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Extrapleural pneumonectomy for sarcoma: outcomes of adult patients at a specialized center and literature review.

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Abstract

Background: Extrapleural pneumonectomy (EPP) is a complex surgical procedure involving en-bloc resection of the parietal and visceral pleura, lung, pericardium, and ipsilateral diaphragm. Small case series of pleural-based sarcoma of predominantly paediatric patients suggest EPP may be a life-prolonging surgical option. We aimed to describe the characteristics and outcomes of adults who underwent EPP at a specialized sarcoma center. Methods: Clinicopathologic variables, surgical details and follow-up information were extracted for eight patients undergoing EPP for pleural-based sarcoma between 2017-2020. Primary outcomes were event-free survival (EFS) and overall survival (OS) from the date of EPP. Secondary outcomes were disease-free interval (DFI) prior to EPP, and early and late postoperative complications. Results: At median follow-up of 22.5 months, median EFS was 6.0 months and OS was 20.7 months. Six patients had disease recurrence; five patients died of progressive disease. Two patients had not recurred: one died of a radiation-related esophageal rupture, and one was alive with no evidence of disease at 37.0 months. Characteristics of those with the longest EFS included low-grade histology and achieving a metabolic response to preoperative chemotherapy. Early postoperative complications included one ventilator-associated pneumonia with new-onset atrial fibrillation and two cases of hydropneumothorax. Late surgical complications included a case of infective endocarditis and septic shock. Conclusions: In adult sarcoma patients, EPP is rarely curative but appears to be a feasible salvage procedure when performed at specialized centers. Patient selection is critical, with a strong consideration for multimodal treatment to optimize oncological outcomes.

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Results: At median follow-up of 22.5 months, median EFS was 6.0 months and OS was 20.7 months. Six patients had disease recurrence; five patients died of progressive disease. Two patients had not recurred: one died of a radiation-related esophageal rupture, and one was alive with no evidence of disease at 37.0 months. Characteristics of those with the longest EFS included low-grade histology and achieving a metabolic response to preoperative chemotherapy. Early postoperative complications included one ventilator-associated pneumonia with new-onset atrial fibrillation and two cases of hydropneumothorax. Late surgical complications included a case of infective endocarditis and septic shock.

Conclusions: In adult sarcoma patients, EPP is rarely curative but appears to be a feasible salvage procedure when performed at specialized centers. Patient selection is critical, with a strong consideration for multimodal treatment to optimize oncological outcomes.

Abstract word count: 244 words

Introduction

Sarcomas in adults are rare, with an incidence of less than 6 per 100,000 per year (1) and primary pulmonary sarcomas are estimated to account for 0.4% to 1.1% of all thoracic malignancies (2). Patients with pleural-based sarcomas, whether found at initial diagnosis or disease recurrence, are challenging to manage and have a poor prognosis with five-year overall survival (OS) of 43-60% (2,3). A radical operation, such as extrapleural pneumonectomy (EPP), can be considered as part of a multimodal therapeutic approach in conjunction with chemotherapy and/or radiotherapy (RT) to obtain long-term disease control in such patients (4). EPP is a complex procedure and consists of en-bloc resection of the parietal and visceral pleura, lung, pericardium and

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ipsilateral diaphragm (4). First described in 1949 for the management of pulmonary tuberculosis, experience with EPP has been chiefly gained in the management of pleural mesothelioma and more recently, for select patients with thymomas, advanced non-small cell lung cancers and sarcomas (3,5,6). Due to the potential for high morbidity, EPP for any tumor type should always be performed by an experienced cardiothoracic team in a high-volume thoracic surgery center (7). Given the rarity of pleural-based sarcoma, literature on outcomes following EPP is sparse and no prospective studies exist. Small, predominantly pediatric case series have reported the outcomes of EPP for the management of pleural-based sarcoma either as treatment for the primary disease or as salvage treatment of sarcoma recurrent to the pleura or lung, and the authors suggest that EPP is a feasible and life-prolonging procedure in selected patients in combination with chemotherapy and radiation (7,8). For this study, we aimed to determine the characteristics and disease outcomes of adult patients who underwent EPP at a tertiary, high-volume cardiothoracic center co-located with a specialized sarcoma center in Sydney, Australia.

Methods

A retrospective chart review was performed on all patients with pleural-based sarcoma who underwent EPP between 2017 and 2020 at the Chris O'Brien Lifehouse / Royal Prince Alfred Hospital sarcoma unit. Patients were identified by review of a prospective database. All patients were discussed at multidisciplinary tumor board. The decision to administer perioperative systemic therapy was individualized and based on tumor chemosensitivity, prior treatment received, patient fitness and preference. The decision to deliver radiation was based on radiosensitivity, margin status and tumor grade.

Patient demographics, histological subtype, treatment and outcome details, and complications were extracted from electronic medical records. The primary outcomes were event-free survival (EFS) and OS. Secondary outcomes were disease-free interval (DFI) prior to EPP and early ([?] 30 days) and late ($>$ 30 days) postoperative complications. EFS was defined as the interval between the date of EPP and the date of the first event, defined as disease recurrence (local or metastatic) or death. OS was defined as the interval from EPP until death from any cause. Patients were censored at the date of the last follow-up. In patients who underwent EPP for recurrent disease, DFI was defined as the interval from the completion of treatment for the last incidence of disease to EPP. Descriptive epidemiological methods were used to illustrate the demographics, tumor characteristics, and treatment patterns of the cohort. Survival probabilities were calculated using the Kaplan–Meier method. Data were collected with the approval of the local institutional review board and waiver of informed consent due to the retrospective nature of this study (HREC #2019/ETH11837).

Results

3.1 Demographics and disease characteristics

Eight patients were identified; the median age was 41 years (range 22 to 70 years) at the time of EPP. Surgeries were performed between 2017 to 2020. Baseline patient demographics and disease characteristics are presented in Table 1. Of the eight patients identified, seven had soft tissue sarcoma (three of synovial sarcoma, one each of intimal sarcoma, malignant solitary fibrous tumor, rhabdomyosarcoma transformed from non-seminomatous germ cell tumor, and undifferentiated pleomorphic sarcoma) and one had bone sarcoma (chondrosarcoma, grade 1-2). Disease status included three patients with primary sarcoma localized to the thorax, one with *de novo* pulmonary sarcoma with solitary brain metastasis, and four with recurrent sarcoma with metastatic disease involving the thorax. All EPP procedures were performed by a cardiothoracic surgeon with extensive experience in complex thoracic oncology.

3.2 Surgical treatment, morbidity, and mortality

Surgical characteristics and postoperative complications are presented in Table 2. Tumor diameter ranged from single lesions measuring 90 mm to 250 mm (occupation of the entire superior mediastinum). Five patients had complicated involvement of local structures, necessitating meticulous dissection. Six patients had clear surgical margins on review of their histopathology. No deaths occurred within 30 days of EPP. Three patients developed early postoperative complications; one developed ventilator-associated pneumonia

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with new-onset atrial fibrillation with rapid ventricular response requiring transesophageal cardioversion, one developed an ipsilateral hydropneumothorax requiring chest tube insertion, and one developed an ipsilateral hydropneumothorax that did not require chest tube insertion. One patient developed severe late postoperative complications with Group A Streptococcal (GAS) bacteremia, with seeding to the mitral valve and resultant septic cardiomyopathic shock. All patients required planned postoperative intensive care support, with subsequent discharge to a specialized thoracic ward for routine postoperative care. The median operation time was four hours (range two to six hours depending on surgical complexity), and the median hospital length of stay was 14 days (range 9 to 45).

3.3 (Neo)-adjuvant treatments

Preoperative systemic therapy was administered to three patients: one received immunotherapy prior to EPP, and two received neoadjuvant doxorubicin/ifosfamide (AI). One patient received postoperative vincristine/actinomycin/cyclophosphamide (VAC) for rhabdomyosarcoma. Two patients received adjuvant radiation (Table 1).

3.4 Disease outcomes

A swimmer plot of the timing of initial sarcoma diagnosis, disease recurrence, EPP and the OS for patients is shown in Figure 1. At a median follow-up of 22.5 months, the median EFS after EPP was 6.0 months (Figure 2) and median OS from EPP was 20.7 months (Figure 3). Six patients had disease recurrence, including four distant and two local recurrences. Five patients died of progressive disease, and one received palliative chemotherapy for local recurrence at the last follow-up. Three patients, one with primary pleural-based sarcoma and two with recurrent sarcoma (Patients 2, 3 and 6), had an early recurrence after EPP at 2.0, 2.7 and 3.2 months, respectively. Patient 2 underwent EPP for primary synovial sarcoma without perioperative treatment, rapidly recurred, and died before planned adjuvant radiation. Patient 3 had disease progression on immunotherapy for metastatic synovial sarcoma within one month prior to EPP; the patient also recurred rapidly after surgery and died. Patient 6 had a short DFI of 2.3 months after bleomycin/etoposide/cisplatin was completed for a non-seminomatous germ cell tumor with subsequent transformation to rhabdomyosarcoma.

The patients who did not recur (Patients 4 and 7), or had an EFS of greater than one year (Patients 1 and 8), were observed to have either low-intermediate grade histology or a demonstrated partial response to neoadjuvant chemotherapy.

Patient 8, with an EFS of 20.7 months, had a partial metabolic response to neoadjuvant chemotherapy on fluorodeoxyglucose (FDG)-positron emission tomography (PET) and resection and irradiation of a solitary brain metastasis before undergoing EPP. This patient subsequently received palliative chemotherapy for inoperable local recurrence and remains alive at 23.0 months from EPP.

Patient 4, who did not recur, also received preoperative chemotherapy for a primary mediastinal synovial sarcoma and achieved a FDG-PET partial metabolic response. The patient then underwent EPP and aortic grafting, followed by adjuvant radiation. Two years after the completion of treatment, the patient developed esophageal rupture and chronic aortic graft infection, which required multiple washouts for polymicrobial sepsis and long periods of hospital admission. The patient was disease-free after follow-up of 42.3 months but ultimately died of chronic sepsis.

Patient 7, who remains disease-free 37.0 months after EPP, did not receive perioperative treatment. In contrast to the other patients in the case series, patient 7 had a low to intermediate grade chondrosarcoma and multiple prior oligometastatic lung recurrences were treated with either resection or radiofrequency ablation. EPP was undertaken 6.7 years after the original diagnosis and 8.4 months after the most recent lung recurrence.

Patient 1 had a primary malignant solitary fibrous tumor and achieved a prolonged EFS of 16.4 months without pre or post operative systemic treatment. The patient died of distant intra-abdominal recurrence

at 20.7 months. Of note, solitary fibrous tumour is considered a soft tissue tumour of intermediate grade malignant potential, which may explain the prolonged EFS despite lack of perioperative treatment.

Discussion

In our case series, EPP for adults with pleural-based sarcoma was not curative for the majority of patients; only one patient remained alive without disease after maximal follow-up (37 months). After a median follow-up of 22.5 months, five patients died of direct disease-related causes, one died of radiation complications, and one received palliative chemotherapy for metastatic disease. Our results appear inferior to two recently published case series from Rodrigues et al. (7) and Hameury et al. (8); however, there are striking differences between our patient population and those described in the two case series.

Rodrigues et al. reported the outcomes of ten patients aged between 4 to 59 years (median 19.5 years) who underwent EPP, including eight with soft tissue sarcoma and one with bone sarcoma. After a median follow-up of 29.2 months, five patients had no evidence of disease, three died of disease, and two died of treatment-related complications, including heart failure due to constrictive pericarditis and radiation-induced secondary sarcoma.

Hameury et al. illustrated a case series of nine children aged between 9 to 17 years (median 15 years) with osteosarcoma (five cases), Ewing sarcoma (three cases) and undifferentiated sarcoma (one case). After a median follow-up of 6.8 years, four patients were in complete remission, one patient was alive with local recurrence and four died of metastatic disease.

In contrast to these case series, a much lower proportion of our cohort received perioperative and multimodal treatment, which may have contributed to inferior outcomes. Only two of 8 patients received neoadjuvant chemotherapy and two patients received RT. In Rodriguez et al. series, nine of ten patients received neoadjuvant chemotherapy (the exception was a patient with low-grade fibromyxoid sarcoma), with 89% achieving a partial response, and all patients received RT either before and/or after EPP. Similarly, in Hameury et al. series of nine patients, all received neoadjuvant chemotherapy and achieved a good radiological response and six patients also received postoperative radiation. Our patient cohort was also much older, with a median age of 41 years compared to 19.5 years and 15 years, respectively.

A literature review also yielded several case reports. In a case report of two adults who underwent EPP for chondrosarcoma and hemangiopericytoma, both patients recurred at 14 months and 43 months, respectively (9). In a case report of four children undergoing EPP, two had sarcoma (spindle cell sarcoma and inflammatory myofibroblastic tumor); both were disease free at seven months and three years, respectively (10). In a case series of 13 patients with primary pulmonary sarcoma who underwent surgical resections of varying techniques and complexity, the three patients who underwent EPP died within one and seven months after surgery; the histologies were one each of synovial sarcoma, malignant peripheral nerve sheath tumour and pleomorphic sarcoma. In general, the histological subtypes and the perioperative treatments reported in the literature are very heterogenous, making comparisons with our cohort difficult.

Regarding surgical mortality and morbidity, our findings of three patients (37.5%) with early postoperative complications and no deaths by 30- and 90-days are comparable to published case series. Rodriguez et al. described one patient with an early complication of empyema that necessitated wound washout and one patient who developed a late complication of fatal pericarditis and died seven months post-surgery. In Hameury et al., three of nine patients had early postoperative complications including one case of pulmonary infection, one case of postoperative bleeding requiring surgery and one case of cardiac tamponade managed with an emergency pericardial window. Two patients developed late postoperative complications, one with ulcerated esophagitis due to hiatal hernia and one with feeding problems which resolved after gastrostomy. Hameury et al. reported that the median hospitalization time after surgery was 14.5 days (range 8 to 24), comparable with the median hospital length of stay of 14 days (range 9-45) in this series.

Our reported surgical complication rate compares favourably with results of EPP performed for malignant pleural mesothelioma. In a systematic review of 2,462 patients from 34 studies who underwent EPP for

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mesothelioma, the overall perioperative mortality rates ranged from 0 to 11.8% and the morbidity rate ranged from 22 to 82% (11). The median operative time ranged from 3.25 to 6.5 hours, and the median length of hospital stay ranged from 8 to 43 days.

The following criteria have been proposed regarding patient selection for EPP: (1) recommendation by consensus opinions of multidisciplinary tumor board discussion, (2) pleural lesions limited to one hemithorax; (3) cases where there is no other alternative apart from palliative treatment; (4) good performance status and (5) "sufficient" response to preoperative chemotherapy (8). Several authors have highlighted the importance of EPP being offered as part of multimodal treatment in conjunction with chemotherapy and/or radiation and that surgery alone is insufficient to provide long-term disease control (3,7,8). Furthermore, what satisfies a "sufficient" response is unclear, but based on our series, we suggest that at least a partial radiological response appears to be associated with superior outcomes.

The patients reported in our study met selection criteria 1 to 4. The small numbers in our case series preclude formal statistical analysis of the impact of clinicopathological characteristics on EFS and OS, however, the characteristics of patients with the longest survival were: low-intermediate grade histology, a DFI of more than six months and a demonstrated response to preoperative chemotherapy. In contrast, patients with DFI less than six months or disease progression on systemic treatment shortly before surgery did not appear to benefit from EPP, indicating an inherently aggressive tumor biology. Therefore, patient selection could also consider histological grade and DFI where available.

The limitations of this study include its retrospective nature, small sample size, and inclusion of a variety of histological subtypes, tumours with varied biological behaviour and treatment sensitivities which undoubtedly influence disease outcomes. Larger series and systematic reviews will be required to deduce who will most likely benefit from EPP and the optimal patient selection criteria.

Conclusions

In conclusion, in adult sarcoma patients, EPP is rarely curative; however, it is a feasible procedure when performed by an experienced thoracic team in specialized centres. Careful patient selection is critical, given the potential for significant morbidity and poor survival outcomes associated with EPP. Building on previously suggested selection criteria, patients with low-intermediate grade histological subtypes, response to preoperative chemotherapy, and a longer disease-free interval (more than six months) from the last incidence of tumor, appear more likely to have longer outcomes after this procedure. Patients being considered for EPP should receive comprehensive counselling regarding the intent of EPP, whether curative or life-prolonging local disease control and the likelihood of achieving this aim, the available evidence on long-term outcomes, and the morbidity associated with EPP.

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Tables

Table 1. Patient demographics and disease characteristics

Patient	Age (years)	Diagnosis	Disease status	Number of recurrences (DFI)	Preoperative treatment	Postoperative treatment	Type of recurrence	EFS from EPP (months)	OS from EPP (months)
1	70	Malignant solitary fibrous tumor	Primary	-	Nil	Adjuvant RT 56 Gy/28#	Distant (intra-abdominal)	16.4	20.7
2	64	Intimal sarcoma	Primary	-	Nil	Nil[a]	Distant (brain)	2.0	2.4
3	22	Synovial sarcoma	Recurrent	2 (DFI 6.3 months)	Progressed on immunotherapy on clinical trial within 1 month before surgery	Nil	Distant (T10-12 epidural space with cord compression)	2.7	8.3
4	36	Synovial sarcoma	Primary	-	Neoadjuvant AI x 3	Adjuvant RT 60 Gy/30#	Nil	42.3 (censored)	42.3
5	43	Synovial sarcoma	Recurrent	2 (DFI 9.7 months)	Nil[b]	Nil	Local recurrence (ipsilateral pleura)	6.0	26.2

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6	38	Rhabdomyosarcoma (transformed from non-seminomatous germ cell tumor)	Recurrent	1 (DFI 2.3 months)	Nil	Adjuvant VAC x 3	Distant (contralateral lung)	3.2	12.5
7	44	Chondrosarcoma, grade 1-2	Recurrent	5 (DFI 8.4 months)	Nil	Nil	Nil	37.0 (censored)	37.0 (censored)
8	26	Undifferentiated pleomorphic sarcoma	De novo metastatic thoracic tumor	-	Neoadjuvant AI x 4	Nil	Local recurrence (right pulmonary artery)	20.7	23.0 (censored)

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a. Planned for adjuvant radiation but progressed and died rapidly b. Nil adjuvant chemotherapy due to the receipt of adjuvant doxorubicin/ifosfamide x 3 for primary tumour treatment and neoadjuvant doxorubicin/ifosfamide x 3 for treatment of first recurrence. Abbreviations: DFI – disease-free interval; RT – radiation; Gy- Gray; EFS – event-free survival;	a. Planned for adjuvant radiation but progressed and died rapidly b. Nil adjuvant chemotherapy due to the receipt of adjuvant doxorubicin/ifosfamide x 3 for primary tumour treatment and neoadjuvant doxorubicin/ifosfamide x 3 for treatment of first recurrence. Abbreviations: DFI – disease-free interval; RT – radiation; Gy- Gray; EFS – event-free survival;	a. Planned for adjuvant radiation but progressed and died rapidly b. Nil adjuvant chemotherapy due to the receipt of adjuvant doxorubicin/ifosfamide x 3 for primary tumour treatment and neoadjuvant doxorubicin/ifosfamide x 3 for treatment of first recurrence. Abbreviations: DFI – disease-free interval; RT – radiation; Gy- Gray; EFS – event-free survival;	a. Planned for adjuvant radiation but progressed and died rapidly b. Nil adjuvant chemotherapy due to the receipt of adjuvant doxorubicin/ifosfamide x 3 for primary tumour treatment and neoadjuvant doxorubicin/ifosfamide x 3 for treatment of first recurrence. Abbreviations: DFI – disease-free interval; RT – radiation; Gy- Gray; EFS – event-free survival;	a. Planned for adjuvant radiation but progressed and died rapidly b. Nil adjuvant chemotherapy due to the receipt of adjuvant doxorubicin/ifosfamide x 3 for primary tumour treatment and neoadjuvant doxorubicin/ifosfamide x 3 for treatment of first recurrence. Abbreviations: DFI – disease-free interval; RT – radiation; Gy- Gray; EFS – event-free survival;	a. Planned for adjuvant radiation but progressed and died rapidly b. Nil adjuvant chemotherapy due to the receipt of adjuvant doxorubicin/ifosfamide x 3 for primary tumour treatment and neoadjuvant doxorubicin/ifosfamide x 3 for treatment of first recurrence. Abbreviations: DFI – disease-free interval; RT – radiation; Gy- Gray; EFS – event-free survival;	a. Planned for adjuvant radiation but progressed and died rapidly b. Nil adjuvant chemotherapy due to the receipt of adjuvant doxorubicin/ifosfamide x 3 for primary tumour treatment and neoadjuvant doxorubicin/ifosfamide x 3 for treatment of first recurrence. Abbreviations: DFI – disease-free interval; RT – radiation; Gy- Gray; EFS – event-free survival;	a. Planned for adjuvant radiation but progressed and died rapidly b. Nil adjuvant chemotherapy due to the receipt of adjuvant doxorubicin/ifosfamide x 3 for primary tumour treatment and neoadjuvant doxorubicin/ifosfamide x 3 for treatment of first recurrence. Abbreviations: DFI – disease-free interval; RT – radiation; Gy- Gray; EFS – event-free survival;	a. Planned for adjuvant radiation but progressed and died rapidly b. Nil adjuvant chemotherapy due to the receipt of adjuvant doxorubicin/ifosfamide x 3 for primary tumour treatment and neoadjuvant doxorubicin/ifosfamide x 3 for treatment of first recurrence. Abbreviations: DFI – disease-free interval; RT – radiation; Gy- Gray; EFS – event-free survival;	a. Planned for adjuvant radiation but progressed and died rapidly b. Nil adjuvant chemotherapy due to the receipt of adjuvant doxorubicin/ifosfamide x 3 for primary tumour treatment and neoadjuvant doxorubicin/ifosfamide x 3 for treatment of first recurrence. Abbreviations: DFI – disease-free interval; RT – radiation; Gy- Gray; EFS – event-free survival;

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Table 2. Surgical characteristics, early and late postoperative complications

Patient	Complex involvement of local structures	Early Complications	Late complications	Margin status
1	Tumor tamponade, pericardial and diaphragmatic involvement and invasion	Nil	Nil	R0
2	Extension to right superior pulmonary vein, right upper/middle lobe collapse, atrial tumor thrombus	Ventilator-associated pneumonia; AF with RVR requiring TOE cardioversion	Nil	R1
3	Nil		Nil	R0
4	Proximal aortic involvement Compression of left main bronchus No plane between the lesion and aortic wall	Nil	GAS bacteremia, infective endocarditis Esophageal and aortic reconstruction Repeated space washouts Candidemia	R0
5	Right costophrenic angle	Ipsilateral hydropneumothorax	Nil	R0
6	Mediastinal displacement, left common carotid	Nil	Nil	Not reported
7	Nil	Nil	Nil	R0
8	Nil	Ipsilateral hydropneumothorax	Nil	R0

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Abbreviations: AF – atrial fibrillation; RVR – rapid ventricular response; TOE – transoesophageal echo; GAS – Group A Streptococcus; R0 – microscopic negative surgical margins; R1 – microscopic positive surgical margins	Abbreviations: AF – atrial fibrillation; RVR – rapid ventricular response; TOE – transoesophageal echo; GAS – Group A Streptococcus; R0 – microscopic negative surgical margins; R1 – microscopic positive surgical margins	Abbreviations: AF – atrial fibrillation; RVR – rapid ventricular response; TOE – transoesophageal echo; GAS – Group A Streptococcus; R0 – microscopic negative surgical margins; R1 – microscopic positive surgical margins	Abbreviations: AF – atrial fibrillation; RVR – rapid ventricular response; TOE – transoesophageal echo; GAS – Group A Streptococcus; R0 – microscopic negative surgical margins; R1 – microscopic positive surgical margins	Abbreviations: AF – atrial fibrillation; RVR – rapid ventricular response; TOE – transoesophageal echo; GAS – Group A Streptococcus; R0 – microscopic negative surgical margins; R1 – microscopic positive surgical margins

Figures

Figure 1. Swimmer plot of the timing of recurrence, timing of EPP, and overall survival for patients

Figure 2. Event-free survival of patients with pleural-based sarcoma after extrapleural pneumonectomy

Figure 3. Overall survival of patients with pleural-based sarcoma after extrapleural pneumonectomy

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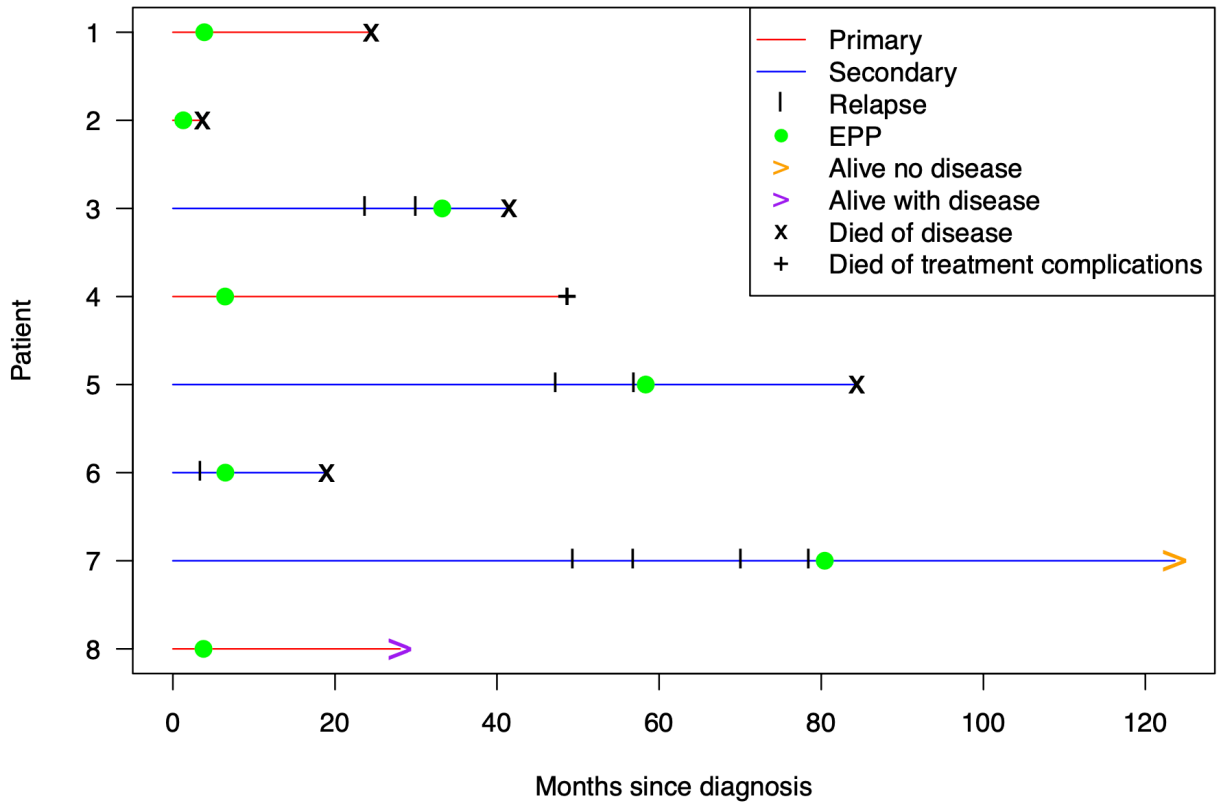

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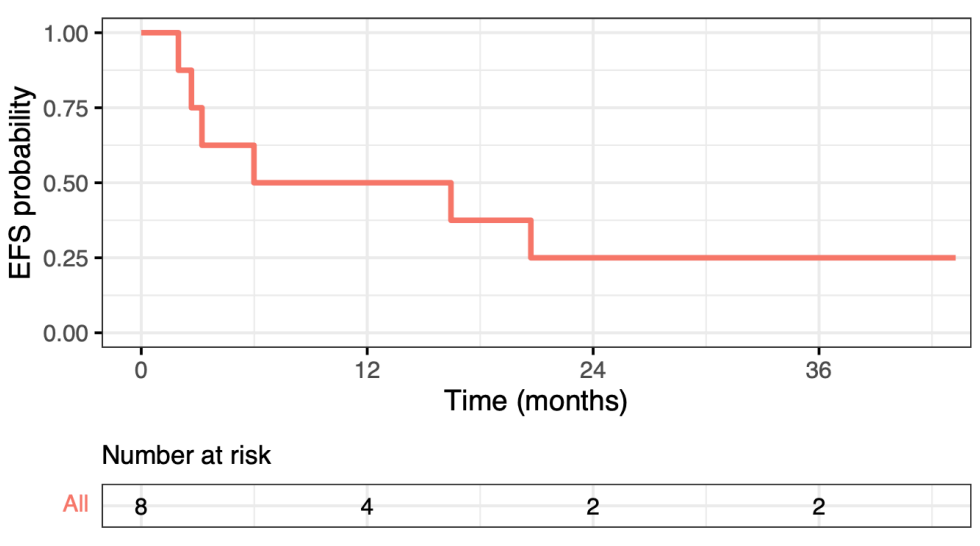

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