

Favorable outcomes of localized synovial sarcoma patients with a high utilization rate of neoadjuvant and/or adjuvant chemotherapy

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Abstract. Synovial sarcoma (SS) is considered to be a chemosensitive, soft tissue sarcoma. Therefore, neoadjuvant and/or adjuvant chemotherapy (N/AC) is used for the treatment of high-risk SS patients. However, the role of N/AC remains controversial. The present study aimed to review the clinical outcomes of surgically treated localized SS and investigate the effects of N/AC with long-term observation. The clinical outcomes of 54 patients with surgically treated localized SS were retrospectively analyzed. The median patient age was 42 years (range, 8-81 years), and the median follow-up period was 94 months for survivors (range, 7-220 months). A total of 38 patients (70%) received chemotherapy. Of these, 32 (59%) patients received neoadjuvant chemotherapy, 33 (61%) received adjuvant chemotherapy, and 27 (50%) received neoadjuvant and adjuvant chemotherapy. Fourteen patients (26%) received adjuvant radiotherapy. Three patients (6%) had local recurrence and 13 patients (24%) developed distant metastasis. The overall survival (OS) rates at 5 and 10 years were 87 and 84%, respectively. N/AC did not improve survival. In conclusion, we found satisfactory long-term OS among patients with a high utilization rate of N/AC. Further study should be necessary to evaluate which population of SS would benefit from N/AC.

Introduction

Synovial sarcoma (SS) is a soft tissue sarcoma (STS) that can occur at many different locations. In Japan, SS has been ranked as the fifth most common STS, with the exception of well-differentiated liposarcoma, and its occurrence has been shown to peak in the third and fourth decades of life (1). The standard treatment for SS is wide surgical resection with or without radiotherapy, which is similar to the approach for other STSs (2). The role of chemotherapy is highly debated. A review of 15 clinical trials demonstrated that advanced SS had a better response to systemic chemotherapy than other subtypes of STS (3). Hence, neoadjuvant and/or adjuvant chemotherapy (N/AC) is frequently used for localized SS, especially in young patients (4). However, the role of N/AC is still controversial. Several large studies have demonstrated a survival benefit with N/AC (5-7), whereas others have not demonstrated such a benefit (4,8-10). Further, the dose efficacy of N/AC remains unclear. The present study aimed to review the clinical outcomes of surgically treated localized SS and investigate the effects of N/AC with long-term observation.

Patients and methods

We assessed our institutional database and identified 54 patients with histological diagnosis of localized SS treated between 2000 and 2016. All patients were staged according to computed tomography (CT) and/or magnetic resonance imaging (MRI) findings. The 8th American Joint Committee on Cancer (AJCC) staging system was used for disease staging (11). The greatest dimension of the tumor was defined as tumor size. Tumor grading was evaluated using the French Federation of Cancer Centres Sarcoma Group (FNCLCC) grading system (12). According to the FNCLCC grading system, the tumor could be either grade 2 or grade 3,

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depending on the mitotic rate, the extent of necrosis, or both; however, no grading information was available. The resection margin status was classified as R0 (macroscopically and microscopically clear), R1 (macroscopically clear and microscopically involved), and R2 (macroscopically involved). Inclusion criteria of N/AC were deep located and ≥ 5 cm tumors. If tumor was attached to critical structures, or seemed to contaminate surrounding tissue after unplanned surgery, the use of N/AC depended on the physician's choice. Exclusion criteria of N/AC was superficial located and < 5 cm tumors and patients > 70 years old. The administered regimen was doxorubicin (60 mg/m^2) in combination with ifosfamide ($6\text{--}10 \text{ g/m}^2$), high-dose ifosfamide ($12\text{--}15 \text{ g/m}^2$), or both. When histology showed the existence of poorly differentiated component, regimens administered were doxorubicin (60 mg/m^2) in combination with vincristine (1.5 mg/m^2) and cyclophosphamide ($1,000 \text{ mg/m}^2$), ifosfamide (5 g/m^2) in combination with etoposide (300 mg/m^2). If surgical margin was contaminated, or close to the tumor, radiotherapy was used based on physician's choice. Patients were followed up at our outpatient clinic every 3 months during first 2 years, every 6 months during next 3 years, then annually until 10 years had passed or death. At each visit, chest radiographs were obtained. Chest CT and/or local MRI were performed at intervals of 3–6 months until 5 years. This study was approved by Osaka University Clinical Research Review Committee, and waived off the requirement for written informed consent from the subjects (certificate no. 14240-2).

Statistical analysis. We assessed local recurrence free survival (LRFS), overall survival (OS), and metastasis-free survival (MFS) using the Kaplan-Meier method with 95% confidence intervals (CIs). Differences between LRFS, OS, and MFS were compared using the log-rank test. Descriptive statistics were used to show the distribution of variables in the population. All statistical analyses were performed using SPSS 23.0 software (IBM Corp., Armonk, NY, USA). $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Patient and treatment demographics. The study included 54 patients (23 male and 31 female patients). The median patient age was 42 years (range, 8–81 years), and the median follow-up period was 94 months for survivors (range, 7–220 months). Fifteen patients were referred after unplanned surgery, 36 had initial definitive treatment at our institutions, and 3 had no records about initial treatment before reference. All patients underwent surgical resection of the primary tumor. Six patients (11%) had positive surgical margins. Of the 6 patients, 3 had R2 resection and 3 had R1 resection. Fourteen patients (26%) received radiotherapy after surgery. Thirty-eight patients (70%) were treated with chemotherapy. Neoadjuvant chemotherapy and adjuvant chemotherapy were used in 32 patients (59%) and 33 patients (61%), respectively. Twenty-seven (50%) patients received both neoadjuvant and adjuvant chemotherapy. All patients with stage III tumors, except 3 patients, received N/AC. One patient did not receive chemotherapy because of high age (81 years) and the other patients because of superficial location. Their tumor size were

Table I. Clinical and treatment characteristics.

Variables	All patients		P-value
	N/AC (-)	N/AC (+)	
Sex			0.911
Male	7	16	
Female	9	22	
Age			0.233
< 40	6	21	
$40 \leq$	10	17	
Unplanned surgery			0.559
Yes	6	9	
No	9	27	
ND	1	2	
Grade			0.005
2	11	15	
3	1	20	
ND	4	3	
Depth			0.008
Superficial	6	3	
Deep	10	35	
Size			< 0.001
< 5 cm	12	9	
$5 \text{ cm} \leq$	3	29	
Site			0.981
Limbs	11	26	
Axial	5	12	
Stage			< 0.001
II	13	9	
III	3	29	
Surgical margin			0.246
Negative	13	35	
Positive	3	3	
RT			0.562
Yes	5	9	
No	11	29	

N/AC, neoadjuvant and/or adjuvant chemotherapy; ND, no data; RT, radiotherapy. χ^2 test was used to analyze the relationships between the variables.

8 and 10 cm. The factors associated with receipt of N/AC were grade 3 histology, deep-seated location, tumor size ≥ 5 cm, and stage III tumor (Table I). The factors associated with receipt of radiotherapy were positive surgical margins, age ≥ 40 , and grade 3 tumor ($P = 0.001$, $P = 0.062$, and $P = 0.08$, respectively; data not shown).

Outcomes. Three patients (6%) had local recurrence (LR) and 13 patients (24%) developed distant metastasis. Of the 13 patients who developed distant metastasis, 8 died of SS, 4 showed no evidence of disease after metastasectomy, and one lost follow-up due to shifting to palliative care.

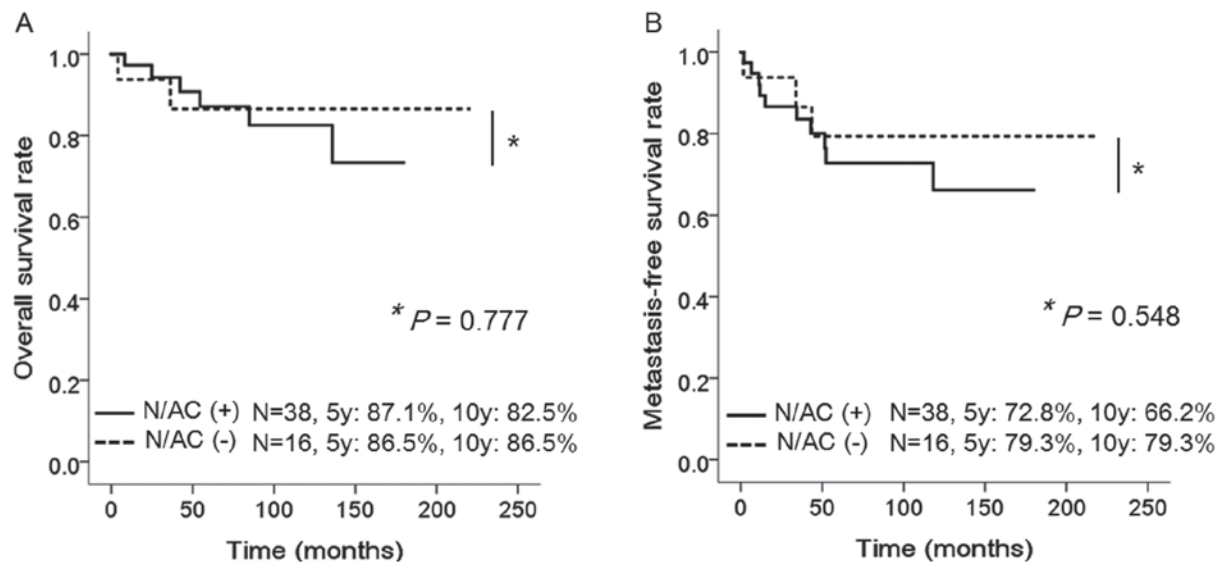


Figure 1. (A) Overall survival in all patients who received (continuous line) and those who did not receive (broken line) neoadjuvant and/or adjuvant chemotherapy. No significant difference is observed between the groups ($P=0.777$). (B) Metastasis-free survival in all patients who received (continuous line) and those who did not receive (broken line) neoadjuvant and/or adjuvant chemotherapy. No significant difference is observed between the groups ($P=0.548$).

One patient died of another cause. The 5- and 10-year LR rates were 93.7% (95% CI, 86.8-100) and 93.7% (95% CI, 86.8-100), respectively. Tumor size <5 cm was associated with worse LRFS ($P=0.033$). The 5- and 10-year MFS rates were 74.7% (95% CI, 62.2-87.2) and 70.0% (95% CI, 55.3-84.7), respectively. Tumor size ≥ 5 cm, and receipt of radiotherapy were significantly associated with worse MFS ($P=0.045$, and $P=0.02$, respectively). The 5- and 10-year OS rates were 87.1% (95% CI, 77.6-96.9) and 83.7% (95% CI, 72.3-95.1), respectively. Receipt of radiotherapy was significantly associated with worse OS ($P=0.02$) (Table II), probably due to selection bias. Because receipt of radiotherapy was associated with positive surgical margins, age ≥ 40 , and grade 3 tumor ($P=0.001$, $P=0.062$, and $P=0.08$, respectively; data not shown) N/AC did not have significant effects on LR, MFS, and OS ($P=0.131$, $P=0.548$, and $P=0.777$, respectively; Fig. 1).

Discussion

In the present study, the 5- and 10-year OS rates were found to be 87.1 and 83.7%, respectively. To our knowledge, this is the best long-term result among published large series involving adult SS patients (Table III), although Krieg *et al* (13) reported that SS tends to develop metastasis late with high mortality. There are 3 possible factors to explain the favorable outcomes. The first is patient and tumor demographics. A number of prognostic factors for localized SS have been reported, and among them, the relatively common favorable factors were small tumor size and young age at diagnosis (4,5,7-9,14). It remains unclear whether the prognostic significance of age is related to biological variables or to historically different treatment approaches adapted in pediatric vs. adult patients (15). The proportion of tumors measuring ≥ 5 cm and the median age at diagnosis in this cohort were comparable to the values in previous studies (Table III). Thus, patient and tumor demographics appear to have less effect on the outcomes. The second is primary treatment. In this study, the status of the surgical

margin was comparable to that in previous studies and the rate of adjuvant radiotherapy use was lower than that in previous studies (Table III). On the contrary, the proportion of patients who received N/AC was higher than that in previous studies (Table III). The third is treatment after tumor relapse. For the last 3-4 decades, there have been few options other than doxorubicin and ifosfamide for the treatment of advanced STS. Recently, 3 new drugs (pazopanib, trabectedin, and eribulin) were approved in Japan for the treatment of advanced STS. The effects of these new drugs on SS have not been clarified yet, but it is possible that these new drugs will prolong the survival of patients with relapsed SS. Furthermore, 4 patients achieved disease free survival after metastasectomy. Hence aggressive treatment after tumor relapse including local and systematic therapy likely contributed to prolong the survival. However, considering that the rates of local recurrence and distant metastasis were lower in this study than those in previous studies (Table III), primary treatment appears to have a more vital role than treatment after tumor relapse. Taken together, the effect of N/AC on survival is considered important in this cohort.

The effect of N/AC on SS has not been proven previously, and study results have been conflicting. Italiano *et al* (10) demonstrated that N/AC did not have a significant impact on OS, using the French Sarcoma Group Database. On the contrary, Chen *et al* (16) reported that adjuvant chemotherapy improved disease-specific survival and prolonged the time to metastasis in stage IIB/III SS patients. Recently, Vining *et al* (17) reported improved outcomes with adjuvant chemotherapy in stage III SS patients from an analysis of the National Cancer Database and recommended less restricted use of adjuvant chemotherapy for stage III SS. These differences might come from varying use of chemotherapy regimens among patients and different proportions of N/AC administration. Besides which population of stage III SS could improve survival by N/AC is still unclear. In this study, all patients with stage III SS, except 3 patients, received N/AC. Of the 3 patients, one died of disease

Table II. Univariate analysis of factors influencing LRFS, MFS, and OS.

Variables	LRFS P-value	MFS P-value	OS P-value
Sex			
Male	0.703	0.511	0.239
Female			
Age			
<40	0.608	0.598	0.357
40≤			
Unplanned surgery			
Yes	0.331	0.061	0.234
No			
ND			
Site			
Limbs	0.198	0.071	0.343
Axial			
Size			
<5 cm	0.033	0.045	0.093
5 cm ≤			
Depth			
Superficial	0.42	0.084	0.193
Deep			
Histology			
Monophasic	0.635	0.272	0.915
Biphasic			
NOS			
Grade			
2	0.513	0.191	0.340
3			
ND			
Surgical margin			
Negative	0.12	0.068	0.118
Positive			
RT			
Yes	0.601	0.02	0.020
No			
N/AC			
Yes	0.131	0.548	0.777
No			

LRFS, local recurrence free survival; MFS, metastasis-free survival; OS, overall survival; RT, radiotherapy; N/AC, neoadjuvant and/or adjuvant chemotherapy; ND, no data. Differences between LRFS, MFS, and OS were compared using the log-rank test.

4 months after surgery, 2 were continuous disease free for 69 and 50 months after surgery. Thus, we could not compare the effects of N/AC in high-risk patients properly and recommend that all stage III patients should have N/AC. Nonetheless, the treatment resulted in better long-term outcomes than those of previous studies. Collectively, our results suggest that patients with stage III SS include the population of patients who benefit

Table III. Published large series on localized synovial sarcoma including adult patients.

	Number of patients	Proportion of tumors measuring ≥5 cm	Age (median)	Follow-up (months)	Surgical margin (% positive)	N/AC (%)	RT (%)	LR (%)	DM (%)	5-y OS (%)	10-y OS (%)
Bergh <i>et al</i> (14)	121	ND	34	118	ND	32	27	31	54	60	50
Lewis <i>et al</i> (8)	112	45	35	72	14	37	46	15	39	75	ND
Trassard <i>et al</i> (9)	128	ND	33	37	24	57	80	24	48	63	ND
Ferrari <i>et al</i> (5)	215	52	ND	65	ND	28	50	37	49	72	ND
Canter <i>et al</i> (7)	255	56	34	72	14	39	63	ND	45	72	60
Palmaerini <i>et al</i> (4)	204	51	36	66	12	52	52	18	27	76	ND
Italiano <i>et al</i> (10)	237	ND	35	58	14<	60	76	24	45	64	<46
Current study	54	59	42	78	11	70	26	6	24	87	84

N/AC, neoadjuvant and/or adjuvant chemotherapy; RT, radiotherapy; LR, local recurrence; DM, distant metastasis; OS, overall survival; ND, no data.

from N/AC and high utilization of N/AC in SS might improve long-term outcomes.

Some studies have shown that adjuvant radiotherapy improved survival in SS patients (18,19). However, we showed that radiotherapy had adverse effects on OS and MFS. Receipt of radiotherapy was associated with positive surgical margins, age ≥ 40 , and grade 3 tumor ($P=0.001$, $P=0.062$, and $P=0.08$, respectively; data not shown); thus, the adverse effects of radiotherapy observed in this study resulted from selection bias and we were not able to evaluate the impact of radiotherapy appropriately. In this study, radiotherapy and surgical margin did not correlate with LRFS probably due to low rate of LR. Surprisingly, tumor size <5 cm was associated with LRFS. Because 2 of the 3 patients who developed LR had unplanned surgery, we speculated the correlation might be affected by unplanned surgery.

The present study has several limitations. The number of patients was too small to draw a definitive conclusion. There were no information of chromosomal translocation. We did not use fluorescent *in situ* hybridization for diagnosis, and that might affect the patient population. We were not able to obtain histological grading information in some cases. It was sometimes difficult to determine FNCLCC grading after neoadjuvant chemotherapy. Administration regimens were not uniform. The rate of positive surgical margins was comparable to that reported in previous series, but the rate was the lowest among previously reported rates. This might be associated with lower local recurrence rates and might influence favorable outcomes. The rate of radiotherapy use was low. Usually, radiotherapy is considered useful for local control, and it can improve survival in SS patients (19). We considered that the low rate of radiotherapy use did not lead to overestimation of the effects of N/AC. Finally, there was possible selection bias with regard to receipt of N/AC. We delivered N/AC to almost all high-risk patients, and we failed to assess the effects of N/AC appropriately.

In conclusion, we demonstrated satisfactory long-term outcomes in localized SS patients with a high utilization rate of N/AC. We failed to show the impact of N/AC on survival probably due to high use of N/AC on stage III patients. Further study should be necessary to evaluate which population of SS would benefit from N/AC.

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Availability of data and materials

The datasets used in the present study are available from the corresponding author on reasonable request.

Authors' contributions

HO conceived and designed the study, collected, analyzed, and interpreted the data, and wrote the manuscript. SK analyzed

data and revised the manuscript. KH and ST collected data and reviewed the manuscript. SN reviewed the histological grading of the tumor specimens. YI, TT, HT, and KO collected and interpreted data. NN, IK, NA, TU, and HY analyzed and interpreted the data and reviewed and revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by Osaka University Clinical Research Review Committee, and waived off the requirement for written informed consent from the subjects (certificate no. 14240-2).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no conflict of interest.

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