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Type and Incidence of Soft Tissue Sarcomas in Korea: 2001–2007

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Background: The Korean Bone and Soft Tissue Pathology Study Group of the Korean Society of Pathologists conducted a nationwide retrospective analysis of soft tissue sarcoma (STS) to provide the clinicopathologic characteristics of STS within the population of the Republic of Korea. **Methods:** The cases of STS were collected during a 7-year period (2001-2007) from 19 institutes in Korea. All cases were classified according to the histologic criteria proposed by the World Health Organization. Clinicopathologic data were reviewed. **Results:** Data from 722 patients (median age, 50 years) were collected. Data showed a slight male predominance. The most frequent types of STS in decreasing order were liposarcoma, malignant fibrous histiocytoma, leiomyosarcoma, and synovial sarcoma. STS occurred throughout the body, although approximately half (47.8%) were located in the extremities. The majority of STS was histologically classified as high grade with a large tumor size (>5 cm). The overall survival rate for the patients was 76.3% (median follow-up time, 26 months; range, 1 to 89 months). Histologic grade, tumor size, American Joint Committee on Cancer stage, tumor site, and resection status were prognostic. Significant independent adverse prognostic factors were large tumor size (>5 cm) and tumor site other than extremities. **Conclusions:** We reported the distribution and characteristics of STS in the Republic of Korea.

Key Words: Sarcoma; Korea; Incidence; Type; Prognosis

Soft tissue sarcoma (STS) is a highly heterogeneous malignancy group consisting of many different histologic types and originating from the nonepithelial extraskeletal tissue of the body exclusive of the reticuloendothelial system. STS, compared with carcinomas and other neoplasms, are relatively rare and constitute less than 1% of the overall human burden of malig-

nant tumors.[1,2] In the United States, approximately 10,000 new cases are diagnosed annually.[3]

Histopathologic classification of STS has evolved considerably over the last few decades. The advances in immunohistochemistry and cytogenetic analysis have had significant impact on the classification of STS. The new World Health Organization (WHO) classification admits to no definable line of differentiation of the categories known as malignant fibrous histiocyoma (MFH), which has been regarded as the most common category of STS in adults for many years.[4] Many reports have described the characteristics of STS based on the previous classification and terminology. A few studies have reported epidemiology and prognosis of STS using population-based series or nationwide studies.[5,6] The incidence and distribution of STS seem to be similar in different regions of the world.

In this study, the Korean Bone and Soft Tissue Pathology Study Group of the Korean Society of Pathologists evaluated the incidence, the clinicopathologic characteristics, and prognosis of STS in the Republic of Korea by conducting a nationwide retrospective review of 722 cases of STS, according to the WHO classification. We believe that this study may not only facilitate more accurate information about the incidence and clinical behavior of STS, but additionally will discern the characteristics of STS according to geography.

MATERIALS AND METHODS

A total of 722 cases of STS diagnosed at 19 institutes between January 2001 and December 2007 in the Republic of Korea were included in the study. We collected all patients from each hospital at the time of diagnosis with STS throughout the body. The patients were diagnosed by experts of soft tissue pathology according to the WHO classification.[4] Conventionally, STS includes the malignant tumors arising from the peripheral nervous system, however patients with malignant peripheral nerve sheath tumors were excluded because this study was strictly designed and standardized to the new WHO classification. Clinical data relating to age, gender, and sites, and follow-up date associated with local recurrence, distant metastasis, and survival, were obtained from the medical records. The same patients who visited two hospitals or more were organized to avoid the data overlap. Therefore, data of this study was based on 722 patients.

The following definitions were used. Tumor size was judged from preoperative imaging or from pathological examination of fresh surgical specimens, and was defined as the maximum length of the tumor. Tumors were classified as small (≤ 5 cm) and large (>5 cm). The anatomic depth of tumors was defined in relation to the fascia and characterized as either superficial or deep. A superficial tumor is located exclusively above the superficial fascia without invasion of the fascia. A deep tumor is located either exclusively beneath the superficial fascia, superficial to the fascia with invasion or through the fascia. Retroperitoneal, mediastinal and pelvic sarcomas are classified as deep tumors. The histologic grade was classified as either high or low by translating the three and four grades of the specific grading system of each institution to a two grade system. Grade 1 of the three grade system and grades 1 and 2 of the four grade system are considered low grade. Grades 2 and 3 of the three grade system and grades 3 and 4 of the four grade system correspond to a high grade. The American Joint Committee on Cancer (AJCC) seventh edition staging sytem was used for staging.[7] Complete resection meant a macroscopically complete resection with no visible tumor remaining. Survival rate was calculated from the date of the first diagnosis to the date of death or the last follow-up.

Associations between categoric variables were studied using a chi-square test and the Kaplan-Meier technique for univariate analysis, whereas the Cox model was applied to search for independent prognostic factors. A p-value <0.05 was considered significant.

RESULTS

Clinicopathologic data

Seven hundred and twenty-two patients with primary STS were identified. Table 1 shows the pathologic characteristics in the patients. The median age at the onset of disease was 50 years (range, 0 to 90 years). The male-to female ratio was 1.15 : 1.

Among all cases, the most common histologic type was liposarcoma (20.2%), followed by MFH (19.1%), leiomyosarcoma (13.0%), synovial sarcoma (12.3%), fibrosarcoma (8.4%), and rhabdomyosarcoma (8.0%) in decreasing order of frequency (Table 2). Age-related incidences vary among the histologic types. The median age of patients with lipoarcoma and MFH was 60 years (range, 20 to 84 years) and 60.5 years (range, 14 to 88 years), with synovial sarcoma 42 years (range, 12 to 77 years), whereas rhabomyosarcoma occurred almost exclusively in young individuals (median, 16.5 years) (Fig. 1). Male predominance or

Table 1. Clinicopathologic data of patients with STS

Variables		No. of patients (%)
Gender (n=722)	Male	387 (53.6)
	Female	335 (46.4)
Tumor site (n=722)	Extremities	345 (47.8)
	Upper extremities	83
	Lower extremities	262
	Retroperitoneum/intra-abdominal	130 (18.0)
	Head and neck	65 (9.0)
	Thoracic region	64 (8.9)
	Abdominal wall	51 (7.1)
	Visceral organ	38 (5.3)
	Others	29 (3.9)
Histologic grade (n=649)	Low	120 (18.5)
	High	529 (81.5)
AJCC stage (n=603)	I	114 (18.9)
	II	198 (32.8)
	III	238 (39.5)
	IV	53 (8.8)
Tumor size (n=673)	≤5 cm	223 (33.1)
	>5 cm	450 (66.9)
Anatomic depth (n=671)	Superficial	138 (20.6)
	Deep	533 (79.4)
Complete resection (n=510)	Complete resection	437 (85.7)
	Incomplete resection	73 (14.3)
Lymph node metastasis at diagnosis (n=722)	NX	277 (38.4)
	N0	420 (58.2)
	N1	25 (3.5)
Distant metastasis at diagnosis (n=722)	M0	677 (93.8)
	M1	45 (6.2)

STS, soft tissue sarcoma; AJCC, American Joint Committee on Cancer.

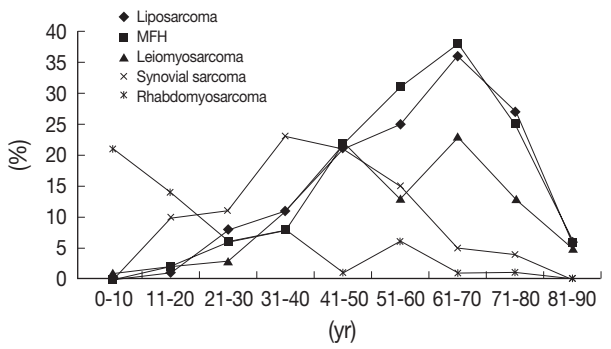

Fig. 1. Age-related distribution of soft tissue sarcoma.
MFH, malignant fibrous histiocytoma.

no apparent sex predilection is shown except for leiomyosarcomas (Fig. 2).

The most common tumor sites were extremities, with the lower extremities involved in 36.2% and the upper extremities involved in 11.5%. The next most common sites were the retroperitoneum/intra-abdominal region (18.0%), head and neck

Table 2. Histologic types of patients with STS (n=722)

Histologic type	Subtypes	No. of patients (%)
Liposarcoma		146 (20.2)
	Well differentiated	21
	Dedifferentiated	27
	Myxoid/Round cell	78
	Pleomorphic	14
	Mixed	6
MFH		138 (19.1)
	Pleomorphic	132
	Giant cell	2
	Inflammatory	4
Leiomyosarcoma		94 (13.0)
Synovial sarcoma		89 (12.3)
Fibrosarcoma		61 (8.4)
	Conventional	12
	Myxofibrosarcoma	35
	Low grade fibromyxoid sarcoma	11
	Sclerosing epithelioid	3
Rhabdomyosarcoma		58 (8.0)
	Embryonal	33
	Alveolar	18
	Pleomorphic	7
PNET/Extraskeletal Ewing sarcoma		31 (4.3)
Angiosarcoma		23 (3.2)
Epithelioid sarcoma		18 (2.5)
Alveolar soft part sarcoma		11 (1.5)
Desmoplastic small round cell tumor		9 (1.2)
Extraskeletal myxoid chondrosarcoma		7 (1.0)
Epithelioid hemangioendothelioma		5 (0.7)
Clear cell sarcoma of soft tissue		5 (0.7)
Extraskeletal osteosarcoma		3 (0.4)
Extra-renal rhabdoid tumor		3 (0.4)
Malignant mesenchymoma		2 (0.3)
PEComa		1 (0.1)
Malignant glomus tumor		1 (0.1)
Sarcoma, type undetermined		17 (2.4)

STS, soft tissue sarcoma; MFH, malignant fibrous histiocytoma; PNET, primitive neuroectodermal tumors; PEComa, neoplasms with perivascular epithelioid cell differentiation.

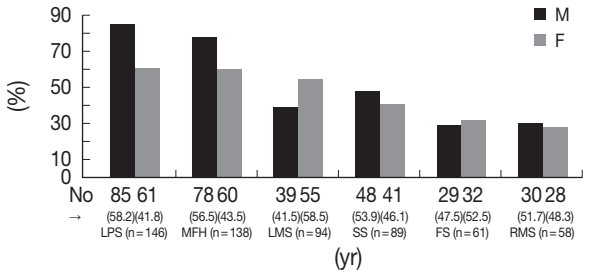

Fig. 2. Gender distribution of soft tissue sarcoma.
LPS, liposarcoma; MFH, malignant fibrous histiocytoma; LMS, leiomyosarcoma; SS, synovial sarcoma; FS, fibrosarcoma; RMS, rhabdomyosarcoma; M, male; F, female.

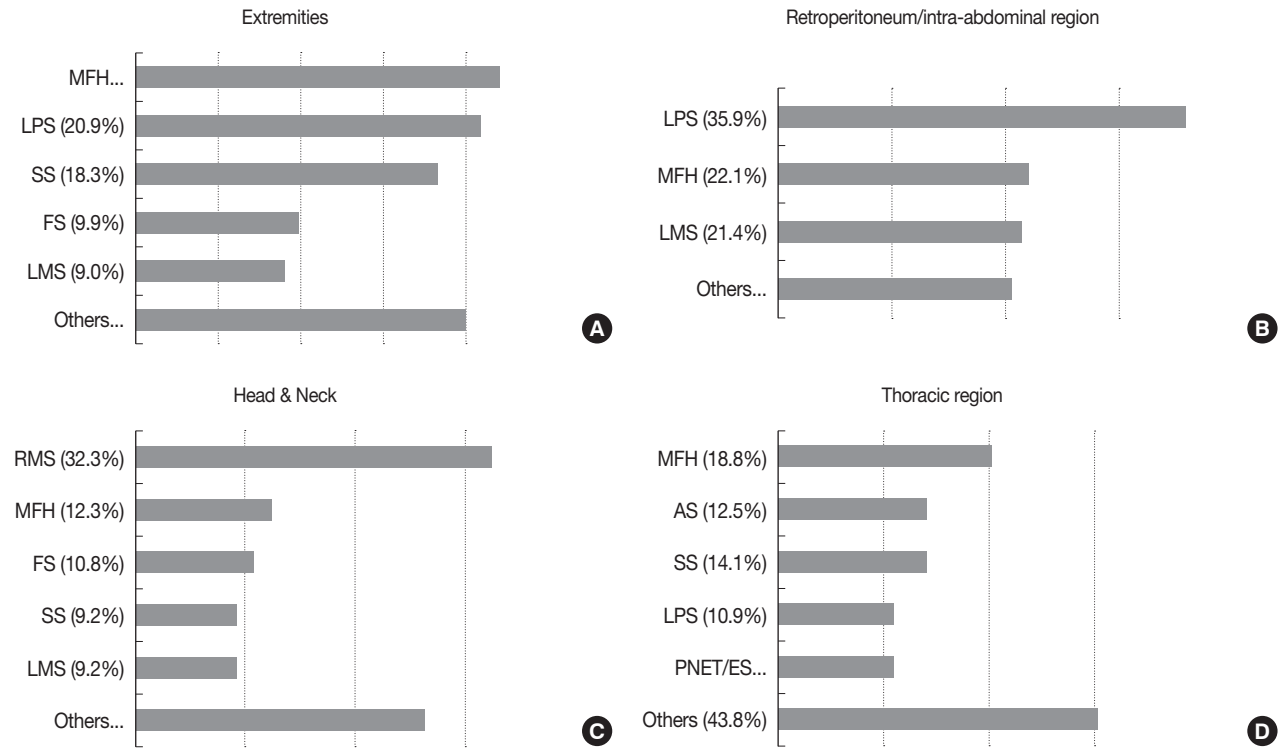

Fig. 3. Site-specific distribution of soft tissue sarcoma (STS). (A) Extremities. (B) Retroperitoneum/intra-abdominal region. (C) Head and neck. (D) Thoracic region.
MFH, malignant fibrous histiocytoma; LPS, liposarcoma; SS, synovial sarcoma; FS, fibrosarcoma; LMS, leiomyosarcoma; RMS, rhabdomyosarcoma; AS, angiosarcoma; PNET/ES, primitive neuroectodermal tumor/Ewing sarcoma.

(9.0%), and thoracic region (8.9%). For extremity sarcoma, the most common histologies were MFH (22.0%), liposarcoma (20.9%), and synovial sarcoma (18.3%). For retroperitoneal/intra-abdominal sarcoma, liposarcoma (35.9%), MFH (22.1%), and leiomyosarcoma (21.4%) were the most common histologic types, whereas, rhabdomyosarcoma (32.3%) represented the major histologic subtype in the head and neck regions. In the thoracic region, malignant fibrous histocytoma (20.3%) was the most common histologic type and angiosarcoma (14.1%) was the second most common type (Fig. 3).

The median size was 7 cm (range, 1 to 39 cm). Sixty-seven percent of patients presented with lesions of more than 5 cm whereas 33% had lesions ≤5 cm. The majority of lesions were located in the deep portion (79.0%). Nearly four-fifths of patients had high-grade lesions. Approximately 25% of the lesions were stage I, with 32.8% stage II, 39.5% stage III, and 8.8% stage IV. Complete excision was achieved in 85.7% of patients.

Metastasis at presentation was diagnosed in 6.2% of the patients (45/722). Metastases at presentation were more common in desmoplastic small round cell tumor (3/9, 33.3%), rhabdomyosarcoma (7/58, 12.1%), epithelioid sarcoma (2/18, 11.1%), and leiomyosarcoma (10/94, 10.6%). Patients with metastases had higher histologic grades (high grade, 40 cases; low grade, 2 cases; unknown, 3 cases). Metastases at diagnosis were seen in only 4.3% of superficial and 7.3% of deep-seated lesions.

Survival and prognostic factors

The overall survival rate was 76.3%, with a median follow-up time of 26 months (range, 1 to 89 months). Prognostic factors for overall survival were studied on 211 patients (Table 3). High histologic grade, large tumor size (>5 cm), high AJCC stage, tumor location other than extremities, and incomplete resection were significant risk factors for poorer survival by univariate analysis. Anatomic depth and gender were not significant. The Kaplan-Meier estimates of survival function in relation to prognostic factors are presented in Fig. 4. At multivariate analysis, large tumor size (>5 cm) and tumor site other than extremities were independently associated with poorer survival (Table 4).

Table 3. Prognostic factors of STS: unvariate analysis

Factors		Survival		p-value
		DOD (n=50)	Alive (n=161)	
Gender	Male	31 (23.0)	104 (77.0)	0.431
	Female	19 (25.0)	57 (75.0)	
Histologic type	Liposarcoma	8 (15.3)	44 (84.7)	0.114
	MFH	9 (28.1)	23 (71.9)	
	Leiomyosarcoma	4 (28.6)	10 (71.4)	
	Synovial sarcoma	4 (12.9)	27 (87.1)	
	Fibrosarcoma	2 (15.4)	11 (84.6)	
	Rhabdomyosarcoma	8 (33.3)	16 (66.7)	
	Others	15 (33.3)	30 (66.7)	
Tumor site	Extremities	16 (15.1)	90 (84.9)	0.005
	Non-extremities	34 (32.4)	71 (67.6)	
Histologic grade	Low	2 (4.8)	40 (95.2)	0.000
	High	48 (28.4)	121 (71.6)	
AJCC stage	I	2 (4.9)	39 (95.1)	0.000
	II	15 (20.8)	57 (79.2)	
	III	25 (32.1)	63 (67.9)	
	IV	8 (40.0)	12 (60.0)	
Tumor size	≤5 cm	11 (14.5)	65 (85.5)	0.013
	>5 cm	39 (28.9)	96 (71.1)	
Anatomic depth	Superficial	14 (25.5)	41 (74.5)	0.426
	Deep	36 (23.1)	120 (76.9)	
Complete resection	Complete	35 (19.5)	145 (80.5)	0.001
	Incomplete	15 (48.4)	16 (51.6)	

STS, soft tissue sarcoma; DOD, died of disease; MFH, malignant fibrous histiocytoma; AJCC, American Joint Committee on Cancer.

Table 4. Multivariate analysis of prognostic factors in STS

Variables	Grouping	p-value	Ratio of risk	95% CI
Tumor site	Extremities vs non-extremities	0.009	2.310	1.117-4.776
Histologic grade	High vs low	0.941	1.110	0.013-1.219
Tumor size	>5 cm vs ≤5 cm	0.015	2.654	1.211-5.817
AJCC stage	II, III, IV vs I	0.971	3.716	0.000-1.297
Complete resection	Incomplete vs complete	0.094	2.106	0.880-5.041

STS, soft tissue sarcoma; CI, confidence interval; AJCC, American Joint Committee on Cancer.

DISCUSSION

The main goal of this study was to assess the incidence rates, histologic distribution, clinicopathologic characteristics, and survival rates of patients with STS in the Republic of Korea. According to an annual report of cancer statistics in Korea, there were 828 new cases of STS in 2008.[8] The Korean Bone and Soft Tissue Pathology Study Group of the Korean Society of Pathologists attempted to collect cases throughout the Korean peninsula and conduct a nationwide retrospective review. Nineteen institutes covering nearly all geographic regions of the Republic of Korea participated and a total of 722 cases were included in this study. This study is the first report to show an overall tendency and comparative materials on the incidence and survival of STS in the Republic of Korea, although there is some weakness in this study related to a relatively small number of cases.

Histological classification was performed according to the WHO Classification of Soft Tissue Tumors[4] to standardize the data. In this study, liposarcoma and MFH were the most common histologic types, followed by leiomyosarcoma, synovial sarcoma, and fibrosarcoma. STS occurred in various sites, but half were located in the extremities and 18% in the retroperitoneum and intra-abdominal region. This distribution concurs with other series.[5,9,10] In the extremities, liposarcoma, MFH, and synovial sarcoma constituted two-thirds of the tumors, while in the retroperitoneum and intra-abdominal region, liposarcoma, MFH, and leiomyosarcoma represented about 80% of the tumors.[11] Rhabdomyosarcoma is the most common histologic type in the head and neck region.[1]

STS occurred more commonly in males (male : female = 1.16 : 1).[9] STS can occur at any age and, similarly to carcinomas, are more common in older patients. In this study, about 7% of affected persons were younger than 15 years, and about 50% of affected persons were 50 years or older. The median age at diagnosis was 50 years. It is unclear why Korean patients with STS showed a somewhat younger median age compared to median ages of 60s in other studies.[1,5,9] There are no data to indicate significant geographic and racial differences compared with the previous studies.[1,5,9,12,13] Age-related incidences varied among the histologic types. For instance, liposarcoma and MFH dominated in the elderly, whereas rhabdomyosarcoma occurred mostly in children. The majority of clinicopathologic data shared many similarities with Western countries.[5,12,13] Most of the STS was deep seated with large tumor sizes and histologically classified as high grade. About 6% of the patients had distant metastasis at diagnosis of the primary tumor.

The overall survival rate of patients with STS was 76.3% in this study. The 5-year-survival rate for STS has been known to be 46-75%, depending on tumor location.[9-11,14-16] The overall survival rate in this study was slightly higher than expected. This may indicate, due to selection bias, the low fraction of patients with available follow-up data. Only one-third of the entire data set had the exact information for analysis. Another selection bias was therefore made, whereby a larger fraction of a relatively better prognostic group was included in the survival analysis. Univariate analysis identified a number of prognostic

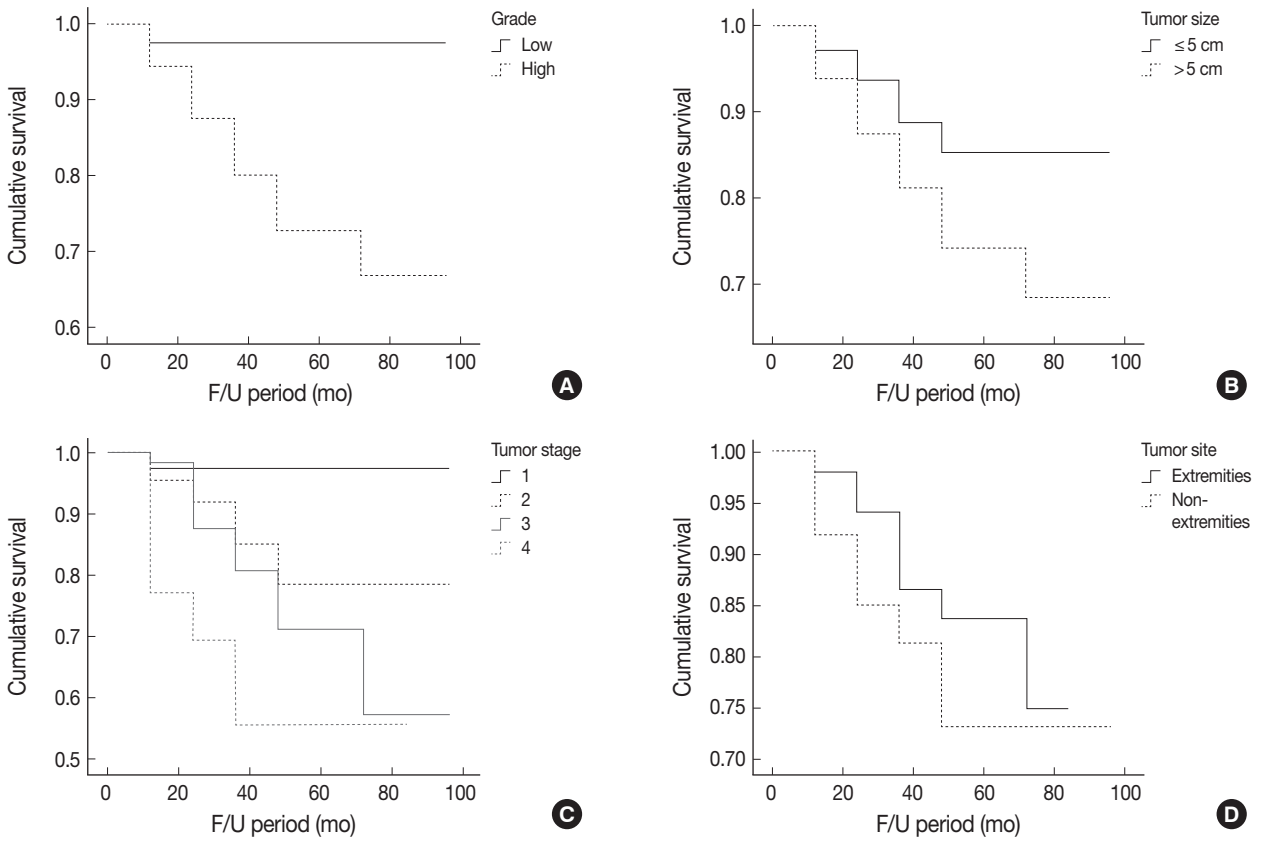

Fig. 4. Kaplan-Meier survival curves of patients with soft tissue sarcoma. (A) Histologic grade and overall survival (p=0.000). (B) Tumor size and overall survival (p=0.013). (C) American Joint Committee on Cancer tumor stage and overall survival (p=0.000). (D) Complete resection status and overall survival (p=0.001).
F/U, follow-up.

factors. High histologic grade, large tumor size (>5 cm), high AJCC stage, tumor location other than extremities, and incomplete resection were significant risk factors for poorer survival. This is similar to the results reported by other authors. Histologic grade has repeatedly been established as a negative prognostic factor in STS.[11-13,17-19] However, there is no consensus as to whether a 2-, 3-, or 4-tiered scale should be used. A positive margin following surgical resection is at increased risk of local recurrence.[10,17,18] Sabolch *et al*.[18] also reported that patients with local recurrence had decreased overall survival. Of the above prognostic factors, tumor size and tumor location other than extremities were independent prognostic factors. In other words, small tumor size (≤5 cm) and extremity sarcoma showed good prognoses. Tumor size represents an established prognostic factor in STS[12,20,21] and the location of sarcoma was important for overall survival. The 5-year survival rate for STS in extremities was 65-75%,[14] but this was less than 50% in retroperitoneal sarcoma.[11,17] We found that age, gender and anatomic depth were of no prognostic importance. However, some series have reported that the sex of the patients is a prognostic factor, and that age of more than 50 years and deep location were adverse prognostic factors.[10] Histologic type had an influence on outcome, particularly in retroperitoneal sarcoma.[11] Stoeckle *et al*.[11] showed that patients with nonliposarcoma tumors had a higher risk of metastasis when compared with liposarcoma in the retroperitoneum.

Several factors, including patient age, tumor size, anatomic depth, histological type, histologic grade, and tumor stage have been used to estimate a patient's prognosis, and some prognostic systems based on combinations of the above factors have been proposed. However refined prognosticators are needed to identify high-risk patients for ajuvant therapy and to avoid adverse effects of unnecessary treatment for low-risk patients. Some authors have emphasized vascular invasion, tumor necrosis and growth pattern to improve prognostication of STS.[21,22] The Scandinavian Sarcoma Group recently suggested a new prognostic model, referred to as SING, based on the factors of tumor size, vascular invasion, necrosis, and growth pattern.[23] They re-

ported that SING represents a promising prognostic model.

These contemporary data illustrate the incidence and survival rate patterns for STS patients in the Republic of Korea. The incidence and distribution of STS seem to be similar in different regions of the world. We did not find significant racial or geographic variation, although there was a younger age of tumor occurrence. The survival rate was slightly higher than that reported in other studies. A possible explanation for the finding may be selection bias and relatively small numbers. Since the exact causes of our findings are not currently known, future investigations could use these data to clarify the prognostic factors on survival. Further investigation, however, is needed to confirm these findings.

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