Resection of Pulmonary and Extrapulmonary Sarcomatous Metastases Is Associated With Long-Term Survival

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Background. **The presence of extrapulmonary sarcomatous metastases has traditionally been a contraindication for the resection of pulmonary metastases. We, therefore, reviewed our experience with resection of pulmonary metastases in patients who had documented extrapulmonary metastases to determine long-term outcome.**

Methods. **From 1998 to 2006, 234 patients underwent pulmonary metastasectomy. They were grouped as follows: group A (lung metastasectomy only); group B1 (with either synchronous or prior extrapulmonary metastasectomy); group B2 (with nonsurgical treatment of synchronous or prior extrapulmonary metastases); group C1 (with later extrapulmonary metastasectomy); group C2 (with later extrapulmonary metastasis which was not resected).**

Results. **Groups A, B1, and B2 consisted of 147 (62.8%), 26 (11.1%), and 13 (5.6%) patients, respectively. The median survival from lung metastasectomy date was 35.5, 37.8, and 13.5 months in groups A, B1, and B2, respectively. Comparison among the three groups showed no significant survival difference in groups A versus B1 ($p = 0.96$), but a survival difference was found comparing groups A versus B2 ($p < 0.001$) and B1 versus B2 ($p < 0.001$). Prognostic factors for increased survival included 3 or greater redo pulmonary operations, greater than 12 month mean time between pulmonary recurrences, greater than 24 month mean time between extrathoracic recurrences, and a prolonged disease-free interval. Prognostic factors for decreased survival included 3 or greater pulmonary metastases and group B2 patients.**

Conclusions. **These results suggest extrapulmonary metastases should no longer be viewed as a contraindication to resection of sarcomatous pulmonary metastases. Long-term survival can be achieved when a complete resection is possible for both the pulmonary and extrapulmonary metastases.**

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Sarcomas are a diverse group of malignant tumors and comprise 1% of adult malignancies [1]. Approximately 11,590 new diagnoses of, and 3,560 deaths from soft tissue and bone sarcoma occur annually in the Unites States [1]. The lung is the most common site of metastasis, with 20% of sarcoma patients presenting with isolated pulmonary metastases [2].

Pulmonary metastasectomy is accepted as a standard approach to treat isolated soft tissue sarcoma [3–7]. Many studies have reported 3-year and 5-year survival rates after pulmonary metastasectomy to range from 39 ± 16% and 32 ± 7%, respectively [2–4, 8]. The role of adjuvant chemotherapy for soft tissue and osteogenic sarcoma is controversial [9–11].

The feasibility of resection of pulmonary metastases is based on several prognostic factors which predict survival in these patients. Important predictors of survival include disease-free interval, histology of the tumor, and age [3, 12]. However, the most significant predictor of survival is complete resection [2, 3, 12, 13]. The number of metastatic nodules and their impact on survival was initially considered to be an independent predictor of survival [14]. However, if complete resection can be achieved, the number of pulmonary metastatic nodules does not seem to influence survival [3, 5, 15–17]. Surgical resection of recurrent pulmonary metastases also should be considered in selected patients [7, 18–20]. In this group of patients, those who are free of tumor at the primary site and have a long disease-free interval have better survival after reoperation for recurrent disease in the lung [19].

Although a survival benefit is seen after resection of sarcomatous pulmonary metastases, the survival after resection of extrathoracic metastases to other organs in conjunction with pulmonary metastasectomy patients is unknown. The aim of this study is to examine

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prognostic factors for survival in pulmonary metastasectomy patients and survival among patients who had sarcomatous extrathoracic metastases resected compared with patients whose extrathoracic metastases could not be resected. The study also compares survival among different groups of patients, one with metastasectomy to lung only, one with metastasectomy to lung with either synchronous or prior extrathoracic metastases, and a third group of patients who underwent pulmonary metastasectomy and later developed extrathoracic metastases.

Material and Methods

Patient Population

From 1998 to 2006, 15,744 patients with soft tissue and bone sarcoma were referred to The University of Texas M.D. Anderson Cancer Center. During this interval, 4,355 (27.7%) patients were diagnosed with sarcomatous pulmonary metastases. They received various combinations of treatment ranging from chemotherapy, radiotherapy, and surgery. Patients were referred for immediate surgery if they presented with a single pulmonary metastasis or a limited number of metastases and a long disease-free interval. Those who developed metastatic disease early with multiple pulmonary nodules were treated initially with chemotherapy to determine the pace of disease progression, if any, on treatment. Patients responding to chemotherapy, those with stable disease, and those with slow progression were referred for resection while those with rapidly progressive metastatic disease received alternative chemotherapy treatment. The regimens used for osteosarcoma and most soft-tissue sarcomas are different, but therapy was individualized based on the patient's prior regimen, if any, and history of response to that regimen. Adjuvant chemotherapy was continued only if there was evidence of clinical benefit from preoperative chemotherapy. Computed tomographic (CT) scanning was routinely used to monitor disease progression with contrast and 3.75 to 5 mm collimation prior to 1998, and with contrast and 2.5 mm collimation after 1998. Routine fluorodeoxyglucose-positron emission tomography (FDG-PET) was not performed. Pulmonary metastasectomy was performed on 234 (5.6%) patients. A prospective surgical database was used to identify metastasectomy patients and missing clinical data were supplemented in a retrospective manner. The pulmonary metastasectomy patients were then categorized according to their presentation and whether or not their disease was resected. Out of 234 patients undergoing pulmonary metastasectomy, 147 (62.8%) required no additional resection (group A). Thirty-nine (16.7%) patients had either synchronous or prior metachronous extrathoracic metastases (group B). Those forty-eight patients undergoing pulmonary metastasectomy and later developing extrathoracic metastases (group C) comprised 20.5 percent of the pulmonary metastasectomy patients. Institutional Review Board approval was granted for this retrospective review along with a waiver of patient consent.

Group A: Metastasectomy to Lungs Only

This group is comprised of every patient who underwent pulmonary metastasectomy and never developed extrathoracic disease. During the initial diagnosis and treatment of patients with soft tissue sarcoma, the histologic type of the tumor was also determined. These patients were followed with chest radiographs and CT scans of the chest when the index of suspicion for pulmonary metastases was high. Selection criteria for pulmonary resection included local control of the primary lesion, resectable pulmonary metastases, and adequate cardiopulmonary reserve.

Various operative approaches (anterolateral thoracotomy, median sternotomy, partial sternotomy, and posterolateral thoracotomy) were used for pulmonary metastasectomy. Recurrent resectable pulmonary metastases meeting the initial criterion for resection underwent repeat excision. Demographic and outcome data were collected from the patient records to allow the study of variables such as age at diagnosis, gender, disease-free interval, surgery type, adjuvant therapy, site of primary tumor, histologic type, number of pulmonary metastases resected, time to first pulmonary recurrence, number of redo lung operations, mean time interval between pulmonary recurrences, and number of local recurrences, which were variables entered into the univariate analysis.

Group B: Metastasectomy to Lungs and Synchronous or Prior Metastases to Other Organs

This group includes patients who, apart from pulmonary metastases for sarcoma, also developed either synchronous or prior metachronous metastases to extrathoracic sites. At the time of evaluation for pulmonary metastasectomy, the thoracic surgeon had knowledge of the extrathoracic metastases. The most common extrathoracic site of metastasis included spine, bone, soft tissue, liver, abdomen, brain, and the pelvis. Group B was further divided into two subgroups depending on the treatment of these extrathoracic metastases. Group B1 includes patients who had at least one resection of extrathoracic metastasis (some patients underwent repeat metastasectomy) and group B2 includes patients whose extrathoracic metastases were treated by chemotherapy, radiotherapy, or chemoradiotherapy, but not surgical resection. Surgical resection of extrathoracic metastases in group B2 patients was either not feasible due to the extent of metastases or patient refusal.

The diagnosis, follow-up, and treatment of pulmonary metastases as well as selection criteria, contraindications, and operative approaches for pulmonary metastasectomy in group B patients were similar to group A patients. Patients who developed extrathoracic metastases were examined clinically and radiographic evaluations were performed to confirm the clinical diagnosis, to evaluate the extent of spread, and for surgical planning. Operative approaches for the resection of extrathoracic

Table 1. Sarcoma Patients With Pulmonary Metastasectomy Divided Into Five Groups

Patient Groups	No.	Percent
Group A		
Metastasectomy to lung only	147	62.8
Group B1		
Metastasectomy to lung and synchronous or prior metachronous metastases to extrathoracic organs resected	26	11.1
Group B2		
Metastasectomy to lung and synchronous or prior metachronous metastases to extrathoracic organs not resected	13	5.6
Group C1		
Metastasectomy to lung and later metachronous metastases to extrathoracic organs resected	25	10.7
Group C2		
Metastasectomy to lung and later metachronous metastases toextrathoracic organs not resected	23	9.8
Total	234	100.0

metastases varied depending on the site of the metastasis.

Apart from the variables mentioned for group A, patients in group B had data collected for additional variables like number of extrathoracic metastases, number of extrathoracic metastatic recurrences, mean time interval between extrathoracic recurrences, and number of sites of extrathoracic metastases. Survival was compared between the most common sites of extrathoracic metastases. The absolute time of occurrence of extrathoracic metastasis in relation to the time of occurrence of first lung metastasis was also determined. Based on this time of occurrence of extrathoracic metastasis, they were classified as "synchronous" to lung if extrathoracic metastasis occurred within the first 6 months before or after the diagnosis of first lung metastasis or "metachronous" to lung if extrathoracic metastasis occurred outside a 6 month interval either before or after the diagnosis of first lung metastasis.

Table 3. Location of the First Extrathoracic Metastases and the Proportion Undergoing Resection

Location	Number Resected	Total No. (%)
Abdomen	3	10 (30)
Abdominal organs	9	24 (38)
Bone	16	21 (76)
Brain	7	15 (47)
Nonpulmonary chest	3	4 (75)
Pelvis	3	5 (60)
Retroperitoneal	2	4 (50)
Soft tissue/skin	7	8 (88)
Scalp	5	5 (100)
Spine	8	16 (50)

Group C: Metastasectomy to Lungs and Later Metachronous Metastasis to Other Organs

This group includes patients who, apart from pulmonary metastases of sarcoma, also developed later (>6 months) metachronous metastases to extrathoracic sites. Group C was further divided into two subgroups depending on the treatment of these extrathoracic metastases. Group C1 includes patients who had at least one resection of extrathoracic metastasis (some patients underwent repeat metastasectomy) and group C2 includes patients whose extrathoracic metastases were treated by chemotherapy, radiotherapy, or chemoradiotherapy, but not surgical resection. Surgical resection of extrathoracic metastases in group C2 patients was either not feasible due

Table 2. Lung Metastases From Sarcoma: Distribution by Patient Characteristics and Histologic Type

Variable	Group A	Group B1	Group B2	Group C1	Group C2	Total No. (%)
Gender:						
Male	79	13	8	11	12	123 (52.6)
Female	68	13	5	14	11	111 (47.4)
Age (years)[a]:						
<50	95	19	8	15	12	149 (63.7)
≥50	52	7	5	10	11	85 (36.3)
Histology[b]:						
Osteosarcoma	32	2	4	3	5	46 (19.7)
MFH	23	3	1	5	1	33 (14.1)
Synovial	22	1	1	3	2	29 (12.4)
Leiomyosarcoma	18	8	0	6	9	41 (17.5)
Others	52	12	7	8	6	85 (36.3)
Total	147	26	13	25	23	234

[a] Age at first pulmonary metastasectomy. [b] Others (chondrosarcoma, liposarcoma, rhabdomyosarcoma, alveolar soft part sarcoma, spindle cell sarcoma, Ewing's sarcoma, unclassified sarcoma).

There was no statistical difference among groups comparing preoperative patient characteristics.

MFH = malignant fibrous histiocytoma.

Table 4. Univariate Analysis of Survival: Patients With Pulmonary Sarcomatous Metastases

Age at first lung metastasectomy surgery date
Preoperative chemotherapy (yes/no)
Time to first pulmonary recurrence in months
Primary histology
Number of redo pulmonary operations, grouped (0, 1, 2, ≥3)
Mean time interval between pulmonary recurrences in months
Mean interval time between extrathoracic recurrences grouped in months
Disease-free interval (months from primary sarcoma diagnosis date to any recurrence)
Maximum number of pulmonary metastases (≤2, ≥3)
Order of presentation and resection (groups A, B1, B2, C1, and C2)

to the extent of metastases or patient consent was not given for surgical therapy.

The diagnosis, follow-up, and treatment of pulmonary metastases as well as selection criteria, contraindications, and operative approaches for pulmonary metastasectomy in group C patients were similar to the other patients. The additional data collected for group C patients were similar to group B data collection.

Statistical Analysis

Multiple clinical variables were evaluated by univariate analysis using Cox proportional hazards model and Kaplan-Meier curves. The variables found significant on univariate analysis (p value < 0.25 was considered significant) were evaluated by multivariable analysis using the Cox proportional hazards model after backward stepwise Wald elimination. A p value of less than 0.05 on multivariate analysis was taken to be significant. The multivariate analysis was done to determine the effect of the combination of various clinical factors on survival.

Survival was calculated from the date of the first pulmonary metastasectomy to the date of last contact or death. Disease-free interval (DFI) was calculated from the date of sarcomatous primary diagnosis to the occur-

Table 5. Multivariable Analysis of Survival: Patients With Pulmonary Sarcomatous Metastases

Variable[a]	No.	Median Survival (Months)	HR (95% CI)	*P* (Cox Model)
Primary Histology:				0.001
Osteosarcoma (ref)	45	28.9	1.00	
MFH	31	16.7	1.74 (0.99, 3.06)	0.053
Synovial	28	30.2	0.91 (0.51, 1.62)	0.739
Leiomyosarcoma	41	41.8	0.59 (0.33, 1.07)	0.085
Other	81	45.3	0.59 (0.36, 0.94)	0.026
Disease-free interval (months):				
(continuous variable)	226		0.99 (0.99, 1.00)	0.042
Resection type:				0.052
Group A	140	35.5	1.008 (0.53, 1.91)	0.981
Group B1 (ref)	25	37.8	1.00	
Group B2	13	13.5	2.79 (1.15, 6.79)	0.024
Groups C1	25	46.2	0.97 (0.43, 2.16)	0.939
Group C2	23	34.8	1.38 (0.63, 3.04)	0.427
Number of redo pulmonary operations:				0.045
0 (ref)	85	26.8	1.00	
1	75	32.5	1.13 (0.72, 1.77)	0.590
2	40	42.9	1.04 (0.58, 1.87)	0.896
≥3	26	60.8	0.44 (0.20, 0.94)	0.034
Mean time between pulmonary recurrences:				0.002
≤6 months (ref)	60	24.8	1.00	
>6-12 months	40	42.9	0.62 (0.36, 1.07)	0.086
>12 months	41	60.8	0.35 (0.19, 0.63)	0.001
No pulmonary recurrence	85	26.8		
Mean time between extrathoracic recurrences:				0.013
≤24 months	45	18.7	1.00	
>24 months	28	59.8	0.36 (0.18, 0.73)	0.005
No extrathoracic recurrence	153	34.8	0.87 (0.56, 1.34)	0.520
Maximum number of pulmonary metastases:				
≤2	94	44.0	1.00	
>2	132	32.5	1.62 (1.10, 2.39)	0.015

[a] After backward stepwise Wald elimination.

CI = confidence interval; HR = hazard ratio; MFH = malignant fibrous histiocytoma.

rence of either a pulmonary or extrathoracic metastasis. Kaplan-Meier curves were used to compare the survival among the five groups (groups A, B1, B2, C1, and C2) with the log-rank test. Similarly, pair-wise comparisons of the groups were also done. A p value of less than 0.05 was reported as significant on the log-rank test. All analyses were conducted using SPSS version 15.0 (SPSS Inc, Chicago, IL).

Results

Patient Characteristics and Histology

Out of 4,355 patients with sarcomatous pulmonary metastases, 234 (5.6%) patients were treated with pulmonary metastasectomy. The mean and median ages at diagnosis of primary sarcoma were 42.5 and 43 years, respectively, and the age range was 8 to 83 years. Of these, 123 (52.6%) were men and 111 (47.4%) were women. The frequency distribution and definition of the different resection groups is shown in Table 1. The frequency distribution of patient characteristics and primary histology according to the different resection groups is shown in Table 2. Osteosarcoma (19.7%) was found to be the most common overall histologic subtype. There was no significant difference between each group with respect to patient characteristics or primary histology.

Primary Location

The majority of patients presented with extremity sarcomas (n = 136, 58.1%). There was no difference among resection groups with respect to location of the primary tumor. The location of the first extrathoracic metastases and the proportion of those undergoing resection are included in Table 3.

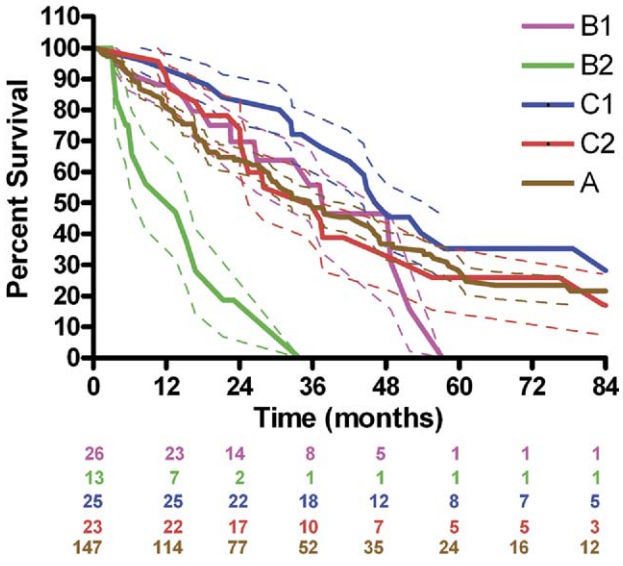

Fig 1. Cumulative survival probability according to type of resection and order of presentation of metastases (groups A, B1, B2, C1, and C2).

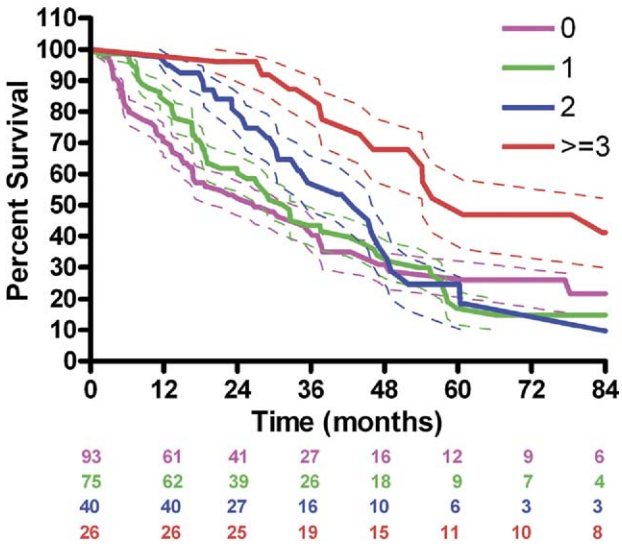

Fig 2. Cumulative survival probability according to the number of redo pulmonary operations.

Type of Resection

Although this was not included in the multivariable analysis, patients underwent various types of resections. From the first pulmonary resection, the majority of patients underwent wedge resections only (n = 200), 18 patients underwent lobectomy, bilobectomy, or sleeve resection, 15 patients underwent segmentectomy, and only 1 patient had a pneumonectomy performed. Only 7 patients had a lymph node dissection performed and 4 patients had a thoracoscopic resection. Fifty patients had incomplete resections (microscopically positive margin, n = 21 and grossly positive margin, n = 29), but this was not included in the multivariable analysis.

Multivariate Analysis of Survival

We studied different variables for their impact on survival. The median follow-up time from the date of pulmonary metastasectomy to last contact date was 27.1 ±

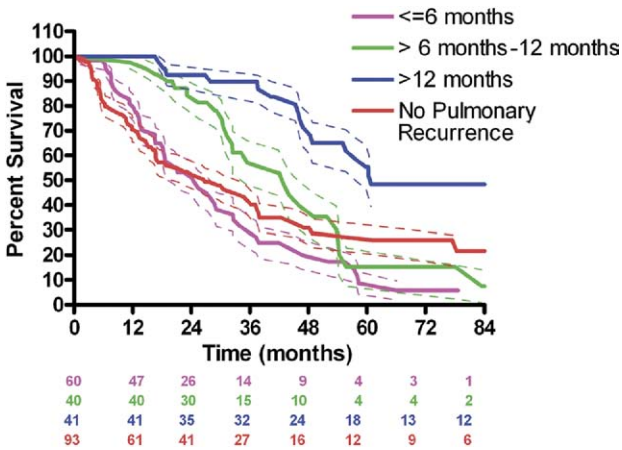

Fig 3. Cumulative survival probability according to mean time between pulmonary recurrences.

32.6 months. Those significantly predicting survival from the univariate analysis are listed in Table 4. From the multivariable analysis, prognostic variables for increased survival included more than three redo pulmonary operations, more than 12 months mean time between pulmonary recurrences, more than 24 months between extrathoracic recurrences, and an increased DFI. Prognostic variables for decreased survival included three or more pulmonary metastases and patients in group B2 (patients undergoing pulmonary metastasectomy but not able to undergo synchronous or prior metachronous extrathoracic metastasectomy). The results of the multivariate analysis are listed in Table 5.

A subgroup analysis of predictors for survival found DFI (>24 months), maximum number of pulmonary nodules, age at diagnosis, and histology to be significant for those patients in Group A. A subgroup analysis of predictors for survival found DFI, the number of redo pulmonary metastasectomies, the number of local recurrences, the mean interval between extrathoracic recurrences, and time to the first pulmonary recurrence to be significant for patients with resected thoracic and extrathoracic disease (groups B1 and C1). For those patients only having pulmonary metastasectomy with an unresected extrathoracic metastasis (groups B2 and C2), the only significant predictors for survival were DFI and the number of pulmonary metastases.

Survival After Resection

Median survival for the entire group was 36.2 months. With regard to survival in the resection groups, the median survival from lung metastasectomy date was 35.5, 37.8, 13.5, 46.2, and 34.8 months in groups A, B1, B2, C1, and C2, respectively (Fig 1). The survival compared among the groups showed no significant survival difference in groups A versus B1 ($p = 0.96$), but a survival difference was found comparing groups A versus B2 ($p < 0.001$) and B1 versus B2 ($p < 0.001$).

The median survival for patients with osteosarcoma, malignant fibrous histiocytoma (MFH), synovial sarcoma, leiomyosarcoma, and other sarcoma types grouped was 28.9, 16.7, 30.2, 41.8, and 45.3, respectively. Cumulative survival probability according to the number of redo pulmonary operations is seen in Figure 2. The median survival for patients with none, one, two, or three or more re-resections of pulmonary metastases was 26.8, 32.5, 42.9, and 60.8, respectively. Cumulative survival probability according to mean time between pulmonary recurrences is seen in Figure 3. The median survival for patients with 6 months or less, greater than 6 months to 12 months, greater than 12 months mean interval between pulmonary recurrences, and those with no pulmonary recurrence was 24.8, 42.9, 60.8, and 26.8, respectively. The median survival for patients with 24 months or less, greater than 24 months mean time between extrathoracic recurrences, and no extrathoracic recurrence was 18.7, 59.8, and 34.8, respectively. Cumulative survival probability according to the number of pulmonary metastases

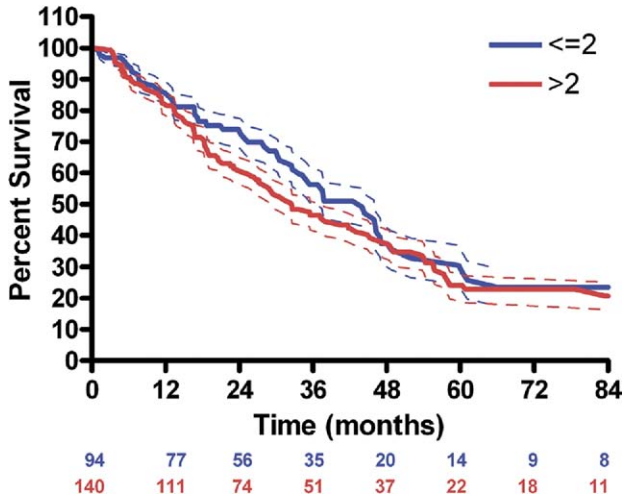

Fig 4. Cumulative survival probability according to number of pulmonary metastases.

is seen in Figure 4. The median survival for patients with 2 or less and greater than 2 pulmonary metastases was 44.0 and 32.5 months, respectively. The pulmonary metastasectomy groups presented in this study had no 30-day mortality, and three patients died within 90 days of pulmonary metastasectomy.

Comment

Sarcomatous pulmonary metastasectomy remains the cornerstone for treatment of isolated pulmonary metastases. Resection of extrathoracic pulmonary metastases in conjunction with lung metastases has to this point not been evaluated. This single-institution review provides new prognostic indicators as well as an evaluation of a previously unvalidated treatment paradigm. Long-term survival can be achieved when a complete resection is possible for both pulmonary and extrapulmonary metastases.

The highly selected pulmonary metastasectomy group presented in this study had a median, 3-year, and 5-year survival of 36.2 months, 50.5%, and 26.3%. Many of these patients underwent repeat metastasectomy both of the lung and extrathoracic metastases, making it in general a more complex patient population than what has traditionally been presented in the literature. In spite of this, their survival compares favorably with survival rates reported for thoracic metastasectomy by numerous authors [2–4, 7, 8, 13, 18–22].

Although the current sarcoma patients with a diagnosis of MFH had a trend toward worse survival, our analysis of the primary histology did not find one specific group of patients to have a more favorable survival. Because there can be more than 50 histologic subclassifications of sarcoma, we grouped patients with the less frequent histologies together, and this generic group had a more favorable survival in our multivariate analysis. Other studies have found histology to predict pulmonary metastasis, resectability, and ultimately survival in ex-

tremity soft tissue sarcomas [2], and to predict survival overall in soft tissue sarcomas in general [3]. The grade and location both were also predictive of survival in the latter study.

The number of redo pulmonary metastasectomies consistently seems to correlate with improved survival [3, 18–20, 22]. As the current study also showed, patients surviving to undergo multiple metastasectomies most likely have a more biologically favorable tumor and their benefit from repeat metastasectomy is less significant with each subsequent resection, but still more improved than if they were not re-resected [3, 20].

In an effort to address time to recurrence, the current study used an average between recurrences to simulate more aggressive tumor activity. The mean times between both the pulmonary recurrences and the extrathoracic recurrences both reflect the rapidity with which recurrence develops. Although this variable has not previously been presented in such a way, this does seem to appropriately reflect the biologic activity of the tumor and predict survival as an independent variable. Recurrence outside the chest is the most likely explanation for the shorter survival associated with patients having no pulmonary recurrence.

As many other studies have shown, DFI appears to be one of the most important prognostic indicators of survival in pulmonary metastasectomy patients after resection [3–6, 19]. Others have not found DFI to predict survival [13, 21], but one of these studies was not strictly sarcomatous metastasectomies [21]. According to the current study, which evaluated this as a continuous variable, for every month increase in DFI there was an improvement in survival.

Although the maximum number of pulmonary metastases often predicts survival in analyses of all patients undergoing pulmonary metastasectomy [5, 14, 21, 17], subgroup analyses have found patients undergoing complete resection of pulmonary metastases, regardless of the number, becomes a stronger predictor of outcome and thus reduces the effect of increased lung metastases on survival [5–7]. It is difficult to discern the difference between early recurrence versus incomplete resection of pulmonary metastases, and caution should be used when classifying resections as "complete versus incomplete" based on pathology reports of a negative margin for each resection alone. Because of the inability to confirm resections as "complete" based on the pathology reports and margin status recorded in our database, the current study did not include completeness of resection in the multivariable analysis. Thus, we are unable to determine the role this important variable plays in these patients. Multiple other analyses have found completeness of resection to be the most important prognostic indicator for survival [3, 13, 21].

Another factor predicting survival includes the interval of time between detection of the pulmonary metastasis and resection. Tanaka and colleagues have found improved survival and decreased relapse after metastasectomy when a longer amount of time (more than three months) exists between detection and resection [23].

By separating our patients into several groups, we were able to analyze survival according to how they present clinically to the thoracic surgeon. This made our data more applicable to a clinical setting where such decisions are made. The selection of patients for resection is an extremely variable process, and those patients not selected for pulmonary metastasectomy are unfortunately not included in this analysis. The retrospective nature of this study is a severe limitation, and does not allow a comparison between pulmonary metastasectomy patients and those not selected for metastasectomy. Gadd and colleagues [2] have looked at entire patient cohorts and made such comparisons, finding a significant (21%) improvement in survival when patients are able to undergo resection of pulmonary metastases from extremity sarcomatous primary tumors.

Similar survival is possible for resectable sarcomatous pulmonary and synchronous or prior nonpulmonary metastasectomy patients compared with patients with only resectable sarcomatous pulmonary metastases. The traditional surgical criteria mandating all disease outside the chest to be controlled prior to pulmonary resection should be amended to include the selection of patients with resectable disease outside the chest as well. Patients who survive to have multiple pulmonary resections who have a more than 12 month mean interval between pulmonary recurrences, who have a more than 24 month mean interval between extrathoracic recurrences, and who have a prolonged disease-free interval are expected to have increased survival.

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DISCUSSION

DR ROBERT J. CERFOLIO (Birmingham, AL): VATS metastasectomy versus open metastasectomy, do you want to talk about your preference and why?

DR BLACKMON: Currently we do open metastasectomy, but I know Dr Miller has presented some data on this before, as many others have. I think the advantage of a VATS [video-assisted thoracic surgery] metastasectomy would clearly be that re-resecting these patients is easier, and if they are recurring at a decent interval, we know that multiple metastasectomy patients continue to benefit from repeat resections, although with each re-resection the benefit declines. So I do think that would be the advantage of that. The disadvantage is finding those deeper lesions that are more difficult to get to, and I think targeting those lesions with some kind of marker might be the best way to get them. I don't have a strong opinion about whether or not it should or shouldn't be done.

DR CERFOLIO: First, do you think you commit them to more operations if you do a VATS because you are not feeling nonimaged nodules, and second, do you feel that maybe by not doing a complete metastasectomy because you have done a VATS that these nonimaged nodules may metastasize to regional nodes? Now, there is no data for that, but that's the concern.

Do you have any opinions or data on those two points?

DR BLACKMON: I think a randomized trial would answer that question, and I think that's probably the only way those questions will be answered. Only four of our patients had a thoracoscopic resection from this group, which is a reflection of our general feeling that a more complete resection can be achieved in an open manner.

DR CERFOLIO: Very good.

DR PAUL SCHIPPER (Portland, OR): I have two questions. In that 96% of patients who had pulmonary metastasis but did not have surgical resection, were they getting a therapy, and what type of therapy?

DR BLACKMON: The patients who did not have any surgical therapy had either chemotherapy or radiation therapy.

DR SCHIPPER: They all went on to a local therapy or a systemic therapy?

DR BLACKMON: Right.

DR SCHIPPER: And then 96% of them did not?

DR BLACKMON: Correct. Some of them were not treated and instead were observed.

DR SCHIPPER: Thank You. My second question. Of the patients that you resected, did you notice where they recurred the second time or the third time? Did you notice a change in the pattern of recurrence or appearance of new disease compared to those patients who were not resected? In other words, I have wondered if in removing known pulmonary metastasis there is a change in a patient's immune system and disease that was previous stable or not known is able to grow. Did you see more recurrences at the site of primary disease for example?

DR BLACKMON: We didn't notice a pattern of recurrence change. We did have many patients who had more than four recurrent resections, and we did notice that there was a trend towards increased survival for those who had three or more recurrences within the lung; however, the mean time between recurrence tended to predict survival more than anything. Some patients were resected as they progressed and others were resected with slow-growing or stable disease. Those with a favorable tumor biology did not appear to become unfavorable after they were resected. I do not have the data to completely answer your question right now, but will certainly try to go back and look at our data to find it.

DR ENRICO RUFFINI (Torino, Italy): Do you recommend lymphadenectomy in this type of patient, and, if yes, did you notice if there is any prognostic significance in patients who are node-positive or node-negative?

DR BLACKMON: We did not look at lymphadenectomy in this study; however, we have looked at it with other studies. Lymphadenectomy was not routinely performed on every case and was especially not performed on repeat metastasectomy cases. However, some of the patients did undergo lymphadenectomy, and I don't have any data to tell you whether or not that made a difference.

DR RUFFINI: What are your criteria for doing or not doing lymphadenectomy in these sarcomatous patients?

DR BLACKMON: As a standard, they don't get a lymphadenectomy. As you know, this disease rarely metastasizes to the lymph nodes. On review of our patients, only two had a positive lymph node resected, and both appeared to have enlarging or clinically suspicious lymphadenopathy.

DR CERFOLIO: But I think we should, and I'll take it a step further. What do you do with a 21-year-old guy who has suspicious nodes and you do a mediastinoscopy and you find that he has metastatic sarcoma in an N2 lymph node? Do you say, hey, the prognosis is so bad, because we know it is, or do you go in there and be aggressive and resect them?

DR BLACKMON: I think it depends on the histology of the tumor.

DR CERFOLIO: He's 19.

DR BLACKMON: Well, again, I think it depends on the histology of the tumor and its responsiveness to adjuvant therapy, but I think in that case, if you can get everything out, as the study has shown, they should have increased survival.

DR CERFOLIO: Okay. Now he's 69 with marginal PFTs [pulmonary function tests] and you're doing a mediastinoscopy and it's positive for metastatic sarcoma and he has two nodules, one in the right upper and one in the right lower. Do you do him?

DR BLACKMON: I think it depends. If he only requires a wedge resection, yes. If he requires a lobectomy or a more extensive resection and has mediastinal positive nodes, then, probably, no.

DR DANIEL L. MILLER (Atlanta, Georgia): That's a good point, because a lot is based on the histology, because if you have a tumor that will have some response, then doing a lymphadenectomy may have some benefit, especially in patients with a history of colorectal or renal cell cancer. The most important point is for the sarcoma patients, in the majority we do not see nodal involvement because they are followed more frequently for the possibility of pulmonary mets and therefore have less of a chance for the development of nodal disease because of less overall tumor burden and shorter time of tumor growth. Whereas for colon cancer patients, they are not routinely followed for the risk of pulmonary mets with CT scans, and when they are finally found to have a pulmonary met they are usually larger lesions that have been present for a longer period of time and thus have a higher chance of developing thoracic nodal involvement.

DR CERFOLIO: But, Dan, I just don't think it's the follow-up. I think it's the biology of the disease.

DR MILLER: I agree somewhat, but also the time of discovery of the met related to primary tumor and how (incidentally or symptomatically) also plays a role.

DR CERFOLIO: They are all hematogenous, but I think they are different. But I think we should be doing lymph node resections when we do them, because then when they come back, if you need an out, a reason not to do them again, and if he is a higher risk, you say, "Look, I did you a year ago. Two or three of your lymph nodes were positive. Your benefit of re-resection is pretty low," and you might not offer him re-resection. Without the lymph node data, and we congratulate our colleagues from Italy for proving this data for us, their prognosis and survival is very low.

DR MILLER: Yes, I agree with that.