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Author/s:

Bae, S;Brnabic, A;Crowe, P;Carey-Smith, R;Andelkovic, V;Singhal, N;Stalley, P;Yip, D;Desai, J

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Managing patients with advanced soft tissue sarcoma: Evolving landscape from an Australian perspective

Susie Bae^{1,2}, Alan Brnabic³, Philip Crowe⁴, Richard Carey-Smith⁵, Vladimir Andelkovic⁶, Nimit Singhal⁷, Paul Stalley⁸, Desmond Yip⁹, Jayesh Desai^{1,2}

1. Peter MacCallum Cancer Centre, Vic, Australia; 2. Sir Peter MacCallum Department of Oncology, The University of Melbourne, Vic, Australia; 3. Eli Lilly Australia, NSW, Australia; 4. Prince of Wales Hospital, NSW, Australia; 5. Sir Charles Gairdner Hospital, WA, Australia; 6. Princess Alexandra Hospital, QLD, Australia; 7. Royal Adelaide Hospital, SA, Australia; 8. Royal Prince Alfred Hospital, NSW, Australia; 9. The Canberra Hospital, ACT, Australia.

Abstract

Background

Despite lack of advances in the first-line systemic therapy, the overall survival has continued to improve in patients with advanced soft tissue sarcoma (STS) with the recent estimation of median overall survival at 20 months. Several systemic therapy options are available now for the second-line and beyond, with more treatment tailored to histology and molecular subtype. The aim of this retrospective study was to characterise current patterns of care in managing patients with advanced STS in Australia.

Methods

Sarcoma databases from seven Australian sarcoma services were accessed to identify patients diagnosed with locally advanced inoperable and/or metastatic STS between 1 Jan 2010 and 31 Dec 2015. Baseline clinicopathological factors and initial treatment patterns were descriptively analysed. For the Victorian cohort where treatment of advanced STS and follow-up details were available, further explorative analysis was conducted to determine the impact of patient and tumour characteristics and the use of palliative-intent treatment on the overall survival.

Results

Of 2261 cases of STS, 671 were deemed as advanced STS. Two thirds were relapsed disease with the average 1.9 years from initial diagnosis of primary STS. Median age at diagnosis of advanced STS was 59 years (18-95 years) and 56.3% was male. Histology classification revealed four main subtypes:

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undifferentiated pleomorphic sarcoma (UPS) (23.1%), leiomyosarcoma (18.2%), liposarcoma (12.8%), synovial sarcoma (8.2%), and other comprising of 13 STS subtypes. For the Victorian cohort (N=361), approximately 80% of patients accessed palliative-intent treatment of various modalities. Nearly 40% of patients underwent tumour debulking surgery or metastectomy, of which lung wedge resection was the most common (N=83, 47.7%). A total of 438 palliative-intent radiotherapy treatments were delivered to 259 patients (71.7%), with the majority in the form of external beam radiotherapy. Palliative-intent systemic therapy was delivered to 51.5% of patients (N=186). Anthracycline-based therapy was the most commonly delivered therapy (N=135, 72.6%). Approximately half of the patients in each line of therapy failed to proceed to the subsequent line of systemic therapy with 29.4% receiving three or more lines of therapy (N=55). 18.3% of patient (N=34) participated in clinical trials or accessed off-label drugs. The median overall survival for the Victoria cohort was 15.4 months (95% CI: 12.1, 18.2). The UPS histology subtype was associated with poorer overall survival whereas receiving any modality of palliative-intent treatment conferred survival benefit.

Conclusion

In Australia advanced STS is managed with diverse treatment approaches comprising various therapy modalities. Further work is planned in describing healthcare resource utilisation and estimating costs by this patient cohort.

A retrospective cohort study was conducted to characterise treatment patterns in managing advanced soft tissue sarcoma at Australian sarcoma referral centres. Our findings highlight the highly variable course of patient journey in this incurable setting with the use of systemic therapy and frequent use of local therapies.

INTRODUCTION

Soft tissue sarcoma (STS) is a rare type of malignancy, accounting for approximately 1% of adult cancers (1). It comprises more than seventy different histology subtypes, many of which have distinct molecular signatures and clinical behaviors (2). For patients with metastatic soft tissue sarcoma, their median survival ranges from 14 to 20 months (3-10). Although doxorubicin remains the gold standard first-line chemotherapy for patients with most STS subtypes of advanced stage, there are now several novel systemic therapy options in the second-line and beyond, which provide progression-free survival or overall survival benefits (3, 6, 7). In parallel, significant progress has been made in techniques of delivering local therapy with surgery and/or radiotherapy for treatment of soft tissue sarcoma. Multiple small series highlight seemingly safe and effective local control

measures of these treatment modalities for a subset of patients with metastatic STS (11). The aim of this retrospective study was to characterize advanced STS being managed at Australian sarcoma referral centers.

METHODS

Electronic databases from seven sarcoma referral services in Australia were queried for patients diagnosed with advanced STS between 2010 and 2015. These included Royal Prince Alfred Hospital and Prince of Wales Hospital from New South Wales, Canberra Hospital from Australian Capital Territory, Peter MacCallum Cancer Centre from Victoria, Royal Adelaide Hospital from South Australia, Princess Alexandra Hospital from Queensland, and Sir Charles Gairdner Hospital from Western Australia. Advanced STS was defined as those with locally advanced unresectable STS and/or metastatic STS, managed with non-curative intent treatment. For the purpose of this study, patients with gastrointestinal stromal tumour and extraskeletal Ewing sarcoma/osteosarcoma/chondrosarcoma were excluded. Cases were classified according to WHO classification of tumors, 4th edition and stage at diagnosis according to American Joint Committee on Cancer (AJCC) Cancer Staging Manual 7th edition (12, 13). Clinicopathological factors were analyzed using descriptive statistics and were presented for categorical and continuous variables. Exploratory analysis was planned using treatment patterns and outcomes from the whole study cohort, however the protocol was amended to use the data from Victorian cohort alone due to deficits in completeness of follow up data. Kaplan Meier (KM) estimates were reported for overall survival.

For the Victorian cohort, exploratory analysis was used to determine the impact on overall survival for the predictors that were available in the database. These variables were lines of chemotherapy (1+ lines versus none), age (70 years and beyond, less than 70 years), gender, STS histological subtype (LMS, leiomyosarcoma; LPS, liposarcoma; synovial, synovial sarcoma; UPS, undifferentiated pleomorphic sarcoma), stage at primary diagnosis, year of advanced STS diagnosis, site of primary STS (extremity, abdomen/pelvis, intrathoracic, other, unknown primary), presentation of aSTS (relapsed versus de novo advanced STS), palliative-intent radiotherapy (yes/no) and palliative-intent surgery (yes/no). Various statistical approaches were used to assess the differences between the chemotherapy and histological subtype groups including Cox regression, parametric models and the restricted mean survival time (RMST) as a sensitivity analysis. Nonparametric models were used when the proportional assumption failed including the Gamma, Lognormal, and Loglogistic. The best model was selected based on Akaike and Bayesian information criterion (AIC, BIC) as well as visual inspection. RMST is a well-established, yet underutilized measure that can be interpreted as the

average event-free survival time up to a pre-specified, clinically important time point (14-16). It is equivalent to the area under the KM curve from the beginning of the study through that time point. The RMST difference means gain or loss in the event-free survival time due to treatment versus control during this period. The cut off selected was 30 or 40 months which is the approximate point at which the survival curves crossed (Figure 2B).

Data analysis was performed using SAS v9.4 with SAS/STAT 15.1 (SAS Institute Inc., Cary, NC, USA). Medical charts were sourced for clarification, accuracy for missing information. No imputation was used. This study was approved by Melbourne Health Human Research Ethics Committee.

RESULTS

Of 2261 cases of STS identified between 2010 and 2015, 671 cases were deemed advanced stage with locally advanced inoperable disease and/or metastatic disease. Annual case numbers of STS showed a slight trend of increase over the six-year period with stable proportion of advanced STS cases of approximately 30% (Table 1). Approximately two thirds of the advanced STS cases were relapsed disease after having had localized disease with the average 1.9 years from initial localized STS diagnosis (N=454, 67.7%). Average age at diagnosis of advanced STS was 59 years. Histology classification revealed four main subtypes: undifferentiated pleomorphic sarcoma (23.1%), leiomyosarcoma (18.2%), liposarcoma (12.8%), synovial sarcoma (8.2%), and other, comprising 14 distinct STS subtypes (37.7%). Common sites of metastases were lung (57.7%), bone (18.5%) and lymph node (13.3%).

Management of localized STS prior to advanced STS diagnosis

Surgery was the mainstay of treatment in localized STS (82.5%) with the majority of patients receiving radiotherapy in preoperative or post-operative setting (44.2%). Neoadjuvant or adjuvant chemotherapy was utilized in a minority of cases (N=31, 8.6%) with the doublet chemotherapy with doxorubicin/epirubicin and ifosfamide as the most commonly used regimen (N=17).

Subset analysis of the Victorian cohort

Palliative treatment of advanced STS was further explored for the Victorian cohort (N=361). Patient characteristics were similar to the overall study population in terms of STS histology subtypes, age, and breakdown of relapsed and de novo metastatic STS (Table 2). Approximately 80% of patients (N=287) received at least one modality of palliative-intent treatment of which radiotherapy was most commonly delivered.

Palliative-intent systemic therapy

A total of 186 patients, accounting for 51.5% of the advanced STS cohort, received palliative-intent systemic therapy. Anthracycline-based therapy was the most commonly delivered therapy (N=134, 72.0%) with the majority receiving in the first line setting (N=119) as a single agent doxorubicin (N=94). The two most frequent reasons for using non-anthracycline-based therapy were STS histology subtype being that of vascular sarcoma (angiosarcoma or epithelioid hemangioendothelioma, N=20) or prior exposure to anthracycline in neoadjuvant/adjuvant setting (N=9). Of patients who received the first-line therapy, 54.0% received the second-line therapy, and of these patients, 54.5% received the third-line therapy. The mean number of lines of systemic therapy received was two (range: 0 - 8). Various second and subsequent lines of systemic therapy were instituted at different times points and individual patient pathway was highly variable as featured in the Sankey diagram (Figure 1). Approximately one third of patients (N=54, 29.0%) received three or more lines of palliative-intent therapy. An oral agent, pazopanib, was used in 37 patients with non-adipocytic STS subtypes, most commonly as the second- or third-line therapies with the average duration of therapy, approximately five months (149 days). Up to 34 patients participated in clinical trials or accessed off-label drugs during their treatment phase, of which half were enrolled in Phase 1 trials.

Palliative-intent local therapies

Nearly 40% of the patients with advanced STS (N=139) underwent 266 palliative-intent surgeries, of those 59 patients had primary STS resected in the presence of metastasis. A total of 174 metastasectomies were performed, of which lung wedge resection was the most common procedure (N=83, 47.7%) with 20 patients undergoing two or more lung metastasectomies.

A total of 438 palliative-intent radiotherapy treatments were delivered to 259 patients. Seventy-six patients received high dose palliative-intent radiotherapy to their primary STS site in the setting of unresectable primary STS and/or in the presence of metastasis. Of those, twenty patients underwent surgical resection of the primary STS either as a complete local therapy in the setting of low metastatic disease burden or due to local failure post radiotherapy. Four patients received stereotactic ablative radiotherapy to sites of metastases for local control. A total of 322 radiotherapy treatments were delivered to metastatic sites of disease. Repeated radiotherapy treatments were common with 163 patients receiving two or more palliative-intent radiotherapy treatments. Most common metastatic sites to receive radiotherapy were bone (N=115), followed by lung/pleura

(N=48), abdomen/pelvis (N=34) and lymph node (N=34). Thirty-nine patients undertook radiotherapy treatments for local recurrence.

Survival analysis

The median overall survival (OS) was 15.4 months (95% confidence interval: 12.1, 18.2) with the mean follow-up time of 22.5 months (SD 24.3) (Figure 2). Survival differences were seen depending on the receipt of palliative-intent treatment and the STS histology subtypes. The median OS for the group who received palliative systemic therapy and those who did not receive systemic therapy were 18.4 months and 8.7 months respectively (Figure 2B). Approximately 20% of patients who received no systemic therapy were long term survivors beyond five years from the diagnosis of advanced STS. In terms of STS histology subtypes, the UPS group had the worst median OS of 9.7 months (LMS, 16.3 months; LPS, 18.8; synovial sarcoma, 19.3; and other histologies, 18.2) (Figure 2C). Differences in survival was evident based on the uptake of palliative-intent surgery with the median survival of 26.5 months for patients who underwent surgery compared to 8.9 months for those who did not (Figure 2D). Age differences were apparent; the group who received palliative systemic therapy was younger overall with the median age of 56 years (range: 19 – 86 years) compared to that of the group who did not receive systemic therapy whose median age was 71 years (22 – 95 years).

Various models were fitted to test the effects of systemic therapy, gender, age at diagnosis of advanced STS, STS histology group, stage at primary diagnosis and year of advanced STS diagnosis on overall survival. Stage at primary diagnosis and year of advanced STS diagnosis were not significant in any models fitted so were omitted from the presented analysis (Table 3.) The cox proportional hazards models were not considered given the violation of the proportional hazards assumption. This was seen by the non-parallel lines for the graph of the $\log(-\log(\text{survival}))$ versus \log of survival time and a significant correlation of the Schoenfeld residuals with the rank of survival time ($P < 0.001$). Of the parametric models, the Gamma was the best fitting followed by the log-normal and log-logistic models based on lowest AIC and BIC (Table 3). For all three models, age, stage at primary diagnosis, year of aSTS diagnosis and presentation of aSTS were not significant predictors and gender was significant only for the log-normal & log-logistic models. However, these demographic variables were forced into the model due to a priori specification. STS histology groups, site of primary STS, having at least one line of chemotherapy, palliative-intent radiotherapy, and palliative-intent surgery all significantly impacted the overall survival for all three models. From the Gamma model patients with 1+ line of chemotherapy had on average 2 times ($=e^{0.7}$) the overall

survival compared to patients with no chemotherapy ($p < 0.001$). (Table 3) This was consistent with the observed median survival times for the two groups (18.4 vs 8.7 months, Figure 3B). In addition, there was a statistically significant difference in OS stratified by the STS histological subtype ($P = 0.0499$ from the Gamma model). In particular, survival benefits for the other STS histologies ranged from 1.3 to 1.6 times ($e^{0.3}$ to $e^{0.5}$, from the Gamma model), better compared to the undifferentiated pleomorphic sarcoma (UPS). For primary site, patients with unknown primary had 2.5 times ($e^{0.9}$) survival benefit compared to patients with extremities, however this should be interpreted with caution given the small patient number in the unknown primary group ($N = 8$). Survival benefits were also observed for patients with palliative-intent radiotherapy and palliative-intent surgery (1.5- and 2.7-times better survival, respectively). Results from the adjusted RMST models (controlling for the same variables as the parametric models) with 30 or 40 months cut-offs yielded consistent results with the parametric models with 3.4 ($p = 0.0028$) and 3.1 ($p = 0.0503$) months on average better survival for those on 1 + lines of chemotherapy compared to those without for the 30 and 40 month cut-offs respectively.

DISCUSSION

Treatment paradigms for patients with advanced STS have evolved significantly over the past decade. Incorporating histology-tailored systemic therapy and instituting local treatment options such as metastasectomy and various radiotherapy modalities at the appropriate time points are critical in providing optimal care to prolong survival whilst maintaining quality of life. Characterizing such real-world patterns of care in the setting of incurable STS was the main goal of this project. Our earlier work based on the data from 2010 and 2012 offered a glimpse of insight into the heterogeneous population of STS in Australia with relatively low systemic therapy use and similar survival outcome to other series (17). The datasets have matured over the years and herein we present an updated analysis.

Compared to the earlier study, there was an increased uptake of palliative-intent systemic therapy with more patients accessing the first-line therapy and beyond. As demonstrated by the treatment flow through lines of therapy in the Sankey diagram (Figure 1), highly complex and variable chemotherapy pathways were seen with individual patients except for the most common use of anthracycline as a monotherapy in the first-line setting. Such variation seen in the choice of therapies and treatment sequence was surprising to some extent, given the limited therapy options. However, this also reflects the inherent heterogeneity of patient population with the clinicians likely to tailor therapy to histology subtypes. Nonetheless some consistent practice emerged – most

patients with angiosarcoma or other vascular-rich STS subtypes such as epithelioid hemangioendothelioma were treated with non-anthracycline-based first-line therapy, often with paclitaxel and more frequently with a small molecule tyrosine kinase inhibitor, pazopanib, consistent with the guidelines from the National Comprehensive Cancer Network and the European Society for Medical oncology (18, 19). Of note, pazopanib is currently not available for reimbursement in Australia when used in the first-line setting or without prior anthracycline treatment for advanced angiosarcoma as per the patient eligibility criteria for the Phase III PALLETE study (3). Our study did not explore the methods by which patients accessed the drugs as this was not captured in the database, however, this will be an important area to investigate in the future studies as difficulties in accessing off-label drugs for these rare sarcoma subtypes are becoming increasingly recognized. Accessing systemic therapy is largely governed by the availability of therapies, also contributing to practice variation across countries. For example, the use of combination therapy, docetaxel and gemcitabine, has been substantially lower in Australia (accounting for 9% of treatment choices in our study) compared to its more frequent use in other countries (20). The patent for docetaxel expired in 2012 in Australia, therefore, accessing this regimen was uncommon prior to this time and may have influenced its less frequent use in more recent years.

There are inherent challenges in designing clinical trials for STS with a heterogeneous patient population being grouped as one cohort to study the drug efficacy. However, there has been the resurgence of Phase III clinical trials for advanced STS through rigorous global efforts over the last decade. Although none of combination drug regimens have been shown to be superior to single agent doxorubicin, an incremental improvement in the overall survival has been seen with the latest estimation of 20 months from the ANNOUNCE trial (10). It is important to acknowledge advances in multidisciplinary care of sarcoma and other ancillary services such as palliative care and allied health services, which have become integral part of patient-centred cancer care. Furthermore, beyond the first-line therapy, therapeutic arsenal has expanded to include a variety of new agents tailored to histology and molecular subtypes – pazopanib for non-adipocytic STS, eribulin for liposarcoma and trabectedin for liposarcoma and leiomyosarcoma (3, 6, 7). In Australia, patients continue to face challenges in accessing these drugs on time. Approximately 24 months of delay was seen from the time of drug approval by the US Food and Drug Administration (FDA) or European Medicines Agency (EMA) until the listing of pazopanib and eribulin on Pharmaceutical Benefits Scheme (PBS) in Australia (21-23). Trabectedin, which was approved by the EMA in 2007 is still yet to be listed on the PBS in Australia.

Our study demonstrates a pertinent finding on the use of local therapy with a substantial proportion of patients with advanced STS undergoing surgery and/or radiotherapy for various indications. Most often this was in the form of palliative-intent radiotherapy delivered for symptom control, including 43% of those patients who did not receive palliative-intent systemic therapy. Interestingly, 16.3% of patients with advanced STS went onto have surgery on their primary tumour in the presence of metastatic disease. In addition, one in five patients with advanced STS had radiotherapy to their primary STS with the high radiation dose, in the order of 50 to 60 Gy, most commonly in the presence of low volume metastatic disease and a large primary tumour. A multidisciplinary team meeting would be the usual platform where such complex cases are discussed. Confirming of a STS histology subtype by an expert pathologist and careful discussion around the pros and cons of immediate local treatment or a close watchful waiting are all cornerstones of gold-standard STS management (18, 19). A significant number of patients underwent metastasectomies, in some instances, multiple times, or stereotactic ablative radiotherapy for distant metastases. Much work has gone into this space with regards to the survival gain of such treatment approach but with lack of evidence supporting repeated surgeries (31-33). Recent advances in surgical techniques and radiotherapy delivery hold promising local therapy options even for patients with advanced STS, when the treatment intent is not cure. This highlights the importance of careful patient selection in determining the right sequence of treatment modalities and involving patients in informed decision-making, judiciously balancing the hope of long-term disease control and likely risks or even futility of aggressive therapies. From our study it is unclear to determine how much of patient's preferences and/or individual clinicians' beliefs in certain approaches have shaped the individual's treatment pathway. As the clinical data mature, this may pave the development of prognostication tools using a large dataset.

The median overall survival of the Victorian cohort was 15.4 months, slightly less than that from the earlier analysis but within the estimated range for the OS for the metastatic STS population from large series (17). We also found the statistically significant survival difference between the UPS histology group compared to the other histology subtypes. This is consistent with findings from other series and is expected as the UPS histology is well known for its presentation as a large high-grade tumour, often in older population and its preponderance for metastatic potential (34-36). The marked age difference between the groups who received systemic therapy and those who did not also raises the question about the bias that age may bring to decision-making about the systemic therapy. However, all three statistical models fitted to test the effects of age at diagnosis of advanced STS on overall survival did not find the age as a significant predictor. A confirmed

histological diagnosis of STS subtype will usually narrow down the therapeutic options for patients before age and other patient factors are taken into account, however, in the current era of rapidly evolving cancer genomics, molecular profiling of tumour may also shed further light in differentiating likelihood of treatment responses and outcomes. It is reassuring to note that access to palliative-intent radiotherapy and surgery was associated with longer survival. However, this may reflect the appropriate patient selection by clinicians in utilising these treatment modalities.

Findings from this study are subject to several limitations inherent to retrospective analysis. The deficits in data completeness surrounding treatment and follow-up details were significant resulting in only one site contributing to analysis of treatment and survival data. Maintaining high-quality cancer data is a labour and resource intensive long-term project, requiring a strategic funding support and dedicated staff. Several works are underway to address this issue at each site participating in data collection with more centralised data quality check. Real-world data provide important insight into the current and evolving landscape of advanced STS management. The study cohort is highly heterogeneous including multiple STS histologies, mirroring the everyday practice of sarcoma referral centres. Marked complexities in individual patient's treatment journey highlight the challenges in making decisions at each time points, which will obviously take into account multiple prognostic variables, some of which were not available for this analysis. Tumour and patient characteristics such as tempo of disease, treatment response to each line, patient's performance status and comorbidities, as well as patient's preference would have influenced this decision-making process.

CONCLUSION

To our knowledge this is the largest series of advanced STS cohort study from Australian sarcoma services. Our findings highlight the highly variable course of patient journey with regards to use of systemic therapy as well as local therapies with improved treatment choices in the non-curative setting. Further work is planned in describing healthcare resource utilisation and estimating costs by this patient cohort.

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Table 1. Proportion of patients with newly diagnosed with STS between 2010 and 2015

Population characteristic	Total n, (%)	NSW ¹ n, (%)	ACT ² n, (%)	SA ³ n, (%)	VIC ⁴ n, (%)	WA ⁵ n, (%)	QLD ⁶ n, (%)
Patients with newly diagnosed STS	2261 (100)	420 (18.6)	98 (4.3)	349 (15.4)	905 (40.0)	245 (10.8)	244 (10.8)
Stage at diagnosis							
Stage I	400 (17.7)	62 (14.8)	2 (2.0)	68 (19.5)	189 (20.9)	13 (5.3)	66 (27.0)
Stage II	455 (20.1)	121 (28.8)	8 (8.2)	46 (13.2)	147 (16.2)	76 (31.0)	57 (23.4)
Stage III	586 (25.9)	68 (16.2)	22 (22.5)	104 (29.8)	267 (29.5)	29 (11.8)	96 (39.3)
Stage IV	247 (10.9)	30 (7.1)	9 (9.2)	28 (8.0)	127 (14.0)	29 (11.8)	24 (9.8)
Missing stage	573 (25.4)	139 (33.1)	57 (58.2)	103 (29.5)	175 (19.3)	98 (40.0)	1 (0.4)
Patient numbers by year	2010	2011	2012	2013	2014	2015	
All stages of STS	373	362	340	362	405	419	
Advanced STS	106 (28.4%)	100 (27.6%)	95 (27.9%)	115 (31.8%)	134 (33.1%)	121 (28.9%)	

1, New South Wales (Royal Prince Alfred Hospital and Prince of Wales Hospital); 2, Australian Capital Territory (Canberra Hospital); 3, South Australia (Royal Adelaide Hospital); 4, Victoria (Peter MacCallum Cancer Centre); 5, Western Australia (Sir Charles Gairdner Hospital); 6, Queensland (Princess Alexandra Hospital).

Table 2. Characteristics of patients with advanced STS¹ between 2010 and 2015.

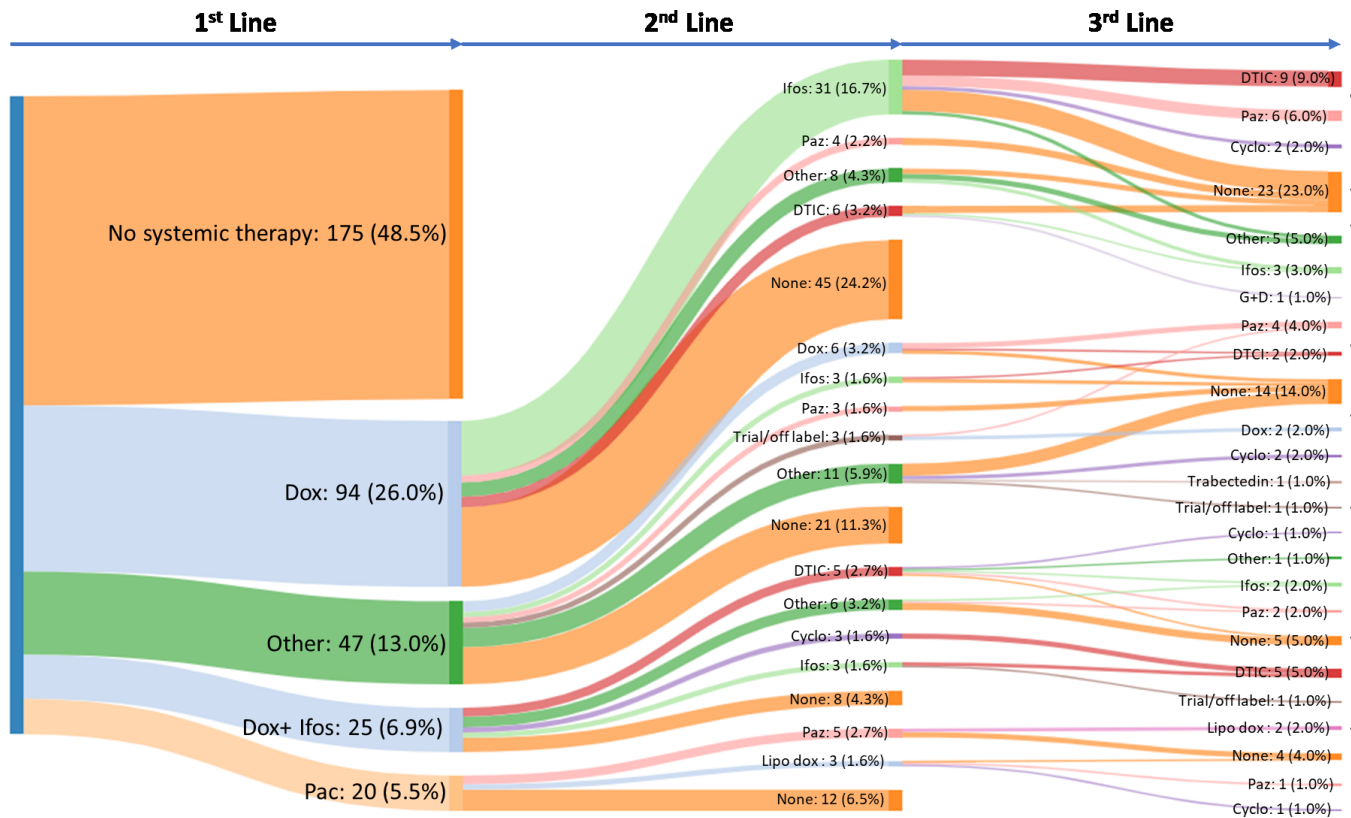
Number of patients with aSTS (N, %)	671 (Total)	361 (Victorian subset)
Gender		
Female	293 (43.7)	170 (47.1)
Male	378 (56.3)	191 (52.9)
Age at initial diagnosis (years)		
Mean (SE)	57.7 (17.7)	58.4 (16.5)
Minimum, Maximum	15, 93	16, 93
Age at advanced STS diagnosis (years)		
Mean (SE)	59.0 (17.6)	60.0 (16.4)
Minimum, Maximum	18, 95	18, 95
Stage at diagnosis		
Stage I	39 (5.8)	25 (6.9)
Stage II	74 (11.0)	29 (8.0)
Stage III	215 (32.0)	134 (37.1)
Stage IV	221 (32.9)	109 (30.2)
Unknown	123 (18.3)	64 (17.7)
Disease status at aSTS presentation		
Relapsed disease	454 (67.7)	250 (69.3)
Denovo advanced STS	217 (32.3)	111 (30.7)
Year of aSTS diagnosis		
2010	105 (15.6)	55 (15.2)
2011	100 (14.9)	59 (16.3)
2012	96 (14.3)	56 (15.5)
2013	115 (17.1)	62 (17.2)
2014	134 (20.0)	66 (18.3)
2015	121 (18.0)	63 (17.5)
Histological classification		
Undifferentiated pleomorphic sarcoma	155 (23.1)	104 (28.8)
Leiomyosarcoma	122 (18.2)	68 (18.8)
Liposarcoma	86 (12.8)	43 (11.9)
Synovial sarcoma	55 (8.2)	26 (7.2)
Other	253 (37.7)	120 (33.2)
Primary disease site		
Extremity	288 (42.9)	144 (39.9)
Abdomen/pelvis	208 (31.0)	120 (33.2)
Intrathoracic	113 (16.8)	16 (4.4)
Other	44 (6.6)	73 (20.2)
Unknown	18 (2.7)	8 (2.2)
Palliative intent treatment for aSTS		287 (79.5)
Chemotherapy		186 (51.5)
Radiotherapy		259 (71.7)
Surgery		139 (38.5)

1, Advanced STS refers to locally advanced, unresectable and/or metastatic disease.

Table 3. Summary of results of fitting parametric models to Overall Survival

MODEL	Gamma	Log-normal	Log-logistic
Intercept	2.3 (1.8,3.0), P<.0001	2.9 (2.4,3.5), P<.0001	2.9 (2.3,3.5), P<.0001
1+ lines of Chemotherapy*	0.7 (0.4,0.97), P<.0001	0.4 (0.1,0.6), P=0.0095	0.4 (0.1,0.7), P=0.0066
70+ years*	-0.05 (-0.3,0.2), P=0.7498	-0.1 (-0.4,0.2), P=0.4448	-0.1 (-0.4,0.2), P=0.5751
Female*	0.2(-0.01,0.5), P=0.0688	0.3 (0.03,0.6), P=0.0267	0.3 (0.03,0.6), P=0.0317
Histology*	<i>P=0.0499</i>	<i>P=0.0104</i>	<i>P=0.0226</i>
LMS	0.5 (0.1,0.9), P=0.0077	0.5 (0.1,0.9), P=0.0148	0.5 (0.1,0.8), P=0.0191
LPS	0.4 (-0.03,0.9), P=0.0729	0.7 (0.2,1.1), P=0.0030	0.7 (0.2,1.2), P=0.0059
Other	0.4 (0.1,0.7), P=0.0128	0.5 (0.2,0.8), P=0.0047	0.5 (0.1,0.8), P=0.0105
Synovial	0.3 (-0.2,0.8), P=0.2168	0.3 (-0.2,0.9), P=0.2451	0.3 (-0.2,0.8), P=0.2787
Stage at primary diagnosis	<i>P=0.3290</i>	<i>P=0.4231</i>	<i>P=0.4792</i>
Year of aSTS Diagnosis	<i>P=0.3072</i>	<i>P=0.4547</i>	<i>P=0.5020</i>
Primary Site*	<i>P=0.0287</i>	<i>P=0.0234</i>	<i>P=0.0257</i>
Abdomen/pelvis	-0.3 (-0.6, 0.05), P=0.1024	-0.4 (-0.7, -0.02), P=0.0358	-0.3 (-0.7, 0.01), P=0.0546
Intrathoracic	-0.3 (-0.8, 0.2), P=0.1926	-0.5 (-1.0, 0.1), P=0.0881	-0.4 (-1.0, 0.1), P=0.1050
Other	-0.2 (-0.5, 0.2), P=0.3180	-0.2 (-0.6, 0.2), P=0.3568	-0.2 (-0.6, 0.2), P=0.3558
Unknown primary	0.9 (0.1,1.8), P=0.0304	0.8 (-0.1,1.7), P=0.0834	0.8 (-0.1,1.6), P=0.0695
Presentation of aSTS* Relapsed vs. <i>denovo</i> aSTS	<i>P=0.1274</i>	<i>P=0.1958</i>	<i>P=0.1755</i>
Palliative-intent radiotherapy*	-0.4 (-0.7, -0.2), P=0.0011	-0.3 (-0.6, -0.1), P=0.0168	-0.4 (-0.7, -0.1), P=0.0037
Palliative-intent surgery*	-1.0 (-1.3, -0.8), P<.0001	-1.0 (-1.3, -0.7), P<.0001	-1.0 (-1.3, -0.7), P<.0001
Scale	1.08 (0.98,1.19)	1.14 (1.04,1.24)	0.66 (0.60,0.73)
Shape	-0.9 (-1.2, -0.5)		
-2 Log Likelihood	2285.5	2302.6	2305.8
AIC (smaller is better)	2337.5	2352.6	2355.8
BIC (smaller is better)	2438.3	2449.5	2452.7
*Reference groups; no chemotherapy, <70 years, male, UPS, extremity, relapsed aSTS, radiotherapy, surgery. 357 observations used.			

Figure 1. Sankey diagram of palliative-intent systemic treatment patterns across lines of therapy.



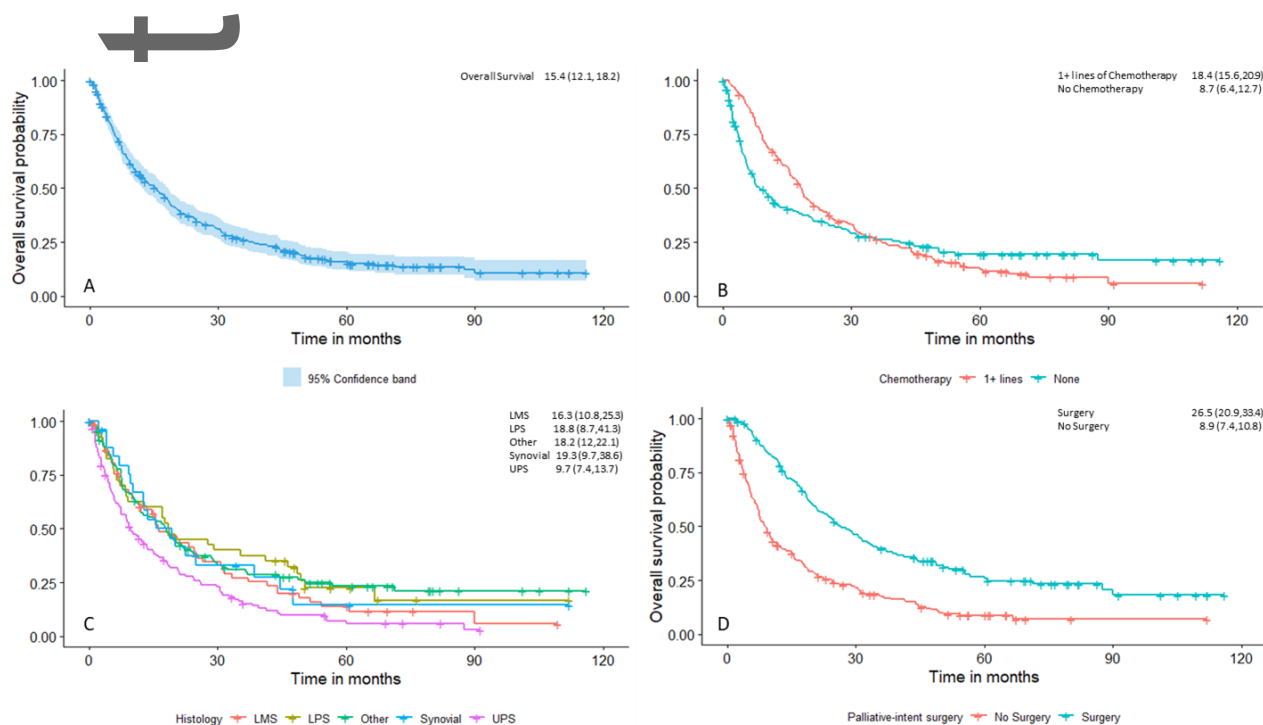
Abbreviations: Chemo, chemotherapy; dox, doxorubicin; ifos, ifosfamide; pac, paclitaxel; paz, pazopanib, DTIC, dacarbazine; lipo dox, liposomal doxorubicin; cyclo, cyclophosphamide; G+D, gemcitabine and docetaxel.

Numbers displayed are n (%) within each treatment line; $n_{1st\ line}=361$, $n_{2nd\ line}=187$, $n_{3rd\ line}=101$.

Other therapy comprised of anastrozole, letrozole, cisplatin, eribulin, sorafenib and sunitinib across all lines.

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Figure 2. Kaplan-Meier curves for overall survival; overall, by lines of chemotherapy and Histology Types



A. Victorian aSTS cohort; B. Palliative-intent chemotherapy vs. no chemotherapy; C. Stratified by STS histology subtypes; D. Palliative-intent surgery vs. no surgery
 Abbreviations: LMS, leiomyosarcoma; LPS, liposarcoma; synovial, synovial sarcoma; UPS, undifferentiated pleomorphic sarcoma.
 Numbers presented are Median survival time (95% Confidence Interval) months

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