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Long-Term Results After Repeated Surgical Removal of Pulmonary Metastases

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Background. Although surgical resection is accepted widely as first-line therapy for pulmonary metastases, few data exist on the surgical treatment of recurrent pulmonary metastatic disease. In a retrospective study, we analyzed patients who were operated on repeatedly for recurrent metastatic disease of the lung with curative intent over a 20-year period.

Methods. From 1973 to 1993, 396 metastasectomies were performed in 330 patients. The study population included patients with any histologic tumor type who had undergone at least two (range, 2 to 4) complete surgical procedures because of recurrent metastatic disease. Surgical and functional resectability of the recurrent lung metastases and control of the primary lesion served as objective criteria for reoperation. A subgroup of 35 patients that included patients with histologic findings such as epithelial cancer and osteosarcoma then was analyzed retrospectively to calculate prognosis and define selection criteria for repeated pulmonary metastasectomy.

Results. The 5- and 10-year survival rates after the first metastasectomy were 48% and 28%, respectively. The overall median survival was 60 months. A mean disease-free interval (calculated for all intervals, with a minimum of two) of greater than 1 year was significantly associated with a survival advantage beyond the last operation. Univariate analysis failed to show size, number, increase or decrease in number or size, or distribution of metastases as factors related significantly to survival.

Conclusions. Although patients with different histologic tumor types were included, the study population appeared to be homogenous in terms of survival benefit and prognostic factors, and it probably represented the selection of biologically favorable tumors in which histology, size, number, and laterality are of minor importance. We conclude that patients who are persistently free of disease at the primary location but who have recurrent, resectable metastatic disease of the lung are likely to benefit from operation a second, third, or even fourth time.


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sectomy was 48% (Fig 1). Twenty-eight percent of the patients lived for more than 10 years. At the last follow-up evaluation, 15 of the 35 patients were alive. Mean survival after the second resection was 26.3 months.

A statistically significant survival advantage was shown for the groups with the longest DFIs. Patients who had a long interval between operation for the primary tumor and the first metastasectomy (DFI1) also had a long interval between the first and second metastasectomies (DFI2). A DFI1 of more than 20 months was associated with longer survival ($p = 0.0043$). Patients with a DFI2 of more than 40 months also had a significant survival advantage ($p = 0.0012$) (Fig 2). In addition, patients with a mean DFI exceeding 1 year had a significant survival advantage ($p < 0.0001$).

The size of the metastases ranged from 0.4 to 11 cm at the first operation, from 0.5 to 18 cm at the second, from 0.8 to 12 cm at the third, and from 2 to 9 cm at the fourth. The number of metastases ranged from 1 to 8 (median, 4) at the first operation, from 1 to 20 (median, 5) at the second, from 1 to 20 (median, 4) at the third, and from 2 to 4 (median, 2) at the fourth.

Trends in the number, size, and viability of the metastases between the first two metastasectomies are shown in Table 1. Neither the number nor the size of the metastases had a significant influence on survival. An increase or decrease in the size or number of the metastases also did not affect survival (data not shown). The viability of the metastases was defined according to the extent of tumor necrosis found at pathohistologic examination. No survival advantage was found for patients in whom the extent of tumor necrosis was either more or less than 50%. Patients with bilateral and unilateral disease had equal survival.

Grouping patients according to the nature of their primary tumor (ie, soft tissue, osteosarcoma, or epithelial cancer) revealed no survival advantage for any group. We also found no advantage for any of the sarcoma

Fig 1. Survival of 35 patients with recurrent lung metastases who underwent two or more lung metastasectomies. Median survival calculated from the first metastasectomy was 60 months. The long-term survival rate was 48% at 5 years and 28% at 10 years. At last follow-up, 15 patients were alive.

Fig 2. Survival in relation to disease-free interval between the first two metastasectomies. A disease-free interval between the first two metastasectomies exceeding 40 months was associated with significantly longer survival ($p = 0.0012$).
groups when these were evaluated separately, but the groups were somewhat small (Fig 3).

Table 2 shows the number of operations performed in the three groups with different primary tumors. Neither a small nor a large number of operations had an influence on survival (data not shown). The surgical procedures performed for the first, second, third, and fourth operations are listed in Table 3. In a total of 87 operations, 31 axillary thoracotomies, 27 sternotomies, and 29 dorsolateral thoracotomies were performed.

Comment

Several studies have shown that operative treatment is effective and safe as first-line therapy for initial, resectable pulmonary metastases [1–3]. However, the resection of recurrent pulmonary metastases remains controversial and has been addressed only in a few series of patients with soft tissue sarcoma [4–6]. In two of these series, resectability and the DFI proved to be prognostic factors. In the other series, only the number of nodules was found to be predictive of survival.

Using resectability and control of the primary tumor as a prerequisite for the surgical treatment of recurrent pulmonary metastases probably would result in the selection of patients with certain favorable tumor kinetics. This possibility appears to be supported by the 5-year survival rate of 48% after repeated metastasectomy, the significant survival advantage we found among patients who had long DFIs, and also the large size of some of the lesions removed. Consistently, patients who experienced a long DFI between operation for the primary tumor and the first metastasectomy also had a long DFI between the first and second metastasectomies.

The DFI and its effect on prognosis is a subject of controversy in the literature. The International Registry of Lung Metastases analyzed 5,206 cases and found a
Table 3. Surgical Procedures Performed in Relation to Number of Metastasectomies

<table>
<thead>
<tr>
<th>Surgical Procedure</th>
<th>No. of Metastasectomies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wedge resection</td>
<td>1 2 3 4</td>
</tr>
<tr>
<td>Extended wedge resection</td>
<td></td>
</tr>
<tr>
<td>Segment resection</td>
<td></td>
</tr>
<tr>
<td>Lobectomy (including sleeve)</td>
<td></td>
</tr>
<tr>
<td>Wedge resection plus lobectomy or segment resection</td>
<td></td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>... 1 1 1</td>
</tr>
<tr>
<td>Mediastinal dissection</td>
<td>2 2 1</td>
</tr>
<tr>
<td>Tumor reduction</td>
<td>... 2 1 ...</td>
</tr>
<tr>
<td>Biopsy only</td>
<td>... ... 1 ...</td>
</tr>
<tr>
<td>Total</td>
<td>35 33 14 3</td>
</tr>
</tbody>
</table>

survival advantage among those with a DFI between operation for the primary tumor and the first metastasectomy exceeding 36 months [1]. They also found an advantage among patients who had metastases of distinct histology (ie, germ cell tumors). Baron and colleagues [10] and Okumura and associates [11] analyzed patients with lung metastases from colorectal cancers and found no association between the DFI and overall survival. In contrast, Van Geel and co-workers [3] found a more favorable outcome among 255 patients with metastases from soft tissue sarcoma who had a DFI of 2.5 years or more.

In our analysis, the DFI appeared to be important to survival regardless of tumor histology. We found a survival advantage for a DFI exceeding 20 months and a DFI exceeding 40 months. In our analysis, the length of the DFI appeared to be associated with the length of the DFI.

Our report was not restricted to a distinct histologic tumor type. The most common diagnosis was epithelial cancer, followed by osteosarcoma and soft tissue sarcoma. In comparing these groups, we found no difference in survival. Although the histology of the primary tumor is important for first-line metastasectomy [12], its influence seems to diminish in recurrent metastatic disease. The latter might be characterized better by favorable tumor biology.

Patients with repeated relapse years after complete clearance of the primary tumor obviously have systemic disease. It has recently been observed in experimental animal models of melanoma that most metastatic cells that enter the circulation appear to survive and extravasate into their target organs, where they remain dormant as long as they lack tumor vasculature [13, 14]. This observation could explain organ-specific metastatic tumor relapse years after complete local clearance of the primary tumor. However, it is not yet known why tumor relapse occurs after different long DFIs in a resectable, local limited, or disseminated manner.

The 5-year survival rate of almost 50% that we found in patients with recurrent pulmonary metastatic disease might reflect the selection of tumors with favorable kinetics. Surgical criteria for resectability seem to function as selection criteria for such tumors. The survival of patients with recurrent pulmonary metastatic disease is not related to the histology of the primary tumor in patients with epithelial cancer and osteosarcoma. We conclude that patients with recurrent resectable pulmonary metastases should be considered for reoperation regardless of the number, size, location, or histology of the metastases. The success of repeated surgical resection of pulmonary metastatic disease probably relies on the selection of tumors with a distinct biologic behavior and environment that has not yet been defined but may include a long DFI.

References

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