Multimodality treatment including surgery for primary pulmonary sarcoma: Size does matter

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Abstract

Background and Objectives: Primary pulmonary sarcoma (PPS) accounts for less than 1.1% of all pulmonary tumors. Few outcome data are reported. We evaluated outcome and prognostic factors in our series.

Methods: We retrospectively reviewed all patients who underwent resection for PPS in our center from 2002 to 2018. Survival was calculated from the date of surgery until last follow-up. Impact on survival of gender, type of lung resection, completeness of resection, grade, size, and TNM staging for lung cancer and soft tissue sarcoma (STS) was assessed.

Results: Thirteen patients were included. Eight (61.5%) patients received neoadjuvant treatment. Median tumor size at diagnosis was 11.5 cm (1-30 cm). Type of lung resection was wedge (n = 2, 15%), lobectomy (n = 4, 31%), intrapericardial (n = 3, 23%), and extrapleural pneumonectomies (n = 4, 31%). In-hospital mortality was 8%. Overall 5-year survival was 60%. Median disease-free survival was 17 months. Tumor size was a predictor for survival (P = .02) and recurrence (P = .05). Gender (P = .04) and type of lung resection (P = .04) were predictors of survival. T stage for STS of trunk and extremity, and TNM stage for lung cancer were predictors for recurrence (P = .03 and P = .04, respectively).

Conclusion: Surgical resection within a multimodality therapy concept in highly selected patients can offer good long-term outcome.

KEYWORDS
induction, lung sarcoma, multimodality treatment, primary pulmonary sarcoma, surgery

INTRODUCTION

Primary pulmonary sarcoma (PPS) is a rare aggressive tumor, accounting for only 0.4% to 1.1% of all lung malignancies.1,2 Due to its rarity, the literature is limited mostly to case reports or small retrospective case series. Surgery is the cornerstone of treatment and most studies have demonstrated a survival benefit after complete resection.3-5 The role of chemotherapy in localized sarcomas is undisputed in Ewing Sarcoma, high-grade osteosarcoma, and pediatric rhabdomyosarcoma. Most sarcoma centers use chemotherapy to treat locally advanced high-grade soft tissue sarcomas (STSs) as well as STS deemed to have a high
risk of metastatic disease and a chemotherapy-sensitive histology.6,8

Staging aims at better stratifying patients’ risk of death and guide therapeutic management. Until shortly, there has been no dedicated staging classification for PPS and different staging systems were used, depending on the background of the authors. Lung cancer staging system was used in three reports.1,4,9 It was found to be well applicable to PPS and was a significant predictor for survival.1,4 In two other studies including the largest PPS series with 365 patients, staging system for STS of trunk and extremity was used.3,10 In the 8th edition of the AJCC (American Joint Commission on Cancer) cancer staging manual, an effort was made to emphasize the anatomic site of primary sarcoma and for the first time, a dedicated staging system was described for STS of the abdomen and thoracic visceral organs, which would be applicable for PPS.11 To our knowledge, the reliability of this dedicated staging system has not been assessed so far. Table 1 summarizes the different staging systems available for PPS as well as their impact on overall survival.

Here, we describe our patient cohort with PPS that was surgically treated within a multimodality therapy concept. We assessed the reliability of the abdomen and thoracic visceral organ STS classification when applied to PPS, as well as the outcome and prognostic factors for survival.

2 | MATERIALS AND METHODS

All consecutive patients with histologically confirmed PPS who underwent resection in a curative intent in our center, from January 2002 to December 2018, were included. Lesions with both lung and chest wall invasions were considered as PPS when more than 95% of tumor volume was located in the lung.1 Tumor resectability was evaluated by the surgeon based on preoperative imaging. Tumors involving structures such as the brachial plexus, esophagus, or heart were considered unresectable. Data were retrospectively retrieved from the patients’ electronic documentation system and all follow-up centers. The study was approved by the institutional ethics committee (19-8751-BO).

Staging included computed tomography (CT) of the chest and upper abdomen, brain imaging with CT or magnetic resonance imaging (MRI), and a whole-body positron emission tomography integrated in CT (PET/CT).

Histological confirmation of malignancy was obtained preoperatively whenever possible. Treatment strategy was discussed on a case-by-case basis during our multidisciplinary tumor board conferences dedicated to thoracic oncology and/or sarcoma. When the diagnosis of PPS was known preoperatively, neoadjuvant treatment was administered with or without radiation. Restaging included CT of the chest and upper abdomen and/or PET/CT.

Surgical approach and extent of lung resection were based on surgeons’ evaluation of preoperative imaging. Anatomic lung resection was favored over wedge resection. Mediastinal lymph node dissection was routinely performed. Resection was defined by the pathologist as complete (R0), or microscopically (R1) or macroscopically (R2) incomplete.

PPS were staged according to the 8th edition of the AJCC cancer staging manual for lung cancer, STS of trunk and extremities as well as for STS of abdomen and thoracic visceral organs.11 Of note, patients with complete response after induction therapy were classified as ypT0 in all three staging systems. Patients with pleural sarcomatosis were defined as T4 in the STS of the abdomen and thoracic visceral organ TNM staging system. Grading was based on the evaluation of tumor differentiation, mitotic count, and necrosis according to the French Fédération Nationale de Centres de Lutte Contre le Cancer (FNCLCC) system.12,13

Recurrence was defined as local (intrathoracic) or distant, based on follow-up imaging. Patients with incomplete resections were not defined as having recurrence until progression was observed on imaging.

| TABLE 1 | Available staging systems for PPS and the impact of their variables on overall survival |
|---------------------------------|--------------------------------------------------------------------------------------|
| **Staging system**              | **Variables used for stage grouping**                                                |
| Lung cancer                     | T, N, M                                                                               |
| STS of the trunk and extremity  | T, N, M, G                                                                             |
| STS of the abdomen and thoracic visceral organs | No defined stage grouping yet |
| Predictors of survival          |                                                                                       |
| T (significant with longer OS for patients with T2 vs T3)1 |
| Stage (significant with longer OS for patients in stage IB vs IIIB)5 |
| Stage (significant with longer OS for patients in stage I vs IIIB)1 |
| Stage (significant with longer OS for patients in stages I, II vs III, IV)9 |
| N (trend in multivariate analysis with longer OS for patients with N0 vs N+)4 |
| G (significant in multivariate analysis with longer OS for patients with G1,2 vs G3,4)11 |
| G (significant with longer OS for patients with G1 vs G2,3)12 |

Abbreviations: OS, overall survival; PPS, primary pulmonary sarcoma; SST, soft tissue sarcoma.
Statistical analysis was performed using IBM SPSS software (IBM Corp, Armonk, NY). The Kaplan-Meier estimate was used to analyze survivals, calculated from the day of surgery until death or last follow-up (overall survival) and recurrence or last follow-up (disease-free survival).

The impact on survival of the following variables—gender, type of lung resection, completeness of resection, tumor grade, tumor size, TNM staging system for lung cancer, and STS, preoperatively confirmed diagnosis of sarcoma—was assessed by Cox regression for continuous and log-rank test for discrete variables. Statistical significance was defined as a P-value of less than .05.

### 3 | RESULTS

Thirteen patients (7 females, 54%) with PPS were surgically treated within a multimodality therapy concept during the study period in our center. Patient characteristics are summarized in Table 2. Median age at surgery was 56 years (21-79). Most of the patients had a preoperative diagnosis of sarcoma (n = 9, 69%). Median tumor size at diagnosis was 11.5 cm (1-30 cm).

Eight patients (62%) received neoadjuvant treatment. One patient had radiotherapy alone and two had combined chemotherapy with a median dose of 50 Gy (range 45-66). Chemotherapy regimen was ifosfamide/doxorubicin (n = 3), VIDE (n = 1), ifosfamide/adriblastin (n = 1), and epirubicin (n = 1). In one patient chemotherapeutic agents given were unknown. One patient with preoperative diagnosis of sarcoma did not receive induction therapy due to his advanced age. Median delay between preoperative imaging and resection was 12 days (from 3 to 41). Surgical resection required a pneumonectomy in most of the patients (n = 7, 54%). On pathologic examination, response to neoadjuvant treatment was complete in two patients. The most common histology was synovial sarcoma (n = 4, 31%). Most of the patients had high-grade (G3) sarcomas (n = 6, 46%). Complete R0 resection was achieved in 81% of patients (9/11).

PPS were pathological T0 (n = 2, 15%), T1 (n = 1, 8%), T2 (n = 2, 15%), T3 (n = 1, 8%), and T4 (n = 7, 54%) based on the classification for lung cancer. Most of the patients had mediastinal lymph node dissection (n = 7, 54%), while sampling was performed in three patients (23%). In two patients in the initial part of the observation period, the reason why no lymph node was resected is unknown. In the third patient, solitary fibrous tumor of the pleura was suspected. None of the patients had any lymph node involvement. Therefore, stages were 0 (n = 2, 17%), I (n = 2, 17%), II (n = 1, 8%), and III (n = 7, 58%). Based on the classification for STS of trunk and extremities, PPS were pathological T0 (n = 2, 15%), T1 (n = 3, 23%), T2 (n = 2, 15%), T3 (n = 2, 15%), and T4 (n = 4, 31%). Taking grading into account, stages were therefore I (n = 5, 39%), II (n = 2, 15%), and III (n = 6, 46%).

Based on the classification for STS of abdomen and thoracic visceral organs, PPS were pathological T0 (n = 2, 15%), T1 (n = 6, 46%), T3 (n = 1, 8%), and T4 (n = 4, 31%).

Postoperative complications occurred in five patients (46%) and included atrial fibrillation, pulmonary embolism, hemothorax, and postoperative anemia requiring transfusion. One patient died in the postoperative period on day 24 consecutively to pneumonia-related septic shock. Therefore, in-hospital and 90-day mortality was 8%.

Overall and disease-free survival curves are depicted in Figures 1 and 2. In our cohort, overall survival is the same as disease-specific survival as all deceased patients died from a cause directly related to sarcoma. Survival rates at 5 and 10 years were 60% and 45%, respectively. Median overall survival was 69 months, while median follow-up was 46 months. Median disease-free survival was 17 months. At the end of follow-up eight patients (62%) developed recurrence, mostly local intrathoracic (54%). One patient had both local and distant recurrence, namely osseous metastases (Table 2).

Results of the Cox regression and log-rank test for identification of predictive factors of survival and recurrence are summarized in Table 3. Tumor size at diagnosis did significantly impact overall survival (P < .023, hazard ratio [HR] 1.022, 95% confidence interval [CI] 1.003-1.041) and disease-free survival (P < .05 HR 1.015, 95% CI 1.000-1.031). Survival, while tumor size measured on operative specimen did not. Completeness of resection did not significantly impact on overall and disease-free survivals in our study. Among the different staging systems used, pathologic stage for lung cancer (P < .041) and pathologic T stage for STS of the trunk and extremity (P < .025) were found to statistically impact disease-free survival.

Figures 3 and 4 show the significant impact of gender and type of lung resection on survival.

### 4 | DISCUSSION

In this single-center retrospective study including 13 patients who underwent resection in a curative intent for PPS, overall survival reached 60% at 5 years. This is in line with the best results from the literature, which range from 27% to 69%.11,14

In STS of the extremity, tumor size and grade are major determinants of overall survival.15,16 These two clinical criteria are also part of the criteria used for stage grouping of STS of the trunk and extremity.11 However, unlike STS of the extremity, PPS tend to be larger at diagnosis, as symptoms appear to occur later. In our study on PPS, tumor size at diagnosis was also found to be a prognostic factor for recurrence and for overall or sarcoma-specific survival rates. This confirms the conclusion of an historical study with 18 patients, where all four survivors (from 3 to 18 years after surgery) had a tumor of 2 to 3 cm in greatest dimension.17 More recently, in a study on 16 operated patients, where tumor size was dichotomized to its median value of 4 cm, survival for patients with larger tumors (>4 cm) was significantly worse (23 months) than for patients with a smaller tumor (≤4 cm—did not reach a median survival value).18 In addition, multivariate analysis of the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute showed a decreased overall survival for patients with tumors less than 5 cm (HR 1.6, 95% CI 1.25-2.19) in 365
| Patient number | Age, y | Sex | Type of sarcoma | Tumor size at diagnosis, cm | Sarcoma preoperatively diagnosed | Neoadjuvant treatment | Lung resection | R | G | Tumor size on operative specimen, cm | Adjuvant treatment | Recurrence type | OS, mo |
|----------------|--------|-----|-----------------|-----------------------------|---------------------------------|----------------------|----------------|---|---|----------------------------------|-------------------|----------------|-------|
| 1              | 36     | F   | Ewing           | 8                           | Yes                             | CHT                  | Bilobectomy    | 1  | 3 | 3.5                              | CHT/RT            | No             | 83+   |
| 2              | 36     | F   | Synovial        | 10                          | Yes                             | CHT                  | IPP            | 0  | NA| 7.5                              | No                | Local          | 63+   |
| 3              | 73     | F   | Synovial        | 3                           | No                              | No                   | Lobectomy      | 0  | 2 | 3                                | No                | Local          | 46+   |
| 4              | 79     | M   | Liposarcoma     | 12                          | No                              | No                   | Wedge          | 0  | 3 | 12                              | RT                | Local          | 11+   |
| 5              | 61     | M   | Sarcoma NOS     | NA                          | Yes                             | CHT                  | IPP            | 0  | NA| 0                                | NA                | No             | 11    |
| 6              | 53     | M   | Synovial        | 11                          | Yes                             | CHT                  | EPP            | NA | 3 | 0                                | RT                | Local          | 7     |
| 7              | 44     | F   | Pleomorphic     | 6                           | Yes                             | CHT/RT               | Lobectomy      | 0  | 3 | 6                                | No                | No             | 55+   |
| 8              | 56     | F   | Synovial        | 1                           | No                              | No                   | Wedge          | 0  | NA| 1                                | No                | Local          | 123+  |
| 9              | 57     | F   | MPNST           | 17                          | Yes                             | CHT/RT               | IPP            | 0  | 1 | 17                               | NA                | No             | 178+  |
| 10             | 22     | M   | Sarcoma NOS     | 12                          | No                              | No                   | Lobectomy      | NA | NA| 12                               | CHT/RT            | Local and distant (OSS) | 69    |
| 11             | 68     | F   | MPNST           | 20                          | Yes                             | RT                   | IPP            | 0  | 3 | 20                               | No                | Local          | 22    |
| 12             | 79     | M   | Leiomyosarcoma  | 30                          | Yes                             | No                   | EPP            | 2  | 3 | 30                               | No                | No             | 1     |
| 13             | 21     | M   | Pleomorphic     | 17                          | Yes                             | CHT                  | EPP            | 0  | 3 | 17                               | CHT               | Local          | 3     |

Abbreviations: CHT, chemotherapy; EPP, extrapleural pneumonectomy; F, female; G, tumor grade; IPP, intrapericardial pneumonectomy; M, male; MPNST, malignant peripheral nerve sheet tumor; NA, not available; NOS, not otherwise specified; OS, overall survival; OSS, organ-sparing surgery; R, completeness of resection; RT, radiotherapy; +, still alive at the time of last follow-up.
In our study, there was only a trend for worse survival in patients with higher tumor grade (G3). To this end, the negative prognostic effect of G3 might have been compensated by chemotherapy treatment, which tends to be more effective in patients with higher grading. In the large population-based cohort study from the SEER database with 365 patients, multivariate analysis identified tumor grade as significant prognostic factor in patients with PPS. Unfortunately, no relation with chemotherapy treatment could be evaluated in that series as chemotherapy treatment is not coded in the SEER database.

In the general population, life expectancy for females are longer than for men. In our work, survival was significantly better for female with PPS compared with male. This was in line with previous published data from multifactorial analysis were the risk of death in
TABLE 3 Predictive factors for survival and recurrence

| Covariates                                | Overall survival P-value | Disease-free survival P-value |
|-------------------------------------------|--------------------------|------------------------------|
| Gender (male vs female)                   | .04                      | .05                          |
| Type of lung resection (wedge/lobectomy vs pneumonectomy) | .04                      | .09                          |
| G (1/2 vs 3)                              | .14                      | .71                          |
| R (0 vs 1/2)                              | .40                      | .09                          |
| Tumor size at diagnosis                   | .02 (HR 1.02, 95% CI, 1.00-1.04) | .05 (HR 1.02, 95% CI, 1.00-1.03) |
| Tumor size on operative specimen          | .12                      | .06                          |
| pT (NSCLC) (0,1,2,3 vs 4)                 | .39                      | .09                          |
| pStage (NSCLC) (0,1,2 vs 3)               | .60                      | .04                          |
| pT (STS trunk and extremity) (1,2,3 vs 4) | .14                      | .03                          |
| pStage (STS trunk and extremity) 1,2 vs 3 | .49                      | .60                          |
| pT (STS abdomen and thoracic visceral organs) (0,1 vs 3,4) | .96                      | .64                          |
| Preoperatively diagnosed sarcoma (yes vs no) | .30                      | .59                          |

P-values are derived from Cox regression for continuous and log-rank test for discrete variables. HR and 95% CI are mentioned for statistically significant P-values from Cox regression. The significant of bold values represent P < 0.05. Abbreviations: 95% CI, 95% confidence interval; G, tumor grade; HR, hazard ratio; NSCLC, non–small-cell lung cancer; R, completeness of resection; STS, soft tissue sarcoma.

Overall survival for patients with unresectable disease is poor. In an analysis of the larger SEER database, a trend was seen for worse survival in patients with nodal involvement in multivariate analysis while the difference was statistically significant in the univariate analysis. Patients with node-negative disease had 5-year OS of 39% compared with 14% for those with node-positive disease. Node involvement per se may yield to unfavorable prognosis or can just be a sign of more advanced disease. Indeed, all three patients with unresectable disease who underwent exploratory thoracotomy had histologically proven lymph node involvement. In our work, despite routine mediastinal lymph node dissection, none of the patients had lymph node involvement. The reason is unclear but

with microscopic complete resection who died from recurrence had local relapse with extended pleural involvement.

women with diagnosed PPS was nearly 7 times lower than in men. Surgery is the mainstay of treatment in sarcoma. However, in high-grade sarcomas, the prognosis usually depends on distant relapse. Undisputed exceptions are sarcomas of the retroperitoneum, for which local relapse usually determines survival. In PPS, no conclusion can be drawn. While in a study, most of the patients died from distant relapse, another showed homogeneous distribution of local and distant relapses as cause of deaths. In our study, both patients
could be potentially explained by the high rate of induction treatment or by the distribution of sarcoma histological subtypes, consisting mostly of subtypes very unlikely to follow a lymphatic pattern of metastasis. Taking existing data together and giving the low morbidity of mediastinal lymph node dissection, we strongly encourage its systemic use to shed light on the real prevalence of lymph node involvement in PPS. Beside the potential curative effect of mediastinal lymph node dissection, it will optimize postoperative staging and will refine the indication for adjuvant treatment, potentially improving patient outcome.

PPS staging can clearly be confusing, as three staging systems can be used, namely TNM staging for lung cancer, for STS of the trunk and extremity, as well as newly for STS of the abdomen and thoracic visceral organs. Lung cancer staging system was found to
be well applicable to PPS and was a significant predictor for survival.1,5 In our work, patients with pathologic stage III—according to lung cancer staging system—had a significantly shorter time to relapse compared with patients with stages 0-II. In another study, variables from the STS of trunk and extremity staging system were evaluated, namely T, N, and grading.3, 14 In the multivariable model of overall mortality, T stage (T1 vs T2) and grading (1.2 vs 3.4) were significantly impairing survivals, while N (N0 vs N1) did only show a trend for worse survival. In our study, pathologic T stage, based on the staging system for STS of trunk and extremity was found to be predictive of recurrence. This is however not surprising as the different T stages are defined by increasing tumor size, namely 0 to 5 cm (T1), 5 to 10 cm (T2), 10 to 15 cm (T3), and more than 15 cm (T4), respectively. Whether the two covariates (clinical tumor size and pathologic T stage) are both independently significant prognostic factors could not be evaluated. Indeed, a multivariate regression analysis was not feasible due to the small sample size of our cohort. In the 8th edition of the AJCC cancer staging manual, for the first time, a dedicated staging system was described for STS of the abdomen and thoracic visceral organs.11 While the staging system is meant to be applied to both abdominal and thoracic visceral organs, primary tumor extension (T) is defined mainly according to abdominal structures and cannot in our opinion be reliably applied to PPS. While a parallel can be drawn for T2a tumors defined by invasion of the visceral serosa (peritoneum or pleura), T2b tumors with extension beyond the serosa (mesentery) is less applicable for PPS. A central bronchovascular hilar extension of PPS carries probably a far worse prognosis than mesenterial tumor extension. There is also a gray zone for definition interpretation of T3 (tumor invading another organ) and T4 (multifocal involvement) tumors in case of PPS. To the best of our knowledge, we defined patients with pleural sarcomatosis as having multifocal involvement or T4 tumors. Unfortunately, from our patient cohort, we could not demonstrate any value of this new staging system in predicting death or relapse. However, we encourage the use of this classification for the purpose of future data collection and potential refinement of a more specific thoracic organ staging algorithm in the future, including different known prognostic factors and specific thoracic anatomic relationships.

In our study, 62% of patients had induction chemo(radiation) therapy before resection. Induction therapy was administered routinely in all but one case with preoperative diagnosis of PPS. While the use of chemotherapy is undisputed in Ewing and osteosarcoma, it is more controversial in STS. However, in recent years, the clinical benefit has been more evident when selected for patients with chemotherapy-sensitive subtypes and at highest risk of metastatic disease. To this end, most centers prefer neoadjuvant treatment to interrupt treatment early in those few patients progressing on chemotherapy.6,7,23,25

Given the rarity of PPS it is not surprising that no prospective data is available. At our center, we feel that given the mostly large tumor size and proximity to vital structures, induction therapy may facilitate resection and offer earliest treatment of micrometastases. In our series, no patient had become unresectable due to early progression under induction therapy.

Our study has the highest proportion of patients with PPS who received induction therapy before resection in a curative intent. Despite its limited sample size, clinical factors such as tumor size, gender, and type of lung resection were found to be predictive of overall and sarcoma-specific survival. These factors, along with other known survival predictors (tumor grade, completeness of resection) should aid the clinician to determine the need for neo- or adjuvant therapy, respectively. Due to the rarity of PPS and so far the lack of collaboration between centers to elaborate common study protocols, there are still more questions related to the optimal management of PPS than concrete answers. Building an international register and improving networking would probably set optimal conditions to more uniformly manage patients with PPS, leading to increasing patient survival and quality of life.

DATA AVAILABILITY STATEMENT
The anonymized data that support the findings of this study are available on request from the corresponding author.

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