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Comorbidity is Independently Associated with Poor Outcome in Extremity Soft Tissue Sarcoma

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Background: Comorbidity has not been examined as an independent prognostic factor in soft tissue sarcoma (STS). We examined the prognostic impact of comorbidity on oncologic outcome in STS with an adjustment for possible confounding factors.

Methods: A retrospective review was performed on 349 patients who had undergone surgery for high-grade localized STS of extremity at our institute. Conditions known to alter the risk of mortality, as defined in the Charlson comorbidity index, were classified as comorbidities and 43 patients (12%) had at least one comorbidity at the time of surgery. The association of comorbidity and oncologic outcomes of local recurrence-free survival (LRFS) and disease-specific survival (DSS) were tested with adjustment for confounding factors.

Results: Comorbidity was associated with old age, high tumor grade, and large tumor size. The presence of comorbidity was independently associated with poor LRFS and DSS, even after adjusting for confounding factors including age and treatment variables.

Conclusions: Our data suggest that the presence of comorbidity is an independent prognostic factor for extremity STS.

Keywords: *Sarcoma, Comorbidity, Prognosis, Age of onset, Treatment outcome*

Soft tissue sarcoma (STS) develops from the mesoderm and constitutes less than 1% of all malignant tumors.[1] The age distribution of patients with STS is relatively younger than that of other cancers.[1,2] However, with increasing life expectancy, STS in the elderly is becoming more common. Although the aging process itself seems to be a poor prognostic indicator for STS,[3-5] many healthy older patients with STS seem to have a greater ability to endure treatments and to experience more favorable outcomes than unhealthy young patients.

Comorbidity, defined as coexisting diseases or conditions, has not been regarded as an independent prognostic factor in cancer patients because the impact of comorbidity on cancer prognoses is complicated as comorbidity increases proportionately with age, an established prognostic factor in many cancer types. Moreover, presence of comorbidities may preclude patients from getting standard treatment. However, comorbidity was recently reported to be an independent prognostic factor in a few cancer types.[6] Charlson comorbidity index (CCI),[7] a measure of comorbidity which has been most frequently used for predicting mortality in hospitalized patients, has been shown to be independently associated with prognoses in certain cancer types.[2,6,7]

Based on these observations, we hypothesized that comorbidity, rather than the chronological age itself, could independently affect the prognosis of STS patients. To test this hypothesis, we performed a series of multivariate analyses to test the impact of comorbidity on oncologic outcome in STS.

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METHODS

Patients

Patients who had undergone surgical removal of STS of the extremities or trunk wall in the authors' institute between May 1990 and February 2012 were reviewed. Of 491 patients who were reviewed, 102 patients were excluded, including patients with metastases at initial work-up (n = 52); those with follow-up durations less than 6 months (n = 36); and those with tumors with uncertain biologic behavior according to the World Health Organization classification for soft tissue tumors,[8] such as hemangiopericytoma, solitary fibrous tumor, atypical fibrous histiocytoma, hemangioendothelioma, and inflammatory myofibroblastic tumor (n = 14). One patient with unavailable comorbidity information was also excluded. The patients with well-differentiated liposarcoma (n = 39) and dermatofibrosarcoma protuberans (n = 15) were also excluded due to their benign course with little metastasis. Finally, 334 patients were considered for the retrospective review. The mean follow-up duration was 52 months (range, 6 to 273 months). Our hospital is a tertiary referral hospital and has a specialized musculoskeletal tumor center with tumor specialists and a specialist team for musculoskeletal tumors. This study was approved by the Institutional Review Board of our hospital.

Subject Variables

Conditions that are known to alter the risk of mortality, as defined in the CCI,[7] were classified as comorbidities. Only the comorbidities present at the time of the patients' initial surgery for their primary STS were considered, and 43 of 334 patients (12.9%) had at least one comorbidity. The specific comorbidities were as follows (some patients were duplicated): myocardial infarction (n = 3), congestive heart failure (3), peripheral vascular disease (3), cerebrovascular disease (2), dementia (1), chronic pulmonary disease (3), connective tissue disease (0), ulcer disease (1), liver disease (6), diabetes (19), hemiplegia (1), moderate or severe renal disease (0), any tumor or metastasis except STS, which is the subject of this study (4), leukemia (1), lymphoma (0), and acquired immunodeficiency syndrome (0). In this report, we refer to the 43 patients with comorbidity as the 'comorbid group' and to those without comorbidity as the 'non-comorbid group.'

Medical records were reviewed for the potential clinicopathologic factors that might influence oncologic outcome in STS: (1) clinicopathologic factors at initial presentation, (2) treatment variables, and (3) age. Regarding initial presentation, the patient's gender, tumor anatomical site, histological tumor type, previous unplanned excisions, histological grade, initial tumor size, and tumor depth were investigated. There were 188 male (56.3%) and 146 female (43.7%) patients. The anatomical sites were the upper extremity (n = 78, 23.4%), lower extremity (n = 213, 63.8%), and trunk (n = 43, 12.9%). The chest wall, back, neck, buttock, pelvis, axilla, and inguinal area were included in the trunk definition. Undifferentiated pleomorphic sarcoma (UPS) was the most common histological type (n = 90, 26.9%), followed by synovial sarcoma (n = 57, 17.1%), liposarcoma (n = 53, 15.9%), leiomyosarcoma (n = 23, 6.9%), malignant peripheral nerve sheath tumor (n = 23, 6.9%), myxofibrosarcoma (n = 16, 4.8%), fibrosarcoma (n = 15, 4.5%), and epithelioid sarcoma (n = 11, 3.3%).[8] The UPS group included the previously-used classification of malignant fibrous histiocytoma. Previously unplanned excisions were defined as any previous surgical excision of the tumor without regard for malignancy, and were performed in 162 patients (48.5%). The mean time duration between the unplanned excision and the re-excision was 36.2 ± 11.8 days. Among the 162 patients, 59 (36.4%) were referred after recurrence. Histological tumor grading was performed using the Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) classification system.[9] There were 47 (15.3%) grade 1, 147 (47.7%) grade 2, and 114 (37.0%) grade 3 tumors. Initial tumor size was defined as the largest diameter on preoperative magnetic resonance imaging (MRI). In the case of a previous unplanned excision with no available data on MRI performed before the excision, the initial tumor size was calculated according to the medical chart of the referring hospital where the unplanned excision was performed. The mean initial tumor size was 7.2 ± 5.4 cm, and the initial tumor sizes were classified as ≤ 5 cm (n = 141, 45.3%), > 5 cm and ≤ 10 cm (n = 104, 33.4%), and > 10 cm (n = 66, 21.2%) for analysis purposes. Tumor depth was classified as superficial (n = 42, 14.0%) or deep (n = 259, 86.0%); tumors located exclusively above the superficial fascia were defined as superficial. There was no survival difference between any consecutive time periods, and varying the cut-off ranges did not change the results.

Investigated treatment variables included pathological resection margin, surgical margin, administration of adjuvant therapy (preoperative chemotherapy and postoperative radiotherapy/chemotherapy), and the completeness of treatment intensity. The administration of preoperative radiotherapy was not included because our cohort did not include any such cases. Any microscopic involvement of the margin of the excised specimen was considered positive for the pathological resection margin. There were 21

cases (6.3%) with positive pathological resection margins. Surgical excision was performed with the intent to achieve a wide margin, and surgical marginal status was evaluated by examining the resected specimen. In cases with previous unplanned excision, re-excision was performed by removing the tumor bed to achieve a wide margin.[10] The re-excision surgical margin was determined on the basis of an enhanced MRI performed shortly before the re-excision; re-excision was undertaken with a wide margin of the normal surrounding tissues. Surgical marginal status was classified as 'wide' or 'other'. Wide excision included wide and radical excision (n = 257, 76.9%); others included inadequate wide, marginal, and intralesional excisions (n = 77, 23.1%). Note that the pathological resection margin was determined by the pathologic report using microscopic examination, whereas the surgical margin was determined by the operative record using gross examination. Following the diagnosis of a patient with STS, the decision to undertake adjuvant therapy was made after discussion of the case at a multidisciplinary conference. In general, chemotherapy and/or radiation therapy was administered when survival gain and/or high risk of local recurrence was thought to exist based on clinical information, such as histological grade and surgical margin. However, no prospectively selected criteria were used for patient selection. Preoperative chemotherapy was performed in 11 cases (3.3%), postoperative chemotherapy in 62 cases (18.6%), and postoperative radiotherapy in 170 cases (50.9%). We included the completeness of treatment intensity as one of the treatment variables; 'incomplete treatment intensity' referred to any of the following: (1) incomplete surgical margin, such as intralesional or marginal, during definitive surgery; (2) reduced or palliative dose or drop-out due to any causes during first-line chemotherapy; and (3) palliative dose or drop-out due to any causes during adjuvant and/or neoadjuvant radiotherapy. There were 110 cases (32.9%) with incomplete treatment intensity.

Finally, the age of the patient at the time of initial surgical removal under the diagnosis of STS was investigated. The mean age was 45.8 ± 18.9 years, and patients were age-grouped as ≤ 30 years (n = 82, 24.6%), > 30 years and ≤ 45 years (n = 83, 24.9%), > 45 years and ≤ 60 years (n = 81, 24.3%), and > 60 years (n = 88, 26.3%) for analysis purposes.

Statistical Analysis

Oncologic outcomes were analyzed using two clinical endpoints: local recurrence and disease-specific death. For local recurrence-free survival (LRFS), any recurrence at or adjacent to the initial primary site (n = 85) was defined as an event. For disease-specific survival (DSS), death due to sarcoma or related treatment (n = 51) was defined as an event. The 8 patients who died from other causes were not counted as an event. To evaluate the prognostic effect in terms of oncologic outcomes, Kaplan-Meier survival curves and the log-rank test were used for univariate analysis and Cox regression analysis was used for multivariate analysis. The factors significantly associated with the presence of comorbidity ($p < 0.05$) and the variables with p-values of < 0.10 in univariate analysis of survival[11] were determined as possible confounding factors on comorbidity for survival, and those possible confounding factors were used in multivariate analysis. To show the confounding effects of age and treatment variables that are generally well known to be associated with comorbidity, we first analyzed the prognostic effect of the presence of comorbidity in multivariate analysis with only initial presentations (namely, analysis without the age and treatment variables as co-variables). Then, patient age and treatment variables were sequentially included in the analysis, and the changes in statistical significance and the hazard ratio of comorbidity were noted.

For the purpose of comparing the patients with and without comorbidity, the significance of differences between means was calculated using the independent t-test. The significance of differences between frequencies was calculated using the chi-square test, and Fisher exact test was used in cases when the frequency was less than five.

Significance was confirmed for p-values of < 0.05. Statistical analyses were performed using SPSS ver. 21 (IBM Co., Armonk, NY, USA).

RESULTS

Factors Associated with Comorbidity

When comparing the comorbid group and the non-comorbid group (Table 1), the comorbid group had older chronological age ($p < 0.001$), fewer synovial sarcomas ($p = 0.017$), and larger initial tumor size ($p = 0.003$). The comorbid group also tended to have a higher FNCLCC grade ($p = 0.052$). LRFS and DSS in the comorbid group were worse than those in the non-comorbid group (Fig. 1).

Prognostic Factors for Oncologic Outcomes

On univariate analysis for LRFS, significant factors ($p <$ 0.10) were treatment intensity, postoperative radiotherapy, pathological resection margin, age, and histological type (synovial sarcoma and malignant peripheral nerve sheath tumor [MPNST]). On multivariate analysis of these factors, along with the factors significantly associated with

Table 1. Patient Characteristics according to the Presence of Comorbidity

Characteristic (n)	Total	Absence (n = 291)	Presence (n = 43)	*p*-value*
Age (yr) (334)	45.8 ± 18.9	43.6 ± 18.3	61.0 ± 15.7	< 0.001†
≤ 30	82 (24.6)	79 (27.1)	3 (7.0)	< 0.001†
> 30 and ≤ 45	83 (24.9)	77 (26.5)	6 (14.0)	
> 45 and ≤ 60	81 (24.3)	74 (25.4)	7 (16.3)	
> 60	88 (26.3)	61 (21.0)	27 (62.8)	
Initial presentation				
Gender (334)				0.114
Male	188 (56.3)	159 (54.6)	29 (67.4)	
Female	145 (43.7)	132 (45.4)	14 (32.6)	
Anatomical site (349)				0.480
Upper extremity	78 (23.4)	69 (23.7)	9 (20.9)	
Lower extremity	213 (63.8)	187 (64.3)	26 (60.5)	
Trunk	43 (12.9)	35 (12.0)	8 (18.6)	
Histological type (349)				0.157
UPS	90 (26.9)	76 (26.1)	14 (32.6)	0.374
Synovial sarcoma	57 (17.1)	55 (18.9)	2 (4.7)	0.017†
Liposarcoma	53 (15.9)	45 (15.5)	8 (18.6)	0.599
Leiomyosarcoma	23 (6.9)	18 (6.2)	5 (11.6)	0.188
MPNST‡	23 (6.9)	19 (6.5)	4 (9.3)	0.516
Myxofibrosarcoma	16 (4.8)	16 (5.5)	0 (0.0)	0.240
Fibrosarcoma	15 (4.5)	14 (4.8)	1 (2.3)	0.703
Epithelioid sarcoma	11 (3.3)	11 (3.8)	0 (0.0)	0.371
Other types	46 (13.8)	37 (12.7)	9 (20.9)	0.145
Previous unplanned excision (332)				0.748
Performed	162 (48.8)	142 (49.1)	20 (46.5)	
With recurrence	103 (30.8)	96 (33.2)	7 (16.3)	
Without recurrence	59 (17.7)	46 (15.9)	13 (30.2)	
Not performed	170 (51.2)	147 (50.9)	23 (53.5)	
FNCLCC grade (308)				0.052
3	114 (37.0)	99 (36.8)	15 (38.5)	
2	147 (47.7)	124 (46.1)	23 (59.0)	
1	47 (15.3)	46 (17.1)	1 (2.6)	
Initial tumor size (cm) (311)	7.2 ± 5.4	6.8 ± 5.1	9.6 ± 6.4	0.003†
≤ 5	141 (45.3)	130 (47.6)	11 (28.9)	0.009†
> 5 and ≤ 10	104 (33.4)	92 (33.7)	12 (31.6)	
> 10	66 (21.2)	51 (18.7)	15 (39.5)	
Tumor depth (301)				0.205
Superficial	42 (14.0)	34 (13.0)	8 (20.5)	
Deep	259 (86.0)	228 (87.0)	31 (79.5)	
Treatment variable				
Pathological resection margin (322)				0.115
Positive	21 (6.5)	16 (5.7)	5 (12.2)	
Negative	301 (93.5)	265 (94.3)	36 (87.8)	
Surgical margin (334)				0.458
Wide excision	257 (76.9)	222 (76.3)	35 (81.4)	
Others	77 (23.1)	69 (23.7)	8 (18.6)	
Preoperative chemotherapy (333)				0.371
Not performed	322 (96.7)	279 (96.2)	43 (100.0)	
Performed	11 (3.3)	11 (3.8)	0 (0.0)	
Postoperative chemotherapy (333)				0.673
Not performed	271 (81.4)	235 (81.0)	36 (83.7)	
Performed	62 (18.6)	55 (19.0)	7 (16.3)	
Postoperative radiotherapy (334)				0.110
Not performed	164 (49.1)	138 (47.4)	26 (60.5)	
Performed	170 (50.9)	153 (52.6)	17 (39.5)	
Treatment intensity (334)				0.324
Complete	224 (67.1)	198 (68.0)	26 (60.5)	
Incomplete‡	110 (32.9)	93 (32.0)	17 (39.5)	
Survival rate				
Local recurrence-free survival rate (%) (334)				< 0.001†
5-Year	70.8 ± 3.0	74.7 ± 3.1	42.7 ± 9.3	
10-Year	63.6 ± 4.0	66.6 ± 4.3	42.7 ± 9.3	
Disease-specific survival rate (%) (334)				0.002†
5-Year	80.9 ± 2.7	84.1 ± 2.6	56.3 ± 11.0	
10-Year	75.1 ± 3.4	77.4 ± 3.6	56.3 ± 11.0	

Values are presented as mean ± standard deviation or number (%).
UPS: undifferentiated pleomorphic sarcoma, MPNST: malignant peripheral nerve sheath tumor, DFSP: dermatofibrosarcoma protuberans, FNCLCC: the Federation Nationale des Centres de Lutte Contre le Cancer.
*Comparison between the groups with the presence and absence of comorbidity. †*p*-value < 0.05. ‡Incomplete treatment intensity refers to any of the following: (1) incomplete surgical margin, such as intralesional or marginal, during definitive surgery; (2) reduced or palliative dose or drop-out during first-line chemotherapy; and (3) palliative dose or drop-out during adjuvant and/or neoadjuvant radiotherapy.

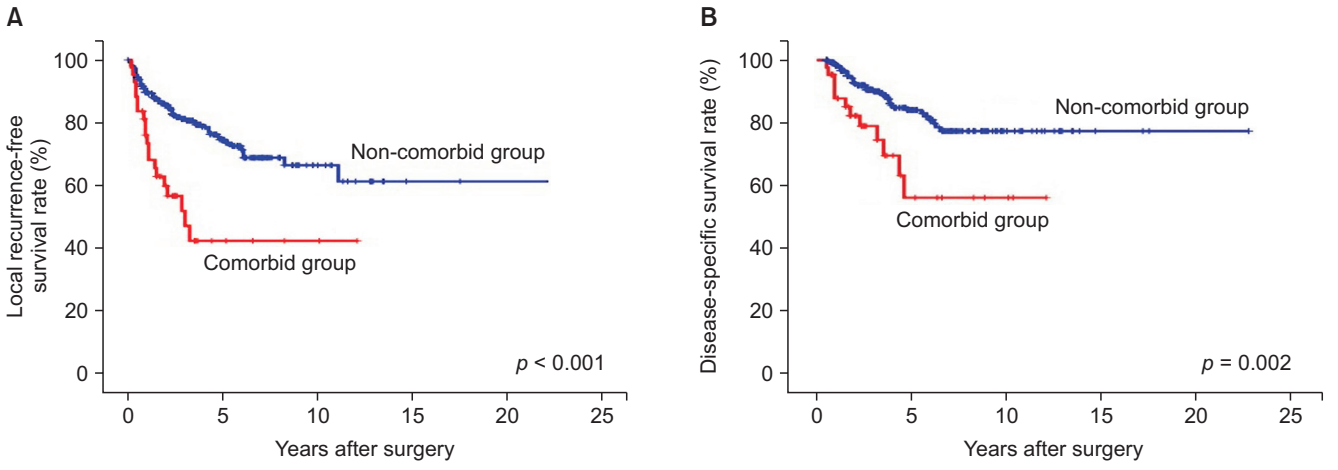

Fig. 1. Survival in the comorbid group was worse than that in the non-comorbid group. (A) Local recurrence-free survival. (B) Disease-specific survival.

comorbidity (age, FNCLCC grade, and initial tumor size), the presence of comorbidity was significantly associated with poor LRFS after adjustment for initial presentation (Table 2). Furthermore, the presence of comorbidity still retained prognostic significance for LRFS even after adjusting for age and treatment variables (Table 2). Besides comorbidity, not performing postoperative radiotherapy was independently associated with poor LRFS.

On univariate analysis for DSS, significant factors ($p < 0.10$) were treatment intensity, postoperative chemotherapy, age, previous unplanned excision, anatomical site, histological type (MPNST), FNCLCC grade, and initial tumor size. On multivariate analysis of these factors, along with the factors significantly associated with comorbidity (age, FNCLCC grade, synovial sarcoma and initial tumor size), the presence of comorbidity was significantly associated with poor DSS after adjustment for initial presentation (Table 3). Furthermore, the presence of comorbidity still retained prognostic significance for DSS even after adjusting for age and treatment variables (Table 3). Besides comorbidity, high FNCLCC grade and large tumor size was independently associated with poor DSS. If the comorbidity was excluded in the analysis, age was significant prognostic factor in LRFS (Table 4).

DISCUSSION

Comorbidity has often been reported to be significantly associated with prognosis in patients with other cancer types.[2,6,12] However, comorbidity is associated with age, and affects treatment modality and intensity, making it difficult to distinguish its respective contributions to prognosis. To prove the independent prognostic effect of comorbidity, we first investigated the characteristics of patients and categorized them into initial presentation, age, and treatment variables. Among the separate categorized characteristics, we determined the possible confounding factors that were significantly associated with comorbidity or affected the survival of STS patients. We then analyzed the prognostic impact of comorbidity on STS outcome with an adjustment for the possible confounding factors including initial presentation, age, and treatment variables sequentially. To our knowledge, this is the first study to address the prognostic effect of comorbidity with a specific focus on STS.

A few things should be considered when interpreting the results of this study. First, our reason for undertaking this study was based on the idea that the assessment of specific factors in geriatric patients could predict the prognosis of STS. The most widely used and representative factor in geriatric assessment has been chronological age. However, with advances in medical technology and increased life expectancy, many healthy elderly patients with STS endure more aggressive treatments and achieve better oncological outcomes than young people. Thus, we sought additional geriatric assessment modalities, which might reflect the prognosis more precisely. We adopted the presence of comorbidity as one of our geriatric assessment tools because it is relatively well established, objective, and advantageous for use in further studies with nationwide cancer registry systems.[7,13] Of course, there is certainly a sufficient possibility that our study did not reveal an actual prognostic factor that reflects geriatric progression. In other words, comorbidity as well as chronological age may merely be a confounder partly reflecting the aging process, and it may be the case that there is another actual prognostic factor, such as functional status, muscular volume, etc., or several factors combined that reflect real

Table 2. Multivariate Results for Local Recurrence-Free Survival

Comorbidity and the possible confounding factors	Age and treatment variables excluded		Age included		Age and treatment variables included	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Comorbidity		< 0.001*		0.001*		0.007*
Presence	3.307 (1.855–5.896)		2.877 (1.576–5.252)		2.391 (1.268–4.510)	
Absence	1 (Reference)		1 (Reference)		1 (Reference)	
Treatment variables						
Treatment intensity	NA		NA			0.065
Incomplete†					1.641 (0.969–2.778)	
Complete					1 (Reference)	
Postoperative radiotherapy	NA		NA			0.001*
Performed					0.426 (0.256–0.709)	
Not performed					1 (Reference)	
Resection margin	NA		NA			0.337
Positive					1.487 (0.661–3.345)	
Negative					1 (Reference)	
Age (yr)	NA					
> 60			1.886 (0.936–3.799)	0.076	1.941 (0.939–4.008)	0.073
> 45 and ≤ 60			1.036 (0.483–2.221)	0.927	1.164 (0.532–2.546)	0.704
> 30 and ≤ 45			0.948 (0.430–2.091)	0.895	1.237 (0.548–2.791)	0.608
≤ 30			1 (Reference)		1 (Reference)	
Initial presentation						
Histological type						
Synovial sarcoma	0.579 (0.260–1.289)	0.181	0.684 (0.299–1.562)	0.367	0.768 (0.335–1.756)	0.531
MPNST	2.024 (0.981–4.176)	0.056	1.863 (0.903–3.844)	0.092	1.956 (0.909–4.206)	0.086
Others	1 (reference)		1 (Reference)		1 (Reference)	
FNCLCC grade						
3	1.781 (0.798–3.974)	0.159	1.570 (0.687–3.589)	0.285	2.260 (0.898–5.686)	0.083
2	1.167 (0.524–2.602)	0.705	1.063 (0.468–2.414)	0.884	1.493 (0.576–3.870)	0.409
1	1 (Reference)		1 (Reference)		1 (Reference)	
Initial tumor size (cm)						
> 10	1.079 (0.586–1.990)	0.806	1.092 (0.588–2.029)	0.780	1.023 (0.530–1.977)	0.946
> 5 and ≤ 10	0.706 (0.400–1.245)	0.229	0.675 (0.380–1.199)	0.675	0.686 (0.376–1.251)	0.219
≤ 5	1 (Reference)		1 (Reference)		1 (Reference)	

On univariate analysis, treatment intensity, postoperative radiotherapy, pathological resection margin, age, and histological types of synovial sarcoma and MPNST showed *p*-values < 0.10. With those variables, as well as the significantly related factors (age, synovial sarcoma, FNCLCC grade, and initial tumor size), multivariate analysis was performed. The presence of comorbidity showed a significantly poor prognostic effect for local recurrence-free survival, and remained significantly associated with the survival after adjusting for age and treatment variables.
HR: hazard ratio, CI: confidence interval, NA: not applied, MPNST: malignant peripheral nerve sheath tumor, FNCLCC: the Federation Nationale des Centres de Lutte Contre le Cancer.
*p-value < 0.05. †Incomplete treatment intensity means any of the following: (1) incomplete surgical margin, such as intralesional or marginal, during definitive surgery, (2) reduced or palliative dose or any drop-out during first-line chemotherapy, (3) palliative dose or any drop-out during adjuvant and/or neoadjuvant radiotherapy.

Table 3. Multivariate Results for Disease-Specific Survival

Comorbidity and the possible confounding factors	Age and treatment variables excluded		Age included		Age and treatment variables included	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Comorbidity		0.005*		0.013*		0.016*
Presence	2.948 (1.392–6.245)		2.683 (1.226–5.869)		2.646 (1.198–5.842)	
Absence	1 (Reference)		1 (Reference)		1 (Reference)	
Treatment variables						
Treatment intensity	NA		NA			0.110
Incomplete†					1.788 (0.876–3.638)	
Complete					1 (Reference)	
Postoperative chemotherapy	NA		NA			0.504
Performed					1.322 (0.582–3.002)	
Not performed					1 (Reference)	
Age (yr)	NA					
> 60			1.573 (0.605–4.089)	0.353	1.644 (0.629–4.297)	0.311
> 45 and ≤ 60			0.922 (0.337–2.525)	0.874	1.052 (0.384–2.883)	0.922
> 30 and ≤ 45			0.975 (0.355–2.677)	0.961	0.986 (0.362–2.686)	0.978
≤ 30			1 (Reference)		1 (Reference)	
Initial presentation						
Previous unplanned excision		0.756		0.772		0.930
Performed	0.896 (0.450–1.786)		0.902 (0.450–1.809)		1.032 (0.508–2.096)	
Not performed	1 (Reference)		1 (Reference)		1 (Reference)	
Anatomical site						
Upper extremity	0.537 (0.166–1.733)	0.298	0.470 (0.141 to –1.565)	0.219	0.474 (0.140–1.604)	0.230
Lower extremity	1.190 (0.487–2.907)	0.702	1.052 (0.416–2.662)	0.914	1.142 (0.437–2.981)	0.787
Trunk	1 (Reference)		1 (Reference)		1 (Reference)	
Histological type						
Synovial sarcoma	0.957 (0.385–2.377)	0.925	1.091 (0.397–3.001)	0.866	1.142 (0.421–3.100)	0.794
MPNST	1.701 (0.587–4.929)	0.328	1.566 (0.537–4.563)	0.411	1.584 (0.535–4.697)	0.406
Others	1 (Reference)		1 (Reference)		1 (Reference)	
FNCLCC grade						
3	4.459 (1.039–19.142)	0.044*	4.156 (0.937–18.423)	0.061	4.680 (1.039 to –21.068)	0.044*
2	1.893 (0.424–8.447)	0.403	1.749 (0.381–8.022)	0.472	1.990 (0.426–9.287)	0.381
1	1 (Reference)		1 (Reference)		1 (Reference)	
Initial tumor size (cm)						
> 10	2.380 (1.048–5.408)	0.038*	2.331 (1.023–5.313)	0.044*	2.347 (1.025–5.374)	0.043*
> 5 and ≤ 10	1.476 (0.661–3.297)	0.343	1.420 (0.635–3.177)	0.393	1.443 (0.641–3.252)	0.376
≤ 5	1 (Reference)		1 (Reference)		1 (Reference)	

On univariate analysis, treatment intensity, postoperative chemotherapy, age, previous unplanned excision, anatomical site, histological type of MPNST, FNCLCC grade, and initial tumor size showed *p*-values < 0.10. With those variables, as well as the significantly related factors (age, synovial sarcoma, FNCLCC grade, and initial tumor size), multivariate analysis was performed. The presence of comorbidity showed a significantly poor prognostic effect for disease-specific survival, and remained significantly associated with the survival after adjusting for age and treatment variables.
HR: hazard ratio, CI: confidence interval, NA: not applied, MPNST: malignant peripheral nerve sheath tumor, FNCLCC: the Federation Nationale des Centres de Lutte Contre le Cancer.
*p-value < 0.05. †Incomplete treatment intensity means any of the following: (1) incomplete surgical margin, such as intralesional or marginal, during definitive surgery, (2) reduced or palliative dose or any drop-out during first-line chemotherapy, (3) palliative dose or any drop-out during adjuvant and/or neoadjuvant radiotherapy.

Table 4. Multivariate Results for Local Recurrence-Free Survival and Disease-Specific Survival When the Comorbidity was Excluded from the Co-Variables

Characteristic	Local recurrence-free survival		Disease-specific survival	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Treatment variable				
Treatment intensity		0.063		0.071
Incomplete[†]	1.645 (0.974–2.778)		1.896 (0.947–3.795)	
Complete	1 (Reference)		1 (Reference)	
Postoperative radiotherapy		< 0.001*	NA	
Performed	0.389 (0.235–0.643)			
Not performed	1 (Reference)			
Resection margin		0.355	NA	
Positive	1.471 (0.650–3.329)			
Negative	1 (Reference)			
Postoperative chemotherapy	NA			0.602
Performed			1.237 (0.557–2.743)	
Not performed			1 (Reference)	
Age (yr)				
> 60	2.390 (1.177–4.851)	0.016*	1.941 (0.750–5.021)	0.172
> 45 and ≤ 60	1.353 (0.624–2.930)	0.444	1.206 (0.451–3.225)	0.709
> 30 and ≤ 45	1.261 (0.560–2.837)	0.576	0.936 (0.345–2.539)	0.897
≤ 30	1 (Reference)		1 (Reference)	
Initial presentation				
Previous unplanned excision	NA			0.798
Done			1.097 (0.539–2.235)	
Not done			1 (Reference)	
Anatomical site	NA			
Upper extremity			0.445 (0.132–1.492)	0.189
Lower extremity			1.070 (0.408–2.801)	0.891
Trunk			1 (Reference)	
Histological type				
Synovial sarcoma	0.740 (0.324–1.687)	0.474	1.015 (0.377–2.732)	0.977
MPNST	1.903 (0.887–4.082)	0.099	1.373 (0.466–4.045)	0.566
Others	1 (Reference)		1 (Reference)	
FNCLCC grade				
3	2.484 (0.990–6.233)	0.053	5.146 (1.150–23.022)	0.032
2	1.821 (0.712–4.660)	0.211	2.547 (0.554–11.705)	0.230
1	1 (Reference)		1 (Reference)	
Initial tumor size (cm)				
> 10	1.276 (0.675–2.409)	0.453	3.055 (1.376–6.782)	0.006*
> 5 and ≤ 10	0.734 (0.404–1.332)	0.309	1.511 (0.671–3.399)	0.319
≤ 5	1 (Reference)		1 (Reference)	

On univariate analysis, the patient's age, which was of no prognostic value when the comorbidity was included in the analysis, showed significant prognostic value for local recurrence.
HR: hazard ratio, CI: confidence interval, NA: not applied, MPNST: malignant peripheral nerve sheath tumor, FNCLCC: the Federation Nationale des Centres de Lutte Contre le Cancer.
*p-value ≤ 0.05. [†]Incomplete treatment intensity means any of the following: (1) incomplete surgical margin, such as intralesional or marginal, during definitive surgery, (2) reduced or palliative dose or any drop-out during first-line chemotherapy, (3) palliative dose or any drop-out during adjuvant and/or neoadjuvant radiotherapy.

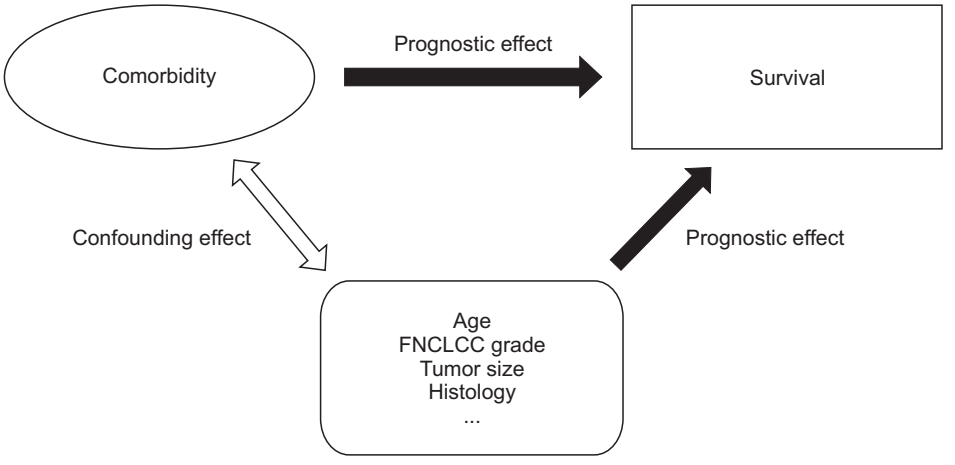

Fig. 2. Comorbidity is suggested to have an independent prognostic effect on the survival of soft tissue sarcoma patients as well as confounding effects with certain poor prognostic factors. FNCLCC: the Federation Nationale des Centres de Lutte Contre le Cancer.

geriatric biology. Second, we simply used the presence of comorbidity as a representative of comorbid conditions instead of the comorbidity burden, such as that measured by the CCI itself. Lung cancer is one of the cancer fields in which the prognostic effect of comorbidity has been most actively investigated. Patients with lung cancer tend to have relatively more comorbidities because they are relatively older[2,12] and because some comorbidities share their etiology with the underlying malignancy. For example, tobacco use is a major risk factor not only for lung cancer but also for the most common medical comorbidities of chronic obstructive pulmonary disease and coronary artery disease.[2] However, patients with STS are relatively young compared to patients with other types of cancer,[1,2] and there is no definite shared cause that results in both the malignancy and the observed comorbidities. For this reason, the proportion of patients in our study with comorbidities was small, and most of them had only one comorbidity. Therefore, we used the presence of comorbidity as a representative of comorbid conditions. We suggest that this could also explain the reason why comorbidity has not been studied as a prognostic factor in STS. Third, the survival for patients with STS has been increasing.[14] Piccirillo et al.[6] reported that comorbidity information was more important in the cancers with longer mean survival and prognostically least informative in the cancers with the worst survival. Therefore, it can be inferred that the prognostic effect of comorbidity in STS may increase as survival rates increase and the population ages. Fourth, there are many demographic differences between the comorbid and non-comorbid groups such as age, histological type, grade, and size. Therefore, the possibilities of unproven bias should be considered when interpreting the results, even though multivariate analyses had been performed. The final consideration is that this study might be limited by its retrospective nature, with a relatively small number of patients studied in a single institute. This limitation may have resulted in some missing data and may theoretically cause observational and selection biases. We presented each available number of characteristics in Table 1 to minimize the misunderstanding of readers.

In the current study, comorbidity showed an independent poor prognostic effect on LRFS and DSS in patients with STS on multivariate analysis, even after adjusting for initial presentation, age, and treatment variables. Comorbidity showed a significant correlation with age ($p < 0.001$). On the other hand, comorbidity showed no significant association with the completeness of treatment intensity. This might be a reflection of our hospital's principle of treating cancer patients as aggressively as possible regardless of the patients' age and comorbidities. Other than age, comorbidity was also associated with fewer synovial sarcomas on histological type, and larger tumor size, and tended to associate with FNCLCC grade. Notably, all those variables were associated with poor prognosis in survival: older age showed a poor prognosis in LRFS in the absence of comorbidity as a co-variable; synovial sarcoma of histological type, although only on univariate analysis, showed a good prognosis in LRFS; and high FNCLCC grade and large initial tumor size showed poor prognosis in DSS. Moreover, the hazard ratio of comorbidity decreased as age and treatment variables were included. Thus, we suggest that comorbidity not only has an independent poor prognostic effect on the survival of STS patients but also has some confounding effects with other poor prognostic factors (Fig. 2). These factors might be related to the actual aging process.

Many explanations for the prognostic or confounding effects of comorbidity have been proposed; suggestions include that comorbidity might affect treatment

selection;[2,12,15,16] might increase the likelihood of experiencing treatment-related adverse effects in addition to exacerbations of the comorbidity;[2,17-19] might decrease the likelihood of completing prescribed treatments, resulting in lower rates of disease control;[2,20] and might limit life expectancy itself, independent of the underlying malignancy.[2,6] In some studies, particularly in breast cancer, the prognostic effect of comorbidity has been explained with special attention to the metabolism of certain comorbidities.[21-24] However, STS is known to have no definite risk factors commonly shared with comorbidity and to be relatively unaffected by metabolism. Therefore, although more studies are needed, we carefully suggest that a certain biological change with the aging process is one of the main prognostic factors in STS, and comorbidity is one of the relevant geriatric assessments.

Our data suggest that the presence of comorbidity is an independent prognostic factor for extremity STS.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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