

Surgical Treatment and Prognosis of Soft Tissue Sarcoma in Patients Aged 85 Years and Older

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Abstract

Background/Aim: The incidence of soft tissue sarcomas (STSs) among older patients is increasing. Although it has been reported that surgical treatment of elderly patients with STS improves prognosis, most of these studies included patients aged <85 years. This study aimed to analyze the clinical features and prognostic factors of STS in excessively elderly patients aged ≥85 or ≥90 years.

Patients and Methods: We retrospectively identified 398 patients with STS who were treated at our two hospitals between 1994 and 2022. Only histological types that existed in ≥20 cases were included. Data on clinical information and detailed assessments were collected. We divided the patients into two subgroups according to 85 or 90 years of age and compared the groups within each subgroup. Furthermore, we examined the factors affecting the prognosis of all and older patients.

Results: Patients ≥85 or ≥90 years old comprised 12.1% and 4.0% of the study population, respectively. In all patients, Kaplan-Meier curves for overall survival demonstrated a significantly poorer prognosis in elderly patients with STS aged ≥85 years ($p=0.0476$) and ≥90 years ($p=0.0164$). However, no significant differences were observed when analyzing only patients who underwent surgical treatment without distant metastasis at diagnosis. In the multivariate analyses, surgical treatment for the primary tumor improved prognosis exclusively in patients ≥85 years old ($p=0.0300$).

Conclusion: Surgical treatment improves the prognosis in elderly STS patients aged ≥85 years and possibly among those aged ≥90 years.

Keywords: Elderly, soft tissue sarcoma, surgery, 90 years old.



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Introduction

In recent years, the rapid aging of the population has become a social problem in developed countries (1). Because soft tissue sarcoma (STS) is generally a malignant tumor that is more likely to occur in middle-aged and elderly people, it is expected that the number of elderly cases of STS is also increasing. Patients with STS aged ≥ 85 and ≥ 90 years accounted for approximately 4.1% and 1.0% of all patients with STS in 2009; however, due to the aging population in Japan the proportion of patients in these age groups increased to 9.1% and 2.5% in 2021 (2, 3).

It has been well reported that older age is one of the poor prognostic factors for STS (4). Although the principal treatment for STS is surgical resection, a less aggressive treatment is sometimes selected for elderly patients owing to comorbidities and decreased performance status. However, in recent years, surgical treatment has been reported to improve the prognoses of elderly STS patients. Most of these studies included patients with STS aged ≥ 65 years, ≥ 70 years, and at most ≥ 80 years (4-14). Although some reports have examined patients with STS aged ≥ 85 years, very few studies are available (15-18). Previous studies comparing STS in patients over 85 years old with those younger showed the possibility of improving prognosis in patients over 85 years old through surgical treatment. However, these studies included a small number of cases (15, 16). In addition, a previous study examining 16 STS cases in patients over 90 years old showed that surgical treatment yielded a better prognosis than radiation therapy but did not compare the prognosis with younger age groups (18).

This study aimed to analyze the clinical features and prognostic factors of excessively elderly patients with STS aged ≥ 85 and ≥ 90 years in a large number of cases.

Patients and Methods

Subjects. We retrospectively identified 460 patients with STS involving the extremities or trunk who began treatment at Akita University Hospital and Sapporo Medical University Hospital, between January 1994 and March 2023. To reduce

the influence of variations in histological characteristics, only histological types with at least 20 cases were included in this study. Finally, we included a total of 398 patients with STS [211 males and 187 females; mean age (range), 64.8 (10-94) years]. The eligible histological subtypes with ≥ 20 cases were as follows: i) myxoid liposarcoma, ii) dedifferentiated liposarcoma, iii) pleomorphic liposarcoma, iv) undifferentiated pleomorphic sarcoma (UPS), v) myxofibrosarcoma, vi) synovial sarcoma, vii) malignant peripheral nerve sheath tumor, and viii) leiomyosarcoma.

Patient records were searched to collect data, including age, sex, period from onset to consultation, presence or absence of unplanned excision, anatomical tumor location, size, malignancy, metastasis at diagnosis, primary tumor treatment (surgical treatment, chemotherapy, and radiotherapy), local and distant relapse, follow-up period, and outcomes. STS specimens were classified using the French Federation of Cancer Center Sarcoma Group (FNCLCC) system (19). Additionally, we collected information on the type of local therapy and surgical margins (Enneking staging system) of patients who underwent surgery (20). In the absence of any adverse events, patients were de-identified at their last follow-up. We defined death from original disease as 'died of disease'.

In our study, we compared clinical courses and outcomes between the younger and older groups. We categorized patients into two age-based subgroups: ≤ 84 vs. ≥ 85 years and ≤ 89 vs. ≥ 90 years, then compared the groups within each subgroup. Moreover, we compared only patients who had surgical treatment and did not have metastasis at the diagnosis. Furthermore, we examined factors affecting the prognosis of all and older patients. This research has been approved by the authors' affiliated institutions.

Statistical analysis. All continuous variables were expressed as mean \pm standard deviation. A Cox proportional hazards model was used to identify the factors affecting prognosis. The curve for overall survival was drawn according to the Kaplan-Meier method, and differences were analyzed using the Log-rank test. Statistical significance was defined as a p -value < 0.05 .

Results

The clinicodemographic characteristics of patients are shown in Table I. There were 48 patients aged ≥ 85 years, accounting for 12.1% of the total population, and 16 patients aged ≥ 90 years, accounting for 4.0% of the total population. The median period from onset to consultation was 16.3 ± 38.4 (0-420) months, and the mean follow-up was 53.2 ± 51.2 (1-373) months. The primary tumors were located in the lower extremities ($n=208$), upper extremities ($n=69$), and axial region ($n=121$). The mean tumor size for all patients was 87.3 ± 56.3 (10-370) mm. Adjuvant therapy for surgical margin was conducted in 63 patients (18.5%) and included absolute ethanol, hot water, and acridine orange (21). Radiotherapy for the primary tumor was performed in 65 patients (16.3%) and included heavy ion radiation ($n=1$), proton beam radiation ($n=4$), and radiotherapy plus surgery ($n=33$). Chemotherapy was administered to 110 patients (27.6%) and included doxorubicin, ifosfamide, dacarbazine, gemcitabine, docetaxel, eribulin, trabectedin, pazopanib, cisplatin, carboplatin, vincristine, etoposide, and actinomycin D. No patients died of complications during the perioperative period.

In all patients, Kaplan-Meier curves for overall survival showed a significant difference between the two subgroups aged 85 and 90 years ($p=0.0476$ and $p=0.0164$), and prognosis was significantly poor in elderly patients with STS (Figure 1). However, among patients who underwent surgical treatment without distant metastasis at diagnosis, there were no significant differences in Kaplan-Meier curves for overall survival between the 85- and 90- year subgroups (Figure 2).

Multivariate Cox regression analysis in all patients revealed that the size of the primary tumor, high histological grade, and the presence of distant metastasis were significant predictors of poor prognosis ($p=0.0001$, <0.0001 , and <0.0001 , respectively) and surgical treatment for the primary tumor improved prognosis ($p<0.0001$) (Table II). In the univariate and multivariate Cox regression analyses, in patients ≥ 85 years old, only surgical treatment for the primary tumor improved prognosis ($p=0.0300$).

Table I. Patient characteristics.

	Number (%)
Number	398
Age	64.8 ± 17.9
Sex - male/female	211/187
Period from onset to consultation (months)	16.3 ± 38.4
Past inappropriate excision	61 (15.3)
Size (mm)	87.3 ± 56.3
Location - extremity/axial	277/121
Histological type	
Myxoid liposarcoma	47 (11.8)
Dedifferentiated liposarcoma	39 (9.8)
Pleomorphic liposarcoma	27 (6.8)
Undifferentiated pleomorphic sarcoma	98 (24.6)
Myxofibrosarcoma	89 (22.4)
Synovial sarcoma	37 (9.3)
Malignant peripheral nerve sheath tumor	34 (8.5)
Leiomyosarcoma	27 (6.8)
FNCLCC classification - Grade I/II/III/unknown	64/158/174/2
Surgical treatment for primary tumor	340 (85.4)
Surgical margin - adequate/inadequate	277/63
Adjuvant therapy for surgical margin	63 (18.5)
All chemotherapy	110 (27.6)
Perioperative chemotherapy	55 (16.2)
All radiotherapy	107 (26.9)
Perioperative radiotherapy	65 (19.1)
Local recurrence	69 (20.3)
Time to local recurrence (months)	27.5 ± 37.7
All distant metastasis	149 (37.4)
Metastasis at diagnosis	37 (9.3)
Time to distant metastasis (months)	13.6 ± 24.1
Follow up period (months)	53.2 ± 51.2
Outcome at the last follow-up - NED/AWD/DOD	181/47/120

Values are expressed as number of patients or mean \pm SD with ranges. FNCLCC: French Federation of Cancer Center Sarcoma Group; NED: no evidence of disease; AWD: alive with disease; DOD: died of original disease.

However, univariate analysis in patients aged ≥ 90 years old revealed that the size of the primary tumor was a significant predictor for poor prognosis ($p=0.0383$) (Table III).

Discussion

Several studies have reported that older age, larger tumor size, high histological grade, and distant metastasis are significant independent predictors of poor prognosis (4-15). In our study, when examining all cases, risk factors included tumor diameter, histological grade, distant metastasis, and local recurrence, and results were similar to previous

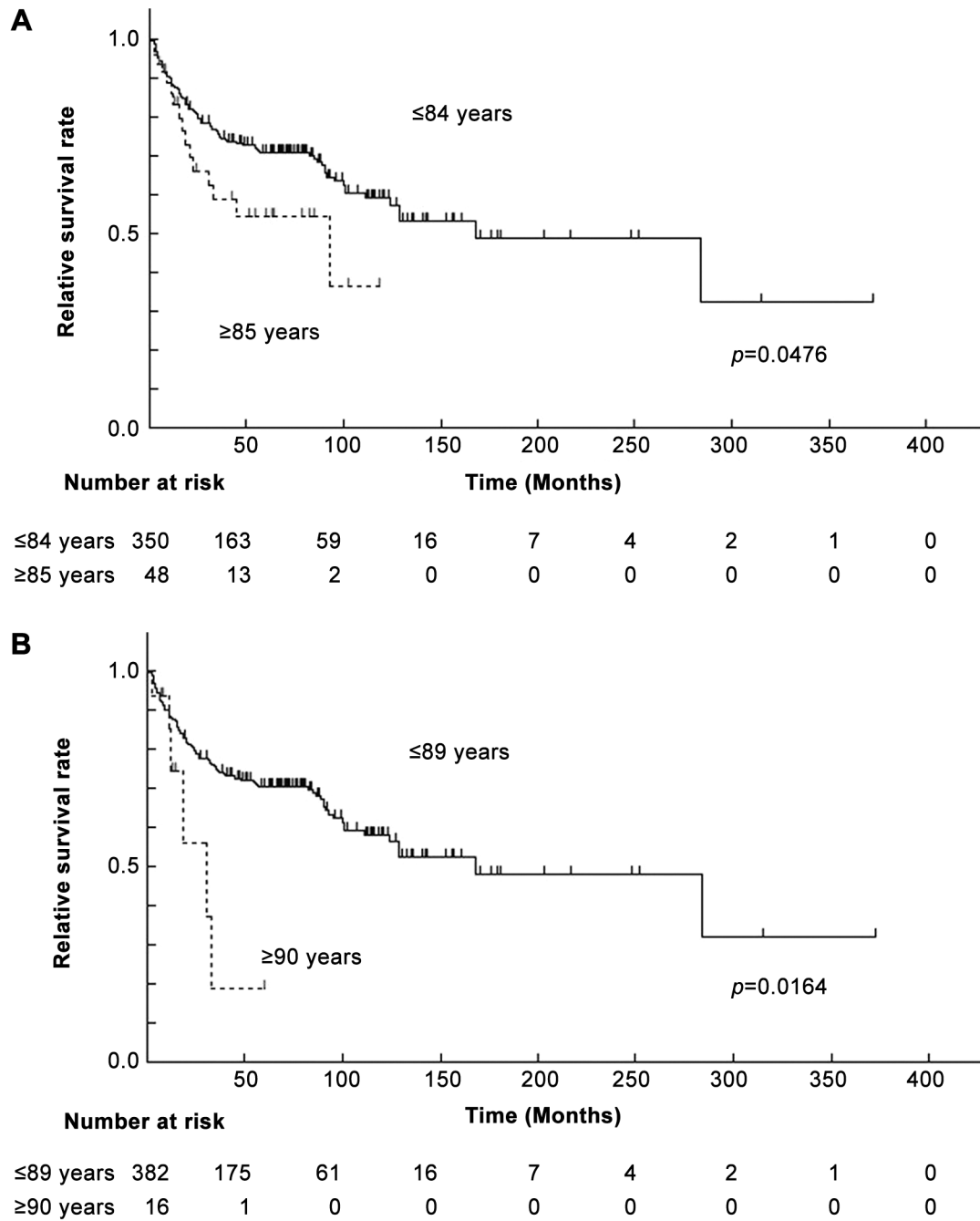


Figure 1. Kaplan-Meier curves for overall survival in all patients, comparing two groups divided by age thresholds of 85 (A) and 90 years (B). The 85 and 90-year-old groups demonstrated significant differences ($p=0.0476$ and $p=0.0164$).

reports. However, when targeting only patients ≥ 85 years, surgical treatment was the only factor improving prognosis. Two previous reports on STS cases in patients aged ≥ 85

years found no adverse effects associated with surgical treatment (15, 16). Furthermore, in the previous work of 107 cases of STS by Tsuchie *et al.* (16), similar to the present

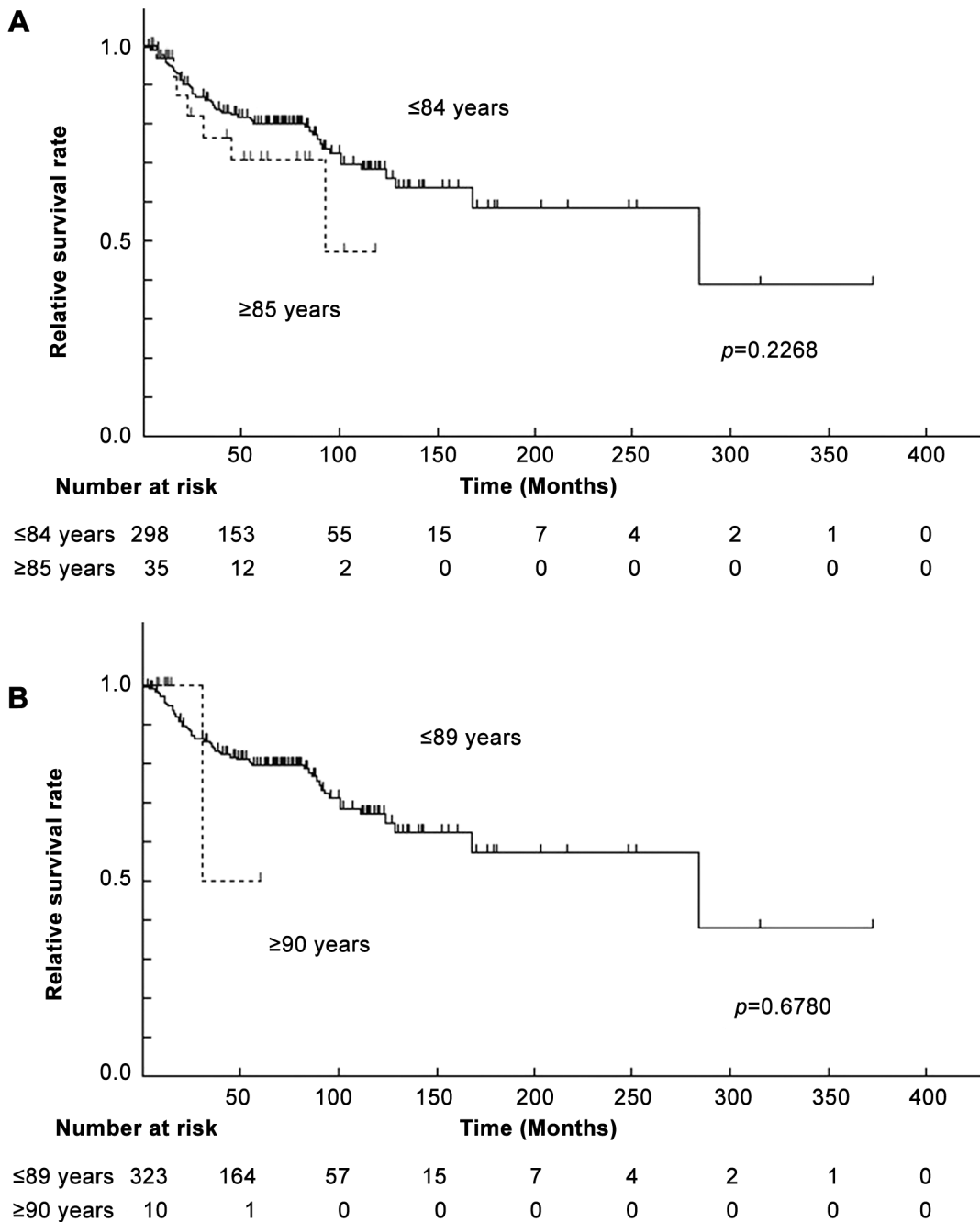


Figure 2. Kaplan-Meier curves for overall survival in patients who underwent surgical treatment without distant metastasis at diagnosis, comparing subgroups divided by age thresholds of 85 (A) and 90 years (B). No significant difference was observed between the subgroups.

study, surgical treatment was the only factor that improved prognosis. Previous reports on elderly patients with STS have shown that aggressive surgical treatment may improve

prognosis (4-16). It has been reported that surgical treatment improves prognosis compared with radiotherapy in patients aged ≥ 90 years, but no comparison has been

Table II. Univariate and multivariate Cox regression analysis of factors affecting the prognosis of all patients.

Variables	Univariate			Multivariate		
	OR	95%CI	p-Value	OR	95%CI	p-Value
Age	1.010	1.000-1.021	0.0606			
Sex – female	0.659	0.456-0.954	0.0271	1.297	0.878-1.918	0.1918
Size	1.010	1.007-1.013	<0.0001	1.006	1.003-1.010	0.0001
Period from onset to consultation	0.997	0.990-1.004	0.3408			
Past inappropriate excision	0.513	0.276-0.954	0.0349	0.813	0.409-1.619	0.5560
Location–axial	1.709	1.183-2.469	0.0043	1.184	0.793-1.766	0.4084
Histological grade – high	2.143	1.601-2.867	<0.0001	1.966	1.468-2.632	<0.0001
All chemotherapy	2.153	1.503-3.084	<0.0001	0.837	0.575-1.218	0.3525
All radiotherapy	2.400	1.674-3.441	<0.0001	0.677	0.448-1.024	0.0644
Surgical treatment for primary tumor	0.141	0.096-0.206	<0.0001	0.192	0.121-0.305	<0.0001
All distant metastasis	14.676	8.529-25.253	<0.0001	10.898	6.143-19.332	<0.0001

OR: Odds ratio; CI: confidence interval.

Table III. Univariate and multivariate Cox regression analysis of factors affecting the prognosis of older patients aged ≥85 or ≥90 years.

Variables	Univariate			Multivariate		
	OR	95%CI	p-Value	OR	95%CI	p-Value
≥85 years						
Age	1.142	0.911-1.433	0.2493			
Sex – female	0.627	0.226-1.738	0.3692			
Size	1.011	0.998-1.024	0.0966			
Past inappropriate excision	1.125	0.315-4.016	0.8558			
Location – axial	1.253	0.385-4.084	0.7081			
Histological grade – high	0.811	0.378-1.741	0.5916			
All radiotherapy	2.169	0.805-5.841	0.1255			
Surgical treatment for primary tumor	0.170	0.059-0.487	0.0010	0.288	0.093-0.886	0.0300
All distant metastasis	5.584	1.794-17.376	0.0030	3.557	1.044-12.116	0.0424
≥90 years						
Age	1.078	0.477-2.437	0.8565			
Sex – female	0.267	0.047-1.507	0.1347			
Size	1.039	1.002-1.077	0.0383			
Past inappropriate excision	0.609	0.105-3.524	0.5795			
Histological grade – high	0.855	0.247-2.957	0.8039			
All radiotherapy	2.435	0.440-13.461	0.3077			
Surgical treatment for primary tumor	0.134	0.015-1.155	0.0673			
All distant metastasis	3.113	0.560-17.297	0.1943			

OR: Odds ratio; CI: confidence interval.

made with younger generations (18). In addition, the only report examining patients aged ≥90 years compared to a younger generation did not evaluate the impact of surgical treatment on prognosis (17). The current study examined factors associated with poor prognosis in patients aged ≥90 years, and although surgical treatment showed a tendency

to improve prognosis, no significant difference was found. A comparison using Kaplan-Meier curves for overall survival showed that patients aged ≥90 years old had a poorer prognosis compared to all patients. However, when only patients who had no distant metastasis at the time of initial diagnosis and underwent surgical treatment were included,

there was no difference in prognosis between patients aged ≥ 90 and those < 90 years. Accordingly, surgical treatment may improve prognosis not only for patients aged ≥ 85 years but also for those ≥ 90 years. Because the number of cases in this study was small, a larger number of patients aged ≥ 90 years old is needed for further analysis.

Elderly patients aged ≥ 90 years are assumed to have more complications than their younger counterparts, with a higher surgical treatment risk. In a previous report examining patients aged ≥ 90 years, 60.2% underwent surgical treatment, a lower percentage compared to other age groups (78.5%) (17). In our study, surgical treatment was performed in 62.5% of patients aged ≥ 90 years, which was also lower compared to other age groups (86.4%). In patients aged ≥ 90 years, doctors or patients' families may often choose radiotherapy instead of active treatment primarily by taking age into account, especially in patients who require amputation. Although it is necessary to take into consideration complications and individual preferences, if the patient and family seek a life-prolonging treatment, surgical treatment may be a viable option as long as the patient's overall condition permits.

In the present study, 12.1% of all patients with STS were aged ≥ 85 years, and 4.0% were aged ≥ 90 years. Japan is one of the developed countries with a rapidly aging population, but there are huge differences between regions. This study was conducted in Akita and Hokkaido, rural areas in northern Japan that differ significantly from the capital, Tokyo. The elderly (≥ 65 years) population in 2022 accounted for 22.8% in Tokyo, whereas it was significantly higher in Akita (38.6%) and Hokkaido (32.8%). Therefore, compared with previous reports, our cases had an overwhelmingly higher proportion of elderly patients. In countries where population aging is expected to progress in the future, we believe it is necessary to conduct research on extremely elderly people, as in this study.

To our knowledge, this report is the first to examine the effects of surgical treatment on STS patients aged > 90 years compared to a younger population. Nevertheless, this study had some limitations, the most notable being the small number of ≥ 90 -year-old patients. As various factors

influence the prognosis of STS, data from more cases are needed to perform detailed analyses that consider these factors. In Japan, where the aging population is expected to continue growing, additional detailed studies with a larger number of patients are required. Secondly, we were unable to collect detailed information on preoperative risk assessment and postoperative complications in all patients, although it was known that there were no deaths due to postoperative complications. Therefore, we were unable to clarify the relationship between preoperative risk assessment and postoperative complications in this series. Further detailed studies about the corresponding complications are warranted.

Conclusion

Surgical treatment improves the prognosis of elderly patients with STS aged ≥ 85 years and may even improve prognosis in elderly patients aged ≥ 90 years. As Japan faces a super-aging society, this issue requires further consideration. Given the limited number of patients aged ≥ 90 years in this study, future research with a larger sample size is necessary.

Funding

None.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

Tsuchie H, Emori M, Teramoto A, and Miyakoshi N were involved in the planning and revision of this research. Tsuchie H, Emori M, Murata S, Murahashi Y, Mizushima E, Shimizu J, and Nagasawa H collected the clinical data. Tsuchie H analyzed the raw data. Tsuchie H wrote this manuscript. Teramoto A and Miyakoshi N reviewed this manuscript.

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