Early after pulmonary metastasectomy. Nodal status should be considered in the selection of patients for lung metastasectomy.

Abstract

Lung metastasectomy is an accepted treatment for selected patients with pulmonary metastases. Resectability, disease-free interval and number of metastases are well characterised prognostic indicators after lung metastasectomy. Patients treated with lung metastasectomy for epithelial tumours were retrospectively reviewed. One hundred and forty-two patients were reviewed. The rate of mediastinal node metastases was 12%. Overall 5-year survival rate was 36% with a median survival time of 47 months. Recurrence rate after lung metastasectomy was 50%. Five-year disease-free survival was 26% with a median of 29 months. Mediastinal nodal status negatively affected survival at univariate analysis (5-years 32% for N+ and 40% for N−, \( P = 0.013 \)). Disease-free survival was significantly different according to nodal status: 5-year disease-free survival 17 and 28% for N+ and N−, respectively (\( P = 0.053 \)). Systemic recurrences were more frequent in patients with nodal involvement (\( P = 0.058 \)). Mediastinal nodal involvement resulted in a significant prognostic factor at multivariate analysis (\( N+ : \text{RRD} = 3.0 ; 95\% \ CI 1.3 - 6.7 \)). Patients with pulmonary metastases and nodal involvement had a poor prognosis and relapsed early after pulmonary metastasectomy. Nodal status should be considered in the selection of patients for lung metastasectomy.

Keywords: Pulmonary metastasis; Epithelial tumours; Mediastinal nodal metastases; Prognosis

1. Introduction

It is currently accepted that, in selected patients with pulmonary metastases, a surgical treatment with curative intent can be proposed, and a significant advantage in long-term survival can be expected. The International Registry of Lung Metastases proposed a prognostic stratification based on three significant prognostic factors: resectability, disease-free interval (DFI) and number of pulmonary metastases [1].

Even if mediastinal nodal status is considered a critical prognostic factor after surgical treatment of non-small cell lung cancer, the prognostic impact of lymph node metastases in patients treated with lung metastasectomy for epithelial tumours is analysed in a few studies with controversial results [2–5].

The aim of this retrospective study is to evaluate the results of lung metastasectomy for epithelial tumours in terms of survival and recurrence, with concern to the prognostic role of mediastinal lymph node metastases.

Abstract

2. Materials and methods

We retrospectively reviewed the patients who underwent a complete lung metastasectomy for histologically proven epithelial tumours at the Division of Thoracic Surgery of the University of Modena and Reggio Emilia, from January 1990 to December 2003.

Criteria to select patients for pulmonary metastasectomy were the following: controlled primary tumour, absence of extrapulmonary metastases (except for colorectal cancer with resectable hepatic and pulmonary lesions), resectability of all pulmonary lesions, pulmonary function able to tolerate lung resections. All patients underwent a CT scan of the chest, abdomen and brain, a bone scintigraphy and pulmonary function evaluation prior to lung metastasectomy. Positron emission tomography (PET) was not available at our institute in the period analysed.

During the period of the study, we did not perform a preoperative mediastinoscopy. Mediastinal adenopathy deemed resectable on preoperative CT scan did not preclude lung metastasectomy whereas, enlarged mediastinal lymph nodes with a bulky presentation excluded the patient from the surgical treatment.

Lung metastasectomy was considered complete if all known intrathoracic cancer was removed, with histologically proven free margin of resections. All patients were operated by lateral thoracotomy. Wedge excisions were the
surgical procedure of choice. Lobectomy or bilobectomy was performed when lesser resections did not allow a complete removal of the disease, in a patient with adequate pulmonary function.

A mediastinal exploration with a systematic sampling (SS) of each ipsilateral mediastinal lymph node stations was routinely performed in each patient. Mediastinal lymph node dissection (MLD) was reserved for macroscopically involved nodes.

For each patient clinical and pathological features were recorded. Disease-free interval (DFI) was calculated from the date of resection of the primary tumour and the date of diagnosis of lung metastases. Disease-free survival (DFS) was calculated between the date of lung metastasectomy and the date of relapsed disease.

2.1. Statistical analysis

Frequencies were compared with the chi-square test for categorical variables and Fisher’s exact test for small samples. Continuous variables were compared with t-test and ANOVA. The overall and disease-free survival were calculated according to the Kaplan-Meier method. Deaths from cancer-unrelated causes were considered as withdrawals. Univariate analysis of survival was performed using the log-rank test. Prognostic factors were matched in a multivariate analysis, using Cox regression models. A probability value < 0.05 was considered statistically significant.

3. Results

One hundred and forty-two consecutive patients who underwent lung metastasectomy for epithelial tumours entered the study. Characteristics of the 142 patients are listed in Table 1. Mean age was 60.9 years (standard deviation 10.7, range 33–89).

Five patients (3%), with lung metastases from colorectal cancer, underwent resection of concomitant liver metastasis (4 patients before and 1 patient after pulmonary metastasectomy).

Median DFI between resection of primary tumour and pulmonary metastasectomy was 34 months (range 0–240).

All patients with unilateral disease were operated by lateral muscle-sparing thoracotomy. Bilateral diseases were approached with staged muscle-sparing thoracotomies in 11 patients (7%), whereas 2 patients (1%) underwent a simultaneous bilateral muscle-sparing thoracotomy.

Matching all the clinico-pathological variables in a univariate analysis we found no association among them, except for the following: patients with lung metastases from breast cancer were younger and with a median DFI longer compared to those with metastases from other primaries (median age: breast 55 years, colon 63 years, kidney 59 years, other primaries 60 months, \( P = 0.022 \); median DFI: breast 69 months, kidney 37 months, colon 40 months, other primaries 39 months, \( P = 0.008 \).

Nodal involvement according to the different histologic type was as follows: 8 in colorectal cancer patients, 3 in kidney cancer patients, 5 in breast cancer patients and 2 in the other less common primaries.

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of patients (%)</th>
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<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>74 (52%)</td>
</tr>
<tr>
<td>Female</td>
<td>68 (48%)</td>
</tr>
<tr>
<td>Primary site</td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>64 (44%)</td>
</tr>
<tr>
<td>Kidney</td>
<td>31 (22%)</td>
</tr>
<tr>
<td>Breast</td>
<td>23 (16%)</td>
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<tr>
<td>Head and neck</td>
<td></td>
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<tr>
<td>Uterus</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>Salivary gland</td>
<td></td>
</tr>
<tr>
<td>Bladder</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Others</td>
<td>9 (6%)</td>
</tr>
<tr>
<td>No of metastasis</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>93 (65%)</td>
</tr>
<tr>
<td>2</td>
<td>27 (19%)</td>
</tr>
<tr>
<td>&gt; 3</td>
<td>15 (11%)</td>
</tr>
<tr>
<td>N Status</td>
<td></td>
</tr>
<tr>
<td>N–</td>
<td>124 (88%)</td>
</tr>
<tr>
<td>N+</td>
<td>18 (12%)</td>
</tr>
<tr>
<td>DFI</td>
<td></td>
</tr>
<tr>
<td>&lt; 36 months</td>
<td>77 (54%)</td>
</tr>
<tr>
<td>&gt; 36 months</td>
<td>65 (46%)</td>
</tr>
</tbody>
</table>

Chemotherapy was administrated in 54 patients with metastases from colorectal cancer (84%), before of after metastasectomy, with 5-fluorouracile alone or associated with oxalyplatin. Seven patients after metastasectomy from renal cancer (23%) were treated with interleukin-2 and interferon alpha, 4 (13%) with vinblastine. Chemotherapy and hormonal regimens in patients with breast cancer and metachronous lung metastases were extremely different and the description is beyond the aims of this paper.

3.1. Analysis of survival

Follow-up was complete for all patients by June 2005. The overall 5-year survival rate was 36% with a median survival time of 47 months. A recurrence of the disease after lung metastasectomy occurred in 74 patients (50%). Five-year DFS was 26% with a median DFS time of 29 months. Four patients died without recurrence because of cancer unrelated causes (2 myocardial infarction, 1 stroke and 1 car accident).

Recurrences were systemic in 62 patients (44%) and solitary intrathoracic in 12 (8%). These latter patients underwent redo-metastasectomy (9 wedge resections and 3 lobectomies) with a median DFI of 11 months between the first and second metastasectomy. Four patients (3%) presented a third intrathoracic solitary recurrence amenable to surgical resection (4 wedge resections). Median DFI between the second and the third metastasectomy was 11 months. Median survival time after redo-metastasectomy for intrathoracic recurrences was 18 months, compared
to 8 months for patients who experienced a systemic recurrence ($P = 0.068$).
A trend toward a higher rate of recurrence after lung metastasectomy was observed for metastases from kidney tumours (kidney 71%, colon 44%, breast 43%, other primaries 48%, $P = 0.074$).

The results of univariate analysis of overall and disease-free survival for clinico-pathological variables are reported in Table 2.

Mediastinal lymph nodes metastases was the only variable affecting overall survival (Fig. 1) and DFS. Age, gender, DFI, type of resection, site and number of lung metastases had no significant impact on survival. Ten patients with nodal involvement (59%) experienced a recurrence during the follow-up period and subsequently died of cancer-related causes. The recurrence rate was not significantly different in respect to node negative patients (recurrence rate: N+ 53% vs. N- 51%; $P = 0.942$). However, DFS was shorter in patients with mediastinal involvement compared to negative ones (Table 2). The pattern of recurrence was influenced by the presence of mediastinal lymph node metastasis (solitary intrathoracic in 2 patients and systemic in 8 patients; $P = 0.058$). No other variables influenced the pattern of recurrence after pulmonary metastasectomy.

All the clinico-pathological features described above, except for histologic types, were matched in a multivariate analysis (Fig. 2). Nodal status resulted in an independent prognostic factor. The relative risk of death was three times higher for N+ patients ($P = 0.003$).

4. Discussion

The involvement of mediastinal lymph node in patients with pulmonary metastases is considered rare. The International Registry of Lung Metastases reported a 5% incidence of lymph node metastases in 5206 cases [1]. Authors that routinely performed MLD during lung metastasectomy for epithelial tumours have reported a higher rate of mediastinal lymph node involvement ranging from 14 to 28% [2,4]. Although we did not routinely perform MLD, our study pointed out that mediastinal lymph involvement from epithelial pulmonary metastases is not so uncommon (12%). Few studies in literature have performed a survival analysis according to mediastinal lymph node metastases in patients who underwent lung metastasectomy for epithelial tumours, and conflicting results are reported. Ercan [2] showed national Registry of Lung Metastases reported a 5% incidence of lymph node metastases in 5206 cases [1]. Authors that routinely performed MLD during lung metastasectomy for epithelial tumours have reported a higher rate of mediastinal lymph node involvement ranging from 14 to 28% [2,4]. Although we did not routinely perform MLD, our study pointed out that mediastinal lymph involvement from epithelial pulmonary metastases is not so uncommon (12%). Few studies in literature have performed a survival analysis according to mediastinal lymph node metastases in patients who underwent lung metastasectomy for epithelial tumours, and conflicting results are reported. Ercan [2] showed
adverse outcomes in terms of recurrence and survival for patients with pulmonary metastases and mediastinal nodal involvement, whereas Kamiyoshihara [3], Lambe [4], and, more recently, Monteiro [5] failed to reveal a prognostic impact for nodal status at the time of pulmonary metastasectomy. In our series of epithelial tumours, the presence of mediastinal lymph node metastasis significantly decreased overall survival after lung metastasectomy. Although we found no difference in recurrence rate according to nodal status, the presence of mediastinal nodal spread in patients with pulmonary metastasis significantly shortens the DFI between pulmonary metastasectomy and recurrence. Moreover, the pattern of relapse is significantly influenced by nodal status: a higher systemic recurrence rate after lung metastasectomy was present in patients with mediastinal nodal involvement compared to negative ones. This high rate of early systemic recurrences after complete surgical resection suggests that epithelial pulmonary metastases with mediastinal nodal involvement represent a rapidly progressive neoplastic disease.

Data from the literature [6–11] suggest that the prognostic impact of mediastinal node metastases could change among different histologic primaries. Several authors [6–8] found that nodal involvement metastasis negatively affect survival after lung metastasectomy for colorectal cancer. These authors suggested to include lymph-node involvement as a criterion to define the indications for lung metastasectomy. Murthy [9], analysing pulmonary metastases from renal cancer, found that patients with metastases in the mediastinum are unlikely to benefit from lung metastasectomy unless a complete resection is performed. Regarding breast cancer, the analysis of cases from the International Registry of Lung Metastases [10] and a large monocentric study by France [11], did not reveal a significant prognostic impact of mediastinal nodal status after lung metastasectomy. A reliable statistical analysis of the prognostic significance of lymph node metastases within the different histologic types was not possible in our series, due to the small number of node positive cases in each subgroup. Further studies are needed to evaluate the impact of mediastinal nodal status in specific primaries.

However, the results obtained from the analysis of the whole cohort of patients of our study, suggest that mediastinal nodal involvement is an independent prognostic factor after lung metastasectomy for epithelial pulmonary metastases. We suggest that preoperative nodal status should be considered in the selection of patients for lung metastasectomy. According to other authors [6–8], we do not currently propose lung metastasectomy to patients with preoperative findings of mediastinal nodal involvement. This strategy requires a careful preoperative evaluation of N status. Invasive techniques, such as mediastinoscopy, in the preoperative setting of patients candidate to lung metastasectomy are already advocated by some authors [8,9]. Our current preoperative approach includes an histological confirmation in all patients with enlarged mediastinal nodes at imaging evaluation.

Another important issue is the approach to mediastinal lymph node excision during lung metastasectomy. Some authors advocate routine MLD in order to improve staging and guide treatment [2,4], but most authors perform less invasive procedures for metastatic disease. For non-small cell lung cancer, the survival advantage of MLD compared to systematic sampling (SS) is far from being demonstrated [12–14]. Comparative studies between MLD and less invasive procedures during lung metastasectomy are lacking. In the absence of strong evidences of survival benefit after MLD, we believe that SS could be a satisfactory procedure. In particular, the rate of N positive patients found in our series (12%), is slightly inferior to that reported by some authors who routinely perform MLD during lung metastasectomy (Loehe and colleagues, 14% [4]). Moreover, the lack of adjuvant therapies with clearly proved effectiveness for most epithelial pulmonary metastases, makes the presumptive more complete pathological staging obtained with MLD, not yet justified.
The high rate of systemic recurrence experienced by patients with mediastinal nodal involvement found during lung metastasectomy makes surgery alone no longer adequate to control the disease. These patients are ideal candidates to adjuvant therapies and further studies are needed to evaluate these multimodality approaches.

In conclusion, complete lung metastasectomy in patients with pulmonary epithelial metastases and mediastinal lymph node involvement is associated to an early systemic recurrence of the neoplastic disease and a subsequent dismal survival outcome. Mediastinal nodal status should be included in the selection criteria of patients for lung metastasectomy and a careful mediastinal staging should be considered in the preoperative setting. Systematic sampling during metastasectomy could be adequate to obtain nodal tissue from the mediastinum, in order to identify patients for adjuvant therapies.

References


