Risk stratification of patients undergoing pulmonary metastasectomy for soft tissue and bone sarcomas

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Objectives: Our objective was to identify risk factors associated with survival in patients who underwent pulmonary metastasectomy for soft tissue or bone sarcoma and to create a risk stratification model.

Methods: A retrospective review of the prospectively maintained University of California Los Angeles Sarcoma Database was performed. Clinical, pathologic, and treatment variables were analyzed for overall survival and disease-free survival. Univariate and multivariate analyses were performed, and variables that were identified as significant were included to create a risk model. A total of 155 patients who underwent pulmonary metastasectomy for soft tissue sarcoma (n = 108 patients) or bone sarcoma (n = 47 patients) from 1994 to 2010 were identified.

Results: Multivariate analysis identified 7 factors associated with poor overall survival: age more than 45 years, disease-free interval less than 1 year, thoracotomy, synchronous disease, location and type of sarcoma (soft tissue vs bone sarcoma), and performance of a lobectomy. The number of factors present was associated with poor overall survival, which varied widely from 64% in patients with 2 factors to 3% in those with 5 factors.

Conclusions: We have identified prognostic variables associated with overall survival after lung metastasectomy. Our model may be used as a risk stratification model to guide treatment decisions on the basis of the number of risk factors present. Although prospective studies are warranted to determine the benefit of surgical intervention in all cohorts compared with other local therapies or medical therapy, given the attendant dismal prognosis in patients with 5 or more risk factors, the benefit of surgical resection in this group is questioned. (J Thorac Cardiovasc Surg 2015;149:85-92)

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Pulmonary metastases occur in up to 50% of patients with sarcoma during the course of their disease,¹⁻³ and the lung is the sole site of metastasis in 19% of patients.⁴ No randomized controlled trials have directly compared surgical resection with chemotherapy alone or the effects of chemotherapy given for metastatic disease on survival. Pulmonary metastasectomy has become an accepted treatment option in select patients with metastatic sarcoma isolated to the lung.^{1-3,5-9} The prognosis for unresected disease is poor with a median survival of 11 months, whereas that for completely resected disease is up to 33 months.² Retrospective studies have shown a survival advantage in patients who underwent complete resection of pulmonary metastases with 5-year survival ranging from 13% to 49%.^{1,10-12}

Although multiple risk factors associated with poor survival have been reported, stratification of these variables into patient cohorts to guide surgical treatment is not well defined.² The objective of this study is to identify prognostic variables of overall survival (OS) and create a risk stratification model to guide surgical treatment of sarcoma metastasis to the lung.

Abbreviations and Acronyms

BS	= bone sarcoma
DFI	= disease-free interval
DFS	= disease-free survival
OS	= overall survival
STS	= soft tissue sarcoma
VATS	= video-assisted thoracoscopic surgery

We report the identification of 7 factors associated with poor OS after lung metastasectomy: age greater than 45 years, disease-free interval (DFI) less than 1 year, thoracotomy, synchronous disease, location and type of sarcoma (soft tissue sarcoma [STS] vs bone sarcoma [BS]), and performance of lobectomy. The combination of these factors was associated with OS, which varied widely from 64% in patients with 2 factors to 3% in those with 5 factors.

MATERIALS AND METHODS**Patient Population**

A retrospective review of a prospectively maintained sarcoma database at our institution was queried to identify all patients who underwent pulmonary metastasectomy for sarcoma at the University of California, Los Angeles Medical Center between February 1994 and June 2010. Patients' records were reviewed to abstract the following data: demographics, type of primary sarcoma, initial therapy, time to pulmonary metastases, type of resection and additional therapy, disease-free survival (DFS), and OS. Follow-up was censored in May 2013. Three patients without any follow-up were excluded from the final analysis. Institutional review board approval was obtained.

Preoperative Evaluation

A multidisciplinary sarcoma tumor board evaluated patients with sarcomas metastatic to the lung preoperatively and postoperatively to determine the appropriateness of neoadjuvant and adjuvant treatments. All patients were considered for neoadjuvant chemotherapy followed by a single-stage or a 2-stage pulmonary metastasectomy for patients with bilateral diseases. Neoadjuvant chemotherapy was considered in those with (1) short DFI; (2) multiple lesions involving both lungs; (3) high-grade STS and high-risk BS (ie, osteosarcomas, Ewing's, and mesenchymal or dedifferentiated chondrosarcomas); and (4) synchronous pulmonary metastasis when neoadjuvant treatment was recommended for the primary lesion. Neoadjuvant therapy was defined as chemotherapy or chemoradiation given within 1 year before the pulmonary metastasectomy.

Pathologic Evaluation

All resected specimens were examined by a dedicated musculoskeletal pathologist. If the primary site resection was performed at an outside hospital, an attempt was made to obtain the original slides for our pathologist to confirm the diagnoses. The completeness of resection for the primary sites was determined from the available operative and pathology reports. The completeness of pulmonary metastasectomies was described using the residual tumor classification (R stage) system. R0 was defined as a complete resection. R1 was defined as residual microscopic tumor. R2 was defined as gross residual tumor left at the time of lung resection, multiple nodules that were not all resected, and unresected primary tumors treated with nonsurgical modalities.

Survival

Patients' survival data were obtained from the hospital records and the Social Security Death Index. DFI was defined as the time from primary tumor resection to pulmonary metastasectomy performed at our institution. OS was defined as the time between the first pulmonary metastasectomy performed at our institution to the date of death or May 2013 (the date when data collection was censored). DFS was defined as the time from pulmonary metastasectomy to the date of recurrence at all sites. The date of pulmonary metastasectomy was used as the date of recurrence if R2 resection was performed at the time of the pulmonary metastasectomy.

The Kaplan–Meier method was used to calculate OS and DFS probabilities. All survival and recurrence dates were calculated from the date of the first pulmonary metastasectomy. In cases when a 2-stage or sequential resection was planned, the date of the second pulmonary metastasectomy was used if no other intervention was performed in between the 2 operations and if the interval between the 2 operations was less than 3 months.

Statistical Analysis

OS and DFS were graphically displayed using Kaplan–Meier curves. Survival estimates for 1, 3, and 5 years were extracted and plotted. Differences between groups were assessed by the log-rank test. Age, gender, sarcoma type, primary location, grade, size, margin, histology, DFI, metastasectomy approach, type of resection, pulmonary metastasis size, grade, margin status, neoadjuvant therapy, adjuvant treatments, and number of further metastasectomies (including other sites) were included as potential predictors of survival. Variables that were statistically significant from the log-rank test were included in a multivariable Cox proportional hazards model. Hazard ratio estimates and 95% confidence intervals were estimated from the final models. To more easily interpret the results, a scoring system was developed by categorically dichotomizing patients' characteristics to whether they displayed the significant prognostic variable or not. The patients were then grouped according to the number of negative prognosis variables. A Kaplan–Meier curve was constructed summarizing the relationship between the scoring system variable and survival. Statistical analyses were conducted in R (version 3.0.2, www.r-project.org).

Patient and Clinical Presentation

A total of 158 patients underwent pulmonary resection for metastatic sarcoma during the study period. Three patients without available long-term data were excluded from this analysis; therefore, the final analysis was based on the remaining 155 patients. Patient and primary tumor characteristics are shown in Table 1. Neoadjuvant and adjuvant therapies surrounding resection of the primary sarcoma are shown in Table 1. Twenty-one patients (13.5%) underwent further resections for local recurrence before diagnosis of pulmonary metastases. Sixteen patients (10.3%) had prior pulmonary metastasectomies at another institution, and 8 patients (5.2%) had prior nonpulmonary metastasectomies.

RESULTS**Characteristics of Pulmonary Metastases**

The characteristics of the resected pulmonary metastases are shown in Table 2. A total of 115 patients underwent open surgeries (74.2%), and 40 patients (25.8%) underwent video-assisted thoracoscopic surgery (VATS). Seven patients (4.5%) underwent staged bilateral exploration. A total of 102 patients (65.8%) underwent wedge resections, 27 patients (17.4%) underwent lobectomy, and 6 patients (3.9%) required pneumonectomy. The survival curves for the different types of resections

TABLE 1. Patient and primary tumor characteristics

	Overall (n = 155)	Percentage (%)
Age, y		
Average	47 ± 17	
Range	11-92	
Sex		
Male	87	56.1
Female	68	43.9
Symptoms		
Asymptomatic	120	77.4
Symptomatic	35	22.6
Cough	13	8.4
Dyspnea	8	5.2
Chest pain	7	4.5
Hemoptysis	4	2.6
Weight loss	2	1.3
Nausea or vomiting	1	0.6
Sarcoma type		
Soft tissue	108	69.6
Bone	47	30.3
Primary tumor location		
Extremity	87	56.1
Nonextremity	52	33.5
Chest wall*	35	22.6
Intrathoracic§	4	2.6
Retroperitoneum	7	4.5
Head and neck	3	1.9
Other	3	1.9
Visceral-gynecologic	16	10.3
Primary tumor diameter (cm)†		
Average	9.9 ± 5.9	
Range	1.5-33.0	
Primary tumor grade‡		
High	105	67.7
Low/intermediate	19	12.2
Unknown	31	20.0
Margin status		
Positive	15	9.7
Negative	101	65.2
Unknown	39	25.2
Neoadjuvant therapy	62	40.0
Chemotherapy	35	22.6
Chemoradiation	26	16.8
Radiotherapy	1	0.6
None	89	57.4
Unknown	4	2.6
Adjuvant therapy	112	72.3
Chemotherapy	55	35.5
Chemoradiation	33	21.3
Radiotherapy	24	15.5
None	42	27.1
Unknown	1	0.6
Reoperation for local recurrence	21	13.5
DFI (mo)‡		
Average	34.4 ± 37.8	

(Continued)

TABLE 1. Continued

	Overall (n = 155)	Percentage (%)
Median	20.4	
Range	0.7-268.1	

DFI, Disease-free interval. *Includes breast. †A total of 55 patients had unknown primary tumor diameters and were excluded. ‡Time between resection of primary tumor and pulmonary metastasectomy; 2 patients with unknown DFI, 4 patients who did not undergo resection or underwent R2 resection were excluded. §Includes pulmonary artery, mediastinum, and pleura. ||Other includes abdomen, prostate, and unknown.

are shown in Figure 1, C. The average number of resected metastases was 4 (range, 1-29) nodules. The average size of a dominant metastatic nodule was 2.9 cm (range, 0.3-16 cm). High-grade histology was seen in the majority (101 patients, 65%) of pulmonary metastases.

R0 resection was achieved in 105 patients (67.7%). Thirteen patients underwent R1 resection, and 12 patients (8.4%) underwent R2 resection. Twenty-three patients (14.8%) had synchronous metastatic disease. The survival curves for type of sarcoma and synchronous metastases are shown in Figure 1, A and C.

Postoperative Complications

The average length of stay was 4.8 days. Fifteen patients (9.7%) experienced postoperative complications. Pneumonia, respiratory failure, atrial fibrillation, and persistent air leak and pneumothorax were most common and occurred in 9 patients (5.8%). There were no 30-day mortalities from the operative date.

Recurrence of Metastases

At an average follow-up of 14 months (range, 1.0-192.4 months), 19 patients showed no evidence of recurrence. Twenty-seven patients were lost to follow-up, and additional areas of metastases developed in 111 patients. Intrathoracic recurrences were seen in 79 patients. Of these, 75 patients developed second lung metastases, making it the most common site of systemic recurrence. Of these 111 patients with additional recurrences, 73 underwent 156 additional resections. Pulmonary re-resection was the most frequent procedure and was performed 94 additional times (range, 1-6). Re-resection of extremity recurrence was performed in 16 cases, and other organ resection was performed in 46 cases (Table 2).

Prognostic Factors for Overall Survival and Recurrence

The overall median survival was 35.4 months in this group of patients with known metastatic disease. The 5-year OS and DFS for the entire study cohort were 34.8% and 7.7%, respectively. However, we identified

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TABLE 2. Surgical resection of pulmonary metastases

	Overall (n = 155)	Percentage (%)
Pulmonary metastases resected		
Average	4 ± 4	
Range	1-29	
Diameter of largest pulmonary metastases (cm)		
Average	2.9 ± 3.0	
Range	0.3-16	
Operative approach		
Open	115	74.2
Thoracotomy	79	51.0
Sternotomy	21	13.5
Clamshell	13	8.4
Hemiclamshell	2	1.3
VATS	40	25.8
Staged operation	7	4.5
Type of resection		
Wedge	102	65.8
Segmentectomy	20	12.9
Lobectomy	27	17.4
Pneumonectomy	6	3.9
Completeness of resection		
R0	105	67.7
R1	13	8.4
R2	12	7.7
Unknown	25	16.1
Grade		
High	101	65.2
Low/intermediate grade	12	7.7
Unknown	42	27.1
Synchronous metastatic disease	23	14.8
Extremity	3	1.9
Nonextremity	20	12.9
Chest wall*	11	7.1
Thoracic†	1	0.6
Other‡	8	5.2
Hospitalization (d)		
Average	4.8	
Range	1-15	
Complications	15	9.7
Pneumonia/respiratory failure	4	2.6
Atrial fibrillation	3	1.9
Persistent air leak/pneumothorax	2	1.3
Pleural effusion requiring chest tube	1	0.6
Wound infection	1	0.6
Empyema	1	0.6
Colitis	1	0.6
Sternal dehiscence	1	0.6
Bronchus injury	1	0.6
30-d mortality	0	0
Outcome		
Recurrence free	19	12.3
Lost to follow-up	27	17.4

(Continued)

TABLE 2. Continued

	Overall (n = 155)	Percentage (%)
Recurrence	111	71.6
Extremity	7	4.5
Nonextremity	104	67.1
Trunk*	18	11.6
Thoracic†	79	51.0
Retroperitoneum	1	0.6
Head and neck	1	0.6
Other‡	5	3.2
Patients who underwent additional metastasectomies	73	47.1
Additional metastasectomies	156	
Pulmonary	94	
Range	1-6	
Extremity	16	
Nonextremity	46	
Chest wall*	10	
Thoracic†	3	
Head and neck	2	
Retroperitoneum	1	
Other‡	30	

VATS, Video-assisted thoracoscopic surgery. *Includes breast. †Other includes liver, spine, back, bowel, abdomen, and brain. ‡Includes lung, heart/pericardium, and mediastinum.

multiple characteristics that were associated with improved OS. Certain histologies were associated with longer survival, with leiomyosarcoma and osteosarcoma having the longest OS (61% and 68% overall 5-year survival, respectively), whereas liposarcoma and synovial sarcomas were associated with the shortest 5-year OS of 17% and 19%, respectively ($P = .02$). There was no significant impact on DFS or OS by histologic grade of the pulmonary metastases or primary tumor characteristics (primary sarcoma grade, margin, and adjuvant therapy).

Patients who underwent wedge resection, segmentectomy, or pneumonectomy also had longer OS compared with those who underwent lobectomy ($P < .01$). The type of operation (open vs VATS) was not associated with improved survival, but there was a trend with longer survival in the 25% of patients undergoing VATS (Table 3).

Synchronous disease, seen in 15% of patients at the time of pulmonary metastasectomy, was a negative predictor for OS (22% vs 49% OS at 5 years; $P < .01$). There was no impact on DFS. The OS at 5 years for R0, R1, and R2 resection was 41%, 46%, and 25%, respectively ($P < .50$), suggesting that margin negativity beyond gross resection for pulmonary metastasectomy does not affect prognosis. Furthermore, 5-year survival for patients who underwent additional metastasectomies was 40% versus 44% for those who had any additional resection ($P = .25$). Table 3 summarizes additional factors that correlate with DFS and OS.

FIGURE 1. Overall 5-year survival in patients who underwent pulmonary metastasectomy according to (A) type of primary sarcoma, (B) presence of synchronous metastatic disease, (C) type of lung resection, and (D) total number of risk factors.

Multivariate analysis identified 7 negative predictors of OS: age greater than 45 years, DFI less than 1 year, thoracotomy, presence of synchronous disease, site of sarcoma (visceral gynecologic site vs not), type of sarcoma (STS vs BS), and performance of lobectomy (Table 4). The total number of negative risk factors (<2, 3, or 4 or >5 factors) correlated with a poor OS at 5 years (72%, 54%, 35%, and 8%, respectively). Corresponding survival curves are shown in Figure 1, D.

DISCUSSION

The lungs are the most common site of metastases in patients with sarcoma. The prognosis of these patients is variable and dependent on a multitude of factors. We report a modern series of patients undergoing pulmonary metastasectomy for sarcoma to identify prognostic factors for DFS and OS. Our findings are consistent with previous reports that age, DFI, presence of synchronous disease, and type of sarcomas (STS vs BS) predict OS.^{2,5,12,14-17}

In addition, the extent of pulmonary resection predicts OS. Lobectomy compared with wedge resection or pneumonectomy was associated with poorer 5-year OS. Although lung-sparing operations are preferred, at times a central solitary lesion may mandate a larger pulmonary

resection, such as pneumonectomy. In our series, patients who underwent lobectomy had worse survival compared with those who underwent pneumonectomy. Lobectomy was performed in patients with multiple metastases located in a single lobe, warranting the anatomic resection, whereas pneumonectomies were performed in patients with solitary central lesions. This may be reflective of greater metastatic disease burden and a more biologically aggressive disease in patients undergoing lobectomy compared with patients who underwent a pneumonectomy for a central solitary metastasis.

Furthermore, we report that the surgical approach to resection was not significant in predicting OS. Thoracotomy, median sternotomy, and clamshell incisions have been the traditional open approaches for pulmonary metastasectomy. Some believe that manual palpation is a critical part in detecting sarcoma pulmonary metastases, justifying an open surgical approach, particularly for patients with osteosarcoma. For instance, Kayton and colleagues¹⁸ published their findings that CT scans underestimate the extent of metastatic disease in up to 35% pediatric and adolescent patients with osteosarcoma metastases to the lung, but they also found that approximately one third of the resected nodules were benign.

TABLE 3. Predictors of disease-free and overall survival at specified times in patients with metastatic sarcoma to the lung

	N	1-Year DFS (%)	3-Year DFS (%)	Log-rank P	N	3-Year OS (%)	5-Year OS (%)	Log-rank P
Gender				.47				.15
Male	76	38	15		87	45	36	
Female	61	34	11		68	56	48	
Sarcoma type				.16				.03
STS	94	30	12		108	44	37	
Bone	43	48	16		47	64	53	
Primary site				.82				.51
Extremity	77	36	14		87	51	41	
Nonextremity	46	35	12		52	43	36	
Visceral-gynecologic	14	44	18		16	63	56	
Histology types				<.01				.02
Leiomyosarcoma	26	49	9		29	69	61	
Osteosarcoma	21	62	24		22	73	68	
Synovial sarcoma	19	21	5		21	33	19	
Chondrosarcoma	14	36	0		14	57	43	
Liposarcoma	10	12	0		12	33	17	
Undifferentiated sarcoma†	7	14	14		9	38	25	
Ewing's sarcoma	5	60	24		7	43	43	
Malignant peripheral nerve tumor	5	20	20		4	40	20	
Alveolar soft part sarcoma	3	0	0		5	75	75	
Rhabdomyosarcoma	2	100	0		3	67	67	
Other	25	27	11		30	30	26	
Primary sarcoma grade*				.75				.27
High	93	34	18		105	46	39	
Low/intermediate	18	49	12		19	68	58	
Primary sarcoma margin				.06				.50
Positive	15	7	0		15	33	22	
Negative	90	40	18		101	50	43	
Adjuvant therapy for primary sarcoma				.31				.25
Yes	101	34	11		112	45	38	
No	35	40	23		42	62	52	
Metastasectomy approach				.40				.49
Open	99	33	11		115	47	37	
VATS	38	46	20		40	58	53	
Type of resection				.07				<.01
Wedge	94	43	17		102	55	46	
Segmentectomy	17	32	8		20	50	50	
Lobectomy	22	19	0		27	30	16	
Pneumonectomy	4	0	0		6	50	50	
Grade of metastases*				.62				.14
High	91	33	15		101	46	37	
Low/intermediate	12	56	9		12	83	75	
Metastasectomy margin				.34				.54
R0	91	41	17		105	50	41	
R1	12	29	10		13	46	46	
R2		n/a	n/a		12	25	25	
Synchronous disease				.11				<.01
Yes	20	17	6		23	38	22	
No	117	39	15		132	53	49	
Neoadjuvant therapy for pulmonary metastases				.18				.15
Yes	81	29	11		93	62	52	
No	56	45	16		62	45	38	
Additional metastasectomies (all sites)				.40				.25

(Continued)

TABLE 3. Continued

	N	1-Year DFS (%)	3-Year DFS (%)	Log-rank P	N	3-Year OS (%)	5-Year OS (%)	Log-rank P
Yes	73	38	7		73	59	44	
No	64	35	23		82	42	40	

DFS, Disease-free survival; OS, overall survival; STS, soft tissue sarcoma; VATS, video-assisted thoroscopic surgery; n/a, not applicable. *Patients with unknown grades were excluded. †Also known as malignant fibrous histiocytoma.

Despite a complete resection, further pulmonary metastases eventually will develop in 21% to 60% of these patients and a large number will require additional lung resections.¹¹ We found that 70% of our patients had further metastatic disease, and in approximately half, the lung was their first site of recurrence after the initial pulmonary metastasectomy. The median time to a second pulmonary metastasis in our patient cohort was 6 months. Given the high pulmonary recurrence rate, microscopically complete resection (R0) and the need for an open approach may not be necessary in all instances. A minimally invasive approach by VATS (thoracoscopy) allows for faster recovery and less pain.^{1,3,12,15,19} In a retrospective study of 60 patients, Gossot and colleagues¹⁹ showed that thoracotomy and thoracoscopy were both feasible options for resection and found no statistically significant differences in survival at 1, 3, and 5 years. In our series, 25% of resections were done by VATS. Although in the univariate analyses, the surgical approach did not predict DFS or OS, in the multivariate analysis, we found that open surgery was actually a negative predictor of OS, reflecting a greater metastatic tumor burden requiring an open approach. Given that recurrence is high and a significant number of subjects will undergo multiple lung resections, a minimally invasive approach, if feasible, may be preferable in certain clinical situations depending on the tumor location and burden.

Pulmonary metastatic disease burden may be the most influential driver of the surgical approach. Weiser and

colleagues¹⁶ showed that the number of metastatic pulmonary nodules (>3) and nodule diameter greater than 2 cm were negative prognostic factors of disease-specific 5-year survival. Completeness of resection was a significant factor and correlated with disease-specific survival in the same study. However, other authors have reported that neither negative margin⁶ nor number of metastatic nodules correlates with survival.^{5,10} Our findings show that a positive microscopic margin did have a negative impact on the DFS but did not have a significant effect on OS (R0 and R1 resections had an OS of 41% and 46%, respectively). Stephens and colleagues¹³ made a similar observation and did not find the completeness of resection to be a significant prognostic factor on OS.

Control of the primary tumor, absence of synchronous metastases, and ability to perform complete resection are traditional factors evaluated when patients are considered for pulmonary metastasectomy.^{3,12,15} Other groups have resected pulmonary metastases even in the presence of synchronous metastases.^{1,14} Blackmon and colleagues¹ found no difference in OS when synchronous disease was present as long as extrathoracic and pulmonary sites of metastasis were resected compared with the patients who did not undergo resection. In addition, Smith and colleagues¹⁴ did not find that the presence of synchronous disease was significant in predicting OS, but complete resection was associated with the ability to attain long-term survival. In our series, 15% of patients had evidence of synchronous metastasis, and this carried a negative

TABLE 4. Predictors of overall survival (multivariate Cox proportional hazards model)

	Hazard ratio	95% CI	P value
Age >45 y	1.99	1.23-3.23	<.01
DFI <1 y (primary to metastasis)	1.62	1.03-2.55	.04
Resection*			
Pneumonectomy	1.66	0.49-5.563	.41
Segmentectomy	1.00	0.54-1.8	.99
Lobectomy	1.81	1.09-3.01	.04
Synchronous disease	2.22	1.23-3.97	<.01
STS	2.23	1.31-3.78	<.01
Primary site†			
Extremity	2.76	1.25-6.08	.01
Nonextremity	2.44	1.12-5.28	.02
Open surgery	2.03	1.17-3.49	.01

CI, Confidence interval; DFI, disease-free interval; STS, soft tissue sarcoma. *Reference category is wedge resection. †Reference category is visceral-gynecologic site.

impact on OS despite the fact that synchronous sites of disease were treated. The impact of synchronous metastasis on OS after lung metastasectomy may be reflective of variable treatments given at the extrathoracic synchronous sites, which included nonoperative modalities, and in some instances local therapies may not have been instituted.

CONCLUSIONS

Our study supports the existing body of evidence demonstrating that lung metastasectomy is associated with long-term OS. We have further defined a novel prognostic model using negative predictors of OS whereby an increasing number of risk factors correlated with worsening prognosis and survival. As such, OS at 5 years varied widely from 64% in patients with 2 risk factors to 3% in those with 5 identified risk factors. This stratification model can be used clinically to differentiate patients in high- and low-risk categories, guide surveillance, and decide on the use of additional therapy after metastasectomy. Future randomized prospective studies are warranted, particularly in patients with a poor risk profile, to define whether any benefit is derived from lung metastasectomy compared with other local therapies or no resection. In the absence of control (nonoperative) data, quantifying the difference in survival among patients who have undergone metastasectomy and attributing it to surgical resection may not be accurate because there is a selection bias for lung metastasectomy.²⁰

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