An Analysis of Patient Characteristics and Clinical Outcomes in Primary Pulmonary Sarcoma

Matthew B. Spraker, PhD, Eric Bair, PhD,† Ryan Bair, MD,‡ Philip P. Connell, MD,‡ Usama Mahmood, MD,§ and Matthew Koshy, MD*‡*

Introduction: Literature concerning primary pulmonary sarcomas (PPS) is limited to small case series. This study examines, in a large cohort, the clinical characteristics and therapeutic strategies of PPS and their impact on overall survival (OS).

Methods: This was a retrospective analysis from the Surveillance, Epidemiology, and End Results database (1988–2008). Eligible patients had primary PPS and underwent local therapy. Survival estimates were obtained using the Kaplan–Meier method and the Cox regression model. OS of PPS patients were compared with a cohort of 10,909 patients with extremity soft-tissue sarcomas.

Results: The cohort included 365 PPS patients with a median follow-up of 21 months. Fifty-five percent of the patients had large tumors (>5 cm), 76% were high-grade, and 16% had node-positive disease. Seventy-five percent of the cohort underwent surgery alone, 14% underwent surgery and radiation therapy, and 11% underwent radiation therapy alone. Multivariate analysis showed reduced OS for patients with tumors more than 5 cm (hazard ratio [HR] 1.6, 95% confidence interval [CI] 1.25–2.19), high tumor grade (HR 3.1, 95% CI 1.26–3.62), and unresectable disease (HR 2.6, 95% CI 1.76–3.88. The 5-year OS for the cohort of pulmonary sarcomas versus sarcomas of the extremities was 35% versus 71% ($p < 0.0001$).

Conclusion: This large study examining PPS patients reveals a high rate of nodal involvement and a markedly worse OS than patients with extremity soft-tissue sarcomas. Thus, given the poor overall prognosis, it is recommended that PPS patients undergo a thorough mediastinal nodal evaluation to rule out locoregional metastasis and proceed with aggressive treatment.

Key Words: Pulmonary, Sarcoma, Survival, Surveillance, Epidemiology, and End Results.

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*Department of Radiation Oncology, University of Illinois at Chicago, Chicago, Illinois; †Departments of Endodontics and Biostatistics, University of North Carolina, Chapel Hill, North Carolina; ‡Department of Radiation Oncology, University of Chicago, Chicago, Illinois; and §Department of Radiation Oncology, MD Anderson Cancer Center, Houston, Texas.

Address for correspondence: Matthew Koshy, MD, Department of Radiation and Cellular Oncology, University of Chicago, 5758 South Maryland Avenue, M/C 9006, Chicago, IL 60637. E-mail: mkoshy@radonc.uchicago.edu

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Primary pulmonary sarcomas (PPS) represent a rare tumor type.[1–6] Existing literature regarding PPS has been limited only to small retrospective case series that have examined the impact of tumor pathology and clinical management strategies on overall survival (OS). However, interpretation of these results has been severely limited by the small sample sizes.[6,7]

Several reports demonstrate a survival benefit associated with surgical resection.[7,8] Yet, there are conflicting data about which patient and tumor characteristics have prognostic value.[7–13]

The purpose of this study is to examine a large cohort of PPS patients to better characterize the pathologic and clinical features of PPS that impact survival. Furthermore, survival in PPS patients was compared with survival in patients with soft-tissue sarcomas of the extremity.

PATIENTS AND METHODS

The Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute collects incidence and survival data from 17 population-based cancer registries covering 28% of the U.S. population. The SEER program registries collect data on patient demographics, primary tumor site and morphology, stage at diagnosis, first course of treatment, and follow-up for vital status.

Eligible patients had histologically confirmed invasive soft tissue sarcoma of the lung, bronchus, carina, or hilum with no known metastasis. Patients were identified using site codes C340-C349 of the International Classification of Diseases for Oncology, third edition. Analysis was restricted to patients aged 20 years and older, who were diagnosed between 1988 and 2008, and underwent surgery, radiation therapy (RT), or both. Detailed information regarding the tumor size and grade were available in the SEER database only after 1988. Patients with Kaposi's sarcoma were excluded because the majority of these patients have acquired immunodeficiency syndrome, which would confound survival outcomes. Patients with rhabdomyosarcoma, Ewing's sarcoma, Askin tumor of soft tissue, peripheral neurectodermal tumor of soft tissue, and extrarenal rhabdoid tumor were also excluded from the analysis because the primary treatment of these tumors includes chemotherapy, which is not coded in the database. The total sample included 365 patients.

Variables

OS was the primary study endpoint. This was defined as the time from diagnosis to death. Variables included whether patients received surgery alone, external beam RT alone, or both. Exact detail regarding the use of adjuvant chemotherapy and specific RT technique (i.e. dose, fraction, beam energy) was not available in the SEER database.

Covariates included in the analysis were all categorical and included: age (20–44, 45–59, 60–74, and 75+ years), sex, SEER registry location, year of diagnosis, T classification (T1 < 5 cm, T2 > 5 cm), node (N) classification, grade (low grade = 1–2, high grade = 3–4), laterality, and histology. Detailed information regarding the margin status at the time of resection, local control, and performance status is not available in the SEER database.

Statistical Analysis

All data were analyzed using R (version 2.13). Pearson's χ^2 tests were used to analyze the frequency distribution of the categorical variables. Estimates of OS were calculated using the Kaplan–Meier method as a function on size, grade, and nodal status. Survival was also calculated for patients who underwent surgery alone, RT alone, or both. The log-rank test was used to determine whether differences in survival curves were statistically significant.

To determine independent predictors of overall mortality, hazard ratios (HR) and their 95% confidence intervals (CI) were calculated using multivariable Cox proportional hazards models adjusted for all covariates of interest. The models were run for the full sample of patients using the covariates that were found to be significant in the univariate analysis. Furthermore, we compared the OS of pulmonary sarcomas with that of extremity soft-tissue sarcomas. All results were considered significant when p was less than 0.05.

RESULTS

This study examined a total of 365 patients with a median follow-up of 21 months (range, 1 month–20 years). Patient and clinical characteristics of the cohort are depicted in Table 1. The median age was 63 years (range, 20–85 years). Fifty-five percent of the cohort had tumors greater than 5 cm, and more than 40% were high-grade. Furthermore, 16% had node-positive disease. There was no correlation between histologic subtype and nodal status. Approximately 75% of the cohort underwent surgery alone and the remaining patients received RT alone or both surgery and RT. The most frequently identified histologies were fibroblastic and myofibroblastic tumors (16.2%).

Univariate Analysis

Among those with pulmonary sarcomas, the 5-year OS was 48% for tumors less than 5 cm and 25% for tumors greater than 5 cm ($p < 0.0001$). The 5-year OS for patients with low- and high-grade tumors was 73% and 23%, respectively ($p < 0.0001$, Fig. 1). The 5-year OS for patients with node-negative disease was 39%, whereas it was 14% for those with node-positive disease ($p < 0.0001$, Fig. 2).

TABLE 1. Patient and Tumor Characteristics

Variable	No. of Cases (%)
Age (yr)	
20–44	53 (15)
44–59	93 (26)
59–75	129 (35)
75+	90 (25)
Sex	
Male	203 (56)
Female	162 (44)
Registry location	
California (excluding LA, SF, SJ)	66 (18)
Los Angeles	43 (12)
Seattle	39 (11)
New Jersey	36 (10)
San Francisco	29 (8)
Connecticut	28 (8)
Iowa	25 (7)
Detroit	23 (6)
Kentucky	16 (4)
Atlanta	13 (4)
Utah	11 (3)
Louisiana	11 (3)
San Jose	10 (3)
Hawaii	9 (3)
New Mexico	6 (2)
Georgia (excluding Atlanta)	0 (0)
Alaska	0 (0)
Race	
White	327 (90)
Black	16 (4)
American Indian, Asian, Alaska Native/Pacific Islander	20 (5)
Unknown	2 (1)
Year of diagnosis	
1988	5 (1)
1989	7 (2)
1990	4 (1)
1991	11 (3)
1992	10 (3)
1993	11 (3)
1994	6 (2)
1995	12 (3)
1996	13 (4)
1997	13 (4)
1998	19 (5)
1999	11 (3)
2000	25 (7)
2001	33 (9)
2002	27 (7)
2003	32 (9)
2004	26 (7)

(*Continued*)

TABLE 1. (*Continued*)

Variable	No. of Cases (%)
2005	28 (8)
2006	29 (8)
2007	22 (6)
2008	21 (6)
Tumor size (cm)[a]	
0–4.99	152 (43)
5+	201 (57)
Diffuse	1 (<1)
Grade[a]	
Low (1–2)	50 (24)
High (3–4)	161 (76)
Node Status	
Node-negative	307 (84)
Node-positive	58 (16)
Histologic type	
Unspecified soft tissue sarcomas	131 (36)
Fibroblastic and myofibroblastic tumors	59 (16)
Leiomyosarcoma	53 (15)
Synovial sarcomas	43 (12)
Fibrohistiocytic tumors	30 (8)
Blood vessel tumors	21 (6)
Nerve sheath tumors	15 (4)
Miscellaneous soft tissue sarcomas	7 (2)
Liposarcoma	2 (<1)
Osseous and chondromatous neoplasms of soft tissue	2 (<1)
Other fibromatous tumors	1 (<1)
Alveolar soft parts sarcoma	1 (<1)
Laterality	
Right	179 (49)
Left	183 (51)
Therapy type	
Surgery alone	274 (75)
Radiation therapy alone	39 (11
Surgery + radiation therapy	52 (14)

[a]Does not include unknown cases.
LA, Los Angeles; SF, San Francisco; SJ, San Jose.

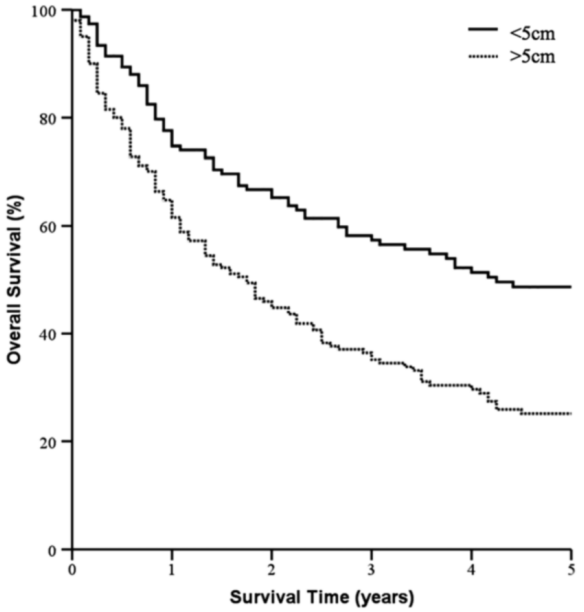

FIGURE 1. Percentage overall survival is depicted for tumors of small (<5 cm) and large (>5 cm) size. Patients with tumors of unknown size are excluded (n = 353).

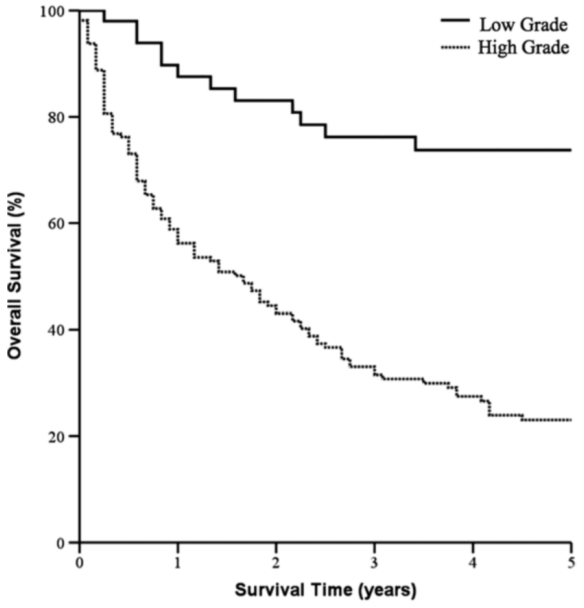

FIGURE 2. Percentage overall survival is depicted for low-grade (grade 1 or 2) and high-grade (grade 3 or 4) tumors. Patients with tumors of unknown grade are excluded (n = 211).

Regarding therapy, the 5-year OS was 41% for those who underwent surgery alone, 25% for those who underwent surgery and RT, and 7% for those who underwent radiation alone ($p < 0.0001$, Fig. 3). On subset analysis, those who received adjuvant RT were more likely to have tumors greater than 5 cm (65% versus 51%), high-grade tumors (94% versus 70%), and node-positive disease (27% versus 10%).

The 5-year OS for the cohort of pulmonary sarcomas compared with soft-tissue sarcomas of the extremities was 35% versus 71%, respectively ($p < 0.0001$). In relation to clinical characteristics, T-stage was similar between extremity and pulmonary sarcomas. Pulmonary sarcomas did have a significantly larger proportion that were node-positive (16% versus 1%), and high-grade (76% versus 54%) compared with extremity soft-tissue sarcomas ($p < 0.05$). Regarding histology, there were a significantly higher proportion of fibrous tumors (33% versus 8%) and liposarcomas (25% versus 1%) in the extremity sarcomas versus the pulmonary sarcomas ($p < 0.05$).

Multivariate Analysis

Patient age, tumor size, tumor grade, and treatment type significantly affected OS on multivariate analysis as shown in

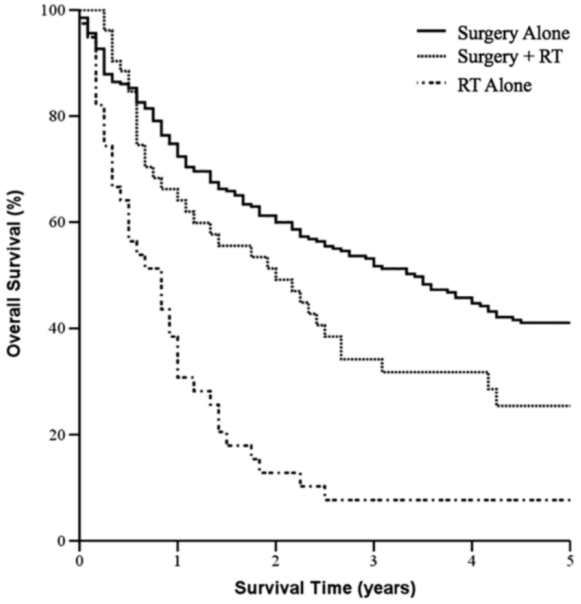

FIGURE 3. Percentage overall survival is depicted for patients who received surgery alone, surgery plus radiation therapy, and radiation therapy alone.

TABLE 2. Hazard Ratios and 95% Confidence Intervals for Multivariable Models of Overall Mortality

Variable	HR	95% CI
Age (yr)		
20–44	1	Reference
44–59	1.53	(0.92, 2.56)
59–75	2.34	(1.47, 3.75)
75+	3.29	(2.03, 5.34)
Sex		
Male	1	Reference
Female	0.86	(0.66, 1.12)
Tumor size (cm)		
0–4.99	1	Reference
5+	1.66	(1.25, 2.19)
Grade		
Low (1–2)	1	Reference
High (3–4)	3.14	(1.85, 5.31)
Unknown	2.14	(1.26, 3.62)
Node status		
Node-negative	1	Reference
Node-positive	1.37	(0.97, 1.94)
Therapy type		
Surgery alone	1	Reference
Radiation therapy alone	2.62	(1.76, 3.88)
Surgery + radiation therapy	1.35	(0.94, 1.96)

Table 2. The estimated HR was 2.6 (95% CI 1.76–3.88) for those with unresectable disease, 1.3 (95% CI 0.94–1.96) for the surgery+RT group, and 1.0 (reference) for the surgery-alone group. High tumor grade was associated with reduced OS compared with low tumor grade (HR 3.14, 95% CI 1.26–3.62). There was also a trend toward reduced OS for patients with node-positive disease compared with node-negative disease (HR 1.37, 95% CI 0.97–1.94).

TABLE 3. Selected Studies Investigating Primary Pulmonary Sarcoma

Authors	N	Mean Age at Diagnosis (yr) (Range)	5-Year Survival (%)
Janssen et al. 1994[13]	22	49.5 (5–76)	44
Bacha et al. 1999[7a]	23	51 (20–78)	69
Régnard 1999[8a]	24	48 (14–73)	48
Porte 2000[11]	18	50 (19–73)	43
Etienne-Mastroianni et al. 2002[9]	12	53 (16–93)	38
Petrov 2003[12]	48	53.3 (13–78)	48
Current study	365	62 (20–85)	41

[a]Five-year survival reported for patients undergoing tumor resection.

DISCUSSION

This is the first large, population-based cohort study to examine patient-specific clinical characteristics and various treatment strategies and their concomitant relationship to OS in patients with primary sarcoma of the lung.

PPS are rare tumors and this study examined the impact of tumor and clinical characteristics on survival. Earlier studies examining PPS have suggested that large tumor size and high tumor grade represent negative prognostic factors,[13] though other case series have not replicated these findings.[7,9,11] This study demonstrates, over a substantially larger cohort, that large size (> 5 cm) and high grade are associated with a significantly worse OS. These findings are consistent with other large series that have examined these factors in soft-tissue sarcomas of the extremities.[14–18]

Earlier studies show that patients able to undergo complete surgical resection have significantly improved survival compared with patients with unresectable tumors or positive surgical margins.[7,8,19] These findings confirm results of an improved survival seen in those who are able to undergo resection. Although significantly worse clinical characteristics made up the subgroup of patients who underwent surgery and RT, the multivariate analysis shows that their OS was not statistically different from that of those who received surgery alone. This may reflect a survival benefit gained from improved locoregional control through the use of adjuvant RT.

This study also demonstrates important prognostic differences between PPS and primary soft-tissue sarcomas of the extremity. PPS had a significantly worse 5-year OS compared with extremity soft tissue sarcomas (35% versus 71%, $p < 0.001$). It is noteworthy that 16% of PPS in this cohort had node-positive disease whereas past studies show that only 2% to 6% of patients with extremity soft-tissue sarcomas have node-positive disease.[20–22] This discrepancy is

likely multifactorial, involving contributions from underlying genetic predispositions for metastasis and differing lymphatic drainage patterns. These results support the routine use of a thorough mediastinal nodal evaluation with positron emission tomography, mediastinoscopy, or mediastinal nodal dissection at the time of resection to rule out locoregional metastatasis. Given the high rate of nodal metastasis and poor prognosis, pulmonary sarcoma patients should be treated aggressively. These data do suggest that patients may benefit from combined surgery and radiotherapy. Likewise, these patients should be considered for chemotherapy when appropriate. These patients might derive a greater potential benefit from systemic chemotherapy than the 5% OS benefit seen with adjuvant chemotherapy in patients with soft-tissue sarcomas of the extremity.[23] The relatively poor survival seen in the node-positive cohort suggests that this group may benefit from neoadjuvant chemoradiation followed by surgical resection in an effort to maximize local control, similar to a treatment strategy that is often used in locally advanced lung cancer.

This study was limited by information that was either not available or not reported in the SEER database. More than one third of cases in this study were classified as a primary sarcoma that is not otherwise specified. This likely reflects the difficulty in the tissue diagnosis of PPS, which has been discussed extensively by Etienne-Mastroianni et al.[9] Rapidly advancing diagnostic techniques may allow future studies to further characterize the relationship between PPS histology and behavior. Although this study adjusted for all available patient and tumor characteristics, there are unreported patient factors that could potentially confound the analysis, such as tumor margin status or patient performance status. Another limitation is that in patients who did not undergo surgery, the nodal staging was based on clinical criteria (American Joint Committee on Cancer tumor, node, metastasis staging criteria), and thus may have been less accurate than in those who underwent surgical resection and had pathologic examination of the resected lymph nodes. Moreover, the SEER database contains no detailed information regarding radiation technique (total dose, fraction size, beam energy) or chemotherapy protocols.

In conclusion, this large study examining PPS revealed that these patients have a markedly worse OS than patients with extremity soft-tissue sarcomas. Furthermore, PPSs are associated with a higher rate of nodal metastasis relative to soft-tissue extremity sarcomas. Thus, it is recommended that pulmonary sarcoma patients undergo a thorough mediastinal nodal evaluation to rule out locoregional metastasis. Given their poor overall prognosis, it is recommended that these patients be treated aggressively.

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