# Surgical Outcomes and Risk Analysis of Primary Pulmonary Sarcoma

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Thorac Cardiovasc Surg 2021;69:101–108.

## Abstract

**Background** Primary pulmonary sarcoma (PPS) is a rare malignant lung neoplasm, and there is very little medical evidence about treatment of PPS. The aim of this study is to clarify the clinical characteristics and therapeutic outcome of patients who underwent surgical resection for PPS.

**Methods** We retrospectively reviewed the records of patients who underwent surgical resection for PPS in our institution between 1995 and 2014. Cases who only underwent biopsy were excluded.

**Results** A total of 24 patients (18 males, 6 females), with a median age of 60 (interquartile range: 44–67) years, were analyzed. The surgical procedures performed in these patients were pneumonectomy ($n = 10$), lobectomy ($n = 11$), and wedge resection ($n = 3$). Complete resection was achieved in 16 patients. The pathological stages (tumor, node, metastases lung cancer classification, 8th edition) of the patients were I ($n = 4$), II ($n = 12$), III ($n = 2$), and IV ($n = 5$), and there were four cases of lymph node metastasis. The 5-year overall survival rate of the patients was 50% (95% confidence interval [CI]: 29–72). Adverse prognostic factors for overall survival were incomplete resection (hazard ratio [HR]: 4.4, 95% CI: 2.1–42), advanced pathological stage (HR 14, 95% CI: 2.8–66), higher pathological grade (HR 4.5, 95% CI: 1.2–17), and tumor size $\geq 7$ cm (HR 4.7, 95% CI: 1.1–21).

**Conclusions** Our series of PPS revealed that incomplete resection, advanced pathological stage, higher pathological grade, and tumor size were unfavorable factors for long-term survival.

**Keywords**
- sarcoma
- tumor
- radiation therapy
- chemotherapy
- surgery/incisions

## Introduction

Primary pulmonary sarcoma (PPS) is a rare malignant lung neoplasm.[1] There is very little medical evidence about treatment of PPS compared with that for sarcoma of the extremities or primary retroperitoneal sarcoma.[2,3] Some studies about PPS, including a large cohort study, have been published that have provided an overview of the disease.[4–10] Several reports suggested a survival benefit associated with surgical resection.[5,6,10] However, the efficacy of neoadjuvant or adjuvant chemotherapy is unknown. Moreover, various histological subtypes have different oncological and biological

**received**
May 8, 2019
**accepted after revision**
July 22, 2019
**published online**
September 9, 2019


Georg Thieme Verlag KG,
Rüdigerstraße 14,
70469 Stuttgart, Germany

**DOI** https://doi.org/10.1055/s-0039-1695784.
**ISSN** 0171-6425.

characteristics, complicating detailed elucidation of the disease. Diagnosis of PPS is suggested only when clinical and imaging evaluation does not identify an alternative primary source. In addition, only detailed immunohistochemistry can provide a definitive diagnosis. A guideline for appropriate treatment of PPS is not yet available. In the current study, we retrospectively investigated the records of patients with PPS in our institute. Our aim was to clarify the clinical characteristics and therapeutic outcomes of patients who underwent surgical resection for PPS.

## Materials and Methods

We performed a retrospective review of the medical records of patients with PPS who underwent tumor resection between 1995 and 2014 at our institute. Patients who only underwent biopsy or explorative thoracotomy were excluded. Reviewed clinical variables were age, gender, clinical history, surgical procedures, postoperative complications, pathological diagnosis, induction or adjuvant treatment, recurrence, and postoperative outcome.

Generally, most cases of malignant mesenchymal tumors of the lung are manifestations of a primary tumor located elsewhere.[4,8] Thus, if our clinical practice encounters a patient with a pulmonary sarcoma histology, diagnosis of PPS can be made only when (1) a systemic clinical and radiological investigation is conducted, and (2) the diagnosis is confirmed by the institutional sarcoma board, which includes oncologists, pathologists, radiologists, and surgeons. For patients who underwent surgery prior to 2004, the diagnosis of PPS was reviewed and confirmed by the pathologist according to the fourth edition of the World Health Organization classification.[11,12] For pathological staging, the eighth edition of the tumor, node, metastases (TNM) classification of lung cancer was applied.[13]

The summary statistics were expressed as medians (range or interquartile range) for continuous variables and as numbers (percentage) for categorical variables. Kaplan–Meier curves were generated to assess overall survival (OS), and 5-year OS rates with 95% confidence intervals (95% CIs) were reported. Univariable Cox regression analyses were performed to identify factors associated with an unfavorable OS, and the significant variables were reported as hazard ratios (HRs) with 95% CIs. A $p$-value $< 0.05$ was considered significant. Statistical analyses were performed using IBM SPSS Statistics, version 22 (IBM Corp, Armonk, New York, United States).

## Results

### Patient Characteristics

A total of 24 patients with PPS were included. The patient characteristics are listed in ►**Table 1**. The ages of the patients ranged from 18 to 83 years, with a median (interquartile range) of 60 (44–67) years. The patient population consisted of 18 (75.0%) males and 6 (25.0%) females. Surgical methods included pneumonectomy ($n = 10$ [41.6%]), lobectomy ($n = 11$ [45.8%]), including sleeve lobectomy ($n = 2$) and bilobectomy ($n = 1$), and wedge resection ($n = 3$ [12.5%]). Eight patients

**Table 1** Patient characteristics

| Characteristic | Patients ($n = 24$) |
|---|---|
| Age (years), median (IQR) | 60 (44–67) |
| Sex | |
| Male | 18 (75%) |
| Female | 6 (25%) |
| Surgical method | |
| Pneumonectomy | 10 (42%) |
| Lobectomy | 8 (33%) |
| Bilobectomy | 1 (4%) |
| Sleeve lobectomy | 2 (8%) |
| Wedge resection | 3 (13%) |
| Additional resection surrounding structures[a] | 8 (33%) |
| Complete resection (R0) | 16 (67%) |
| Tumor size (cm), median (IQR) | 5.3 (3.4–8.1) |
| Histology, WHO classification | |
| Angiosarcoma | 7 (29%) |
| Malignant peripheral nerve sheath tumor | 3 (13%) |
| Fibro/myofibroblast sarcoma | 3 (13%) |
| Follicular dendritic cell sarcoma | 2 (8%) |
| Liposarcoma | 2 (8%) |
| Clear cell sarcoma | 1 (4%) |
| Ewing sarcoma | 1 (4%) |
| Kaposi sarcoma | 1 (4%) |
| Leiomyosarcoma | 1 (4%) |
| Synovial sarcoma | 1 (4%) |
| Unclassified | 2 (17%) |
| Pathological grade | |
| G1 | 4 (17%) |
| G2 | 5 (21%) |
| G3 | 15 (63%) |
| Node-positive disease | 4 (17%) |
| p-Stage[b] | |
| I | 4 (17%) |
| II | 12 (50%) |
| III | 2 (8%) |
| IV | 5 (21%) |
| Surgery alone | 14 (58%) |
| Induction or adjuvant therapy | 10 (42%) |
| Chemotherapy/surgery | 2 (8%) |
| Chemotherapy/surgery/ radiotherapy | 1 (4%) |

**Table 1** (*Continued*)

| Characteristic | Patients ($n = 24$) |
|---|---|
| Surgery/radiotherapy | 3 (13%) |
| Surgery/chemotherapy | 4 (17%) |
| Postoperative complications | 5 (21%) |
| Recurrence | 7 (44% of R0 patients) |

Abbreviations: IQR, interquartile range; p-Stage, pathological stage; WHO, World Health Organization.
[a]Resection of chest wall, intrathoracic nerves, left atrium, pericardium, and pulmonary artery.
[b]The eighth edition of the TNM lung cancer classification was applied for pathological staging.

(33.3%) had undergone resection of surrounding structures, such as pericardium, intrapericardial pulmonary artery, intrathoracic nerves, left atrium, and chest wall. Complete resection (R0) was achieved in 16 (66.7%) patients. The tumor sizes ranged from 0.8 to 24 cm, with a median (interquartile range) of 5.3 (3.4–8.1) cm. Pathological stage based on the eighth edition of the TNM lung cancer classification included IA ($n = 3$ [12.5%]), IB ($n = 1$ [4.2%]), IIA ($n = 6$ [25.0%]), IIB ($n = 6$ [25.0%]), IIIA ($n = 2$ [8.3%]), and IV ($n = 5$ [20.8%]). Lymph node metastasis was observed in four patients (16.7%), and all cases were N1. The pathological subtypes included angiosarcoma ($n = 7$), malignant peripheral nerve sheath tumor ($n = 3$), fibro/myofibroblastic sarcoma ($n = 3$), follicular dendritic cell sarcoma ($n = 2$), liposarcoma ($n = 2$), and other types or unclassified sarcoma ($n = 7$). Pathological grades were G1 ($n = 4$ [16.7%]), G2 ($n = 5$ [20.8%]), and G3 ($n = 15$ [62.5%]). Perioperative therapies included induction therapy ($n = 3$ [12.5%]), adjuvant chemotherapy ($n = 4$ [16.7%]), and adjuvant radiotherapy ($n = 4$ [16.7%]). Of the three patients receiving induction chemotherapy, one each was treated with cisplatin–etoposide (stable disease), carboplatin–paclitaxel (complete remission), and ifosfamide–epirubicin (partial remission). Most of the adjuvant therapy regimens consisted of ifosfamide and epirubicin (or doxorubicin). Postoperative complications were observed in five patients (20.8%). Comorbidity rates in patients with pneumonectomy and other surgical procedures were 50.0 and 14.3%, respectively ($p = 0.13$). Seven patients experienced tumor recurrence (43.8% in R0 patients). During the postoperative follow-up period (median: 762 days; range: 22–5,955 days), 12 patients (50.0%) died; notably, 1 patient died within 30 days after surgery. Patient characteristics stratified by histological subtypes are shown in ►**Table 2**. Mean survival times differ between histological subtypes, although the numbers of patients are small.

**Table 3** Univariable analyses of risk factors for overall survival

| | HR (95% CI) | *p*-Value |
|---|---|---|
| Incomplete resection | 4.4 (2.1–42) | 0.004[a] |
| Advanced pathological stage (III, IV vs. I, II) | 13.6 (2.8–66) | 0.001[a] |
| High pathological grade (G2, G3 vs. G1) | 4.5 (1.2–17) | 0.028[a] |
| Tumor size $\geq 7$ cm | 4.7 (1.0–21) | 0.044[a] |
| Additional resection of surrounding organs | 4.0 (0.9–17) | 0.060 |
| Node-positive disease | 1.1 (0.3–5.0) | 0.87 |

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a]Significant difference.

## Survival Analysis

The 5-year OS rate of the patients was 50.1% (95% CI: 28.5–-71.7%), and the 5-year disease-specific survival rate was 52.4% (95% CI: 30.3–74.5%). ►**Table 3** shows the results of the univariable Cox regression analyses of factors associated with an unfavorable OS, including incomplete resection (HR 4.4, 95% CI: 2.1–42; $p = 0.004$) (►**Fig. 1A**), advanced pathological stage (stages III and IV compared with I and II; HR 13.6, 95% CI: 2.8–66; $p = 0.001$) (►**Fig. 1B**), high pathological grade (G2 or G3 compared with G1; HR 4.5, 95% CI: 1.2–17; $p = 0.028$) (►**Fig. 1C**), and tumor size $\geq 7$ cm (HR 4.7, 95% CI: 1.0–21; $p = 0.044$) (►**Fig. 1D**). The 5-year OS of patients with resection of surrounding structures was worse (HR 4.0, 95% CI: 0.9–17; $p = 0.060$). Other clinical variables, including age, gender, smoking status, lymph node metastasis, induction therapy, and adjuvant therapy, were not identified as unfavorable factors.

**Table 2** Patient characteristics by histological subtype

| Histological type | Patients, *n* | Surgery, *n* (PN/LB/WR) | R0, *n* | Induction chemo, *n* | Adjuvant chemo, *n* | Postop radio, *n* | MST, months |
|---|---|---|---|---|---|---|---|
| Angiosarcoma | 7 | 5/1/1 | 2 | 0 | 2 | 0 | 38 |
| MPNST | 3 | 1/2/0 | 2 | 0 | 0 | 0 | 17 |
| Fibro/myo-fibroblastic | 3 | 0/3/0 | 3 | 0 | 0 | 0 | 76 |
| FDCS | 2 | 0/2/0 | 2 | 2 | 0 | 1 | 14 |
| Liposarcoma | 2 | 1/1/0 | 1 | 1 | 0 | 1 | 0.8 |
| Others | 5 | 1/2/2 | 4 | 0 | 1 | 1 | All alive |
| Unclassified | 2 | 2/0/0 | 2 | 0 | 1 | 1 | 8.4 |

Abbreviations: Chemo, chemotherapy; FDCS, follicular dendritic cell carcinoma; LB, lobectomy; MST, median survival time; MPNST, malignant peripheral nerve sheath tumor; PN, pneumonectomy; Postop Radio, postoperative radiotherapy; R0, complete resection; WR, wedge resection.

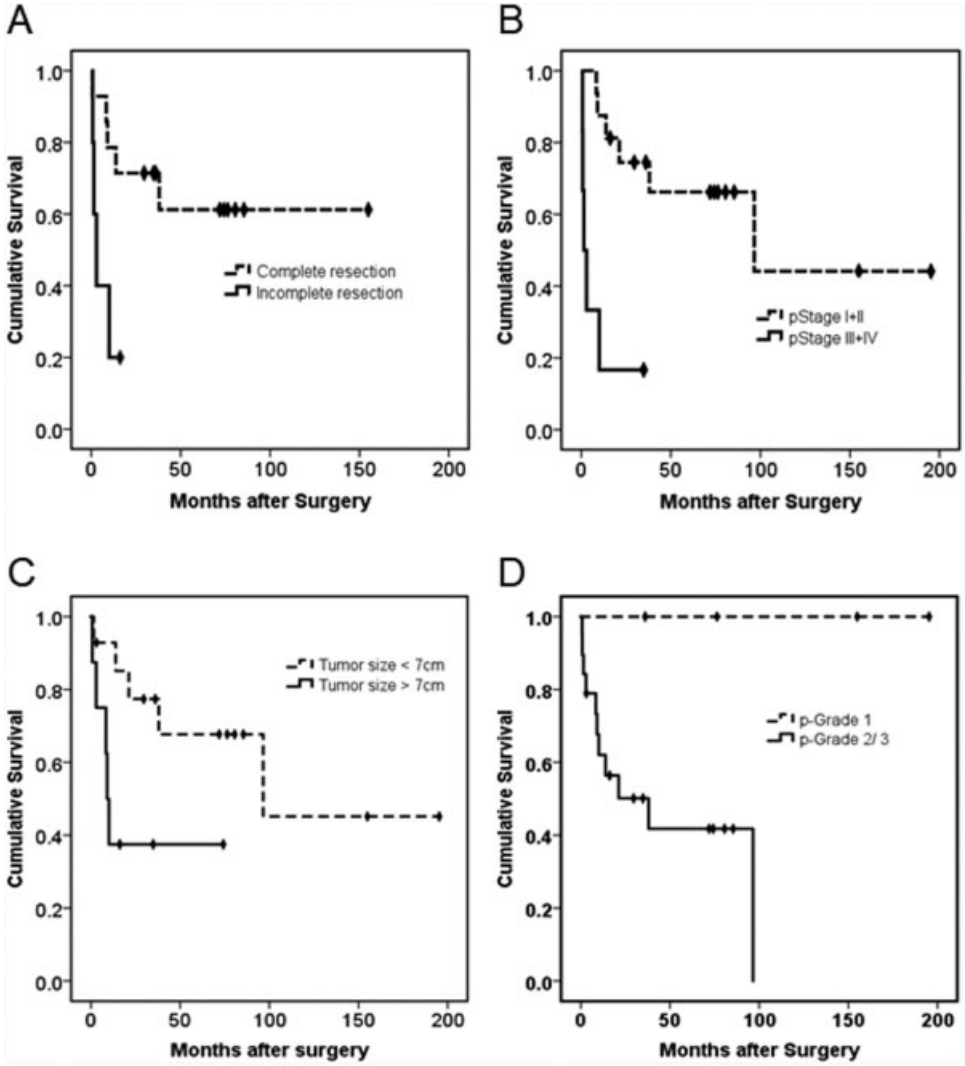


**Fig. 1** Kaplan–Meier curves for overall survival are presented according to (**A**) resection completeness, (**B**) pathological stage (I and II vs. III and IV), (**C**) tumor size ($<7$ vs. $\geq 7$ cm), and (**D**) pathological grade (G1 vs. G2 and G3).

## Case Report

A 48-year-old male ex-smoker (8 pack-years) who had a fever underwent chest X-ray, which showed an abnormal shadow in the left mediastinum. Computed tomography (CT) revealed a poly-lobulated soft tissue mass in the anterior left mediastinum adjacent to the aortic arch, pulmonary artery trunk, proximal left pulmonary arteries, pericardium, and mediastinal fat tissue, with a size of $6.5 \times 3$ cm (►**Fig. 2**). A parasternal biopsy with mini-thoracotomy revealed a high-grade undifferentiated tumor. He received induction chemotherapy with two cycles of cisplatin–etoposide, which resulted in stable disease. Biopsy diagnosis by second opinion suggested epithelioid angiosarcoma. His forced expiratory volume in 1 second was 3.14 L (75%). He underwent a left upper sleeve lobectomy, plasty of the intrapericardial pulmonary artery trunk, en bloc chest wall resection including the second and third ribs, partial resection of the pericardium, mediastinal lymph node dissection, and reconstruction of the chest wall and pericardium. The pathological diagnosis was follicular dendritic cell sarcoma (►**Fig. 3**). Subsequently, he received adjuvant radiotherapy at the tumor site and the mediastinum, with a total dose of 60 Gy. One year after surgical resection, CT scans revealed metastatic lesions in the left thoracic cavity. He underwent a wedge resection in the left lower lobe, and diaphragmatic partial resection and reconstruction. He received another course of postoperative radiotherapy on the left basal costophrenic space, with a total dose of 54 Gy. He is alive without progression of disease at a follow-up of 3 years.

## Discussion

Although a definitive guideline for PPS has not been developed yet, surgical resection is generally regarded as the first choice for resectable disease. Indeed, a retrospective analysis of the Surveillance, Epidemiology, and End Results (SEER) database demonstrated that the 5-year survival of PPS patients was 41% after surgery alone, 25% after surgery and adjuvant radiation, and 7% after radiation alone.[10] However, because of the rareness of this disease, several factors remain to be elucidated, such as causative factors, disease development, metastatic process, prognosis, appropriate treatment, including induction or adjuvant therapy,

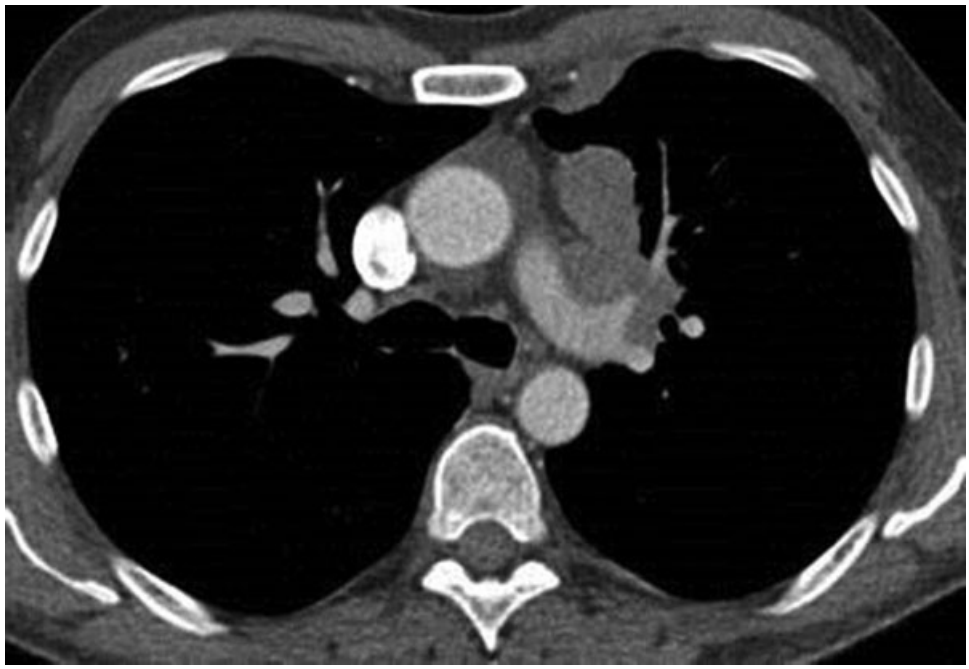

**Fig. 2** A computed tomography axial image from one of our patients showed a poly-lobulated soft tissue mass in the anterior left mediastinum adjacent to the aortic arch, pulmonary artery trunk, proximal left pulmonary arteries, pericardium and mediastinal fat tissue.

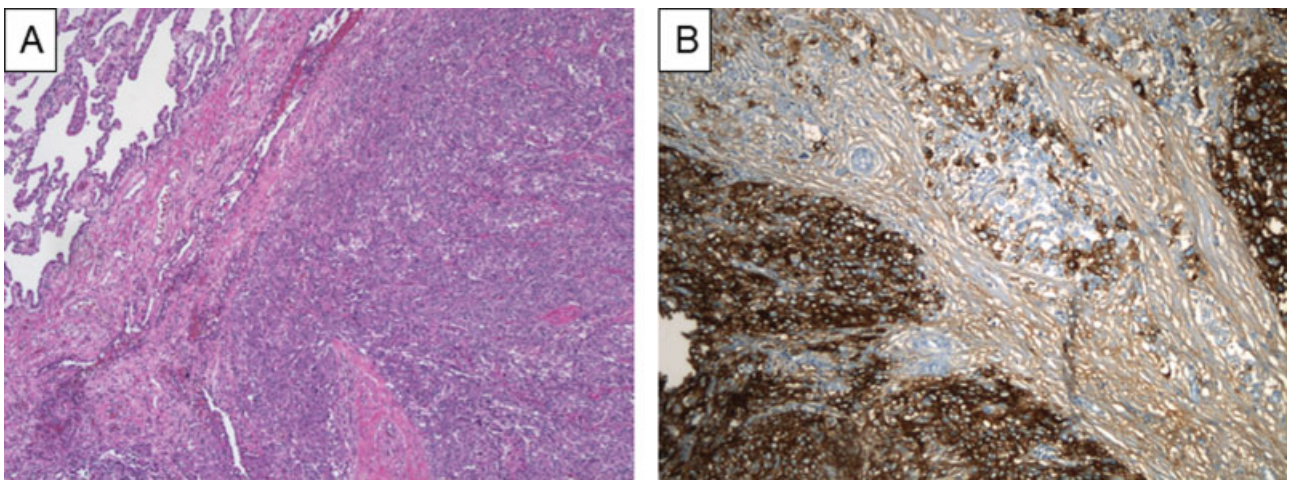


**Fig. 3** (**A**) Proliferating spindle-to-ovoid cells with a variety of growth patterns were observed by hematoxylin and eosin staining (x25). (**B**) Strong CD21 positivity was observed in the tumor cells (x 25).

and relevance of gene mutations. It is, therefore, quite important to accumulate data from case reports of patients with this disease.

This study identified incomplete resection, advanced pathological stage, high pathological grade, and larger tumor size as unfavorable prognostic factors. These results are consistent with previous studies of PPS (►**Table 4**).[4–10] Patients with more advanced disease are expected to have a worse prognosis.

Notably, complete resection is essential for the treatment of PPS. In some advanced cases of the disease, complete resection may be difficult to achieve due to the location of tumor extension. For instance, the rate of complete resection was lower for the angiosarcoma cases in our cohort compared with other types of sarcoma. In the angiosarcoma cases, tumor cells were occasionally found in the vessel stumps. To achieve complete resection, evaluation of tumor extension preoperatively and confirmation of a tumor-free status by frozen-section pathology intraoperatively are necessary, in addition to the requisite surgical technique and experience to perform extended resection.

The current study found that nodal status was not related to prognosis. Our cohort included four cases of lymph node metastasis, all of N1 status. We did not identify any factors related to nodal metastasis. We assume that PPS cells are less likely to migrate via lymphatic vessels. According to the literature, PPS metastasizes primarily via the bloodstream and only rarely via the lymphatic system.[4,14–16] Nevertheless, lymph node dissection should still be performed during PPS surgery to achieve complete resection, because lymph node metastases have been observed occasionally.[6,7,9,10]

**Table 4** Previous studies on surgical cases of primary pulmonary sarcoma

| Author, year | Surgical patients, *n* | Induction therapy, *n* (%) | Adjuvant therapy, *n* (%) | Complete resection, *n* (%) | Recurrence, n (% of R0 patients) | 5 years OS, (%) | Unfavorable overall survival factors |
|---|---|---|---|---|---|---|---|
| Janssen et al 1994[4] | 18 | – | CT 1 (6)<br>RT 2 (11) | 11 (61) | 3 (27) | 44 | Tumor size, p-Grade |
| Bacha et al 1999[5] | 20 | – | CT 11(55)<br>RT 8 (40) | 14 (70) | 0 (0) | 69 | Incomplete resection |
| Régnard et al 1999[6] | 23 | – | CT 5 (22)<br>RT 5 (22)<br>CRT 2 (9) | 20 (87) | 13 (65) | 48 | Incomplete resection, p-Stage |
| Porte et al 2000[7] | 18 | CT 3 (17) | CT 4 (22)<br>RT 2 (11) | 16 (89) | 6 (38) | 43 | p-Stage |
| Etienne-Mastroianni et al 2002[8] | 9 | – | CT 1 (11)<br>RT 2 (22) | 7 (78) | 3 (43) | 38 | |
| Petrov et al 2003[9] | 48 | – | – | 43 (90) | 1 (2) | 49 | p-Stage |
| Spraker et al 2013[10] | 326 | | RT 52 (16) | – | – | 41 | Tumor size, p-Grade, incomplete resection |
| Current study | 24 | CT 3 (13) | CT 4 (17)<br>RT 4 (17) | 16 (67) | 7 (44) | 50 | Tumor size, p-Grade, incomplete resection, p-Stage |

Abbreviations: CRT, chemoradiotherapy; CT, chemotherapy; p-Grade, pathological grade; p-Stage, pathological stage; OS, overall survival; R0, complete resection; RT, radiotherapy.

Multimodal therapy is an important consideration. In thoracic oncological diseases such as lung cancer, mesothelioma, and thymoma, multimodal therapy is an effective addition to surgical resection.[17,18] Furthermore, there is abundant evidence of the effects of multimodal therapy on bone and soft tissue sarcomas. Not only conventional chemotherapies but also molecular targeted therapies have been applied in bone and soft tissue sarcomas.[19,20] Consequently, thoracic clinicians generally share the view that multimodal therapy may also be feasible for PPS. Wu et al presented a patient with hemangiopericytoma who experienced a good response to induction chemotherapy.[21] Porte et al also reported patients preoperatively diagnosed with unresectable PPS who received preoperative chemotherapy and achieved complete resection.[7] Adjuvant chemo- or radiotherapy is also performed for PPS. Régnard et al administered additional therapy to 60% of patients who underwent complete resection for PPS.[6] Other studies also reported high rates of adjuvant therapy administered for PPS.[5,8] Additional therapy has been recommended for PPS cases with higher oncological risks, such as incomplete resection, node-positive disease, invasion to surrounding structures, and tumors with a higher pathological grade or greater size.[5,7,10,22]

Empirically, regimens consisting of doxorubicin and/or ifosfamide are recommended for the additional therapy for PPS. Actually, there is no definite evidence regarding the regimens, but it might be possible to refer to clinical studies for metastatic soft tissue sarcoma. There have been multiple studies showing efficacies of doxorubicin and ifosfamide. Although a phase III trial of the combination revealed no increase in OS, it improved response rates and progression-free survival.[23–27] Lately, olaratumab (a monoclonal antibody directed against platelet-derived growth factor) has been investigated for clinical application. A phase II trial with doxorubicin + olaratumab presented significant improvement in the median OS compared with doxorubicin alone.[28] However, the recent announcement from the phase III trial revealed no significant difference in median OS.[29] It might be necessary to re-establish the strategy with olaratumab, aiming for an appropriate biomarker.[30]

In addition to the conventional cytotoxic agents for malignant diseases, another option of therapy is becoming available due to oncological innovation. Immunotherapy utilizing immune checkpoint inhibitors has yielded significant benefit in a variety of cancers, including metastatic melanoma, non–small-cell lung cancer, and renal cell carcinoma. According to recent preclinical data, there is good evidence to support the use of immunotherapy in sarcoma. In a large analysis of over 2000 sarcomas, more than 50% of all sarcomas displayed expression of PD-L1 with immunohistochemistry.[31,32] Accordingly, there have been several clinical trials using immune checkpoint inhibitors for soft tissue sarcomas.[33–35] However, trials with a single agent found a limited benefit for sarcomas. Alternatively, combination therapies with the agents are undergoing more investigations.[36] Although there have been no reports so far regarding immunotherapy for PPS, future investigations might provide novel insight for the treatment of PPS.

In another point of view, the biological characteristics of this disease differ among the various histological subtypes of PPS. Indeed, the data presented in ►**Table 4** suggest that both the oncological behavior and prognosis vary according to subtype. Consequently, the appropriate combination of treatments, including surgery, radiation, chemotherapy, and immunotherapy, for PPS may depend on the histological subtype. However, a clinical investigation of each subtype demands a large database, as demonstrated by Spraker et al.[10] In that study, they detected the independent risk factors for OS, such as larger tumors, higher tumor grade, and unresectable disease, by multivariate analysis based on data from the SEER database. Further investigation of PPS histological subtypes in terms of multimodal therapy will necessitate the establishment of a larger database.

One of the limitations of this study was the small number of patients. Another was that some of the findings, such as the prognostic factors, have already been presented in previous studies. Nevertheless, we believe that the study possesses certain strengths by some reasons. First, because of the rareness of the disease, it is still important to accumulate cases despite a small cohort. Indeed, our study could corroborate the findings that had been presented by previous studies. Second, because it was a single-center study, all patients were treated in a consistent manner. Third, we were able to review the neoadjuvant/adjuvant therapies administered for PPS, which the SEER database does not cover. Third, although the SEER database contains numerous cases, many clinical issues still require elucidation. To address these questions, implementation of a big-data project is needed to evaluate the clinical characteristics and etiology of each subtype of PPS. Therefore, we deem it important to continue clinical investigations on this disease and accumulate more cases.

In summary, this retrospective analysis of patients with PPS in a single institution showed favorable surgical outcomes. Adverse factors for OS were incomplete resection, advanced pathological stage, higher pathological grade, and tumor size. The variety of characteristics by histological subtype calls for a study with analyses stratified by these subtypes in a larger patient cohort in the future.

Conflict of Interest
None.

Acknowledgment
We thank Prof. Dr. Burkhardt Seifert from the Division of Biostatistics of the University of Zurich for advice on statistical analysis.

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