HHS Public Access

Author manuscript

Ann Thorac Surg. Author manuscript; available in PMC 2018 December 01.

Published in final edited form as:

Ann Thorac Surg. 2017 December ; 104(6): 1837–1845. doi:10.1016/j.athoracsur.2017.07.024.

Is Repeat Pulmonary Metastasectomy Indicated for Soft Tissue Sarcoma?

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Abstract

Background—As recurrence is high following pulmonary metastasectomy (PM) for soft tissue sarcoma (STS), repeat PM is commonly performed. Our objective was to define the selection criteria for repeat PM among patients experiencing recurrence and to identify factors associated with survival.

Methods—We reviewed a prospectively-maintained database of 539 patients undergoing PM for STS. Characteristics of the primary tumor, metastatic disease, treatment, and recurrence were examined. Multivariable Cox models were constructed to identify factors associated with the likelihood of operative selection following recurrence. Overall survival between patients with or without repeat PM was estimated using the Kaplan-Meier method, with prognostic factors identified using Cox models. Both analyses incorporated propensity score matching weights. Factors associated with survival after repeat PM were assessed with multivariable Cox models among those who underwent repeat PM.

Results—Following initial PM, 63% of patients (n=341) experienced pulmonary recurrence; 141 (41%) underwent repeat PM. Patients who were younger (p=0.033), underwent minimally invasive resection at first PM (p=0.041), had a longer disease-free interval following first PM (p=0.009), were without extrapulmonary disease (p<0.001), and had fewer nodules on recurrence (p<0.001) were more likely to undergo repeat PM. Comparison between the repeat and non-repeat PM groups demonstrated an increased hazard of death among patients managed nonoperatively. Factors associated with an increased hazard of death following second PM included preoperative chemotherapy (p=0.008) and R1/R2 metastasectomy (p<0.001).

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Conclusions—Although operative selection occurs, when prognostic factors are controlled for, repeat PM for STS remains independently associated with prolonged overall survival.

Up to 50% of patients with soft tissue sarcoma (STS) develop lung metastases [1–5]. Effective systemic treatment for metastatic STS is limited [6]. Therapeutic pulmonary metastasectomy (PM) has been selectively used, with an associated survival benefit over no surgery, based on Level II evidence. Guidelines for the use of pulmonary metastasectomy do not currently exist [7].

Treatment of STS is further complicated by high recurrence rates following initial PM, as >50% of patients develop lung recurrence [1, 3, 8, 9]. A subset of these patients is selected for repeat PM, with the potential to undergo several operations during their disease course [10]. In the International Registry of Lung Metastases study, 33% of patients with sarcoma examined (n=642) underwent a second PM [8]. Data specific to repeat PM, however, are limited. Several studies document a longer median overall survival (OS) with an increasing number of metastasectomies [3, 8, 11–14]. Repeat PM has thus been considered an acceptable treatment for recurrent disease [3, 15]. Direct comparison between single and multiple PMs, however, has been criticized due to differences within patient characteristics in each of these groupings [16]. In particular, data on nonoperatively managed patients have been scarce [17]. Therefore, the presumed survival benefit ascribed to repeat resection has been questioned.

The objectives of this study are to (1) identify factors associated with selection for repeat PM among patients experiencing pulmonary recurrence; (2) compare OS between patients with pulmonary recurrence who undergo repeat PM and patients who do not have surgery, with a consideration of the differences in clinicopathologic variables at presentation; and (3) identify factors associated with OS among patients who undergo repeat PM.

PATIENTS AND METHODS

Patient Selection

A database of patients undergoing PM for primary STS is prospectively maintained at Memorial Sloan Kettering Cancer Center (MSK). We identified 539 patients undergoing PM with therapeutic intent for STS between September 1991 and June 2014 and have previously reported on these patients [18]. All data were collected with approval of the Institutional Review Board.

Clinicopathologic Variables

Patient demographics, primary and metastatic disease characteristics, and details of treatment, recurrence, and survival were collected. Histologic subtype, size, and grade of the primary tumor were verified by review of pathology reports. Operative reports were reviewed to identify surgical access (open or minimally invasive), as well as extent of resection (wedge resection, lobectomy, or pneumonectomy). The number of metastases identified and/or resected and “R” status at the initial PM were obtained from operative and pathologic reports. Data on chemotherapy were obtained through review of clinical documentation.

Recurrence Following Initial PM

After their initial metastasectomy, patients were monitored with periodic clinical examinations and imaging. Recurrence was defined as the first documentation of disease following initial R0 PM. Upon lung recurrence, data on synchronous extrapulmonary disease and the number of clinical lung metastases were collected. The Karnofsky Performance Status (KPS) scale, used to assess patient fitness, was obtained through documentation during office visits. For patients undergoing repeat PM, treatment details and outcomes were obtained.

Statistical Analyses

Clinicopathologic variables for patients undergoing repeat PM and those not were compared using Fisher's exact test for categorical variables and the Wilcoxon rank sum test for continuous variables. Cox proportional hazards models were constructed to identify factors associated with the probability of undergoing repeat PM. Time to event was measured from the time of recurrence to the date of repeat PM; otherwise it was censored on the date of last follow-up. Variables with a significant association in univariable analyses ($p \leq 0.05$) and clinically relevant were included in a multivariable Cox model.

Comparison of OS between patients who underwent a second PM and those who did not required attention to factors associated with selection. To address this, we used the matching weights method [19]. This approach is a weighting analogue to the 1:1 pair matching method, although shown to be more efficient, that provides better balance across covariates. Unlike 1:1 pair matching, which excludes any unmatched patients, the matching weights approach never discards any patients; instead, it only down-weights some of the patients. The matching weights approach is a variant of the inverse probability weights method; the matching weights can be considered the probability of being selected to the matched data set. With the application of the patient-level matching weights, each patient contributes a fraction of itself to the overall cohort used in the analyses.

Variables for inclusion in the logistic model were selected based on clinical factors associated with the likelihood of undergoing repeat PM. These included age at diagnosis of the primary tumor; age at first PM; sex; histologic subtype, site, and grade of the primary tumor; surgical access; extent of resection; duration between the first PM and relapse; synchronous extrapulmonary recurrence; number of recurrent nodules; and KPS scale. Performance of the matching-weight approach was assessed through evaluation of the standardized mean differences in variables between the two groups. Covariate balance was confirmed by an absolute standardized mean difference (ASMD) ≤ 0.1 for each variable following the application of matching weights. The distribution of propensity scores before and after application of the matching weights is presented as a mirror histogram, to visually assess the success of the approach [19]. Overall survival was measured from the time of first pulmonary recurrence to the time of death, or censored at the time of last follow-up. OS was estimated by the Kaplan-Meier approach and compared between groups by the log-rank test, with the application of matching weights. In addition, the association between receiving repeat PM and death was assessed using Cox models. The matching weights were incorporated as weights at the patient-level, and the second PM status was considered a

time-varying covariate, where all patients initially begin in the non-repeat PM group at the time of recurrence and switch over to the repeat PM group on the date of the second PM.

Factors associated with the hazard of death following repeat PM were assessed with Cox models among patients who received repeat PM. The time to event was measured from the time of the second PM to the time of death or was censored on the date of the last follow-up. Variables that were significant in the univariable analyses ($p \leq 0.05$) and clinically relevant variables were included in a multivariable model. All analyses were conducted in R 3.1.1 (R Development Core Team, Vienna, Austria). The matching weight procedure was performed with the *survey* and *tableone* packages. All statistical tests were two-sided, and $p<0.05$ was considered statistically significant.

RESULTS

Patient Characteristics

Between September 1991 and June 2014, 539 patients underwent 760 PMs with therapeutic intent for STS at MSK. Following R0 resection, 63% of the cohort (n=341) experienced pulmonary recurrence. Of these, 141 underwent repeat PM. Thirty-three patients undergoing repeat PM had bilateral disease, and of these, 14 were staged resections. The remaining 200 patients did not undergo subsequent PM (Fig. 1). Median follow-up was 23.9 months (interquartile range [IQR], 11.2 – 44.4 months) from initial PM. Table 1 demonstrates baseline clinicopathologic characteristics of these two groups as well as details on recurrence. Patients in the repeat PM group were younger ($p<0.001$), and a larger percentage of these patients underwent a minimally invasive procedure at their initial surgery ($p=0.002$). Patients undergoing repeat PM also had longer disease-free intervals (DFIs) from their initial PM ($p<0.001$), fewer pulmonary nodules at recurrence ($p<0.001$), lower occurrence of synchronous extrapulmonary metastases ($p<0.001$), and higher overall fitness, represented by KPS scale ($p<0.001$).

Selection for Repeat PM

We subsequently created multivariable Cox models to identify factors significantly associated with selection for repeat PM (Table 2). Older patients had a lower likelihood of repeat PM (HR: 0.98; 95% CI: 0.97 to 1.00). Minimally invasive resection at the initial PM was associated with an increased likelihood of repeat PM (HR: 1.58; 95% CI: 1.02 to 2.45). Patients with a longer DFI from the initial PM were more likely to be selected for repeat PM (HR: 1.02; 95% CI: 1.00 to 1.04). Patients with a greater number of recurrent pulmonary nodules (HR: 0.73; 95% CI: 0.63 to 0.83) and synchronous extrapulmonary disease (HR: 0.13: 95% CI: 0.08 to 0.23), were less likely to undergo repeat PM. KPS scale (HR: 1.01; 95% CI: 0.99 to 1.06), and receipt of perioperative chemotherapy at initial PM (HR: 0.67; 95% CI: 0.41 to 1.09) were not significantly associated with selection for repeat PM. Of the 200 patients who did not undergo repeat PM, 143 (71.5%) went on to receive chemotherapy.

Propensity Score Matching Weight Analysis of Repeat PM Versus No Surgery

Patients selected for repeat PM had a median OS of 44.9 months from the first recurrence at any site, compared with 14.0 months among patients without repeat PM ($p<0.001$). As

described previously, however, several differences exist between these groups. The matching weight approach was subsequently performed to compare OS between the repeat and non-repeat PM groups among comparable patients, to reduce potential selection bias. Baseline factors pertaining to the primary tumor, characteristics of the index metastasectomy, and clinicopathologic variables on recurrence, as described in the Methods, were used in the calculation of propensity scores and corresponding matching weights for each patient.

The standardized mean differences for each parameter, before and after applying the matching weights, are displayed in Supplemental Table 1. Before applying the matching weights, values for the ASMD were >0.1, confirming known baseline differences between the groups. After applying the matching weights, the ASMD was ≤0.1 for every covariate, indicating balance across all clinically relevant factors (Supplemental Fig. 1). The distribution of propensity scores showed good overlap between the repeat and non-repeat PM groups after application of the matching weights (Supplemental Fig. 2). After applying the matching weights, the effective sample sizes were 68.6 contributions in the non-repeat PM group and 67.7 contributions in the repeat PM group.

Hazard ratios for the hazard of death from the time of the first recurrence were subsequently estimated incorporating these matching weights. Patients who did not undergo repeat PM had a 2.13-fold greater hazard of death, compared with patients who did (95% CI: 1.39 to 3.26; $p<0.001$). Thus, when characteristics of the primary tumor and metastatic disease are controlled for, repeat PM remains associated with a survival benefit (Fig. 2).

Factors Associated with Overall Survival Following Repeat PM

Data on patients who underwent repeat PM ($n=141$) are presented in Supplemental Table 2. Leiomyosarcoma and synovial sarcoma were the most commonly represented primary histologic subtypes in the repeat PM group. Thirty-two patients had synchronous extrapulmonary disease. Most patients ($n=100$) underwent surgery directly; a smaller fraction received chemotherapy before resection. Twenty-three percent of patients ($n=33$) underwent a minimally invasive procedure for repeat PM, compared with 29% for the initial PM. Wedge resection was the most commonly performed procedure ($n=110$). A single pulmonary metastasis was resected in sixty-nine patients. R0 resection was achieved in 86% of cases ($n=121$), which is comparable to the 91% R0 resection rate for first PM.

The rate of recurrence remained high, with 98 patients (70%) experiencing a recurrence at any site following an R0 second PM. Ninety patients had lung recurrence following complete resection. Median time to recurrence for these patients was 5.0 months (range, 2.0 to 9.0 months). Median OS for patients undergoing a second PM was 4.1 years from the first PM and 2.7 years from the second PM (Fig. 3). Thirty-eight patients (42%) underwent a third PM.

Log-rank analyses of OS from the second PM demonstrated differences for several clinicopathologic variables. A DFI >12 months from the first PM was associated with an increased median OS of approximately 27 months ($p=0.007$). Likewise, the initial DFI between resection of the primary lesion and the first PM continued to have a significant association with survival in those undergoing repeat resection. Patients who received

preoperative chemotherapy had shorter OS than patients treated with surgery directly ($p<0.001$). No differences were seen between minimally invasive and open procedures ($p=0.055$), and the extent of resection was also not significant ($p=0.319$). Patients with more recurrent nodules generally had poorer survival ($p=0.025$). Complete resection was associated with an increased median OS of 28 months ($p<0.001$).

We subsequently constructed a multivariable Cox model for the hazard of death following repeat PM (Table 3). Patients with leiomyosarcoma had a lower hazard of death (HR=0.48; 95% CI, 0.25 to 0.92) than patients with PS/MFH. Primary tumor grade was not associated with OS ($p=0.14$). Similarly, the DFI from the first PM was not associated with hazard of death (HR: 0.98; 95% CI: 0.96 to 1.00). Patients treated with preoperative chemotherapy had a significantly greater hazard of death (HR: 1.94; 95% CI: 1.19 to 3.18). More metastatic nodules were not associated with a greater hazard of death (HR: 1.13; 95% CI: 0.99 to 1.28). The factor most strongly associated with OS was resection outcome: patients with incomplete PM had a 4-fold greater hazard of death compared to those with complete resection (HR: 4.15; 95% CI: 2.26 to 7.62).

COMMENT

Repeat PM is commonly used for several tumor types [3, 13, 20–23]. A survey of 146 members of the European Society of Thoracic Surgeons found that 53% of respondents would not place a limit on the number of repeat metastasectomies they would perform. [24]. A frequent criticism of the positive relationship between survival and number of PMs is the inability to differentiate the effect of selection bias from treatment benefit [16, 17, 25]; however, level I evidence of this association remains lacking.

Factors associated with selection for repeat PM in our study have been shown to be associated with improved survival in patients undergoing PM [1, 8, 9, 26, 27]. Noting the overlap of selection and prognostic factors, we performed a matching weight propensity score analysis. When potential confounders were controlled for, a statistically significant reduced risk of death was still associated with repeat PM, compared with no surgery. Previous reports on PM, initial or repeat, have not performed propensity-matched analyses which are a significant advance of this study. Our study is therefore novel in that we have attempted to evaluate the previously indefinable denominator from which patients are selected, and control for variability in baseline characteristics that might indicate a bias toward a repeat PM or nonoperative management. The result of this more rigorous analysis indicates that the survival curves for the nonsurgical and repeat PM groups remain significantly divergent.

Previous studies investigating repeat PM for sarcoma focused on relatively small series [17, 28, 29]. Our institution previously reported on 86 patients who underwent repeat PM between 1982 and 1997, where 5-year survival was 36%. [3]. In the present study, 5-year OS was similar, at 35%, with a median OS of 32.4 months. On univariable analyses, longer DFI, treatment with preoperative chemotherapy, number of recurrent pulmonary metastases, and completeness of resection were significantly associated with survival, as described in various

series [3, 26, 29]. On multivariable analysis, leiomyosarcoma histologic subtype was significantly associated with longer OS as previously reported [13].

Preoperative chemotherapy was also associated with a greater risk of death on multivariable analysis. This likely represents a bias toward patients with a more-aggressive underlying disease biology being selected for multimodality treatment. It has been suggested that progression of disease while receiving chemotherapy is an independent prognostic factor for worse survival [30]. The current analyses demonstrate that, for patients undergoing repeat PM, selection for preoperative chemotherapy is itself a negative predictor, regardless of response.

Several studies have emphasized the importance of achieving an R0 resection [1, 3, 15, 29]. Complete resection was achieved in 86% of patients who underwent repeat PM, with an associated survival benefit that remained significant on multivariable analysis. Selection of patients for resection is of paramount importance, as resectability has been shown to be prognostic. Factors we found to be associated with selection for repeat PM may apply to resectability overall, and careful consideration of these factors may help to ensure that the high rate of R0 resections is maintained.

Limitations of this study include its retrospective design, and the data are derived from a single institution. Although our analysis includes weight-based propensity matching to control for factors associated with selection for surgery, the study is not a randomized controlled trial. The variables we have included for matching, although inclusive of factors associated with selection, may also not capture all of the intricacies involved in the decision-making process, which is often individualized for each patient. Our database also focuses on surgical management; other treatment modalities, such as radiofrequency ablation and stereotactic body radiation therapy that are being increasingly used were not evaluated.

Metastatic disease is frequently relegated to the category of non-operative management. Our results indicate that surgical intervention, even in cases of recurrent metastases, can be associated with a survival benefit. Multidisciplinary disease management teams ought to be used to identify these patients, as is routinely performed at our institution. Specifically, the disease-free interval from the preceding PM, the number of recurrent nodules, the presence of other synchronous sites of disease, and resectability are considered. Furthermore, we plan to use our data for the creation of a nomogram, such that patients can be appropriately identified for referral to a thoracic surgeon.

In summary, we have identified several prognostic variables associated with repeat PM for STS. The high recurrence rate after initial and repeat PM remains one of the greatest challenges in treating this disease. However, compared with patients managed without repeat PM, patients who undergo repeat PM have superior survival and improved outcomes based on matching weights propensity score analysis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ABBREVIATIONS

ASMD	absolute standardized mean difference
DFI	disease-free interval
GU	genitourinary
GYN	gynecological
KPS	Karnofsky performance status
MIS	minimally invasive surgery
MPNST	malignant peripheral nerve sheath tumor
MSK	Memorial Sloan Kettering Cancer Center
OS	overall survival
PM	pulmonary metastasectomy
PS/MFH	pleomorphic sarcoma, malignant fibrous histiocytoma
STS	soft tissue sarcoma

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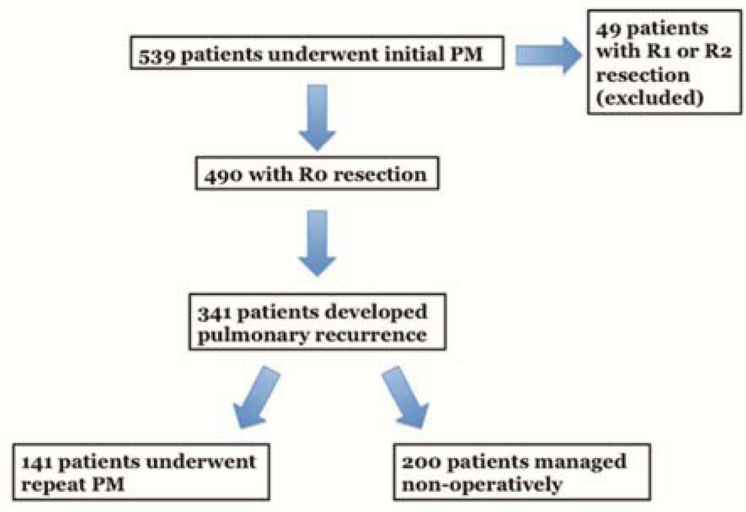

Figure 1.
Consort diagram for inclusion into analysis. PM, pulmonary metastasectomy.

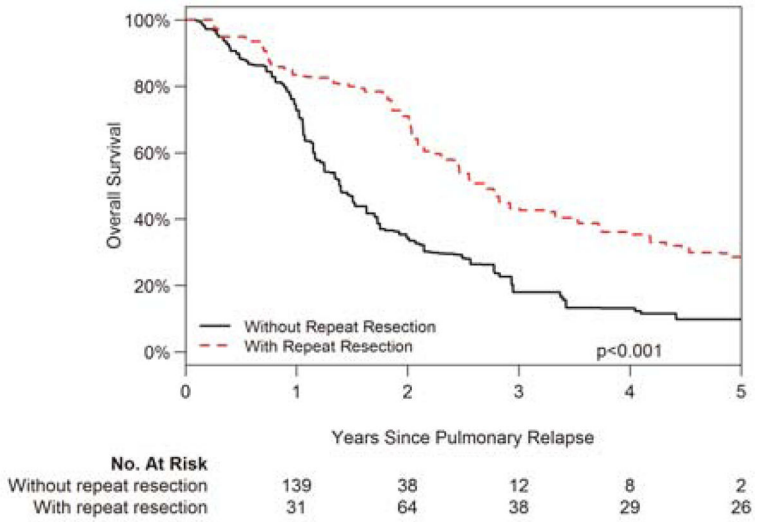

Figure 2.

Overall survival with recurrent metastatic pulmonary soft tissue sarcoma based on treatment following weight-based propensity matching.

**P* value calculated from Cox proportional hazards model incorporating matching weights, and repeat PM is considered a time-dependent variable.

**Considering repeat PM as a time-dependent variable, the number at risk reflects the number of patients who have undergone repeat PM by the indicated time point. The number may increase as patients are selected for repeat PM during their follow-up.

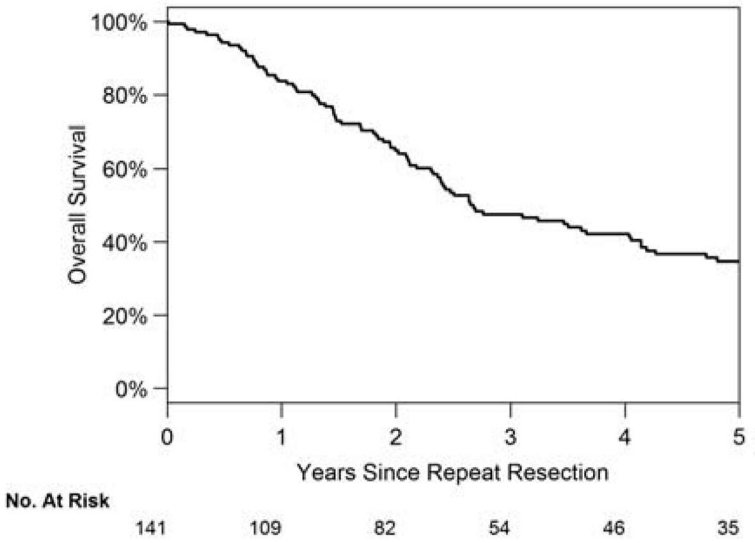

Figure 3.
Overall survival of patients undergoing repeat pulmonary metastasectomy from second resection.

Table 1

Clinicopathologic Characteristics in Patients with Pulmonary Recurrence Based on Subsequent Treatment

Variable	No Surgery *n*=200 (%)	Repeat PM *n*=141 (%)	*P*
Sex			0.179
Female	126 (63.0)	78 (55.3)	
Male	74 (37.0)	63 (44.7)	
Age at diagnosis of primary tumor[a]	53.0 (41.6, 62.4)	48.0 (36.0, 56.7)	<0.001
Histologic subtype of primary tumor			0.002
PS/MFH	59 (29.5)	21 (14.9)	
Synovial	21 (10.5)	32 (22.7)	
Leiomyosarcoma	71 (35.5)	42 (29.8)	
Liposarcoma	10 (5.0)	9 (6.4)	
Fibrosarcoma	8 (4.0)	14 (9.9)	
MPNST	5 (2.5)	4 (2.8)	
Other	26 (13.0)	19 (13.5)	
Site of primary tumor			0.087
Extremity	96 (48.0)	71 (50.4)	
Trunk	25 (12.5)	13 (9.2)	
Retroperitoneal/abdomen/pelvis	24 (12.0)	10 (7.1)	
Visceral-GU/GYN	51 (25.5)	37 (26.2)	
Head and neck	4 (2.0)	10 (7.1)	
Size of primary tumor			0.107
≤10 cm	97 (48.5)	75 (53.2)	
>10 cm	90 (45.0)	50 (35.5)	
Unknown	13 (6.5)	16 (11.3)	
Grade of primary tumor			0.230
Low	16 (8.0)	18 (12.8)	
High	180 (90.0)	122 (86.5)	
Unknown	4 (2.0)	1 (0.7)	
Interval to first PM			0.128
Synchronous	29 (14.5)	17 (12.1)	
<12 months	74 (37.0)	40 (28.4)	
≥12 months	97 (48.5)	84 (59.6)	
Type of surgery at first PM			0.002
Open	155 (77.5)	87 (61.7)	
Minimally invasive	45 (22.5)	54 (38.3)	
Extent of resection at first PM			0.064
Wedge	151 (75.5)	121 (85.8)	
Lobectomy	45 (22.5)	18 (12.8)	
Pneumonectomy	4 (2.0)	2 (1.4)	
Disease-free interval[b]			<0.001
<12 months	175 (87.5)	98 (69.5)	

Variable	No Surgery *n*=200 (%)	Repeat PM *n*=141 (%)	*P*
≥12 months	25 (12.5)	43 (30.5)	
Number pulmonary nodules at recurrence			<0.001
1	42 (21.0)	70 (49.6)	
2	25 (12.5)	21 (14.9)	
3	43 (21.5)	15 (10.6)	
4	24 (12.0)	6 (4.3)	
5	7 (3.5)	1 (0.7)	
>5	42 (21.0)	20 (14.2)	
Unknown	17 (8.5)	8 (5.6)	
Synchronous extrapulmonary disease at recurrence			<0.001
No	74 (37.0)	110 (78.0)	
Yes	126 (63.0)	31 (22.0)	
KPS scale at recurrence			<0.001
≤70	18 (9.0)	0 (0.0)	
80	45 (22.5)	12 (8.5)	
90	77 (38.5)	71 (50.4)	
100	19 (9.5)	15 (10.6)	
Unknown	41 (20.5)	43 (30.5)	

GU, genitourinary; GYN, gynecological; MPNST, malignant peripheral nerve sheath tumor; PM, pulmonary metastasectomy; PS/MFH, pleomorphic sarcoma/malignant fibrous histiocytoma; KPS, Karnofsky Performance Status.

[a] Represented as median (25th, 75th percentile)

[b] From first pulmonary metastasectomy to recurrence at any site.

Table 2

Multivariable Cox Proportional Hazards Models for Likelihood of Undergoing Repeat Pulmonary Metastasectomy (PM)

Variable	Hazard Ratio (95% CI)	*P*
Age at diagnosis of primary tumor	0.98 (0.97 to 1.00)	0.033
Perioperative treatment at initial PM	0.67 (0.41 to 1.09)	0.10
Minimally invasive surgery at initial PM	1.58 (1.02 to 2.45)	0.041
Disease-free interval[a]	1.02 (1.00 to 1.04)	0.009
No. of pulmonary nodules at recurrence	0.73 (0.63 to 0.83)	<0.001
Synchronous extrapulmonary disease at recurrence	0.13 (0.08 to 0.23)	<0.001
KPS scale at recurrence (%)	1.01 (0.99 to 1.06)	0.14

KPS, Karnofsky Performance Status.

[a]From first pulmonary metastasectomy to recurrence at any site per month.

Table 3

Multivariable Cox Proportional Hazards Models for the Hazard of Death After Repeat Pulmonary Metastasectomy

Variable	Cox Hazard Ratio (95% CI)	*P*
Histologic subtype of primary tumor		
PS/MFH[a]	1.00	—
Synovial	0.65 (0.33 to 1.28)	0.2
Leiomyosarcoma	0.48 (0.25 to 0.92)	0.026
Liposarcoma	0.42 (0.14 to 1.28)	0.13
Fibrosarcoma	0.44 (0.17 to 1.10)	0.077
MPNST	0.70 (0.16 to 3.13)	0.6
Other	1.04 (0.43 to 2.55)	0.9
High-grade primary tumor	1.89 (0.81 to 4.38)	0.14
Disease-free interval[b]	0.98 (0.96 to 1.00)	0.11
Preoperative chemotherapy	1.94 (1.19 to 3.18)	0.008
No. of pulmonary nodules	1.13 (0.99 to 1.28)	0.073
Incomplete (R1/R2) resection	4.15 (2.26 to 7.62)	<0.001

PS/MFH, pleomorphic sarcoma/malignant fibrous histiocytoma; MPNST, malignant peripheral nerve sheath tumor.

[a]Reference group.

[b]From first pulmonary metastasectomy to recurrence at any site per month.