Surgical results for multiple primary lung cancers

Federico Rea*, Andrea Zuin, Donatella Callegaro, Luigi Bortolotti, Giovanni Guanella, Francesco Sartori

Division of Thoracic Surgery, University of Padua, Policlinico Universitario, 35128 Padua, Italy

Received 11 October 2000; received in revised form 9 May 2001; accepted 13 June 2001

Abstract

Objective: The development of a multiple primary lung cancer (MPLC) is not rare in long-term survivors after curative resections. We analysed our experience in order to verify surgical results and long-term survival in our patients.

Methods: From 1971 to 1999, 80 patients with MPLC (two tumours each, total 160) were treated at the Division of Thoracic Surgery of the University of Padua. Our criteria for the definition of a synchronous or metachronous cancer are those proposed by Martini and Melamed. We had 19 patients with a synchronous tumour and 61 patients with a metachronous tumour. We performed 95 lobectomies, 5 completion pneumonectomies and 53 segmentectomies. Of 160 MPLCs, 60 were squamous carcinomas, 78 adenocarcinomas, 8 small cell lung cancers, 9 large cell lung cancers and 5 other tumours. Of 160 MPLCs, 140 were N0 disease (87.5%) and 20 were N1 or N2 disease (12.5%).

Results: The overall 30-day mortality was 2.5% (2 patients). Eighteen patients (22.5%) had postoperative complications. Survival at 5 and 10 years for all patients was 72% and 58%, respectively. Five-year survival for patients with metachronous and synchronous disease from the time of initial diagnosis of cancer was 85% and 20% (P<0.001), and 10-year survival was 58% and 0% (P<0.001), respectively. Survival after the development of a metachronous lesion was 51% at 5 years and 20% at 10 years. The 5-year survival of patients with metachronous tumours undergoing standard surgical procedures of the second tumour was 52%; the 5-year survival of patients undergoing atypical or segmental resections was 55%.

Conclusions: Careful follow-up is recommended in all patients surviving curative resection. More accurate selection criteria for MPLC is required. An aggressive surgical approach is justified in patients with MPLC and offers the greatest chance for long-term survival even in the case of limited resection. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Lung; Bronchial cancer; Multiple cancer; Resection

1. Introduction

Multiple primary lung cancer (MPLC) is not an uncommon event and several authors report an incidence of 0.2–20%. More recently an estimate from the available information is that the risk of developing second lung cancer in patients who have been treated with surgical resection of an early-stage lung cancer is approximately 1–2% per patient per year [1–8].

Second lung cancer was first reported by Beyreuther in 1924 [9]; Martini and Melamed in 1975 [3] outlined the criteria for differentiation between MPLC and recurrence.

The aim of the study is to verify the surgical results and long term survival in our patient and the appropriateness of definition criteria.

2. Material and methods

From 1971 to 1999, 80 patients with MPLC were treated at the Division of Thoracic Surgery of the University of Padua.

Tumours were designated ‘synchronous’ when detected or resected simultaneously and ‘metachronous’ when the second tumour was found some time later.

Our criteria for the definition of a synchronous or metachronous cancer are those proposed by Martini and Melamed (Table 1).

Synchronous tumours were noted in 19 patients (23.5%) and metachronous tumours in 61 patients (76.5%).

There were 72 male and eight female patients ranging in age from 33 to 86 (median age 63 years).

Staging was according to the TNM classification [25,26]. Staging procedures from 1971 to 1981 (12 pts.) consisted in chest roentgenograms, bronchoscopy, mediastinoscopy and, from 1982 (68 pts.), we added the CT-scan of the thorax.
CT-scan or ultrasound of the abdomen, CT-scan or MNR of the brain and bone nuclear scan.

We performed 95 lobectomies, five completion pneumonectomies, 53 segmentectomies.

Pathologic diagnosis was obtained through the study of surgical specimens in all patients. Of 160 MPLCs, 60 were squamous carcinomas, 78 adenocarcinomas, eight small cell lung cancers, nine large cell lung cancers and five others tumours. Of 160 MPLCs, 140 were N0 disease (87.5%) and 20 were N1 or N2 disease (12.5%), as resulted from systematic radical lymphnode dissection.

2.1. Metachronous tumours

The median time for diagnosis of metachronous disease was 25 months, with a range of 2–201 months.

The surgical procedures for the first tumour consisted in 49 lobectomies, two pneumonectomies, and 10 segmentectomies.

Pathologic diagnosis was obtained through the study of surgical specimens in all patients. Of 160 MPLCs, 60 were squamous carcinomas, 78 adenocarcinomas, eight small cell lung cancers, nine large cell lung cancers and five others tumours. Of 160 MPLCs, 140 were N0 disease (87.5%) and 20 were N1 or N2 disease (12.5%), as resulted from systematic radical lymphnode dissection.

Histologic examination revealed 49 squamous carcinomas, 53 adenocarcinomas, seven small cell lung cancers, nine large cell lung cancers and four other tumours.

The same histologic type occurred less frequently if the first primary tumour was a squamous carcinoma as opposed to an adenocarcinoma (16 of 49 patients (32.6%) and 19 of 53 (35.8%), respectively) ($P = 0.17$).

Metachronous tumour occurred in the lung contralateral to the initial lesion in 44 cases (72.1%).

The first tumour resulted N0 in 52 patients, N1 in six patients and N2 in three patients.

Metachronous second cancer was N0 in 53 patients, N1 six patients, N2 in two patients.

46 patients had N0 disease in the first cancer and also in the second.

2.2. Synchronous tumours

The surgical procedures consisted in 17 lobectomies, two pneumonectomies and 17 segmentectomies (Table 2).

In nine patients the synchronous tumour was located in the ipsilateral lung and in 10 patients was located in the contralateral lung. In this last group the histology was the same in seven patients and different in three.

All the ipsilateral synchronous tumours were found in different lobes: the histology was the same in six patients and different in three.

Three patients received a bilateral surgical approach at the same time.

Histologic examination revealed 11 squamous carcinomas, 25 adenocarcinomas, one small cell carcinoma and one mesenchymal tumor.

Pathologic staging in the 19 index tumors revealed N0 disease in 17 pts., N1 disease in one, N2 disease in one. In the second tumors revealed N0 disease in 18 pts., N1 disease in one and N2 disease in zero.

Survival rate was calculated with the Kaplan–Meier method and differences in survival were determined by log-rank analysis. Comparisons were also made using $\chi^2$ analysis, as appropriate.

Significance was defined as $P$ less than or equal to 0.05.

3. Results

Overall 30-day mortality was 2.5% (two patients). The incidence was 1.6% for metachronous tumours and 5.2% for synchronous tumours. The causes of death were respiratory failure in one patient and myocardial infarction in the other one.

Eighteen patients (22.5%) had postoperative complications: 13 patients had atelectasis, one haemothorax, two atrial fibrillation, one post-pneumonectomy broncho-pleural fistula and 1 broncho-pleural fistula post left upper lobectomy.

The incidence was 26.2% for patients with metachronous tumour and 10.5% for patients with synchronous tumour ($P = 0.15$).

Five- and 10-year survivals for all patients with MPLC included in the analysis, from the time of initial diagnosis were 77 and 58%, respectively (Fig. 1).

Five-year survival from the time of initial diagnosis for patients with metachronous and synchronous lesions was
85% (95% CI; 85.8–118.4) and 20% (95% CI; 18.8–52.1), respectively (P < 0.001) (Fig. 2).

Ten-year survival was 58% and 0%, respectively (P < 0.001).

Five- and 10-year survival for patients with metachronous disease, measured from the time of diagnosis of the second tumour was 51% (95% CI; 33.0–55.3) and 20%, respectively. This survival was not significantly different from the survival for patients with synchronous disease (P = 0.31) (Fig. 3).

Five- and 10-year survival from the time of the first diagnosis of patients in whom metachronous disease developed at an interval equal to or greater than 2 years was 91% (95% CI; 101.9–142.4) and 62%, respectively. The 5- and 10-year survival of patients in whom metachronous disease developed at an interval less than 2 years was 52% (95% CI; 42.6–79.2) and 0%, respectively (P = 0.002) (Fig. 4).

Five-year survival of patients with metachronous tumours undergoing standard surgical procedures (lobectomies and pneumonectomies) of the second tumour was 52% (95% CI; 27.8–62.5); 5-year survival of patients undergoing segmentectomy was 55% (95% CI; 29.6–56.0) (P = 0.31) (Fig. 5).

Five- and 10-year survival from the time of the first diagnosis of patients with the same histology in both metachronous was 82% (95% CI; 77.7–115.7) and 44%, respectively; in those patients with different histology it was 86% (95% CI; 81.7–150.2) and 70%, respectively. The difference was not statistically different (P = 0.31) (Fig. 6).

Five-year survival from the time of the second diagnosis of lung tumour in those patients with N0 disease in both
tumours was 45%; for those patients with N1-2 disease, 5-year survival was 23%.

Between the 19 synchronous tumours, 13 were found with the same histology in both diseases: the 1-year, 2-year and 5-year survival was 77, 46 and 15% respectively.

All patients with lung cancer were examined postoperatively by our staff every 3 months for 1 year, then every 6 months for 2 years and then on an annual basis. Chest X-ray films, abdominal ultrasound, tumoral markers and a general physical examination are accomplished at each visit; CT scan and, recently, high-resolution spiral CT scan is performed once a year. No patients were lost to follow-up. Mean and median follow-up was 86 and 82 months respectively.

4. Discussion

In clinical studies it is difficult to establish with absolute certainty whether the second tumour is a recurrence, a metastasis or indeed a new primary lesion.

Criteria for multiple primary lung cancer were proposed by Warren and Gates in 1932 [10]. Several authors have since revised these criteria [4,11–13] but the most recent and recognised criteria for differentiation between MPLC and recurrence are those of Martini and Melamed, which have been used by most subsequent authors, including ourselves.

Some authors [14,15] consider that the distinction between synchronous and metachronous cancer is arbitrary, because it refers to the moment of diagnosis and not to the moment of development. Even the question of whether a newly discovered lung lesion after resection is actually a second primary tumour or a recurrence remains a theoretical one.

Although the majority of locally recurrent disease will become manifest within the designated 2-year exclusion interval by Martini and Melamed, extending this interval might be expected to improve specificity of this criteria [14,16–19]. We did not experience a significant difference in survival when the histology of metachronous tumour was the same as the index tumour compared to the metachronous tumour with different histology (Fig. 6).

Instead the group of patients with an interval between the first and second cancer longer than 2 years experienced a significantly better prognosis compared to the group of patients with an interval shorter than 2 years. Patients with synchronous and early metachronous disease did experience significantly reduced survival compared with those with late metachronous disease, similar to results in other published reports [18–20].

Although the decreased survival noted in these patients cannot be related to specific determinant responsible for this poor outcome, the possibility that in the group of patient with synchronous and early metachronous lung cancers could be included some cases of solitary pulmonary metastases always exists.

Perhaps in this subgroup of patients we have to adopt adjuvant or neoadjuvant therapy even in the early stage.

These different criteria to collect patients with MPLC can explain the variety of incidence reported by different authors [3,18,20,21]. Although there is no uniform agreement as to the definition and prevalence of a second primary lung cancer, most thoracic surgeons would agree that the new cancer should be resected if the lesion is solitary in lung parenchyma, if the local and distant staging is negative and if the patient will tolerate lung resection [3,18,20,21].

In our study the survival from the time of initial diagnosis of lung cancer was significantly better for patients having metachronous cancers than for those having synchronous cancers, which is in agreement with many authors [16–20,22].
Survival for patients with metachronous disease, measured from the time of diagnosis of the second tumour, was not significantly better than the survival for patients with synchronous disease: this is in agreement with some authors [18,20,22] and in contrast with others [15,19]. This may indicate that in these papers the patients were selected with different criteria and in different stages of disease (Table 3).

Therefore there is no clear evidence, in the literature, whether the prognosis is better in metachronous or synchronous MPLC.

Anyhow our 5-year survival of 51% for metachronous cancers and 20% for synchronous cancers is better than that for metastatic or locally recurrent disease reported in the literature ranging between a 9 and 23% 2-year survival respectively [17,23].

Our poor results in the group of patients with synchronous disease, compared with those of other authors [15,19] could be correlated with the small number of cases in our study, but we cannot exclude the possibility that some patients with metastatic disease have also been included in this group.

The 5- and 10-year survival rate observed in our patients with metachronous disease is better than results of other authors; we believe that our results are related to the very high percentage of early stage in the group of patients with metachronous disease.

In our study, 5-year survival, from the time of second diagnosis, of those 62 patients with N0 disease in both cancers was 57%, while of 7 patients with N0 in the first disease and N1 or N2 in the second one, only one patient is alive and disease free at 5 years.

Unfortunately we have not enough patients in the group of N1–N2 disease in the second cancer to make any conclusion; other authors [15,16] reported a survival for patients with early stage MPLC significantly better than those with advanced tumours.

In our group of synchronous MPLCs, 13 had the same histology: six tumours were in the ipsilateral lung and seven in the controlateral lung. The survival rate after 1, 2 and 5 years was 77, 46 and 15% respectively.

Actually, however, according with the latest TNM classification, these patients are reclassified M1 with a very low expected survival: 20, 5 and 1% after 1, 2 and 5 years [26].

We have not enough patients with synchronous tumours and same histology to compare with the survival rate of patients with M1 lung cancer, but our good results suggest

<table>
<thead>
<tr>
<th>Author</th>
<th>Classification</th>
<th>5-year survival (%)</th>
<th>10-year survival (%)</th>
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<tbody>
<tr>
<td>Rosengart [19]</td>
<td>Synchronous</td>
<td>44</td>
<td>23</td>
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<td>111 patients</td>
<td>Metachronous after I surgery</td>
<td>70</td>
<td>42</td>
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<tr>
<td></td>
<td>Metachronous after II surgery</td>
<td>23</td>
<td>9</td>
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<tr>
<td>Verhagen [22]</td>
<td>Synchronous</td>
<td>15</td>
<td>-</td>
</tr>
<tr>
<td>55 patients</td>
<td>Metachronous after I surgery</td>
<td>53</td>
<td>-</td>
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<tr>
<td></td>
<td>Metachronous after II surgery</td>
<td>18</td>
<td>-</td>
</tr>
<tr>
<td>Ribet [14]</td>
<td>Synchronous</td>
<td>23*</td>
<td>-</td>
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<tr>
<td>75 patients</td>
<td>Metachronous after I surgery</td>
<td>58*</td>
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<td>Metachronous after II surgery</td>
<td>**</td>
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<td>Mathisen [18]</td>
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<td>0</td>
</tr>
<tr>
<td>90 patients</td>
<td>Metachronous after II surgery</td>
<td>60</td>
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<td>Metachronous after II surgery</td>
<td>33</td>
<td>20</td>
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<tr>
<td>Antakli [1]</td>
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<td>54 patients</td>
<td>Metachronous after I surgery</td>
<td>23</td>
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<td>Metachronous after II surgery</td>
<td>**</td>
<td>-</td>
</tr>
<tr>
<td>Deschamps [20]</td>
<td>Synchronous</td>
<td>16</td>
<td>14</td>
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<td>80 patients</td>
<td>Metachronous after I surgery</td>
<td>55</td>
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<tr>
<td></td>
<td>Metachronous after II surgery</td>
<td>33</td>
<td>27</td>
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<tr>
<td>Okada [15]</td>
<td>Synchronous</td>
<td>70</td>
<td>-</td>
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<td>57 patients</td>
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<td>66</td>
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<tr>
<td></td>
<td>Metachronous after II surgery</td>
<td>51</td>
<td>20</td>
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*3-year survival; **not specified if follow-up from 1st or 2nd tumour.
that this group would represent a selected population different from patients with wide metastatic disease. Actually the latest TNM classification contradicts some criteria for synchronous tumours established by Martini, even if we believe that there could be a difference in the case of a single nodule or multiple nodules.

Therefore, we think that there could be a role for surgery in those patients with two synchronous lesions, with the same histology and without mediastinal nodes involvement, either as double primary tumour or as solitary metastasis.

A further help to exclude the presence of other intrathoracic or distant disease could be the PET scan, that we now perform in all of these patients.

The 30-day mortality in our study was 2.5%; our mortality rate compares favourably with the 5–12% range reported by others [3,18,20,24].

A greater number of MPLCs were treated with segmental resection, but we did not find any difference in long term results when we analysed the group of patients with standard procedure (lobectomy or pneumonectomy) compared to the group of patients with limited resection.

In conclusion we believe that an aggressive approach is justified in patients with MPLC and that lifelong follow up, that includes the high resolution spiral CT scan, is recommended in all patients surviving curative pulmonary resections.

Perhaps we need more accurate selection criteria for MPLCs.

Pulmonary resection conserving as much lung parenchyma as possible is safe and offers the greatest chance for long term survival.

References

Dr Al Kattan: Just doing a pneumonectomy is aggressive. You don’t know the end status. A lot of times you might just by a mediastinal lymphadenectomy find that this patient turned out to be N2 disease, and then you will say it’s probably M1, N2, and you still did a pneumonectomy for him, and any morbidity from that procedure would not be justified at that time. That’s a dilemma we always face.

Dr Rea: But if you had intraoperatively a frozen section of a mediastinal node and it’s negative?

Dr Al Kattan: Yes, but 1 node, 2, 3, but we take out 15 and 16, and you can get one positive and still it’s an N2 disease.

Dr Molnar (Pecs, Hungry): The presentation should be aimed at the pneumologists rather than us because they are the ones who refuse a second operation or a third.

Could you explain how you found N2 lymph nodes or N1 lymph nodes in a second operation? At the first operation you should remove or at least sample nearly all other N1 and N2 lymph nodes. On your slides you showed N2-positive and N1-positive cases again after a previous hypothetically complete resection of the mediastinal lymph nodes.

Dr Rea: The second tumor?

Dr Molnar: Yes.

Dr Rea: Your question is why we have N-positive in the second tumor?

Dr Molnar: No, how you can clear the mediastinum twice.

Dr Rea: In the metachronous group for example you can operate on the right side while previously at the first operation you were on the left side. So you can find N1 disease in the left hilum, and then even on the other site.