Interactive CardioVascular and Thoracic Surgery 2022, 35(4), ivac238
https://doi.org/10.1093/icvts/ivac238 Advance Access publication 6 September 2022

**ORIGINAL ARTICLE**



Cite this article as: Pieropan S, Mercier O, Mitilian D, Pradère P, Fabre D, Ion DI *et al.* Feasibility and long-term outcomes of surgery for primary thoracic synovial sarcoma. Interact CardioVasc Thorac Surg 2022; doi:10.1093/icvts/ivac238.

# Feasibility and long-term outcomes of surgery for primary thoracic synovial sarcoma

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Received 15 July 2022; received in revised form 2 September 2022; accepted 6 September 2022

**Key question**

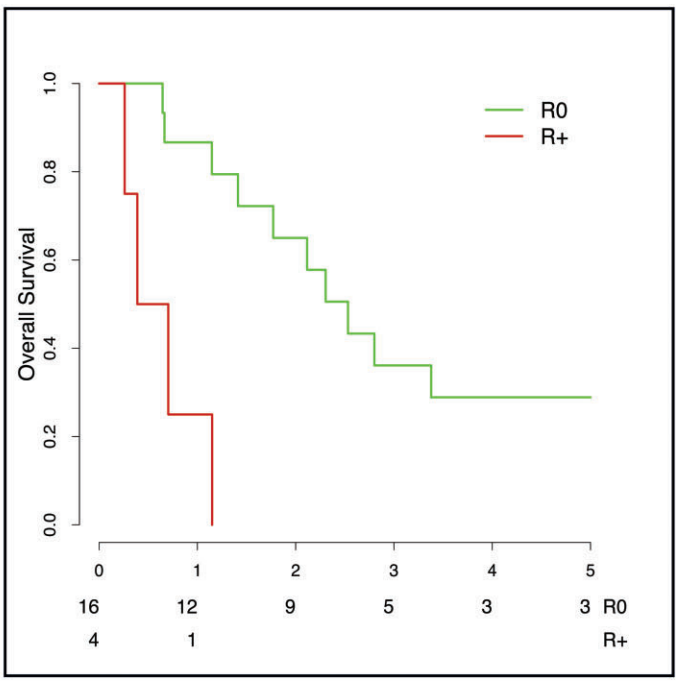
Is surgery for primary thoracic synovial sarcoma feasible and does it provide good survival?

**Key finding(s)**

Surgery might achieve a good survival, provided R0 resection is obtained, with low postoperative morbidity and mortality.

**Take-home message**

In selected patients and for resectable disease, surgery should always be proposed as part of a multimodal strategy.




## Abstract

**OBJECTIVES:** Primary thoracic synovial sarcoma (SS) is a rare, high-grade, malignancy. Involvement of vital organs is frequent and may decrease the benefits of surgical resection. We reviewed our practice at a highly experienced thoracic-surgery centre to assess early- and long-term outcomes after surgery.

**METHODS:** We conducted a retrospective, observational, single-centre study of patients undergoing curative-intent surgery for primary thoracic SS between 1 January 2000 and 31 January 2021 as part of a multidisciplinary management. We assessed demographics, medical history, histopathology and follow-up information.

**RESULTS:** We enrolled 20 patients (13 males) with a median age of 40 years old and a median tumour size of 11 cm. Neoadjuvant chemotherapy was administered to 13 patients. Surgery consisted in extrapleural pneumonectomy ($n = 7$), extrapleural lobectomy ($n = 5$), chest wall resection ($n = 4$) or tumour resection ($n = 4$). R0 resection was achieved in 16 (80%) patients. Adjuvant therapy was given to 13 patients. 6 patients developed postoperative complications. The median hospital stay was 11.5 days. Overall survival at 2 and 5 years was 51% and 22%, respectively; median overall survival was 25 months and median disease-free survival was 8.5 months. Relapses occurred in 15 patients. By univariate analysis, incomplete resection was the only significant predictor of survival ($P = 0.01$).

**CONCLUSIONS:** Primary thoracic SS is an aggressive disease. Surgery included in a multimodal treatment may contribute to achieving a good outcome, providing that an R0 resection is obtained. Given the considerable technical challenges of surgery, patient selection and referral to an experienced centre are crucial to minimize morbidity and mortality.

**Keywords:** Primary thoracic synovial sarcoma • Surgical treatment • Feasibility

**ABBREVIATIONS**

| | |
|---|---|
| CT | Computed tomography |
| DFS | Disease-free survival |
| EPP | Extrapleural pneumonectomy |
| ICU | Intensive care unit |
| MDT | Multidisciplinary team |
| OS | Overall survival |
| PTSS | Primary thoracic synovial sarcoma |
| SS | Synovial sarcoma |

## INTRODUCTION

Synovial sarcoma (SS) accounts for only 5–10% of all soft tissue sarcomas [1] and usually develops in the extremities. SS is a high-grade malignancy classified as a mesenchymal spindle-cell tumour of uncertain differentiation [2] and is characterized in over 90% of the cases by the t(X; 18) (p11; q11) translocation, which is pathognomonic [3, 4]. Primary thoracic SS (PTSS) is extremely rare, contributing to 4–14% of all SSs, and mostly affects adults in the third and fourth decades [5].

The treatment of SS is frequently multimodal. Neoadjuvant chemotherapy is recommended for non-resectable disease, while adjuvant chemotherapy may be administered to high-risk patients [6, 7]. Surgical resection should be considered in all patients with localized SS [8]. However, because of the potential involvement of vital organs and need for extensive resection, surgery can be very demanding and may be followed by major complications [9]. If resection is incomplete, adjuvant radiotherapy should be given to improve local control [8].

Five-year overall survival (OS) of patients with SS arising from any site ranges from 52% to 66% [10]. However, location within the thorax is associated with a far poorer prognosis, with only 30% of patients being alive 5 years after surgery [3, 11].

As PTSS is rare, experience on treatment, notably surgery, is limited. Only case reports and small cohort studies are available [9, 12], and data on early- and long-term outcomes are particularly scarce.

The primary aim of our study was to evaluate OS in patients undergoing curative-intent surgery for PTSS. The secondary aims were to assess the feasibility of surgery based on the hospital stay duration, postoperative complications and 30-day mortality and to determine disease-free survival (DFS).

## PATIENTS AND METHODS

We conducted a retrospective, single-centre study of consecutive patients who underwent curative-intent surgery for PTSS between 1 January 2000 and 31 January 2021 at our thoracic surgery department. Patients were identified by searching the histopathology laboratory database. We excluded patients with thoracic metastasis of a primary SS of another site and patients who underwent only diagnostic procedures or first surgical treatment at another institution.

We collected demographics, preoperative data (risk factors, comorbidities, clinical and radiological presentation, preoperative histological diagnosis, neoadjuvant therapy and functional preoperative evaluation), details on the surgical procedure, postoperative data [intensive care unit (ICU) admission, mechanical ventilation duration, postoperative complications classified according to Clavien–Dindo [13] and hospital stay length] and follow-up data (relapses and subsequent treatments, vital status at last follow-up and cause of death).

As our centre is exclusively surgical, follow-up was not performed in our hospital. For the purpose of the study, we collected information on follow-up by a combination of contact with patients or primary physicians and oncologists and data linkage to a national death register. We did not have any missing data.

R software version 4.1.0 was used for the statistical analysis (http://www.cran.r-project.org/doc/FAQ/R-FAQ.html#Citing-R). Data were described as the median [interquartile range] or absolute frequency (percentage). Kaplan–Meier plots were used to describe OS and DFS. Cox regression was chosen for the univariate analysis to identify factors associated with outcomes. Comparing the results with the log-rank test, we did not find any difference between the 2 methods. As the sample size is small, we did not perform a competing risk analysis nor a multivariable analysis as they would not have a statistical power. *P*-Values smaller than 0.05 were considered statistically significant.

The study protocol was approved by the ethics committee of the French society for cardiovascular and thoracic surgery (*Société Française de Chirurgie Thoracique et Cardio-Vasculaire*, CERC-SFCTCV-2021-02-22). In keeping with French law about

retrospective studies of anonymized patient data, informed consent was not required.

## RESULTS

Through the histopathology database, we identified 65 patients. Twenty patients met our selection criteria (Fig. 1). In 17 cases, the diagnosis was confirmed by identification of the t(X; 18) translocation. In the remaining 3 patients, tissue alterations by the fixative precluded fluorescence in situ hybridization, but the diagnosis was confirmed by retrospective review of the slides by expert histopathologists.

13 patients were males and 7 females, the median age was 40 [28–54] years old. 16 patients had no history of major comorbidities at the diagnosis, one patient had atrial fibrillation, 1 chronic obstructive pulmonary disease, 1 diabetes and 1 a history of breast cancer treated by radiotherapy on the same side of the PTSS. Nine (45%) patients had a history of smoking.

The tumour was symptomatic in 18 patients, causing chest pain ($n = 11$), dyspnoea ($n = 5$), haemoptysis ($n = 3$), cough ($n = 3$), dysphagia ($n = 2$), thoracic bulge ($n = 1$) and/or arm swelling ($n = 1$). In 2 cases, the diagnosis was incidental.

The initial tumour was pleuropulmonary in 11 patients (55%), some of which had a chest wall infiltration. Other locations were the mediastinum ($n = 4$), chest wall ($n = 4$) and trachea ($n = 1$). The median tumour diameter was 11 [8–15] cm.

Preoperative diagnosis was obtained in 18 patients, by computed tomography (CT)-guided percutaneous biopsy ($n = 10$) or surgical biopsy ($n = 8$). The histopathological diagnosis was SS in 12 patients, sarcoma other than SS in 4 patients and undetermined malignancy in 2 patients.

Neoadjuvant treatment, consisting of 4–6 cycles of chemotherapy, was given to 13 patients. Surgery consisted of extrapleural pneumonectomy (EPP) ($n = 7$), extrapleural lobectomy ($n = 5$), chest wall resection ($n = 4$) and tumour-mass resection ($n = 4$). Surgery was performed by excising the tumour *en bloc* with all the structures and/or tissues macroscopically infiltrated. For chest wall resections, a macroscopical margin of at least 3 cm was considered safe for complete resection. If a preoperative biopsy was performed, the biopsy tract and the scar were safely removed.

All patients underwent surgery by an open approach. EPP, extrapleural lobectomies and posterior mediastinum resections were performed by a posterolateral thoracotomy. EPP was systematically associated with a diaphragm resection and reconstruction with a Goretex mesh as well as a pericardium resection and reconstruction with a Vycril mesh (Fig. 2). In the extrapleural lobectomy, as the tumour was adherent to the chest wall, the parietal pleura was excised *en bloc*.

An anterior transclavicular approach was preferred for tumours involving the apex, as it allowed optimal control of the vascular and nervous structures of the thoracic inlet. Because of the number of resected ribs (maximum 4 ribs) and the location of the chest wall defect, chest wall resections did not need reconstruction. The only case requiring osteosynthesis was a sternal resection. Reconstruction was made with 3 Titanium bars and a Goretex mesh.

Histopathological examination showed a complete resection (R0) in 16 patients. R1 was found in 3 patients:

- In a right EPP with chest wall resection, R1 was detected on a chest wall nodule and on the superior pulmonary vein.
- In a right EPP, the resection appeared to be R1 on the pulmonary artery.
- In the resection of a posterior mediastinal tumour, R1 was found on the aortic and the oesophageal adventitia.

A macroscopic incomplete resection (R2) was found in a patient who underwent a resection of a posterior mediastinal mass.

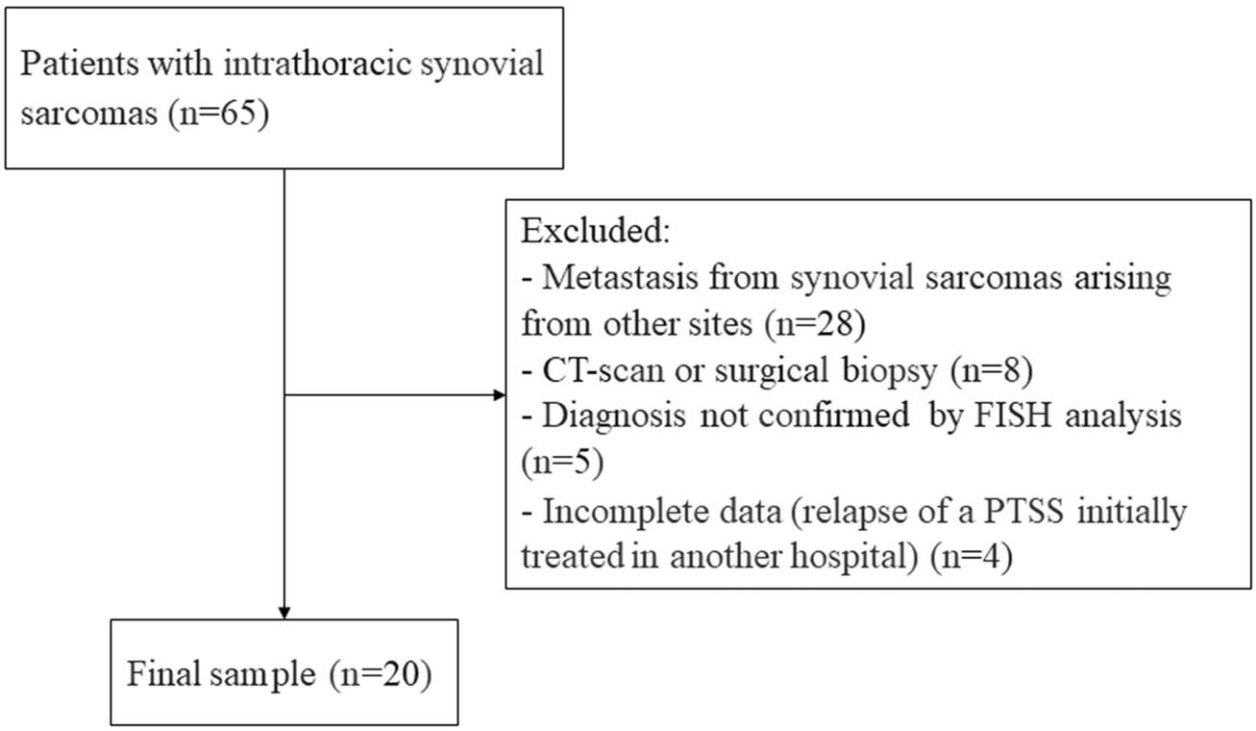



**Figure 1:** Patients' selection flow chart.

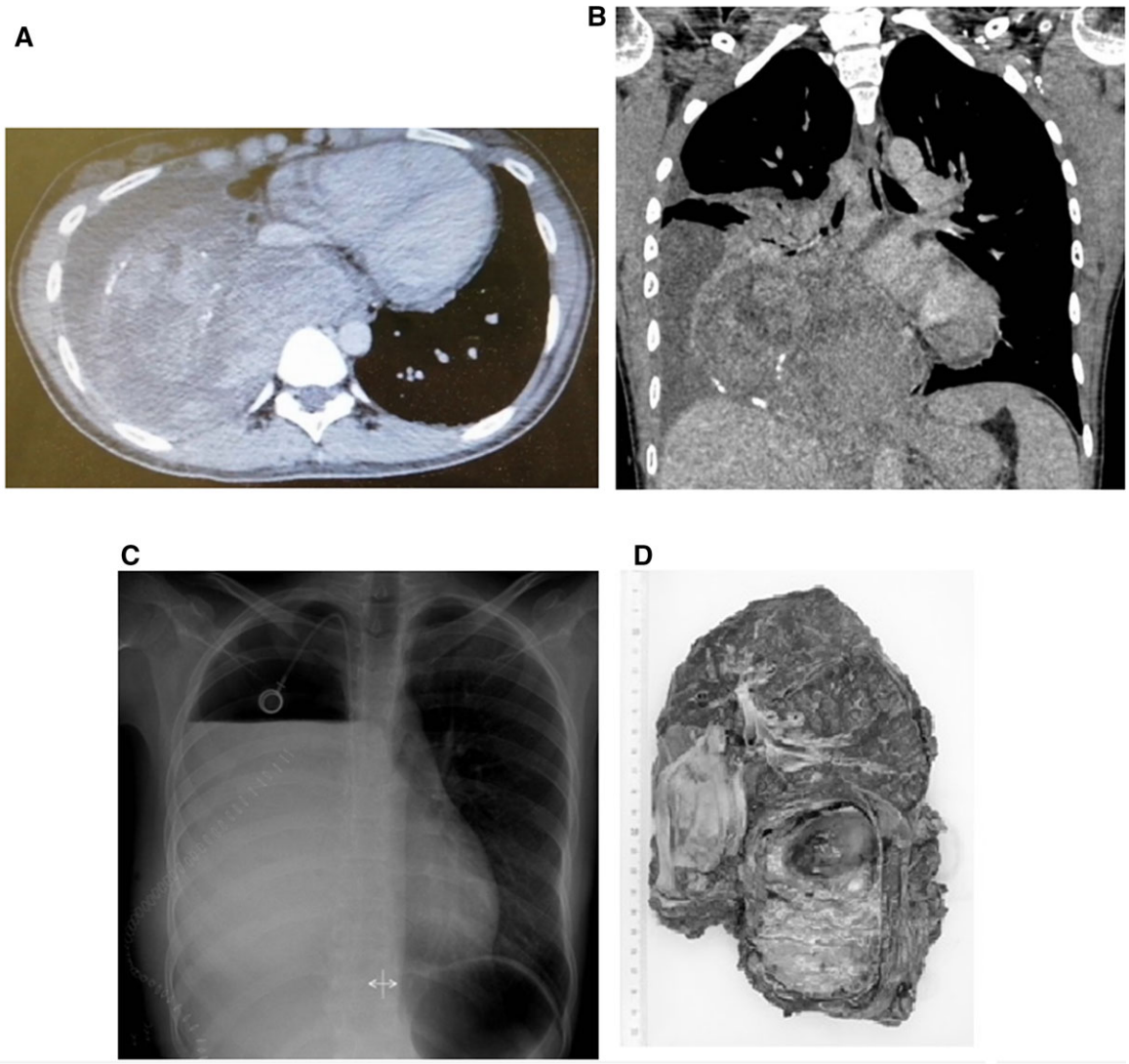



**Figure 2:** Example of a patient with a pulmonary and pleural tumour. (**A** and **B**) Twenty-six-year-old female with a 10 cm × 12 cm × 12 cm right intrathoracic mass, pleural lesions and a pleural effusion. (**C**) She had a partial response to 5 chemotherapy cycles then underwent a right EPP. The postoperative course was uneventful. (**D**) Operative specimen: histology showed an R0 resection of a biphasic synovial sarcoma that measured 10.5 cm × 7.5 cm × 3 cm and partially infiltrated the diaphragm; the tumour contained a necrotic haemorrhagic component, cystic areas and microcalcifications.

R2 was confirmed on the specimen in multiple intra-pericardiac zones.

Seven patients required ICU admission with a median ICU stay of 4 days. Only 1 patient required postoperative mechanical ventilation. The median hospital stay was 11.5 [8–14] days.

Postoperative complications occurred in 6 patients, some of whom experienced >1 complication. They are summarized in Table 1. No patients died within 30 days after surgery.

Adjuvant treatment was given to 13 patients: 11 received radiotherapy and 2 received chemotherapy. Globally, 11 patients received both neoadjuvant chemotherapy and adjuvant radiotherapy, 2 only neoadjuvant chemotherapy, 2 only adjuvant chemotherapy and 5 only surgical treatment.

A local recurrence was diagnosed in 15 patients, of whom only 1 also had a distant metastasis (liver). Recurrences were treated by chemotherapy in 7 patients, and pazopanib in 2 patients. Three patients received palliative care. Surgery was performed in 2 patients. Unfortunately, in both cases, the resection was incomplete (R1). One of the patients received second-line chemotherapy and died 1 year after the second surgery, and the other received chemotherapy and radiotherapy and died 2.5 years after the second surgery.

Two- and five-year OS was 51% and 22%, respectively (Fig. 3). The median OS was 25 months. Two-year DFS was 24% (Fig. 4), with a median of 8.5 months. All patients presenting a recurrence died from the disease. In the 16 patients with R0 resection margins, 5-year OS and DFS were both 29%. Five patients were still alive at the time of the last follow-up with no evidence of disease. Three of them had long follow-ups of 10, 11 and 18 years, with a median follow-up of 127 months.

By the univariate analysis, incomplete resection was the only variable significantly associated with lower OS ($P = 0.01$) (Fig. 5). Age, tumour size, additional treatment (either neoadjuvant or adjuvant or both) and type of surgery did not appear to influence survival (Table 2).

**Table 1:** Postoperative complications, according to the Clavien–Dindo classification

| Grade of complication | Number of events and type of complication | Treatment |
|---|---|---|
| I | 0 | – |
| II | • Pleural or pericardial bleeding in 2 patients<br>• Acute pulmonary ooedema and gastric ulcer in 1 patient | • Blood cell transfusion<br>• Medical treatment |
| IIIa<br>IIIb | • Delayed pneumothorax in 1 patient, prolonged air leak in 1 patient<br>• Bronchial obstruction by secretions in 1 patient<br>• Haemothorax in 1 patient | • Chest drainage<br>• Bronchoscopy<br>• Surgery |
| IV | 0 | – |
| V | 0 | – |

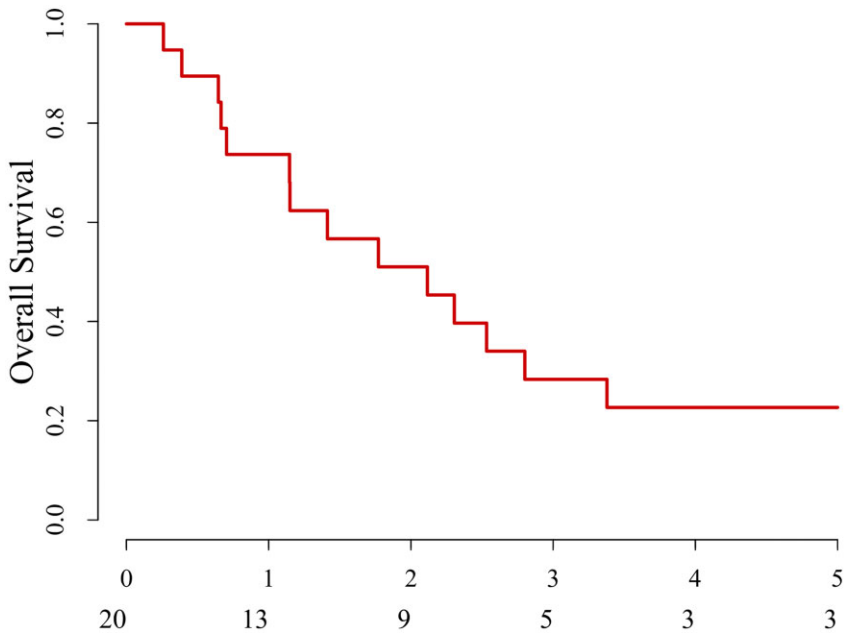



**Figure 3:** Kaplan–Meier estimate of overall survival after the diagnosis of primary thoracic synovial sarcoma.

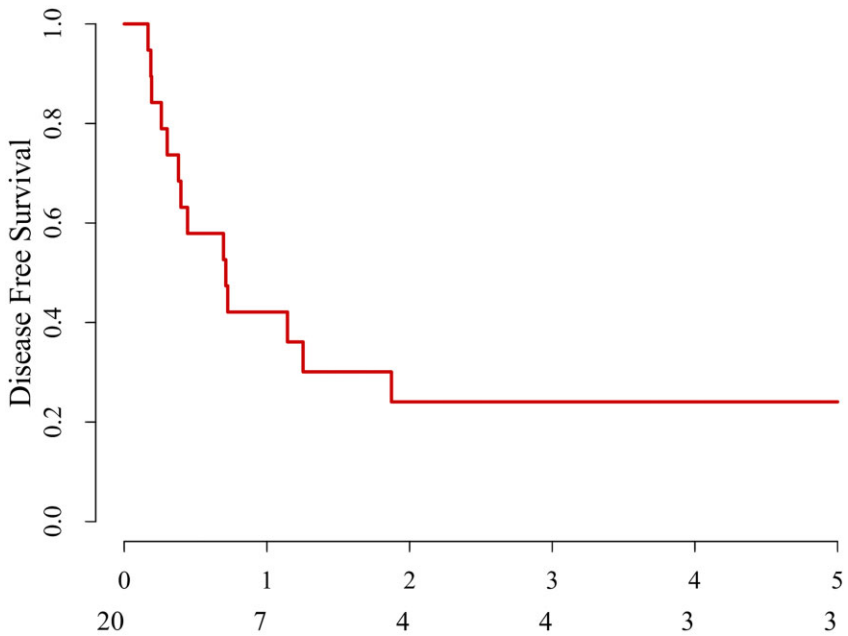



**Figure 4:** Kaplan–Meier estimate of disease-free survival after the diagnosis of primary thoracic synovial sarcoma.

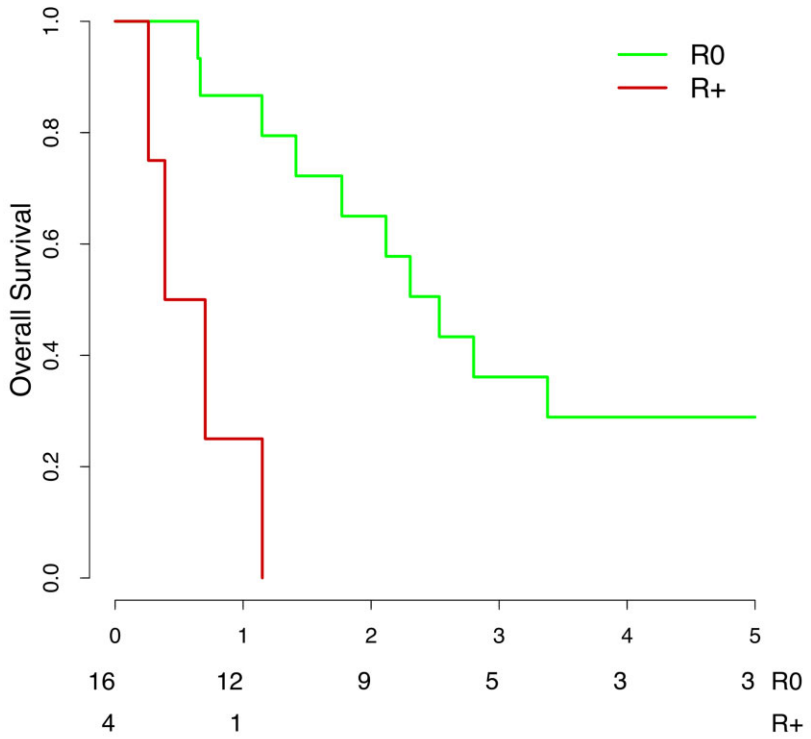



**Figure 5:** Kaplan–Meier estimate of overall survival after the diagnosis in the groups with tumour-free resection margins (R0) versus contaminated resection margins (R+).

**Table 2:** Univariate analysis to identify factors associated with overall survival

| Factors | *N* (%) | Hazard ratio | 95% CI | *P*-Value |
|---|---|---|---|---|
| Age | Not applicable | 1.02 | 0.99–1.06 | 0.07 |
| Tumour size | | | | |
| <11 cm | 10 (50) | Ref | | |
| >11 cm | 10 (50) | 0.44 | 0.28–2.68 | 0.16 |
| Neoadjuvant treatment | | | | |
| No | 7 (35) | Ref | | |
| Yes | 13 (65) | 0.86 | 0.39–0.56 | 0.80 |
| Adjuvant treatment | | | | |
| No | 7 (35) | Ref | | |
| Yes | 13 (65) | 1.17 | 0.39–3.56 | 0.77 |
| Type of surgery | | | | |
| Other than EPP | 13 (65) | Ref | | |
| EPP | 7 (35) | 1.53 | 0.47–4.92 | 0.48 |
| Resection margins | | | | |
| R0 | 16 (80) | Ref | | |
| R1 and R2 | 4 (20) | 0.14 | 0.03–0.62 | 0.01 |

CI: confidence interval; EPP: extrapleural pneumonectomy; Ref: reference value.

## DISCUSSION

PTSS is a very rare malignancy, and surgically resectable patients represent an even smaller subgroup of PTSS patients. In the current study, we found that in highly selected patients, surgery included in a multimodal strategy might contribute to achieve a good survival. The main determinant to obtain this result was complete resection without perioperative mortality, underlining the importance of performing these procedures in expert thoracic surgical centres.

The median age of 40 years old in our population is consistent with earlier reports, while the predominance of males in our study contrasts with the usually more even sex distribution in previous works [14, 15]. Also, in keeping with published data, the symptoms were not specific and consisted chiefly of chest pain, dyspnoea, cough or haemoptysis [16, 17]. PTSS is typically diagnosed as a large mass, with a median diameter of 11 cm in our cohort and up to 13 cm in earlier studies [18].

As indicated in the ESMO-EURACAN guidelines, clinical staging should be completed by a CT scan of the abdomen and pelvis. Imaging of the brain is not standard for SS and should be performed based on the clinical presentation. Fluorodeoxyglucose positron emission tomography scan may be reserved for characterizing equivocal CT findings such as lymph node involvement [8]. In our series, the clinical staging was achieved by performing either a fluorodeoxyglucose positron emission tomography scan or a total body CT scan. Further examinations, such as a flexible bronchoscopy, a thoracic magnetic resonance imaging or a gastroscopy were performed in specific cases.

Preoperative histopathological diagnosis should be sought routinely to guide treatment decisions [19]. In our cohort, the presence of a malignancy was established in 90% of patients, but the diagnosis of SS was made in only 67%, illustrating the challenges raised by the differential diagnosis. Difficult cases must therefore be referred to specialized centres to ensure correct diagnosis. In our study, three cases needed confirmation of the diagnosis by our expert pathologists, who belong to the French soft tissue and visceral sarcoma pathology review network (RRePS).

The variability in treatment strategies in our cohort reflects the absence of consensus regarding the optimal management of PTSS. Induction chemotherapy was proposed when the tumour was not eligible for R0 resection, with the aim of obtaining a tumour shrinkage. However, the topic of neoadjuvant chemotherapy in soft tissue sarcoma remains controversial. Several ongoing trials are trying to address this question (NCT04307277 and NCT03805022).

Adjuvant chemotherapy was considered in patients aged <40 years and able to tolerate doxorubicin and/or ifosfamide and those with R1 resection [20].

In our series, 5 patients had a resectable disease at diagnosis and did not have the criteria for adjuvant therapy; therefore, they received an exclusive surgical treatment. It is important to underline that every decision of the treatment process was taken through a multidisciplinary team (MDT) dedicated to sarcoma and discussed with the patients.

The importance of MDT management has been widely established, notably for rare malignancies [21]. Recently, He *et al.* [11] published a study on the impact of MDT management for PTSS. Although MDT discussion was not independently associated with outcomes, the median OS of patients managed by an MDT was longer than that of patients who were not (46.0 vs 18.0 months). At our institution, the MDT included experts from national referral centres for sarcoma and thoracic surgery.

Surgery should be considered part of the multimodal treatment of PTSS. However, due to the aggressiveness of PTSS and possible infiltration of vital organs, surgery is often very demanding. Morbidity and mortality in nowadays oncological thoracic surgery have been widely investigated. The 30-day mortality rates and the postoperative complication rates for pneumonectomy range from 4% to 7% and 20% to 40%, respectively [22]. Turbendian *et al.* [23] described a morbidity of 37% and a mortality of 6% in patients undergoing surgery for mediastinal sarcomas. The only previous study detailing postoperative complications for PTSS had 15 patients, of whom 1 (6.6%) died postoperatively, 3 had major complications requiring reoperation and 5 had minor complications. [9]. The lower complication rates in our cohort may be explained by the high selection of patients and the expertise of the surgical team.

Referral of patients to tertiary-care centres with high thoracic-surgery volumes and considerable experience in performing complex procedures is crucial to minimize morbidity and mortality. An extensive body of literature has emphasized the impact of institutional and surgeon experience on outcomes. However, studies about lung resection surgery have shown conflicting results. An analysis of a large database found that lung cancer resection volume did not predict mortality [24]. Nevertheless, when analyzing more complex procedures such as pneumonectomies, surgery performed in high-volume centres seems to be associated with reduced odds of mortality and lower rates of failure to rescue after postoperative complications [25].

The poor prognosis of PTSS is well documented. A literature review of 15 clinical trials on chemotherapy as first-line treatment for locally advanced and metastatic SS showed an OS of 15 months and a progression-free survival of 6.3 months [26]. In our cohort, the median OS was 25 months, and OS at 2 and 5 years was 51% and 22%, respectively. Comparisons with earlier studies are difficult due to the variability in data-reporting methods, incomplete follow-up information and probable differences in patient selection for surgery [27, 28]. Table 3, summarizing previously reported long-term outcomes, shows similar OS to ours in some studies [9, 29] and better OS in others [3, 18]. The high frequency of recurrence shortly after surgery in our cohort is consistent with earlier data [30].

Nonetheless, long survivals have been achieved. In our series, 3 patients were alive 10, 11 and 18 years after initial surgery. Similarly, in his series of 25 patients, Zeren *et al.* [17] reported 3 long survivors, with an OS between 12 and 16 years.

However, no factors associated with long-term survival have been identified [4, 5, 18]. Age, sex, tumour size, preoperative and postoperative treatments, histological subtype, SSX-SS18 fusion type, Ki-67 expression and mitotic rate were prognostic factors for survival in some studies but not in others. In our study, the only factor significantly associated with OS by univariate analysis was incomplete resection, which was also consistently significant in other studies [9, 14]. More specifically, when analyzing the R0 patients' subgroup, we found the same 5-year OS and DFS of 29%, which supports the conclusion that we should strive for an R0 resection, even if it can be very demanding, as it is the only factor that seems to make a difference in the outcome of these patients.

## Limitations

A major limitation of our study is the retrospective design and the absence of a control group. Moreover, the high patients' selection and the single-centre recruitment may have induced selection bias. As our institution is a purely surgical centre and does not have an oncological department, we did not have a group of patients undergoing medical treatment or palliative care to compare to our series.

Another major limitation is represented by the small sample size, which mainly depends on the rarity of this disease, thus precluding a multivariable analysis and limiting difference detection and results' interpretation. Randomized trials comparing surgery to other treatments would be unethical, and multicentre observational studies in larger populations are therefore needed to provide more reliable results for the diagnosis and treatment of PTSS. Molecular targeted therapies and immunological strategies are under investigation, and trials evaluating genomic features as potential predictive markers are ongoing and may improve outcomes in the near future.

## CONCLUSION

In conclusion, in patients with resectable PTSS, surgery as part of a multimodal strategy may contribute to achieve a good survival, provided R0 resection is obtained. Given the considerable technical challenges raised by complete PTSS resection, it is of utmost importance that patients are carefully selected and treated in experienced tertiary referral centres to minimize morbidity and mortality.

**Table 3:** Cohort studies on the treatment and long-term outcomes of primary thoracic synovial sarcoma

| Author, year of publication | Sample size | Treatment | R0 | FU available information (% of patients) | OS | DFS and information on recurrence |
|---|---|---|---|---|---|---|
| Zeren *et al.*, 1995 | 25 | 100% surgery | NR | 72% | 40% died of disease within 1–7 years<br>16% died of unrelated causes | 16% alive with disease, 16% alive without disease after 2–20 years |
| Gartner *et al.*, 1996 | 5 | 100% surgery | NR | 100% | 80% died within 3 years | NR |
| Aubry *et al.*, 2001 | 5 | 100% surgery | 100% | 80% | 100% (median FU 9 months) | 100% |
| Essary *et al.*, 2001 | 12 | 8% NR<br>92% surgery | NR | 100% | 2.5-Year OS 58% | 2-Year DFS 25% |
| Duran-Mendicuti *et al.*, 2003 | 5 | 100% surgery | 100% | 100% | Median OS 22 months | 80% recurrence at 2–14 months |
| Okamoto *et al.*, 2004 | 11 | 10% NR<br>90% surgery | NR | 91% | 50% died of disease within 1–9 years | 60% recurrence |
| Begueret *et al.*, 2005 | 40 | 10% NR<br>82% surgery<br>8% CT ± RT | NR | 83% | 2-Year DSS 65.3%<br>5-Year DSS 31.6% | Median DFS 43 months |
| Suster *et al.*, 2005 | 15 | 80% surgery<br>20% RT | 83% | 40% | NR | 80% had recurrence 1–3 years after diagnosis |
| Hartel *et al.*, 2007 | 60 | 8% NR<br>68% surgery<br>23% other treatment | NR | 90%<br>63% information on recurrence | 48% died at a mean of 23 months<br>46% died within 5 years | 18% had local recurrence<br>Mean DFS 17 months |
| Galetta *et al.*, 2013 | 15 | 100% surgery | 60% | 100% | Median OS 27 months<br>10-Year OS 33.5% | 75% recurrence<br>5-Year DFS 30%, median 15 months |
| Kim *et al.*, 2015 | 14 | 7% NR<br>64% surgery<br>28% CT ± RT | NR | 93% | 21.4% died | 57% recurrence<br>2-Year DFS 35.7% |
| Lan *et al.*, 2016 | 26 | 77% surgery<br>12% CT<br>13% supportive care | NR | 73% | Median DSS 14.5 months<br>2-Year DSS 27.7% | Median DFS in surgical patients 8.5 months |
| Terra *et al.*, 2018 | 21 | 52% NR<br>43% surgery<br>5% CT + RT | NR | 74% | 69% died of disease within 5–32 months<br>24% alive with disease at 6–45 months | 88% recurrence |
| He *et al.*, 2021 | 13 | 77% surgery<br>23% CT ± RT | NR | 100% | 2-Year OS 58,3%<br>5-Year OS 30% | Median DFS 13 months |
| Present study | 20 | 100% surgery | 80% | 100% | Median OS 25 months<br>2-Year OS 51%<br>5-Year OS 22% | Median DFS 8.5 months<br>2-Year OS 24% |

CT: chemotherapy; DFS: disease-free survival; DSS: disease-specific survival; FU: follow-up; NR: not reported; OS: overall survival; R0: complete resection; RT: radiotherapy.

## Funding

The authors received no financial support for the research, authorship and/or publication of this article.

**Conflict of interest:** none declared.

## Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

## Author contributions

**Sara Pieropan**: Conceptualization; Formal analysis; Investigation; Writing—original draft; Writing—review & editing. **Olaf Mercier**: Conceptualization; Supervision. **Delphine Mitilian**: Conceptualization; Supervision. **Pauline Pradère**: Resources; Supervision. **Dominique Fabre**: Conceptualization; Supervision. **Daniela Iolanda Ion**: Resources; Supervision. **Olivier Mir**: Investigation; Writing—review & editing. **Barbara Galbardi**: Data curation; Formal analysis; Methodology. **Vincent Thomas De Montpreville**: Investigation; Writing—review & editing. **Elie Fadel**: Conceptualization; Validation; Writing—review & editing.

## Reviewer information

Interactive CardioVascular and Thoracic Surgery thanks Petre Vlah-Horea Botianu, Abdullah Erdogan, Monica Casiraghi and the other, anonymous reviewer(s) for their contribution to the peer review process of this article.

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