral), presence of co-morbidity, histology (same vs different), type of surgery (lobar vs sublobar) and administration of adjuvant therapy.

On univariate analysis, only lymph node metastasis and surgery before the year 2000 significantly worsened survival, and both factors maintained a statistical significance on multivariate analysis (Tables 4 and 5).

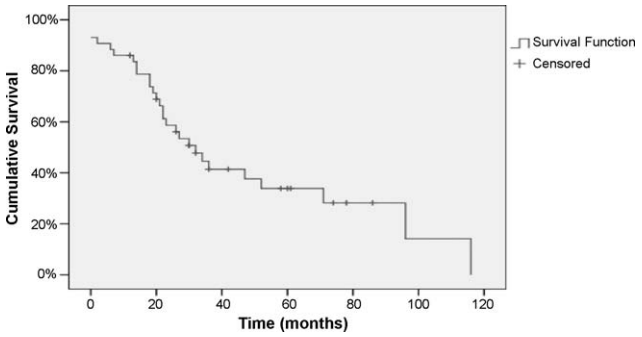

Fig. 1. Cumulative survival of population.

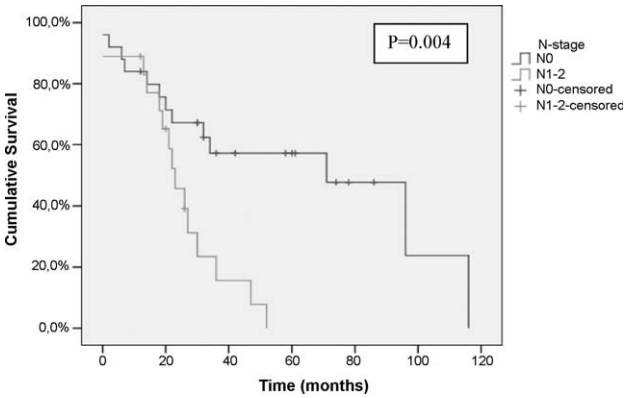

Fig. 2. Survival according to nodal status.

The 5-year survival was 57% and 0% for patients without ($n = 25$) and with ($n = 18$) lymph node metastasis, respectively ($p = 0.004$), and 43% and 18% for patients operated upon after ($n = 27$) and before ($n = 16$) the year 2000, respectively ($p = 0.01$) (Figs. 2 and 3).

At the mean follow-up of 33.5 months (range: 0—116 months), 15 patients (35%) were still alive and 28 (65%) had died.

The cause of late death was related to cancer in 23 of 25 patients. The first site of recurrence was local (defined as any disease in the chest) in nine (39%) patients and systemic in 14 (61%). Disease-free survivals were 37% at 3 years and 27% at 5 years.

4. Discussion

The appropriate diagnosis and management of patients with synchronous MLCs remain controversial. Difficulties mainly consist in defining an additional focus of cancer in the lung separated from the main tumour, which may represent a haematogenous metastasis, a lymphatic spread metastasis or a second primary lung cancer. While an additional focus of tumour in the same lobe does not change the treatment and prognosis substantially, it is arduous to know how best to treat patients with a second same histology cancer focus located in a different lobe or lung. The American Joint Committee on Cancer (AJCC) staging system classifies this anatomical situation as M1, with the consequence that most patients are not usually referred to surgery. However, the highly variable frequency of synchronous tumours in surgical series ranging from 0.8% to 21% [13—17] indicates that some units probably have a more aggressive attitude to surgery, a strategy that may be justified since complete resection offers the best chance for prolonged survival. In addition, a highly variable 5-year survival ranging from 0% to 70% for patients with synchronous MLCs has been reported in the 1990s, consistent with the difficulty of reliably classifying these tumours [13—17].

In this study, the 5-year overall survival of the 43 patients with MPLC who underwent resection of all lesions was 34% with a median survival of 32 months.

Furthermore, the intent-to-treat survival analysis of all 50 patients showed a satisfactory 5-year survival of 31%. Obviously, this is a highly selected group of patients and we do not have information on patients with MLCs who were not offered surgery to compare their survival.

We tried our best to reduce possible bias in interpreting the results. We excluded important confounding variables, such as carcinoid and pure BAC, because of their more indolent biological behaviour. We also excluded patients with same-lobe lesions who present a clear indication to surgery, without requiring an extra work-up other than is required for primary tumour or requiring a different surgical approach.

Alternatively, we included only patients whose lesions had been discovered preoperatively, considering that lesions detected during or after surgery are smaller and then associated with a better prognosis.

Even after excluded these subcategories of patients, our results in terms of survival rates are undoubtedly much better than those reported for stage IV NSCLC [2] and show that some selected patients with synchronous MLCs may indeed benefit from an aggressive surgical attitude.

Our analysis demonstrates that lymph node involvement is the strongest prognostic factor, as reported by other authors [14,17—19]. In particular, Okada et al. found a 5-year survival

Table 3
Histology (percentages reported within columns).

	Unilateral ($n = 15$)		Bilateral ($n = 28$)		Total ($n = 43$)
Same histology	Adk—Adk	9 (60)	Adk—Adk	13 (46.4)	27 (63)
	Epi—Epi	1 (6.7)	Epi—Epi	4 (14.3)	
Different histology	Epi—Adk	2 (13.3)	Epi—Adk	6 (21.4)	16 (37)
	Epi—SCLC	1 (6.7)	Epi—Large C	2 (7.1)	
	Adk—SCLC	1 (6.7)	Adk—Adenosq	1 (3.6)	
	Epi—Adenosq	1 (6.7)	Large C—Adk	1 (3.6)	
			Large C—Adenosq	1 (3.6)	

Abbreviations: Adk: adenocarcinoma, Epi: epidermoid carcinoma, Large C: large cell anaplastic carcinoma, Adenosq: adeno-squamous carcinoma, SCLC: small-cell lung carcinoma.

Table 4
Univariate analysis of predictors of survival.

	Patients (*N*)	Median survival (Months)	5-year survival (%)	*p*
Age				
<67[a]	21	32	27.6	0.84
≥67[a]	22	27	36.6	
Sex				
Male	40	32	33.4	0.738
Female	3	23	50	
Location				0.670
Ipsilateral	15	52	43	
Bilateral	28	30	27	
Histology				0.625
Same	27	36	34	
Different	16	22	33	
Type of resection				0.678
Sublobar	28	34	29	
Lobar	15	32	42	
Co-morbidity				0.387
Yes	14	26	26	
No	29	34	37	
Lymph node involvement				*0.004*
Yes (N1–N2)	18	23	0	
No	25	71	57	
Period				*0.016*
1990–1999	16	20	18	
2000–2007	27	52	43	

Italics: statistically significative.
[a] Median age of population.

rate of 45% in node-negative patients and that lymph node involvement was a better predictor of survival than the number and location of pulmonary metastasis [20]. Tung et al. reported an excellent 5-year survival rate of 66.7% in node-negative patients with ipsilateral multifocal NSCLC in different lobes [21].

In our cohort of patients with synchronous MLCs, classified as stage IV, we found a good 5-year survival of 57%, among the node-negative patients, compared with 0% in node-positive patients. These findings argue in favour of accurate assessment of nodal status at the clinical evaluation. All patients deserve PET scan and mediastinoscopy to exclude from surgery patients with involvement of mediastinal lymph nodes. The significant better survival found in patients with bilateral MLCs operated on after 2000 (and staged with PET)

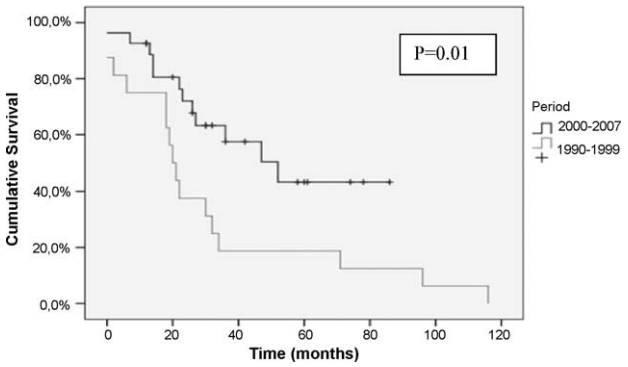

Fig. 3. Survival according to period of surgery.

seems to confirm the benefit of improved selection in a category of patients with potential higher metastatic disease.

Data suggest that even N1 disease is associated with a relatively poor prognosis: so these patients should be scheduled for surgery only after any effort has been made to exclude lobar-node metastasis using more recent diagnostic tools (e.g., PET/CT and cytological confirmation by endoscopic ultrasonography-guided fine-needle aspiration). In case of doubt, a decision should be made on the basis of operative risk and feasibility of radical anatomical resection with acceptable residual pulmonary function.

It is reasonable to believe, although not demonstrated, that determining the second tumour to be a metastasis would change staging, prognosis and management. In 60% of our patients, the pulmonary lesions presented an identical histology. This result, in association with that of literature [6,7,14,15,18,20], illustrates that synchronous MLCs can be considered as metastasis in more than half of patients. We made no attempt to differentiate between synchronous MPLCs and intrapulmonary metastasis, because the criteria of Martini and Melamed [22] are not easily applicable in the clinical setting and no other clinical criteria to distinguish them have been defined [13]. Although it is an important biological question, from a practical point of view it may not be relevant because our results, as those of other series, showed no statistically different survival between patients with multiple tumours of the same histology (which include the subgroup with intrapulmonary metastasis) and patients with multiple tumours of different histology (synchronous MPLC) [4,6,7,14,15,18,20]. Probably, some patients with

Table 5
Multivariate analysis for survival (Cox regression).

	Factor	R.R.	95% CI	*p*
Age	<67[a] versus ≥67 years	0.667	0.207–2.144	0.496
Sex	Male versus female	3.050	0.327–28.477	0.328
Smoke	Yes versus no	1.959	0.188–20.412	0.574
Location	Unilateral versus bilateral	0.597	0.225–1.584	0.300
Type of resection	Sublobar versus lobar	1.048	0.389–2.823	0.926
Histology	Same versus different	0.519	0.185–1.454	0.212
Adjuvant treatment	No versus yes	0.603	0.195–1.862	0.379
Co-morbidity	None versus 1 or more	0.496	0.186–1.327	0.163
N stage	pN0 versus pN1–2	0.202	0.075–0.546	*0.002*
Period	1990–1999 versus 2000–2007	4.221	1.742–10.410	*0.001*

Italics: statistically significative.
[a] Median age of population.

multifocal NSCLC tend to have widespread disease; therefore, these patients should undergo an extensive search for mediastinal lymph node involvement and distant metastasis. In addition to a CT scan of the chest, all these patients should undergo a PET scan and brain CT or MRI to rule out metastatic disease. Mediastinoscopy should also be performed routinely to identify for surgery-only patients with no mediastinal lymph node involvement.

In the absence of distant metastasis and lymph node involvement, the question whether a patient had two synchronous primary tumours or a primary tumour with an isolated metastasis remains quite academic since it does not imply different surgical approach, and long-term results after surgery are comparable.

Other authors have recently reported good results in patients who underwent resection of synchronous MLCs [4—8,18,23], with 5-year survival rate ranging from 15% to 38%. These results seem to be better than those in studies published during the early 1990s and probably depend on a more accurate selection of patients, thanks to recent advances in the diagnostic tools.

Our study differs from many of these series since we have included only patients whose lesions were identified preoperatively. In the second period of our study (2000—2007) patients showed a significantly better outcome than those operated on in the first period (1990—1999) with a 5-year survival rate of 43% and 16%, respectively. Since we did not find any difference in the prognostic factors, complications and operative mortality between the two groups of patients (data not shown), we can only speculate that these improved results reflect a better selection process related to PET-CT scan that was introduced and routinely used in these patients after 2000. Although the incidence of node metastasis before and after introduction of PET scan did not significantly differ in surgically resected patients, it is likely that the routine use of PET allowed us to select only cases of minimal N2 disease and/or to exclude from surgery patients with occult distant metastasis. Unfortunately, we have no data on patients with node or distant metastasis discovered preoperatively since these patients were not candidates for surgery.

In patients with bilateral lesions, sequential delayed resections are safer and can be performed with acceptable morbidity and mortality. Our surgical mortality rate of 7% is in line with that reported in recent studies ranging from 1.1% to 8.5% [6—8,18,23].

We did not find any difference in long-term survival when we compared the group of patients who underwent lobectomy or pneumonectomy with the group of patients who underwent sublobar resection, although it could be pointed out that lobar resections grants better long-term results at the cost of slightly higher postoperative mortality. Thus we believe that lobectomy should be performed in presence of optimal respiratory reserve, although sublobar resections are an acceptable alternative for patients with resectable disease but marginal cardiopulmonary function tests.

In preparation for the new TNM classification, incoming in 2009, the IASLC Staging Committee proposes to reclassify ipsilateral nodules in a different lobe as T4 disease and contralateral nodules as M1a disease. This assumption is based on the observation that patients with ipsilateral nodules in a different lobe had a similar 5-year survival (22%) to patients with T4 disease [24] and prognosis of patients with contralateral nodules (5-year survival, 3%) was similar to patients with pleural dissemination [25].

Although not significant, possibly because of small number of patients, we also found a decrease in survival when the additional nodule was located contralaterally than ipsilaterally to other lobe, with 5-year survival rate of 27% and 40%, respectively. Other studies have reported contrasting results with better survival in case of bilateral synchronous tumours than in ipsilateral other lobe lesions [4—18]. This is possibly related to selection bias, considering that patients with bilateral tumours are selected more accurately, particularly regarding to staging accuracy, as acknowledged by the authors [18].

The limitations of this study are those inherent to all retrospective studies, such as selection bias and consequently lack of data regarding prognosis and survival of non-surgically treated patients: no conclusion can be inferred from the small percentage of patients who did not undergo the second planned contralateral intervention.

5. Conclusions

Surgical resection of synchronous MLCs could be recommendable after an extensive work-up (including PET scan and mediastinoscopy routinely) to select node-negative patients.

Provided there is no evidence of node and distant metastasis, the hypothesis of synchronous MPLCs should prevail on that of metastatic disease even in patients with a second focus of the same type of cancer and surgery should be performed in patients with adequate cardiopulmonary reserve.

Results after surgery have improved in recent years, probably due to better selection of patients.

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