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Impact of Acridine Orange in Patients With Local Recurrent Soft Tissue Sarcoma

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Abstract. *Background/Aim: Local recurrence in soft tissue sarcoma (STS) is a risk factor of worse prognosis. Although a few studies have shown that adjuvant therapy with acridine orange (AO) is effective for local control of primary STS, there have been no reports examining its effectiveness for local recurrence. Patients and Methods: This retrospective study included 36 patients with first local recurrence of STS. Of them, 23 patients received wide excision without AO therapy (Wide group); the other 13 patients received marginal excision with AO therapy (AO group). We compared re-recurrence rates between these two groups. Results: The total re-recurrence rate was 43.5% in the Wide group and 46.2% in the AO group. There was no significant difference in local re-recurrence-free survival and overall survival between the two groups. Conclusion: Adjuvant AO therapy combined with a marginal excision suppresses local re-recurrence rates of individuals with local STS recurrence.*

Soft tissue sarcoma (STS) is relatively rare compared with other types of cancer. Radical resection with an adequate margin is important in the treatment of STS for the prevention of local recurrence. However, when tumors are in contact with important tissues such as major nerves or blood vessels, removing these important tissues can cause serious dysfunction. If resection is conducted in the area where the tumor is in contact with the tissue, the recurrence rate increases. Local recurrence itself is a risk factor of local re-recurrence and a worse prognosis; once local recurrence occurs, it is more difficult to control the STS (1).

Kusuzaki *et al*. were the first to report the effectiveness of acridine orange (AO) treatment as an adjuvant therapy in soft tissue sarcomas in various different studies (2-8). AO accumulates in acidic environments. As sarcoma cells have many large acidic vesicles, AO specifically binds to malignant tumors and immediately accumulates in tumor cells after local administration (9-13). AO has a strong cell-destructive effect on tumor cells after a single session of blue light excitation or low-dose radiation, which kills residual tumor cells after tumor resection.

Several studies have shown that adjuvant therapy with AO is effective on the local control of primary STS (2-8, 14). However, there have been no reports examining the effectiveness of AO treatment for local recurrence cases of STS. The aim of this study was to clarify the efficacy of AO therapy by comparing marginal excisions with adjuvant AO therapy and wide excisions in STS patients with local recurrence.

Patients and Methods

Patients. Forty-two STS patients with local recurrence involving the extremities or trunk were treated with surgical resection, with the exception of amputation surgery, conducted in the Akita University Hospital and Sapporo Medical University Hospital between January 1994 and December 2019. They had not developed distant metastases prior to the surgery for the local recurrence. We defined marginal excision as a resection through the capsule of the tumor and intralesional excision as resection through the tumor; we excluded 4 cases of marginal excision without AO therapy and 2 cases of intralesional excision in this study. Consequently, 36 patients with local STS recurrence treated with wide excision or marginal excision with AO therapy, with a mean age of 66.9 years (range=32-88 years), were included in this study. Twenty-three of the 36 patients underwent wide excision on the recurrent lesion (Wide group), and the other 13 patients were treated by marginal excision with AO therapy on the recurrent lesions (AO group).

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Key Words: Acridine orange, local recurrence, soft tissue sarcoma.

Table I. *Comparison of patient characteristics between those in the wide excision and those in the acridine orange groups.*

	Wide group (%)	AO group (%)	*p*-Value
Number	23	13	
Age (years)	68.4±17.9	64.4±16.6	0.518
Gender – Male/Female	12/11	6/7	1.00
Histological diagnosis			
Undifferentiated pleomorphic sarcoma	6 (26.1)	2 (15.4)	
Myxofibrosarcoma	10 (43.4)	2 (15.4)	
Dedifferentiated liposarcoma	2 (8.7)	2 (15.4)	
Pleomorphic liposarcoma	0 (0)	1 (7.7)	
Myxoid liposarcoma	3 (13.0)	1 (7.7)	
Synovial sarcoma	0 (0)	2 (15.4)	
Low grade fibromyxosarcoma	0 (0)	1 (7.7)	
Extraskeletal myxoid chondrosarcoma	0 (0)	1 (7.7)	
Leiomyosarcoma	2 (8.7)	0 (0)	
Alveolar soft-part sarcoma	0 (0)	1 (7.7)	
Location – Extremity/Axial	13/10	6/7	0.802
Size at first consultation (mm)	69.3±50.0	99.5±71.9	0.170
FNCLCC classification			0.930
Grade I/II/III/Unknown	4/5/13/1	2/4/7/0	
AJCC stage			0.530
Stages I/II/III/Unknown	4/11/7/1	2/5/6/0	
Adjuvant therapy in the first perioperative period			
Chemotherapy – Present/None	0/23	2/11	0.239
Radiotherapy – Present/None	2/21	2/11	0.951
Surgical margin – Adequate/ Inadequate	11/12	5/8	0.848
Time to local recurrence (months)	30.1±22.4	17.5±14.3	0.077
Size at recurrence (mm)	52.4±29.6	49.1±24.1	0.729
Adjuvant therapy in the second perioperative period			
Chemotherapy – Present/None	2/21	0/13	0.7364
Radiotherapy – Present/None	0/23	0/13	–
Local re-recurrence – Present/None	10/13	6/7	0.846
Total re-recurrence rate (%)	43.5	46.2	
5-year local re-recurrence rate (%)	47.1	33.3	0.797
Number of local recurrences	1.6±1.0	2.1±1.4	0.256
Metastasis after recurrent surgery – Present/None	5/18	5/8	0.691
Total follow up period (months)	59.8±40.8	53.3±36.0	0.552
Follow up period after re-operation (months)	39.2±27.9	34.2±54.5	0.765
Outcome at the last follow-up			0.548
Alive without disease/ Alive with disease/Dead	15/1/7	7/4/2	

Values are expressed as the number and proportion of patients or means±standard deviations (SD) with ranges. AO: Acridine orange; FNCLCC: French Federation of Cancer Center Sarcoma Group; AJCC: American Joint Committee on Cancer.

Table II. *Univariate logistic regression analysis of factors affecting the local "re-recurrence" of patients.*

Variables	Univariate		
	OR	95%CI	*p*-Value
Age	1.012	0.981-1.044	0.452
Gender – Female	0.318	0.113-0.894	0.030
Location – axial	1.685	0.623-4.554	0.304
Size at first consultation	1.002	0.994-1.010	0.640
FNCLCC classification	0.999	0.519-1.923	0.997
AJCC stage	1.240	0.566-2.714	0.591
First surgical margin – Inadequate	0.790	0.285-2.186	0.649
Time to local recurrence	1.000	0.976-1.024	0.972
Size at recurrence	0.995	0.975-1.015	0.617
Second surgery–AO+ Marginal excision	1.413	0.504-3.956	0.511
Metastasis after recurrent surgery	2.062	0.741-5.736	0.166

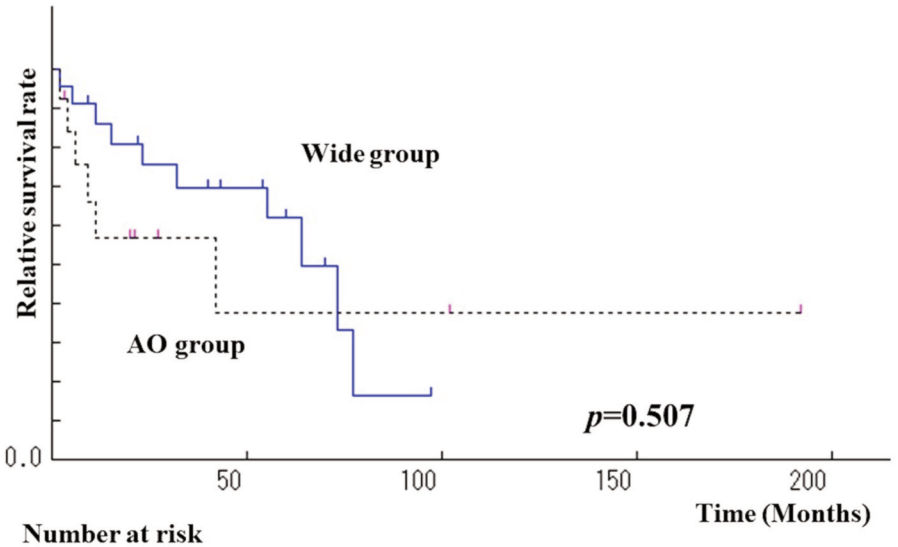
OR: Odds ratio; 95%CI: 95% confidence interval; FNCLCC: French Federation of Cancer Center Sarcoma Group; AJCC: American Joint Committee on Cancer; AO: acridine orange.

Marginal excision with AO therapy was performed on patients when the recurrent tumor was contacting major nerves or vessels, bones, and/or major organs without any signs of massive invasion upon pre-surgery imaging evaluation.

This study was approved by the Institutional Review Board for Clinical Research at Akita University (approval number: 221), and informed consent was obtained from all patients.

Data variables and definitions. Information collected from the patients included: age, gender, histological diagnosis of the tumor, anatomical location of the tumor, primary and recurrence tumor sizes, histological grade, stage of the primary tumor, treatments for the primary and recurrence tumors, local re-recurrence, distant relapse, time to the local recurrence, follow-up period, and outcomes. The stage of the primary tumor was determined based on the staging system of the American Joint Committee on Cancer (AJCC), 7th edition (15). Histological grade of the specimens was classified using the French Federation of Cancer Center Sarcoma Group (FNCLCC) classification. This classification is based on the mitotic index, necrotic extension, and histological differentiation of the tumor (16). In the absence of death, the date of the last follow-up was defined as the end of the follow-up period. The local re-recurrence-free survival (LRRS) was defined as the period from the surgery for the recurrent tumor till the diagnosis of local re-recurrence. Overall survival (OS) was defined as the period from the date of the primary tumor diagnosis to the last follow-up or death. As there were no deaths due to postoperative complications in this study, we defined the deaths from STS as "died of disease" (DOD). Cases were regarded to have a surgical indication if all lesions, including distant metastases, were able to be excised.

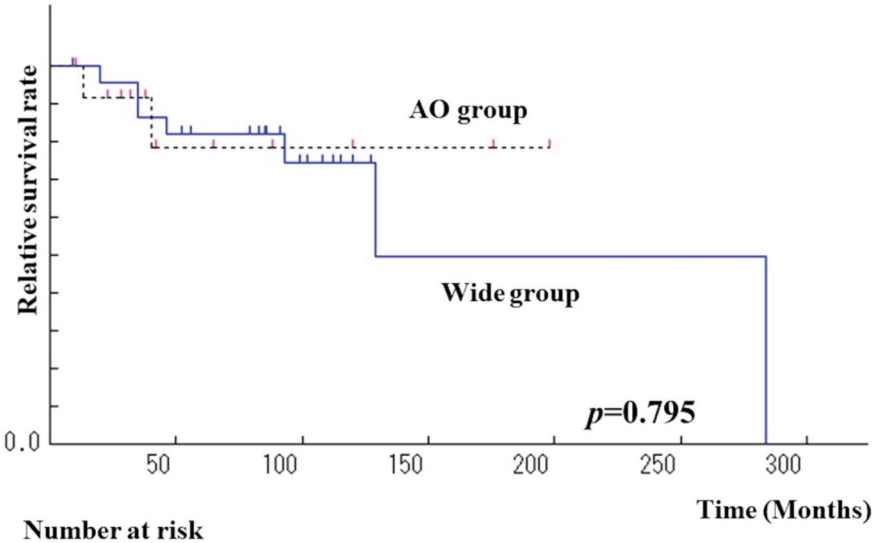
Procedures for AO therapy. We conducted AO therapy, including photodynamic surgery (PDS), photodynamic therapy (PDT), and radiodynamic therapy (RDT), according to methods previously reported (2-7). After marginal excision of STS, a 1 μg/ml solution



Number at risk

Wide	23	10	0	0	0
AO	13	2	2	1	0

Figure 1. *Kaplan-Meier local re-recurrence-free survival curves based on the use of acridine orange in all patients. There was no significant difference between the two groups. AO: Acridine orange.*



Number at risk

Wide	23	18	9	1	1	1	0
AO	13	5	3	2	0	0	0

Figure 2. *Kaplan-Meier overall survival curves based on the use of acridine orange in all patients. There was no significant difference between the two groups. AO: Acridine orange.*

of AO (Sigma Aldrich Co, St Louis, MO, USA) was sprayed around the major nerves, vessels, and organs. Microscopic curettage was conducted using an ultrasonic surgical knife (Olympus Co. Ltd., Tokyo, Japan), a high-power xenon lamp (500 mW; >100,000 lux), and special interference and resorption filters (450-490 nm) to select only the blue light emitted by a xenon lamp (PDS). Administration of the AO-fluid and microscopic curettage was repeated until the green AO-fluorescence area marking the remaining tumor cells had disappeared completely. PDT was followed by PDS. PDT was subsequently applied to the resected area of the tumor by

Table III. *Univariate and multivariate analysis of factors affecting prognosis.*

Variables	Univariate			Multivariate		
	OR	95%CI	*p*-Value	OR	95%CI	*p*-Value
Age	1.016	0.973-1.060	0.477			
Gender – Female	0.076	0.009-0.635	0.017	0.165	0.019-1.429	0.102
Location – axial	1.179	0.292-4.753	0.817			
Size at first consultation	1.006	0.995-1.016	0.282			
FNCLCC classification	2.200	0.569-8.515	0.253			
AJCC Stage	3.318	0.869-12.662	0.079			
Chemotherapy in the first perioperative period	1.650	0.195-13.982	0.646			
Radiotherapy in the first perioperative period	2.193	0.437-11.010	0.340			
First surgical margin -Inadequate	0.994	0.233-4.249	0.994			
Time to local recurrence	0.978	0.942-1.015	0.235			
Size at recurrence	1.032	1.010-1.054	0.004	1.045	1.010-1.081	0.011
Second surgery–AO+Marginal excision	0.808	0.161-4.060	0.796			
Local “re-recurrence”	1.134	0.281-4.570	0.860			
Number of local recurrences	1.296	0.774-2.170	0.323			
Metastasis after recurrent surgery	7.535	1.502-37.797	0.014	13.618	1.465-126.564	0.022

OR: Odds ratio; 95%CI: 95% confidence interval; FNCLCC: French Federation of Cancer Center Sarcoma Group; AJCC: American Joint Committee on Cancer; AO: acridine orange.

illuminating it with >100,000 lux of unfiltered light from a xenon lamp for 10 min. The final step, RDT, was performed in patients who agreed to undergo RDT. After closure of the surgical wound, without washing of the AO solution, single-session radiotherapy with 5 Gy was immediately administered to the resected area. Although it was policy to conduct RDT in all cases, we did not conduct RDT when patients did not agree to it or when the radiation room was not available immediately after surgery.

Statistical analysis. We compared the clinical courses and results between the Wide and the AO groups, and analyzed the factors affecting the local re-recurrence and prognosis after the recurrence.

All continuous variables were expressed as means±standard deviations (SD). Student’s *t*-tests, Welch *t*-tests, and Chi Squared (χ^2) tests were used to compare characteristics between the two groups. The curves for LRRS and OS were drawn using the Kaplan-Meier method, and differences were analyzed using the generalized Wilcoxon test. A Cox proportional hazards model was used to identify the factors associated with local re-recurrence and prognosis. Probability (*p*) values less than 0.05 were considered significant.

Results

The mean follow-up period for all patients was 82.4±57.8 months (range=9-284 months). The histological diagnoses were myxofibrosarcoma in 12 cases (33.3%), undifferentiated pleomorphic sarcoma in 8 cases (22.2%), dedifferentiated liposarcoma in 4 cases (11.1%), myxoid liposarcoma in 4 cases (11.1%), synovial sarcoma in 2 cases (5.6%), leiomyosarcoma in 2 cases (5.6%), and 1 case each (2.8%) of pleomorphic liposarcoma, low grade fibromyxosarcoma, extraskeletal myxoid chondrosarcoma, and alveolar soft-part sarcoma. The sites of the primary lesions were in the extremities in 19 patients (52.8%) and in axial sites in 17 patients (47.2%). The mean tumor size at the primary lesion and recurrence was 81.6±60.7 mm (range=18-250 mm) and 51.2±27.4 mm (range=14-130 mm), respectively. The FNCLCC classifications were grade I for 6 patients, grade II for 9 patients, grade III for 20 patients, and unknown for 1 patient. According to the AJCC staging system, the disease stages of the primary tumor were IA for 2 patients, stage IB for 4 patients, stage IIA for 14 patients, stage IIB for 2 patients, stage III for 13 patients, and unknown for 1 patient. Neoadjuvant chemotherapies in the perioperative period, involving doxorubicin and ifosfamide, were administered to 2 patients for the primary tumor and 2 patients for the recurrent lesions. Adjuvant radiotherapy was performed for 4 patients in the primary perioperative period. Adequate tumor-free margins for the primary tumor were achieved for 16 patients (44.4%). The mean period until the appearance of local recurrence for all patients was 25.6±20.6 months (range=2-68 months). In the AO group, the combined treatment of PDS and PDT for the recurrent lesion was performed in 11 (84.6%) patients; PDS, PDT, and RDT for the recurrent lesion were performed in 2 (15.4%) patients. A total of 16 patients (44.4%) developed local re-recurrence. The number of local recurrences, including the first recurrence within the follow-up period, was 1.8±1.2 times (range=1-5 times). Ten patients (27.8%) developed metastases after the initial local recurrence surgery. At the end of the study, no evidence of disease was found in 22 patients, 5 patients were classified as alive with disease, and 9 patients died of disease. No patients died because of complications during the perioperative period.

There were no significant differences in clinical information between the Wide group and the AO group (Table I). The 5-

year local re-recurrence rate was 47.1% in the Wide group and 33.3% in the AO group; the total re-recurrence rate was 43.5% in the Wide group and 46.2% in the AO group. There were no significant differences in the Kaplan-Meier curves for local re-recurrence survival and overall survival between the two groups (Figures 1 and 2). In the univariate logistic analysis, which investigated factors associated with the local re-recurrence, only male gender was identified as a risk factor for local re-recurrence ($p<0.05$) (Table II). In univariate analysis, which investigated factors associated with prognosis, male gender, tumor size at the recurrence, and metastasis after the surgery for the recurrence were identified as risk factors for poor prognosis. Multivariate analysis identified the tumor size at recurrence and metastasis after the surgery as risk factors for poor prognosis ($p<0.05$) (Table III).

Discussion

Clinical results of marginal excision with AO have been reported to be equivalent to wide excision (2-8). In our previous research, we reported that local control of STS by marginal excision with AO therapy was significantly better than that of marginal excision without adjuvant therapy (14). Our current study showed that a marginal excision with AO can provide local control equivalent to a wide excision, even in local and aggressive recurrent STS cases. Marginal excision with AO requires less tissue to be resected than wide excision, and functional preservation can be expected. Due to the suppressive effects on recurrence and preservation of postoperative function, marginal excision with AO therapy is considered to be an effective treatment.

In the present study, the local re-recurrence rate was relatively high; 43.5% after the extensive resection and 46.2% after the marginal excision with AO. Previous reports of local re-recurrent rates of STS ranged from 20-47%, and the results of surgical treatment for local recurrence generally tended to be worse than the results of the initial surgical treatment (1, 17-24). Among these reports, Sugiura *et al*. analyzed re-recurrence in STS cases, and reported a low re-recurrence rate (20%). Furthermore, they reported that a resection with a margin of 2 cm or more has a local control rate of 87.2% (17); they had also removed all the scar tissue in the resection area of the initial operation. In some of the present cases, we did not perform sufficient excision of the scar tissue after the initial excision. In addition, the Wide group in the present study included cases whose resection margin is not marginal but less than 2 cm. The lack of a stricter definition of the surgical margin may have led to the present high re-recurrence rate. Although our research shows the effectiveness of adjuvant AO therapy, in cases of local recurrence that was difficult to control locally, AO therapy did not show more efficacy than extensive excision.

This study identified male gender as a risk factor for local re-recurrence. Risk factors for local re-recurrence, such as the excision margin, occurrence in the upper limbs, and no adjuvant therapy, have been reported (1, 17, 18). In our study, there were no cases of adjuvant radiotherapy in the perioperative period of local recurrence, and few patients received chemotherapy. The relatively low local control rate in our cases may have been affected by not administering adjuvant therapy. However, Torres *et al*. also reported that adjuvant radiotherapy for local recurrence did not show effectiveness (18). Because there are still conflicting opinions, more cases should be examined in the future to clarify the risk factors of re-recurrence.

The risk factors of prognosis in the cases of local recurrence reported in past studies include the size of the locally recurrent tumor, male gender, and the tumor being histologically high grade (1). In our study, the size of locally recurrent tumor was identified as a poor prognostic factor, along with the appearance of distant metastases. This result shows that a careful follow-up after the first operation is imperative in order to identify local recurrences early.

One of the main limitations of this study was the small number of patients. Several factors may have led to biases, such as histological malignancy, size, and location of the tumor; a larger number of patients are needed to sufficiently analyze these factors. Although we initially targeted more patients, by refining our cases to exclude patients with distant metastasis or amputation, the number of cases in this study was reduced.

This study shows that the inhibitory effect of a marginal excision with adjuvant AO therapy on local re-recurrence of local recurrent STS is just as efficacious as a wide excision. The size of the locally recurrent tumor, and distant metastasis after the surgery for the recurrent lesion affect prognosis, which demonstrates the importance of these factors in the careful follow-up of patients after the first operation.

Conflicts of Interest

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Authors' Contributions

All Authors were involved in the planning and revising for this research; Tsuchie H, Nagasawa H, Emori M, Murahasi Y, Mizushima E, and Shimizu J collected the clinical data; Tsuchie H analyzed the raw data; Tsuchie H wrote this manuscript; Miyakoshi N, Okada K, Yamashita Y, and Shimada Y reviewed this manuscript.

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