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Treatment and outcomes for synovial sarcoma patients in Western Australia: the role of neoadjuvant chemoradiotherapy

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Abstract

Background: This is a retrospective review of synovial sarcoma (SS) patients treated over the last 12 years in Western Australia (WA). SS is both chemo and radiotherapy sensitive. Results of trials in adjuvant chemotherapy are conflicting and there is limited support for neoadjuvant chemotherapy. The use of combined chemoradiotherapy is based on institutional preferences.

Aim: We reviewed the outcomes for SS patients treated in WA over a 12 year period focusing on patients who received neoadjuvant chemoradiotherapy (NACRT).

Methods: Patient details including demographics, histopathology, treatment details, were obtained from the WA sarcoma database (2006-2018). Progression free survival (PFS) and overall survival (OS) were derived for whole cohort.

Results: Twenty seven patients were identified with SS with equal gender incidence. Median age of the cohort was 36 (14-76) years. The most common primary site of disease was extremity (81.5%). 22/27 patients presented with only localized disease and 59.2% of these received neo-adjuvant treatment. Of those who received neo-adjuvant treatment, 56.2% had NACRT, while 25.0% and 18.7% of patients had chemotherapy and radiotherapy respectively. Mesna, doxorubicin, ifosfamide, dacarbazine (MAID) was the most commonly used chemotherapy regimen as

neoadjuvant or adjuvant treatment while ifosfamide (93.7%) was the most commonly used chemotherapy drug in any setting. There was no reported case of disease progression in group of patients who received NACRT apart from one patient who had oligometastatic disease at diagnosis. Median OS of the whole cohort was 38 months while median PFS was 24 months. Bone marrow toxicity was the most commonly reported high grade toxicity in NACRT group (55.5%) but there were no treatment related deaths.

Conclusion: NACRT is not widely adopted and treatment is based on institutional preferences, however our data shows that NACRT is a feasible therapy option. NACRT should be evaluated prospectively in a randomized trial.

1 | BACKGROUND

Synovial sarcoma (SS) is a rare malignancy with unique molecular characteristic of translocation t(X;18)(p11.2;q11.2) in 90% of the patients resulting in fusion of SS18-SSX, which is the main oncogenic driver.[1] SS is a misnomer as it does not arise from synovium but the name is attributed to the morphological similarity with synovial tissue. It primarily originates from soft tissues of the extremities but virtually can involve any site of the body. Its incidence is on the rise,[2] and accounts for 5% to 10% of soft tissue sarcomas predominantly affecting a younger population.[3-6] It is considered to be an aggressive disease with 5-year overall survival (OS) of around 60% in adults.[1] Distant metastasis remains a major problem for localized SS despite achieving good local control with surgery and radiation. 50% to 70% of patients develop metastasis and a high proportion develops late metastasis.[7]

There is limited data for SS with a few small prospective studies available in the literature which makes it difficult to derive any clear conclusions. There is currently no single standard of care for the treatment of SS in either localised or metastatic disease.[8-10] It is a radiotherapy and chemotherapy[11-14] sensitive disease especially to alkylating agents like ifosfamide,[15] however, data is conflicting from randomized trials regarding the benefit of adjuvant or neoadjuvant chemotherapy.[16,17] The role of neoadjuvant radiotherapy is established however an optimal neoadjuvant chemotherapy regimen and its integration with radiotherapy is not known. Tanaka et al prospectively assessed ifosfamide and doxorubicin as neoadjuvant treatment for stage III and intermediate to high grade SS and reported pathological response rates of 28.6% and 5-year OS of 82.6%.[18] Radiotherapy was not part of the neoadjuvant treatment however it was allowed to be added to the protocol as adjuvant treatment for the patients with marginal or intralesional resection. Similarly, a histotype tailored randomized phase III trial favoured combination of neoadjuvant ifosfamide and anthracycline for SS as compared to single agent ifosfamide.[19] Preoperative radiotherapy was allowed in the trial. Ferrari et al conducted a nonrandomized trial and administered 3 cycles of neoadjuvant ifosfamide and doxorubicin for high risk group

and reported pathological response rate of 55.5% and the 3-year event free survival and OS of 77.3% and 94.3% respectively.[20]

There is no head to head comparison of neoadjuvant chemoradiotherapy (NACRT) with neoadjuvant radiotherapy or neoadjuvant chemotherapy and hence we find some degree of variation in the management of SS across the world. In this retrospective review, we looked at the outcomes for all SS patients treated through centralized state sarcoma service in WA in the last 12 years. We focused on reviewing the outcomes of patients receiving NACRT particularly the rates of recurrence and development of metastatic disease compared to patients receiving either surgery or radiotherapy alone.

2 | METHODS

This retrospective review was approved by The Governance, Evidence, Knowledge, and Outcomes (GEKO) committee of Sir Charles Gairdner hospital, WA. Patients with SS were identified from the WA sarcoma database from 2006 to 2018. Data collected included age, gender, histology on biopsy and final pathology, treatment characteristics, and treatment related toxicities. OS was defined as the time from diagnosis to death, while progression free survival (PFS) was defined as the time from diagnosis to first evidence of disease progression. Pathological response to neoadjuvant therapy was identified as minimal, moderate or good as reported on the postoperative pathology report. Time to first clinical review was defined as the date of referral from the primary care provider to first sarcoma clinic review. Extremity sarcoma was defined as a tumor at or distal to shoulder or pelvic girdle. A patient with an axillary tumor abutting chest wall was grouped under nonextremity sarcoma. High risk SS was defined as either the tumor size of at least 5 cm or grade 3 on histopathology. Low risk group was defined as tumor size of less than 5 cm and grade 2 or less on histopathology. Common terminology criteria for adverse events (CTCAE) Version 5 was used to grade treatment toxicities.

2.1 | Statistical analysis

Descriptive summaries were based on frequency distributions. OS and PFS were estimated using Kaplan-Meier survival probabilities and summarized using medians and 95% confidence intervals (CIs). Comparisons of OS and PFS between prognostic factors, including patient and tumor characteristics, were made using Log Rank tests. Data was analyzed using IBM SPPS version 24.0 (Armonk, NY). All hypothesis tests were two-sided, and P values of <.05 were considered statistically significant.

3 | RESULTS

3.1 | Clinicopathological characteristics

In the years from 2006 to 2018, 27 patients were identified with SS from the WA sarcoma database. The median age of the cohort was 36 years with a range of 14 years to 76 years. There was no difference in incidence between males 48.1% (13/27) and females 51.8% (14/27). 81.5% (22/27) patients had localized disease at diagnosis. The most common primary site of tumor was the extremity with majority (17/27) being lower extremity sarcoma (Table 1). 29.6% of patients had their primary sarcoma originating from thigh (Supplementary Table 5). Thirteen patients had SS with high risk features of grade 3 on pathology or primary tumors of greater than 5 cm. Of these patients, four had metastatic disease at diagnosis.

The median size of grade 3 tumor was 6.3 cm (2.4-14.2) as compared to 3 cm (1-14.7) for grade 2 tumors. The predominant site of distant metastasis was the lung (53.3%) followed by liver (13.3%) (Table 1). Histology subtype was not reported in 37% of the patients, however when reported, monophasic (SSX2) and biphasic (SSX1) subtypes were equally distributed among rest of the patients. Similarly,

histological grading was not reported in 63% of patients and high risk histological grade (ie, grade 3) was found in 18.5% of the patients.

3.2 | Treatment

For the whole cohort (n = 27), the median time to first clinical review was 2 days (range 0-15) following referral from the primary clinician. 8 (29.6%) patients underwent amputation, 12 (44.4%) had wide local excision while 7 (25.9%) did not have any surgical intervention. In 16 of 27 patients (59.2%) received neoadjuvant treatment. Out of these, nine had NACRT, four had neoadjuvant chemotherapy and three had neoadjuvant radiotherapy (Figure 1). Concurrent chemoradiotherapy was given to eight of the nine patients receiving NACRT. Mesna, doxorubicin, ifosfamide, dacarbazine (MAID) was the most commonly used chemotherapy regimen (8/9) in patients receiving NACRT. MAID was given every 3 weeks and doses consisted of doxorubicin 20 mg/m^2 daily for 3 days, dacarbazine 300 mg/m^2 daily for 3 days and ifosfamide 2.5 g/m^2/day for 3 days. Doxorubicin was omitted during radiotherapy. Ifosfamide (93.7%) was the most commonly used chemotherapy drug either as a single agent or in
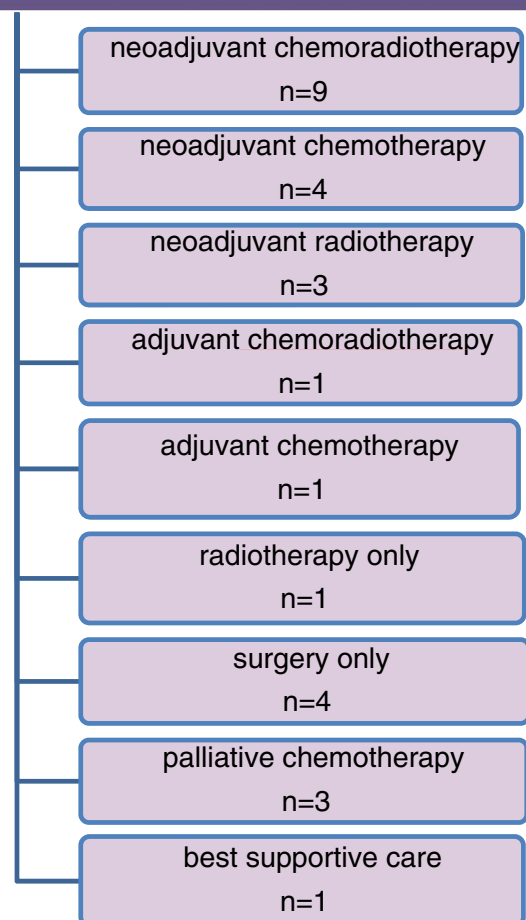
FIGURE 1 Treatment given

TABLE 1 Patient and Tumor characteristics

Age (median)	36 (14–76) years
Gender	Male 13 (48.1%)
	Female 14 (51.8%)
Primary site	Extremity 22 (81.5%)
	Nonextremity 5 (18.5%)
Metastasis site	Lung 8 (53.3%)
	Liver 2 (13.3%)
	Others 5 (33.3%)
Tumor size (median)	4.5 (1-35) cm
Subtype	Monopahsic 9 (33.3%)
	Biphasic 8 (29.6%)
	Not reported 10 (37.0%)
Grade	Grade 2 5 (18.5%)
	Grade 3 5 (18.5%)
	Not reported 17(63.0%)

TABLE 2 Pathological response in NACRT group (n = 9) by tumor grade

Grade	No. of patients	Minimal	Moderate	Good
Grade 2	2	1 (50%)	1 (50%)	
Grade 3	4	2 (50%)	1 (25%)	1 (25%)
Not reported	3	2 (66.6%)	1 (33.3%)	

Abbreviation: NACRT, neoadjuvant chemoradiotherapy.

combination in any setting. Radiotherapy doses ranged from 45 to 54 Gy. 9 of 27 patients had intralesional resection before referral to the state sarcoma service and two of these patients subsequently developed metastatic disease. Only one patient with intralesional resection had NACRT prior to wide local excision.

3.3 | Outcome

For the neoadjuvant cohort, moderate to good pathological response rates were seen in 44.4% of patients in NACRT group vs 25.0% in single modality neoadjuvant treatment group. Out of the four patients with grade 3 histology where pathological response was evaluated, two patients had moderate to good pathological response while the remaining two patients had minimal response (Table 2). For patients with grade 2 tumors, one patient each had minimal, moderate and good pathological response. Down-staging of tumor size was achieved in all the patients receiving NACRT irrespective of pathological responses. Limb salvage surgery rate was 100% in NACRT group while it was reduced to 57.1% in the single modality neoadjuvant group. Rates of treatment failure were low with only 1 of 9 (11.1%) developing progression in the NACRT group. Of note, this patient had oligo-metastatic disease at diagnosis and progressed 12 months after completing the treatment. 57.1% patients progressed in the single modality neoadjuvant treatment group and they all had distant recurrence.

For the entire cohort, median follow up time was 25 months (range 1-109). There were four patients who did not receive either neoadjuvant or adjuvant treatment as they were considered low risk however one of these patients developed distant recurrence 5 months after primary surgery. 9/27 patients had sub-optimal initial surgery performed by referring medical practitioners and four of these patients ended up having an amputation and two of these patients developed distant metastasis. Median OS of the whole cohort was 38 months (95% CI 18.9-57.1) while median PFS was 24 months (95% CI 0-60.2) (Figure 2). Patients who did not have reported grade or histology subtype had worse PFS with statistically significant P values of .014 and .020 respectively (Table 3). For the patients where we were able to record at least 2 year of data before they were censored, 2-year PFS was 44.4% (8/18) and 2-year OS was 83.3% (15/18).

3.4 | Adverse events

In the NACRT group, acute bone marrow toxicity (66.6%) and nausea/vomiting (66.6%) were the most common adverse events of any grade
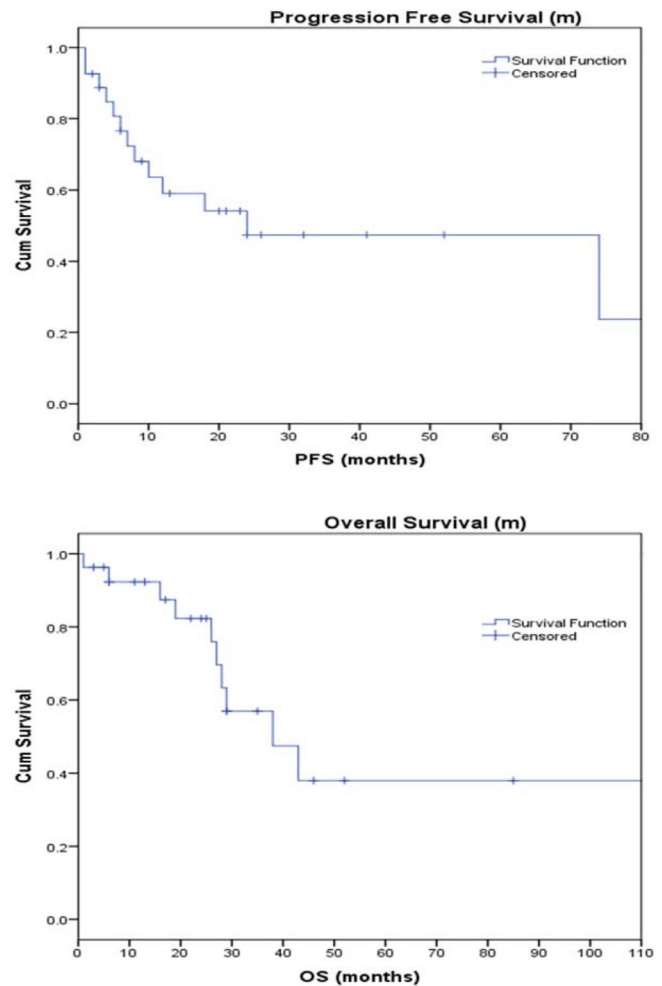
FIGURE 2 Progression free survival and overall survival

(Table 4) while acute bone marrow toxicity was the most common high grade toxicity (55.5%). There were no treatment interruptions or treatment related deaths. Three patients required dose reduction due to toxicities and it did not result in local or distant disease failure or amputation.

Similarly, in the entire cohort (Supplementary Table 6 and Table 7) who received any form of systemic therapy, the most commonly observed toxicity was bone marrow (36.3%) followed by nausea/vomiting (31.8%). There was one case of high grade ifosfamide induced encephalopathy which required methylene blue administration and admission to the intensive care unit.

TABLE 3 Prognostic factors for OS and PFS in months (m)

Variable	Category	Median OS (m)	P value	Median PFS (m)	P value
Size	< 5 cm	Not reached	.097	Not reached	.135
	> 5 cm	28		17	
Gender	Female	43	.181	24	.765
	Male	27		17	
Histology subtype	Monophasic	28	.299	17	**.020**
	Biphasic	Not reached		Not reached	
	Not Reported	38		7	
Grade	2	28	.937	Not reached	**.014**
	3	Not reached		Not reached	
	Not Reported	38		9	

Abbreviations: OS, overall survival; PFS, progression free survival.

TABLE 4 Adverse events in NACRT group

Number of patients receiving treatment, n = 9 (%)				
	Any event	Grade 1	Grade 2	Grade 3/4
Nausea/Vomiting	6 (66.6)	5 (55.5)		1 (11.1)
Lethargy	4 (44.4)	3 (33.3)	1 (11.1)	
Neutropenia	2 (22.2)			2 (22.2)
Febrile neutropenia	2 (22.2)			2 (22.2)
Hepatic dysfunction	2 (22.2)	1 (11.1)	1 (11.1)	
Thrombocytopenia	1 (11.1)			1 (11.1)
Anaemia	1 (11.1)	1 (11.1)		

Abbreviation: NACRT, neoadjuvant chemoradiotherapy.

4 | DISCUSSION

As SS is a rare tumor subtype, the number of patients is small in this retrospective review. Though these results cannot be generalized, our study shows that concurrent NACRT with ifosfamide based therapy is a plausible approach for localized SS and warrants further evaluation through properly designed randomized trials. In this retrospective review we found a high rate of limb salvage surgery with NACRT and no reported progression apart from one case of oligometastatic disease at diagnosis. There was increased rate of disease progression with single modality neo-adjuvant treatment.

A high proportion of our study population did not have histological grade reported. This may be explained by the prior convention of considering all SS cases as being high grade.[21,22] In our univariate analysis, we observed worse outcomes for the subgroup that did not have their histology grade reported. This raises the possibility of under representation of the actual high risk population in our study.

The benefit of NACRT was seen across all grades of tumor. The risk of disease recurrence is generally considered to be low in patients with tumors of histological grade 2 or less and tumor size of less than 5 cm and hence neoadjuvant or adjuvant treatment is not offered routinely to patients with tumors considered as low risk. In our review, 1/4 patients in the low risk group had disease recurrence. Moreover

this patient had distant failure. Various retrospective studies have suggested wide range of clinicopathological features as high risk or poor prognostic factors. Amongst these factors, Intralesional resection of the tumor is consistently associated with high risk of local and distant disease recurrence as well as poor OS.[7,23] Age greater than 25 years of age has also been reported as one of the high risk features in some of the published literature.[24] This low risk patient with distant failure had both intralesional resection as well as age greater than 25 years. This shows that risk of disease recurrence is not completely eliminated in low risk group and a select subgroup may benefit from systemic therapy. A revised risk stratification would be helpful in identifying these patients where additional factors need to be incorporated to categorize the patients into low and high risk group.

Distant disease recurrence is much more common in SS patients as compared to local recurrence. Survival outcomes still remain poor for these patients due to development of metastasis which can be as late as 10 years post initial treatment.[7] Thus, using chemotherapy upfront as part of neoadjuvant treatment carries a good scientific rationale. Chowdhary et al performed a retrospective review of the patients with soft tissue sarcoma treated with NACRT using concurrent chemoradiotherapy and showed a statistically significant improved OS for SS patients with HR of 0.24.[25] As treatment paradigm in medical oncology is rapidly shifting towards precision medicine based on molecular features and identification of predictive markers,

development of effective therapies directed towards driver oncogene SS18-SSX are needed to achieve better outcomes for these patients.

We found a high rate of suboptimal initial surgery for localized SS before getting referred to WA state sarcoma service. Local control was achieved in these patients with further surgery however it did increase the morbidity as 4/9 patients required amputation on their revision surgery and two patients developed distant disease failure despite achieving local control. These two patients with distant failure did not receive any systemic therapy in neoadjuvant or adjuvant setting. A serious consideration should be given to offer systemic therapy either before or after definitive surgery for the subgroup of patients with suboptimal initial surgery irrespective of the risk group category at the time of diagnosis as reported outcomes for patients have been poor historically.

Concurrent chemo-radiotherapy was delivered in almost all the patients receiving NACRT using MAID regimen and this was not associated with increased toxicities or treatment interruptions. Bone marrow toxicity was the most commonly seen higher grade toxicity in our cohort which is expected with combination of multiagent chemotherapy with radical doses of radiotherapy however it did not result into any deaths. Long term follow-up data in survivors is critical to assess delayed toxicities. Potential late complications can impact the morbidity as well as mortality for the survivors especially toxicities affecting bone marrow, cardiovascular system, bladder function, and sexual health. RTOG 9514 evaluated interdigitated chemoradiotherapy with MAID as neoadjuvant treatment for soft tissue sarcoma. High rates of disease control were reported in this trial however there was significant increase in acute and delayed bone marrow toxicities which resulted in two deaths from acute myeloid leukemia.[26] A single institution retrospective study reported its experience using modified MAID regimen for interdigitated chemoradiotherapy. Dacarbazine was omitted in the modified MAID regimen and showed much less toxicities without compromising the treatment outcomes.[27] Up until the data cutoff date there were no observed cases of late haematological complications in our cohort of patients but it reiterates the need of longer follow up for these patients.

A limitation of this study is that it is retrospective. As SS is a rare entity, it poses a challenge to clinicians and researchers to achieve an adequate cohort size to reach any meaningful conclusion whether it is done prospectively or retrospectively. Our study cohort was also relatively small. A larger study cohort was not achievable as the SS database was not available before 2006. A further limitation is that the MAID protocol showed a preponderance in our retrospective analysis because it was historically the preferred protocol for SS at our site. There are other institutions in the world where varying protocols of ifosfamide and anthracycline based chemotherapy are being integrated with radiotherapy due to toxicity concerns. In the short term we did not observe any increased toxicities in NACRT group. As SS is associated with late disease recurrence, these patients require longer ongoing follow up with their cancer clinicians to detect disease recurrence in a timely manner. Our study had a median follow up of 24 months for NACRT group and majority of these patients were treated 2013 onwards. Hence, long term follow up data was not available on these patients.

5 | CONCLUSION

Our data shows that NACRT with ifosfamide based treatment was well tolerated and did not result in poor outcomes. Higher pathological response rates as well as limb sparing surgeries were achieved with NACRT as compared to single modality neoadjuvant treatment. There was no case of local or distant disease relapse on NACRT for the patients with localized disease at the time of data cut off. NACRT is a feasible therapy option for localized SS and should be evaluated prospectively in a randomized trial.

AUTHOR CONTRIBUTIONS
Yasir Khan: Conceptualization; data curation; formal analysis; methodology; validation; writing-original draft; writing-review and editing. **Richard Carey-Smith:** Formal analysis; validation; writing-review and editing. **Mandy Taylor:** Formal analysis; validation; writing-review and editing. **Jennifer Woodhouse:** Validation; writing-review and editing. **Angela Jacques:** Formal analysis; validation; writing-review and editing. **David Wood:** Formal analysis; validation; writing-review and editing. **Anne Long:** Conceptualization; data curation; formal analysis; methodology; supervision; validation; writing-original draft; writing-review and editing.

DATA AVAILABILITY STATEMENT
The data used during the current study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.