Primary pulmonary synovial sarcoma

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ABSTRACT

Objective: Primary pulmonary synovial sarcoma (PPSS) is extremely rare. This study aims to identify the clinicopathologic and therapeutic factors determining survival in PPSS.

Methods: We performed a retrospective analysis of 121 patients from the Surveillance, Epidemiology, and End Results Database as well as 12 patients from our own institution diagnosed with PPSS. Patient survival was evaluated using the Kaplan-Meier method.

Results: The median survival time for 12 PPSS patients in our institution was 78 months. Postoperative chemotherapy ($P = .027$ for overall survival and $P = .035$ for disease-specific survival) was associated with superior survival, whereas pneumonectomy ($P = .011$ for overall survival and $P = .006$ for disease-specific survival) was associated with worse survival. Single lobe involvement ($P = .022$) and the absence of lymph node involvement ($P = .045$) were associated with improved disease-specific survival and overall survival, respectively. In the Surveillance, Epidemiology, and End Results Database, the median survival time was 23 months. Significantly superior survival was observed in patients with earlier American Joint Committee on Cancer stage (I-II) ($P < .001$ for both overall survival and disease-specific survival). Patients who were diagnosed within the recent decade did not achieve a better survival ($P = .599$ for overall survival and $P = .596$ for disease-specific survival).

Conclusions: PPSS was aggressive with a very poor prognosis. The seventh American Joint Committee on Cancer stage might aid in predicting survival. Pneumonectomy and lymph node involvement might be associated with worse survival, whereas single lobe involvement and postoperative chemotherapy might be associated with improved survival. (JTCVS Open 2022;10:404-14)

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Synovial sarcoma (SS) is a rare subtype of malignant soft tissue sarcoma (STS), accounting for 5% to 10% of all STS, 1 with an incidence of 0.12 to 0.18/100,000 people per year. 2 These tumors are more likely to occur in lower limbs or large joints of the extremities. 3,4 Pulmonary sarcoma is rare, comprising 0.5% of all primary lung malignancies, 5 whereas primary pulmonary synovial sarcoma (PPSS) is even more uncommon and accounts for only 16% of pulmonary sarcomas. 6 The diagnosis of PPSS is based on clinical, radiological, pathological, and immunohistochemical examinations to exclude other primary tumors and metastatic sarcomas. 7,8 SS is histopathologically complex and characterized with the specific t(x; 18) (p11.2; q11.2) translocation, resulting in the SYT-SSX fusion protein in more than 95% of cases. 9 Fewer than 100 cases of PPSS have been reported in the international literature, 1,11,12, thus, the features and outcomes of PPSS are uncertain. Because neither a prospective cohort study nor a randomized controlled trial is feasible due to the
low prevalence, using a population-based cancer database to evaluate the clinical characteristics and outcomes is a reasonable approach to better understand this orphan disease. The purpose of the present study is to analyze the characteristics and prognostic factors of PPSS using data collected in our institution and the Surveillance, Epidemiology, and End Results (SEER) Database. Overall survival (OS) and disease-specific survival (DSS) were the primary outcomes in this study.

MATERIALS AND METHODS
Single-Center Observational Study
We conducted a retrospective study on PPSS patients collected prospectively in our institution (Shanghai Pulmonary Hospital). This database enrolled consecutive patients with PPSS from January 2007 to March 2019. Metastatic pulmonary SS, as well as mediastinal, thoracic wall, pleural, and cardiac primary sarcomas were excluded from the study. Patients were followed-up in clinic every year for routine care as part of our institutional protocol. The diagnosis of PPSS was confirmed according to histological samples evaluated by a panel of expert pathologists, as described in our previous study.\(^5\) Video 1 recorded a uniporal VATS right upper lobe lobectomy of a patient with PPSS. Medical records were reviewed, and clinical data, including age, sex, tumor laterality, tumor size, tumor grade, lymph node (LN) involvement, local/distant metastasis, American Joint Committee on Cancers (AJCC) stage (the seventh edition), surgical resection, radiotherapy, chemotherapy, recurrence, follow-up time, and vital status were recorded. The study protocol was approved by the institutional review board of Shanghai Pulmonary Hospital on December 8, 2020 (K20-088Y). Data collection and analyses were approved, and informed consents were obtained from patients.

Data Collection of SEER Database
The search of patients diagnosed with PPSS was performed using the case-listing session protocol of the SEER database (http://www.seer.cancer.gov). This was exempted from institutional review board approval for the public nature of the SEER registry. SEER*Stat software (version 8.3.8; National Institutes of Health) was used to extract clinical, pathologic, and survival information from 1975 to 2016, the widest range of date available in the latest version of the SEER software at present. Histology type was identified in accordance with the International Classification of Diseases codes: synovial sarcoma, not otherwise specified (9040/3); synovial sarcoma, spindle cell (9041/3); synovial sarcoma, epithelioid cell (9042/3); and synovial sarcoma, biphasic (9043/3). Patients with other malignancies or if not the first primary tumor were excluded. Site-specific code was used to identify the primary site (tumor originated in single lobe of lung or involving more than 1 lobe). We collected data for analysis such as sex, age, race, histopathologic information (histologic subtype, tumor extent, tumor grade, tumor size, and tumor laterality), LN and distant metastasis status, treatment modalities (surgery and radiotherapy), vital status, follow-up time, and cause of death. Tumor size is an important factor reflecting the severity of tumor. In the seventh edition of the TNM staging system, T1 stage was defined as tumor ≤5 cm and T2 stage was defined as tumor >5 cm.\(^4\) Thus, we adopted 5 cm as the cutoff point for analysis. Tumors were divided into low grade (well-differentiated, grade I and moderately differentiated, grade II) and advanced grade (poorly differentiated, grade III and undifferentiated, grade IV). The AJCC stage at presentation was retroactively determined by tumor size, tumor extent, LN involvement, and distant metastasis, using the extent-of-disease staging codes and collaborative-stage in the SEER registry.\(^4\)

Statistical Analysis
OS was defined as the time in years from diagnosis to death of any cause, whereas DSS was defined as the time interval from diagnosis to death specifically caused by PPSS. Survival analysis was performed using the Kaplan-Meier method. Continuous variables were analyzed using the 2-sample \(t\) test, whereas categorical variables were compared using Pearson \(\chi^2\) test. Univariate analysis was formally tested by using the log-rank test and Cox proportional hazards model was conducted to adjust variables with \(p < .1\) in the univariate analyses. Statistical analysis was performed by SPSS version 25 (IBM-SPSS Inc) and all tests were 2-sided.

RESULTS
Single-center Case Series
Eighteen patients were diagnosed with PPSS in our institution. After carefully reviewing the medical history and reassessing the histological specimens, 6 cases were excluded: 3 were identified as pleural SS invading part of the lung, and another 3 were identified as pulmonary metastasis of osseous SS. Thus, a total of 12 patients with PPSS were included. The patient cohort selection process is summarized in Figure E1. The median age at diagnosis was 48.0 years (range, 21.0-72.0 years) and the median survival time was 78.0 months, with the 5-year OS of 60.2% and DSS of 69.3%. The male to female ratio was 3:1 and all patients were Chinese. All patients received radical resection, including 5 pneumonectomies, and all the surgical margins...
were negative. The median tumor size was 7.5 cm (range, 3.0-12.0 cm). Four patients had grade II tumors and 8 cases had grade III tumors. Seven cases were in AJCC stage II and 5 cases were in stage III. Local metastasis occurred in 4 patients, with tumors invading into adjacent tissues such as diaphragm, pleura, and chest wall. Only 1 case had regional LN involvement (hilary LN, patient ID: 8). No distant metastasis was found according to the bone scan, brain magnetic resonance imaging, and positron-emission tomography or computed tomography. Eight patients received postoperative chemotherapy, whereas only 1 case received postoperative radiotherapy (patient ID: 6). Local recurrence was found in 3 patients and all the recurrence occurred within 1 year after operation. The diagnosis of PPSS was confirmed by pathological examination and/or SS18-SSX translocation demonstrated by fluorescence in situ hybridization (Figure 1, A and B). A total of 5 patients died, of whom 4 died of PPSS (80%) and 1 died of pneumonia 2.5 years after surgery (Table 1).

Univariate Kaplan-Meier analysis revealed that postoperative chemotherapy ($P = .027$ for OS and $P = .035$ for DSS) was associated with superior survival, whereas pneumonectomy ($P = .011$ for OS and $P = .006$ for DSS) was associated with worse survival. Single lobe involvement ($P = .022$) and the absence of lymph node involvement ($P = .045$) were associated with improved DSS and OS, respectively, whereas OS and DSS, for single lobe involvement and absence of LN involvement, did not reach statistical significance. Other factors, including sex, age, tumor size, tumor grade, AJCC stage, radiotherapy, local metastasis, and recurrence were not significantly associated with survival. Due to the limited sample size, Cox-regression analysis was not performed.

SEER Database Study: Clinicopathological Characteristics of PPSS

After the cohort selection, a total of 121 patients were identified in the SEER Database. Clinicopathological characteristics are reported in Table 2. Men (n = 64, 52.9%) and Caucasian (n = 104, 86%) patients were predominant in the population with the median age at diagnosis of 50 years (range, 12-82 years). Spindle cell (n = 52, 31.1%) was the most common histologic subtype. Only 51 patients (48.1%) had complete tumor grade information, and as high as 44 cases were histologically confirmed to be advanced grade (grade III and grade IV). The median tumor size was 8.1 cm (range, 1.5-21.0 cm). Only 12 patients had LN involvement, whereas distant metastasis occurred in 41 cases. The number of patients classified into TNM stage I, II, III, and IV were 38 (31.4%), 4 (3.3%), 10 (8.3%), and 41 (33.9%), respectively. A total of 25 (20.7%) patients received bimodal therapy (surgery and radiotherapy), whereas 64 (52.8%) patients underwent surgical resection only, and 7 (5.8%) patients received radiotherapy only.

SEER Database Study: Survival Analysis

The 5-year OS and DSS for PPSS patients in the SEER Database were 29.2% and 31.2%, respectively, with the median OS of 23.0 months (Figure 2, A and B). Significantly superior survival was observed in patients with tumor size ≤5 cm, younger age, single lobe involvement, surgical resection, radiotherapy, LN negative, no distant metastasis, and earlier AJCC stage (I-II). Histologic subtype, race, sex, tumor grade, and tumor laterality were not significantly associated with prognosis (Table 3). The information of tumor location, tumor size, LN involvement, and distant metastasis is included in the AJCC stage system; thus, AJCC stage system plays an important role in survival prediction. Because the information of the chemotherapy was unavailable in the SEER Database, multivariate Cox-regression analysis could not be performed.

Subgroup Analysis

We further compared the treatment modalities and survival status for subpopulations, stratified on year at diagnosis (dichotomized into 2 periods, 1975-2006 and 2007-2016, the same period with our single institution). Patients who were diagnosed within the recent decade (2007-2016) did not have a better survival than those diagnosed between 1975 and 2006 (5-year OS of 27.4% vs. 32.7%; $P = .599$ and 5-year DSS of 29.5% vs. 34.5%; $P = .596$). Besides, no significant difference was found in the proportion of patients receiving surgical resection and radiotherapy (Table E1).

**FIGURE 1.** A. Hematoxylin and eosin staining of the incisional specimens of primary pulmonary synovial sarcoma (PPSS) in our institution, showing spindle cells and numerous mitotic figures, the amplification is 100 $\times$ and 400 $\times$, respectively. B. Fluorescence in situ hybridization analysis performed on the incisional specimens of PPSS, showing separation of the 5’ and 3’ SS18 signals in many of the tumor cell nuclei, as shown by the arrows.
### TABLE 1. Clinical features of patients with primary pulmonary synovial sarcoma (PPSS) in Shanghai Pulmonary Hospital, China

| ID  | Sex | Age at diagnosis (y) | Primary site | Tumor laterality | Preoperative biopsy | Surgery performed | Pneumonectomy | Radiotherapy | Chemotherapy | LN status | Local metastasis | Histologic subtype | Tumor grade | Tumor size (cm) | AJCC stage | OS status | DSS status | Survival mo | Recurrence time (mo) |
|-----|-----|----------------------|--------------|-----------------|--------------------|-------------------|-----------------|--------------|--------------|-----------|----------------|-----------------|-------------|-----------------|-----------|-----------|-----------|-------------|------------------|
| 1   | Male| 62                   | Single lobe  | Right           | TBNA (+)           | Yes               | No              | No           | Yes          | No        | No            | Spindle cell     | III         | 3               | II         | Alive     | Alive     | 76          | Yes                  | 5 |
| 2   | Male| 7                    | Involving more than 1 lobe | Right | TBNA (+) | Yes | Yes | No | No | No | No | No | No | Spindle cell | II | 6 | II | Died | Dead due to PPSS | 20 | No | No recurrence |
| 3   | Female| 53                  | Single lobe  | Right           | TBNA (-)          | Yes               | No              | No           | Yes          | No        | No            | Spindle cell     | III         | 4               | II         | Alive     | Alive     | 64          | No | No recurrence |
| 4   | Female| 49                  | Involving more than 1 lobe | Right | TTNA (+) | Yes | No | No | Yes | No | No | No | No | Spindle cell | III | 4 | II | Alive | Alive | 52 | No | No recurrence |
| 5   | Male| 60                   | Involving more than 1 lobe | Left  | TTNA (+) | Yes | Yes | No | No | No | Yes | Yes | Spindle cell | III | 12 | III | Died | Dead due to PPSS | 10 | No | No recurrence |
| 6   | Male| 22                   | Single lobe  | Left            | TTNA (+)          | Yes               | No              | Yes          | Yes          | No        | Yes           | Spindle cell     | III         | 9               | III        | Alive     | Alive     | 12          | Yes | 10 |
| 7   | Male| 25                   | Involving more than 1 lobe | Left  | TBNA (-) | Yes | Yes | No | Yes | No | No | No | No | Spindle cell | III | 8 | III | Alive | Alive | 8 | No | No recurrence |
| 8   | Female| 45                  | Involving more than 1 lobe | Left  | TTNA (+) | Yes | Yes | No | Yes | Yes | No | Yes | Yes | Spindle cell | III | 9 | III | Died | Dead due to PPSS | 14 | No | No recurrence |
| 9   | Male| 47                   | Single lobe  | Right           | TBNA (+)          | Yes               | No              | No           | Yes          | No        | No            | Spindle cell     | III         | 7               | III        | Alive     | Alive     | 96          | No | No recurrence |
| 10  | Male| 21                   | Involving more than 1 lobe | Right | TTNA (+) | Yes | Yes | No | No | No | Yes | Yes | Yes | Spindle cell | II | 8 | II | Died | Dead due to PPSS | 80 | No | No recurrence |
| 11  | Male| 47                   | Single lobe  | Left            | TBNA (+)          | Yes               | No              | No           | Yes          | No        | No            | Spindle cell     | II         | 4               | II         | Alive     | Alive     | 13          | Yes | 5 |
| 12  | Male| 72                   | Single lobe  | Right           | TBNA (+)          | Yes               | No              | No           | No          | No        | No            | Spindle cell     | II         | 4               | II         | Died     | Alive     | 32          | No | No recurrence |

LN, Lymph node; AJCC, American Joint Committee on Cancer; OS, overall survival; DSS, disease-specific survival; TTNA, transthoracic needle aspiration; TBNA, transbronchial needle aspiration; (+), atypical cells found, but the histological type could not be identified.
Cases in our institution were all Chinese (non-Caucasian), although there were only 17 (14.08%)
cases of non-Caucasians in the SEER Database. Due to the different genetic background, environmental, and social factors, there were some differences in the clinical characteristics and management of PPSS between the 2 groups. A comparison of the clinical characteristics and treatment modalities between our institution and the SEER Database was performed. Tumor size was larger in the SEER Database than that in our institution (9.17 cm / 6.83 cm; \( P = .018 \)). There were more patients with multiple lobes involvement in our institution than those in the SEER Database (50% vs 5.6%; \( P < .001 \)). No distant metastasis occurred in our institution, although 33.9% of patients were associated with distant metastasis in the SEER Database (\( P = .014 \)). Although the 5-year OS in the SEER Database was obviously lower than that in our institution (29.2%)

### Table 2. Baseline characteristics of patients with primary pulmonary synovial sarcoma (PPSS) in the Surveillance, Epidemiology, and End Results (SEER) Database

| Variables (n = 121) | Result |
|---------------------|--------|
| Age at diagnosis (y) |        |
| Mean ± SD           | 50.7 ± 18.2 |
| Median (range)      | 50 (12-82) |
| Sex                 |        |
| Female              | 57 (47.1) |
| Male                | 64 (52.9) |
| Race/ethnicity      |        |
| Caucasian           | 104 (86.0) |
| Non-Caucasian       | 17 (14.0) |
| Histologic subtype  |        |
| Synovial sarcoma, not otherwise specified | 66 (54.5) |
| Spindle cell        | 44 (36.4) |
| Epithelioid cell    | 1 (0.8) |
| Biphasic            | 10 (8.3) |
| Tumor grade, n = 51 |        |
| I                   | 2 (1.7) |
| II                  | 5 (4.1) |
| III                 | 27 (22.3) |
| IV                  | 17 (14.0) |
| Unknown             | 70 (57.9) |
| Laterality          |        |
| Left                | 55 (45.5) |
| Right               | 66 (54.5) |
| Primary site        |        |
| Upper lobe          | 49 (40.5) |
| Middle lobe         | 7 (5.8) |
| Lower lobe          | 46 (38.0) |
| Involving more than 1 lobe | 6 (5.0) |
| Lung, not specified | 13 (10.7) |
| AJCC stage, n = 93  |        |
| I                   | 38 (31.4) |
| II                  | 4 (3.3) |
| III                 | 10 (8.3) |
| IV                  | 41 (33.9) |
| Unknown             | 28 (23.1) |
| Surgery performed, n = 118 |        |
| Yes                 | 89 (73.6) |
| No                  | 29 (24.0) |
| Unknown             | 3 (2.5) |
| Radiotherapy, n = 99 |        |
| Yes                 | 34 (28.1) |
| No                  | 65 (53.7) |
| Unknown             | 22 (18.2) |
| Treatment modality, n = 97 |        |
| Surgery with radiotherapy | 25 (20.7) |
| Surgery only        | 64 (52.8) |
| Radiotherapy        | 7 (5.8) |
| No therapy          | 1 (0.8) |
| Unknown             | 24 (19.8) |

(Continued)
vs 60.2%), no statistical significance was found due to the limited sample size. No significant difference was detected regarding to sex, age, histologic subtype, tumor laterality, tumor grade, radiotherapy, LN involvement, and AJCC stage (Table E2).

DISCUSSION

This study reports a total of 121 patients from the SEER Database, as well as 12 patients from our institution, which is the largest study population at present. PPSS had a poor prognosis with the median survival of 23 months at the population level. The OS was not significantly improved within the recent decade and advanced AJCC stage might indicate worse outcome. Although in our institution, the outcome was encouraging with the median survival of 78 months, and tumor primary site, postoperative chemotherapy, pneumonectomy, and LN involvement might be associated with survival.

The T stage in current eighth AJCC staging system is based on invasion of serosa of viscera and the existence of multifocal lesions, and it is not being applied to old data because it was not in use during the period of the study. Therefore, we used the seventh edition of the staging system in the present study, which includes the information of tumor location, tumor size, LN involvement, and distant metastasis. The survival analysis of SEER Database revealed that advanced AJCC stage was associated with worse survival, suggesting that the seventh AJCC stage might aid in predicting survival in PPSS.

The prognosis of PPSS was poorer in the SEER Database comparing with that in our institution. One possible explanation should be that all patients in our institution had no distant metastasis. In addition, the majority of patients in the SEER population had grade III or IV tumors, whereas tumor grades were limited to grade II and III in our institution. Moreover, the proportion of patients receiving postoperative adjuvant treatment in our institution was also higher than that in SEER Database.

No significant difference was found in survival comparing recent (2007-2016) with the previous (1975-2006) SEER Database cohorts. Although the results might be biased because more PPSS patients were being identified during the recent decade, this finding still suggested that at the population level, little significant progress had been made in the treatment of this uncommon disease. In line with this, Wang and colleagues revealed that the prognosis of SS did not improve throughout 1983 and 2012 (1983-1992, 1993-2002, and 2003-2012), with 5-year survival rates of 69.4%, 61.1%, and 60.5%, respectively ($P > .05$), indicating the pressing need for novel and effective treatments.

The standard treatment for primary SS is wide surgical resection combined with radiation. In accordance with this, surgery performance was the main treatment for PPSS in our study, and it was associated with better outcome in the univariate analysis of SEER Database. Pneumonectomy and multiple lung lobes involved were associated with worse survival in our institution, indicating that PPSS patients with multiple lung lobes involved might not benefit from pneumonectomy.

Positive surgical margin is a strong predictor of local recurrence for extremity STS. In our institution, all patients undertook radical tumor resection with negative surgical margins, however, 25% of patients had recurrence within one year after operation. One possible explanation might be that the size of PPSS was relatively large at diagnosis. Besides, it could also reflect the characteristics of PPSS, which were very aggressive and easy to metastasize, and might be more likely to recur than other STS.

![Kaplan-Meier curves for overall survival and number at risk (A) and disease-specific survival analysis and number at risk (B) of patients with primary pulmonary synovial sarcoma (PPSS) in the Surveillance, Epidemiology, and End Results (SEER) Database. Survival curves were truncated when total number of patients at risk <10. The dotted lines indicate the range of 95% CI for the corresponding survival curve.](image-url)
Less than one-third of patients in the SEER Database and only 1 case in our institution received radiotherapy, much less common than SS of the head and neck, suggesting that radiotherapy is less likely to be used in PPSS for disease control, which is in line with a previous report. Improved survival was found in patients receiving radiotherapy according to the SEER database. Notably, the mean size of PPSS was larger than SS of other sites reported in literature; thus, traditional radiotherapy might bring more side effects. Particle beam therapy was superior in dose concentration and cell-killing effect, with efficacy and safety reported in STS, and it might be an alternative treatment for PPSS.

### TABLE 3. Univariate analysis of variables of overall survival and disease-specific survival in the Surveillance, Epidemiology, and End Results (SEER) Database

| Characteristic                      | Overall survival |  | Disease-specific survival |  |
|------------------------------------|------------------|---|--------------------------|---|
|                                    |  |                      |  |                          |  |
| Race                               |  | .665                  |  | .514                     |  |
| Caucasian                          | 1.000 (reference) |  | 1.000 (reference)        |  |
| Non-Caucasian                      | 1.147 (0.618-2.129) |  | 1.231 (0.660-2.298)     |  |
| Sex                                |  | .445                  |  | .615                     |  |
| Female                             | 1.000 (reference) |  | 1.000 (reference)        |  |
| Male                               | 1.197 (0.755-1.898) |  | 1.131 (0.700-1.828)     |  |
| Age at diagnosis (y)               | 1.020 (1.006-1.034) |  | 1.018 (1.004-1.032)     |  |
| Primary site                       |  | .048                  |  | .033                     |  |
| Single lobe                        | 1.000 (reference) |  | 1.000 (reference)        |  |
| Involving more than 1 lobe         | 2.875 (1.011-8.176) |  | 3.154 (1.098-9.058)     |  |
| Tumor grade                        |  | .625                  |  | .751                     |  |
| Low grade (I-II)                   | 1.000 (reference) |  | 1.000 (reference)        |  |
| Advanced grade (III-IV)            | 1.301 (0.453-3.731) |  | 1.189 (0.409-3.448)     |  |
| Laterality                         |  | .138                  |  | .137                     |  |
| Right                              | 1.000 (reference) |  | 1.000 (reference)        |  |
| Left                               | 0.702 (0.440-1.121) |  | 0.691 (0.425-1.124)     |  |
| Histologic subtype                 |  | .245                  |  | .296                     |  |
| Spindle cell                       | 1.000 (reference) |  | 1.000 (reference)        |  |
| Epithelioid cell                   | 4.600 (0.586-36.090) |  | 4.341 (0.553-34.104)    |  |
| Biphasic                           | 0.693 (0.266-1.806) |  | 0.745 (0.284-1.953)     |  |
| Surgery performed                  |  | <.001                 |  | <.001                    |  |
| No                                 | 1.000 (reference) |  | 1.000 (reference)        |  |
| Yes                                | 0.261 (0.156-0.438) |  | 0.243 (0.138-0.399)     |  |
| Radiation therapy                  |  | .004                  |  | .003                     |  |
| Yes                                | 1.000 (reference) |  | 1.000 (reference)        |  |
| No                                 | 2.250 (1.303-3.885) |  | 2.392 (1.344-4.260)     |  |
| Treatment modality                 |  | .007                  |  | .003                     |  |
| Surgery with radiotherapy          | 1.000 (reference) |  | 1.000 (reference)        |  |
| Surgery only                       | 0.500 (0.273-0.914) |  | 0.462 (0.246-0.869)     |  |
| Radiotherapy only                  | 1.992 (0.708-5.602) |  | 2.272 (0.791-6.522)     |  |
| LN involvement                     |  | <.001                 |  | <.001                    |  |
| No                                 | 1.000 (reference) |  | 1.000 (reference)        |  |
| Yes                                | 3.436 (1.782-6.625) |  | 3.684 (1.896-7.158)     |  |
| Distant metastasis                 |  | <.001                 |  | <.001                    |  |
| No                                 | 1.000 (reference) |  | 1.000 (reference)        |  |
| Yes                                | 2.559 (1.538-4.259) |  | 2.724 (1.613-4.598)     |  |
| Tumor size, cm                     |  | .001                  |  | .001                     |  |
| ≤5                                 | 1.000 (reference) |  | 1.000 (reference)        |  |
| >5                                 | 3.540 (1.665-7.525) |  | 3.887 (1.741-8.677)     |  |
| AJCC stage                          |  | <.001                 |  | <.001                    |  |
| I-II                               | 1.000 (reference) |  | 1.000 (reference)        |  |
| III-IV                             | 3.098 (1.760-5.453) |  | 3.241 (1.817-5.780)     |  |

Values are presented as hazard ratio (95% CI). LN, Lymph node; AJCC, American Joint Committee on Cancer; Met, metastasis.
Adjuvant chemotherapy was demonstrated to be beneficial for survival in our institution. However, the benefit of chemotherapy remains controversial in literature and could be considered in patients at high risk of systemic relapse. Although no controlled studies of chemotherapy for PPSS was permitted due to rarity, the pathologic diagnosis of the entity is based on the genetic rearrangements of SS18:SSX, and that studies of systemic therapy for extremity SS may be somewhat applicable to PPSS. For advanced disease, cytotoxic chemotherapy, and especially anthracyclines, ifosfamide, trabectedin, and pazopanib, are the treatments of choice, and chemotherapy may increase disease-free survival.

Limitations
Our study reported the first analysis of PPSS from an epidemiologic perspective at the population level, and the data of our institution provided an additional insight contemporarily. However, some limitations still exist. Firstly, for the rarity of this orphan disease, the study population was relatively small. Secondly, the SEER Database had no centralized review by pathologists, and there are some concerns about misclassification. In addition, some information such as chemotherapy was incomplete and unanalyzable, which made the conclusions less convincing.

CONCLUSIONS
PPSS had a very poor prognosis and no survival improvement was seen in recent decades, calling for novel treatment. The seventh AJCC stage might aid in predicting survival. Besides, single lobe involvement and postoperative chemotherapy might be associated with improved survival, whereas pneumonectomy and LN involvement might be associated with worse survival (Figure 3). However, more data and evidence are needed to verify these conclusions.

Conflict of Interest Statement
The authors reported no conflicts of interest.

The Journal policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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**Key Words:** primary pulmonary synovial sarcoma, single center study, SEER database, outcomes
TABLE E1. Treatment modalities and survival by year group based on the Surveillance, Epidemiology, and End Results (SEER) Database

| Treatment modality and survival | 1975-2006 (n = 42) | 2007-2016 (n = 79) | P value |
|---------------------------------|-------------------|-------------------|---------|
| Surgery performed               |                   |                   | .647    |
| No                              | 8                 | 21                |         |
| Yes                             | 33                | 56                |         |
| Unknown                         | 1                 | 2                 |         |
| Radiation therapy               |                   |                   | .423    |
| No                              | 24                | 41                |         |
| Yes                             | 13                | 21                |         |
| Unknown                         | 5                 | 17                |         |
| Five-year OS (%)                | 32.70             | 27.40             | .599    |
| Five-year DSS (%)               | 34.50             | 29.50             | .596    |

OS, Overall survival; DSS, disease-specific survival.

FIGURE E1. Flow chart for selection of primary pulmonary synovial sarcoma (PPSS) in our institution.
| Characteristic                     | SEER                          | Single center | P value |
|-----------------------------------|-------------------------------|---------------|---------|
| Tumor size (cm), n = 114          |                               |               |         |
| Mean ± SD                         | 9.17 ± 4.92                  | 6.83 ± 2.69   | .018    |
| Race, n = 133                     |                               |               | <.001   |
| Non-Caucasian                     | 17 (14.0%)                   | 12 (100%)     |         |
| Caucasian                          | 104 (86.0)                   | 0 (0)         |         |
| Sex, n = 33                       |                               |               | .142    |
| Female                             | 57 (47.1)                    | 3 (25.0)      |         |
| Male                               | 64 (52.9)                    | 9 (75.0)      |         |
| Age at diagnosis (y)              |                               |               | .603    |
| Mean ± SD                         | 50.70 ± 18.22                | 47.83 ± 17.62 |         |
| Primary site, n = 120             |                               |               | <.001   |
| Single lung lobe                  | 102 (94.4)                   | 6 (50.0)      |         |
| Involving more than 1 lobe        | 6 (5.6)                      | 6 (50.0)      |         |
| Lung, not specified               | 13                           | 0             |         |
| Grade, n = 63                     |                               |               | .235    |
| Low                               | 7 (13.7)                     | 4 (33.3)      |         |
| Advanced                          | 44 (86.3)                    | 8 (66.7)      |         |
| Unknown                           | 70                           | 0             |         |
| Laterality, n = 133               |                               |               | .801    |
| Right                             | 66 (54.5)                    | 7 (58.3)      |         |
| Left                              | 55 (45.5)                    | 5 (41.7)      |         |
| Histologic subtype, n = 67        |                               |               | .248    |
| Monophasic                        | 45 (81.8)                    | 12 (100)      |         |
| Biphasic                          | 10 (18.2)                    | 0 (0)         |         |
| SS, not specified                 | 66                           | 0             |         |
| Surgery performed, n = 130        |                               |               | .113    |
| No                                | 29 (24.6)                    | 0 (0)         |         |
| Yes                               | 89 (75.4)                    | 12 (100)      |         |
| Unknown                           | 3                            | 0             |         |
| Radiotherapy, n = 111             |                               |               | .133    |
| No                                | 65 (65.7)                    | 11 (91.7)     |         |
| Yes                               | 34 (34.3)                    | 1 (8.3)       |         |
| Unknown                           | 22                           | 0             |         |
| LN involvement, n = 119           |                               |               | 1       |
| No                                | 95 (88.8)                    | 11 (91.7)     |         |
| Yes                               | 12 (11.2)                    | 1 (8.3)       |         |
| Unknown                           | 14                           | 0             |         |
| Distant metastasis, n = 112       |                               |               | .014    |
| No                                | 59 (59.0)                    | 12 (100)      |         |
| Yes                               | 41 (41.0)                    | 0 (0)         |         |
| Unknown                           | 21                           | 0             |         |
| AJCC stage, n = 105               |                               |               | .389    |
| I-II                              | 42 (45.2)                    | 7 (58.3)      |         |
| III-IV                            | 51 (54.8)                    | 5 (41.7)      |         |
| Unknown                           | 28                           | 0             |         |
| 5-year OS (%), n = 133            | 29.2                         | 60.2          | .185    |
| 5-year DSS (%), n = 133           | 31.2                         | 69.3          | .186    |

Values are presented as n or n (%) unless otherwise noted. SS, Synovial sarcoma; LN, lymph node; AJCC, American Joint Committee on Cancer; OS, overall survival; DSS, disease-specific survival.