Long-Term Results After Repeated Surgical Removal of Pulmonary Metastases

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Ann Thorac Surg 1998;65:909-912

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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.**

(Ann Thorac Surg 1998;65:909–12)

Pulmonary metastasectomy is accepted widely as standard therapy for isolated pulmonary metastases of different tumor types. The overall 5-year survival rate is reported to be about 36% when all the primary sites are combined [1–3].

Although some reports on lung metastasectomy include data on relapse, the isolated efficacy of operation for recurrent lung metastases remains controversial and has been evaluated only for soft tissue sarcoma [4–6]. The aim of this retrospective study was to determine the benefit of repeated pulmonary metastasectomy and to evaluate the prognostic factors in patients with recurrent metastases including patients with histologic findings such as epithelial cancer, osteosarcoma, and soft tissue sarcoma.

Patients and Methods

Between 1973 and 1993, 82 metastasectomies were performed in 35 patients with recurrent pulmonary metastatic disease. Patient selection criteria for reoperation with curative intent included surgical and functional resectability only. There were no perioperative deaths. Patient age ranged from 15 to 66 years (mean, 44 years). Primary tumors included 20 epithelial carcinomas (mainly colon and breast cancers), 10 osteosarcomas, and 5 soft tissue sarcomas.

Disease-free intervals (DFIs) were defined as follows: The first DFI (DFI1, defined as the number of months between operation for the primary tumor and the first metastasectomy) was calculated for three groups (less than 20 months, 20 to 50 months, and more than 50 months). The second DFI (DFI2, defined as the number of months between the first and second metastasectomies) also was calculated for three groups (less than 10 months, 10 to 40 months, and more than 40 months). Survival curves were computed by the product limit estimate method and tested for significance using the Mantel-Cox test. An alpha level of significance was set at 5%. The influence of diverse factors on survival was tested with univariate analyses using log-rank tests and the Kaplan-Meier method [7–9].

Results

In our study population of patients who had undergone repeated metastasectomy (ie, two or more operations), the actuarial 5-year survival rate after the first metasta-

Accepted for publication Oct 10, 1997.

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Published by Elsevier Science Inc

0003-4975/98/$19.00
PII S0003-4975(98)00019-8

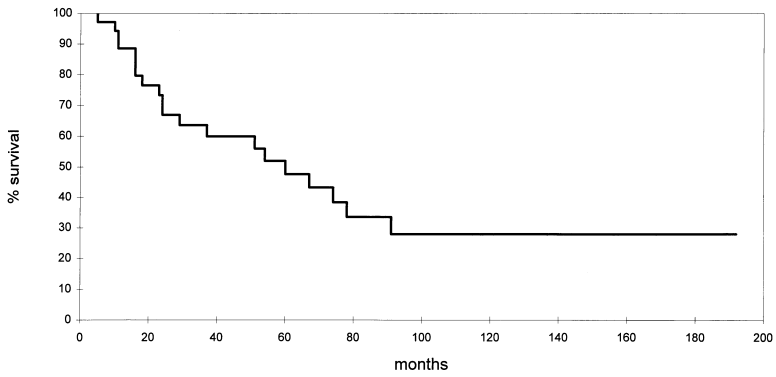

Fig 1. Survival of 35 patients with recurrent lung metastases who underwent two or more lung metastasectomies. Median survival calculated from the first metastasectomy was 60 months. The long-term survival rate was 48% at 5 years and 28% at 10 years. At last follow-up, 15 patients were alive.

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

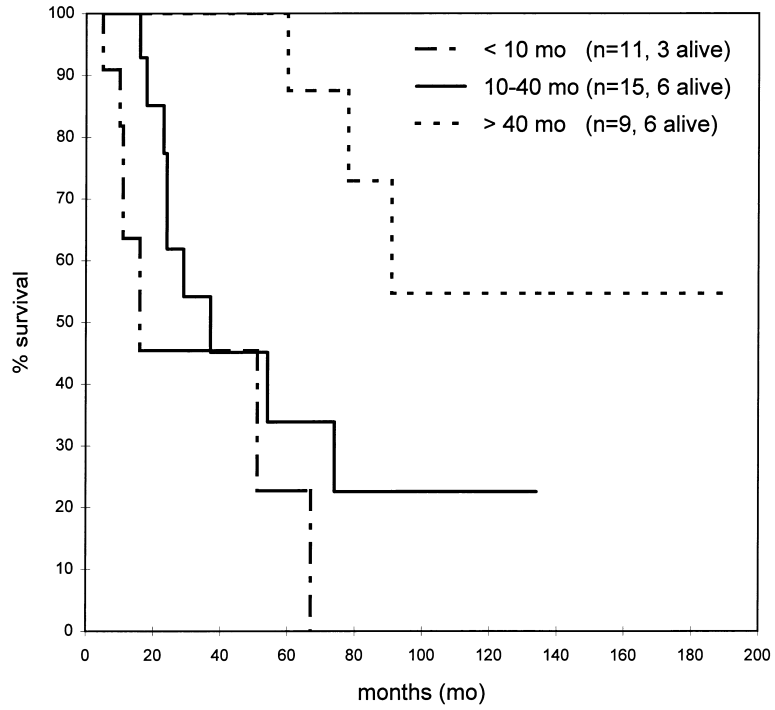

Fig 2. Survival in relation to disease-free interval between the first two metastasectomies. A disease-free interval between the first two metastasectomies exceeding 40 months was associated with significantly longer survival (p = 0.0012).

Table 1. Trends in the Number, Size, and Viability of Metastases Between the First and Second Metastasectomies

Parameter[a]	No. of Patients (%)
Number of metastases	
Fewer	7 (20)
Same	11 (31)
More	13 (37)
Undetermined	4
Size of metastases	
Smaller	9 (26)
Same	11 (31)
Larger	12 (34)
Undetermined	3
Viability of metastases[b]	
Decreased	5 (14)
Same	21 (60)
Increased	5 (14)
Undetermined	4

[a] None of the parameters or their degree of change had any influence on survival. [b] Tumors were grouped for calculation according to the extent of necrosis found at pathohistologic examination (<50% or >50%).

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 2. Number of Metastasectomies in Relation to Type of Primary Tumor

Type of Primary Tumor[a]	No. of Patients	No. of Metastasectomies[b]			No. of Operations
		Two	Three	Four	
Osteosarcoma	10	4	6	. . .	26
Soft tissue sarcoma	5	3	2	. . .	12
Epithelial cancer	20	14	3	3	49

[a] No difference in survival was detected between the different histologic groups. [b] To correlate survival with the number of metastasectomies performed, groups with 2 and more than 2 metastasectomies were compared, no survival advantage was found (data not shown).

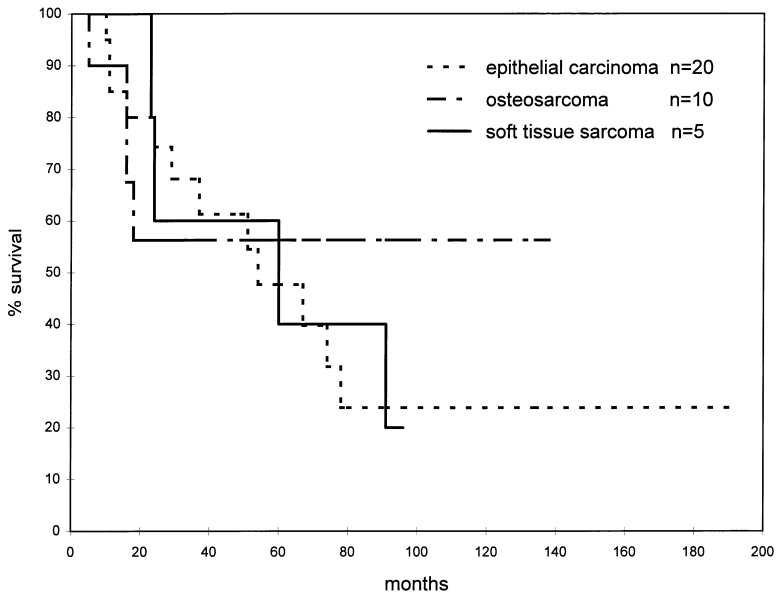

Fig 3. Survival in relation to the histologic type of the primary tumor. In our patient cohort that had undergone two or more metastasectomies, no survival advantage for any group could be found.

Table 3. Surgical Procedures Performed in Relation to Number of Metastasectomies

Surgical Procedure	No. of Metastasectomies			
	1	2	3	4
Wedge resection	24	14	3	1
Extended wedge resection	2	2	3	...
Segment resection	3	4	3	...
Lobectomy (including sleeve)	1	2	...	...
Wedge resection plus lobectomy or segment resection	3	6	2	...
Pneumonectomy	...	1	1	1
Mediastinal dissection	2	2	...	1
Tumor reduction	...	2	1	...
Biopsy only	...	...	1	...
Total	35	33	14	3

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 DFI1 exceeding 20 months and a DFI2 exceeding 40 months. In our analysis, the length of the DFI1 appeared to be associated with the length of the DFI2.

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 recently has 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.

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