Role of surgical resection in adult urological soft tissue sarcoma: 25-Year experience

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Role of Surgical Resection in Adult Urological Soft Tissue Sarcoma: 25-year Experience

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Short title: Adult urological soft tissue sarcoma

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Abstract

Introduction: As adult urological soft tissue sarcomas are rare, there have been few recent large-scale studies of these tumors. This report describes a single institutional experience of adult urological soft tissue sarcomas over 25 years.

Materials and Methods: The study population consisted of 25 adult patients with histologically diagnosed soft tissue sarcoma arising in the urinary tract, male genital system, or retroperitoneum between January 1983 and July 2008. The study endpoint was overall survival. The crude probability of survival was estimated using the Kaplan-Meier method. Univariate and multivariate analysis of differences between patient groups was performed with the log rank test and Cox proportional hazards model.

Results: Overall survival rate at 5 years was 54.2%. On univariate analysis, unfavorable prognostic variables for overall survival were presence of metastasis at diagnosis (P=0.0005), absence of surgical resection (P=0.0003), histological subtype of rhabdomyosarcoma (P=0.0068), and primary organs other than retroperitoneum

(*P*=0.0410). On multivariate analysis, absence of surgical resection remained a significant predictor of unfavorable prognosis (HR 2.67, 95% CI 1.03 to 7.76, *P*=0.044).

Conclusions: Surgical resection, regardless of status of surgical resection margin, contributed to a favorable prognosis in adult patients with locally advanced or metastatic urological soft tissue sarcoma.

Introduction

Soft tissue sarcomas (STS) constitute a heterogeneous group of rare solid tumors of mesenchymal cell origin with distinct clinical and pathological features. The annual incidence of STS in the USA for 2007 was estimated to be about 10,390 cases, with an overall mortality rate of approximately 3,680 cases per year [1]. Less than 5% of STS arise from the genitourinary tract, accounting for only 1 to 2% of all malignant genitourinary tumors [2]. Due to the rarity of urological STS, clinical research is limited and there have been few recent large, institution-based studies. The largest series with 131 cases was collected at the Memorial Sloan-Kettering Cancer Center (MSKCC) between July 1977 and July 2003 [3]. In their study, tumor size and absence of metastasis at diagnosis remained significant predictors of disease-specific survival on multivariate analysis. In the present study, a series of 25 adult urological STS at our institution were reviewed and their prognostic factors were analyzed. This is the largest such series reported to date in Japan.

Materials and Methods

Patients

Patients histologically diagnosed as having STS arising in organs treated by urologists, such as the urinary tract, male genital system, or retroperitoneum, from January 1983 to July 2008 were included in this study. All patients were 15 years or older at diagnosis. Variables analyzed were patient age, sex, tumor size, and histological subtype, primary organ, metastasis at diagnosis, and status of the surgical resection margins. Postoperative adjuvant therapies and treatment after recurrences were also described. Although 2 patients were operated with palliative intent to improve local symptoms, we basically intended to resect tumors completely with curative intent at operation. However, as a result, complete resection was not accomplished in all cases. Surgical resection margins were documented by both the surgeon and the pathologist in evaluating resected specimens. In accordance with the National Comprehensive Cancer Network [4], the status of surgical resection margins was defined as follows: R0 resection, no residual microscopic disease; R1 resection, microscopic residual disease; and R2 resection, gross residual disease. Local recurrence or metastasis was defined as the first recurrence of disease at the primary tumor site or distant site detected by

radiographic modality, such as computed tomography.

Statistical analysis

The date of surgery or biopsy was used as the start of observation. Overall survival was the study endpoint. The crude probability of survival was estimated using the Kaplan-Meier method. Univariate analysis of differences between patient groups was performed with the log rank test. Multivariate analysis of variables that were significant on univariate analysis was analyzed with the Cox proportional hazards model. Statistical significance was defined as $P<0.05$.

Results

Patient characteristics

Patient characteristics are shown in table 1. A total of 25 cases were included in this analysis. The most common site was the retroperitoneum (14 cases, 56%), followed by bladder, kidney, and paratesticular tumors each with 3 cases (12%) and the prostate with 2 cases (8%). The most common histological subtype was rhabdomyosarcoma (7 cases, 28%), followed by liposarcoma with 5 cases (20%), malignant fibrous histiocytoma (MFH) and leiomyosarcoma each with 4 cases (16%). The remaining five cases had other histological subtypes (20%), which included angiosarcoma, malignant hemangiopericytoma, malignant schwannoma, malignant solitary fibrous tumor, and unclassified sarcoma. Of the 25 patients, 5 (20%) presented with metastatic disease and 21 (84%) underwent surgical resection. Of these 21 patients, 19 (90%) underwent surgical resection with curative intent and 2 (10%) underwent surgical resection with palliative intent (R2 resection). Of the 19 patients who underwent surgical resection with curative intent, 8 (42%) underwent complete resection (R0 resection), 6 (32%) underwent incomplete resection with microscopically residual disease (R1 resection) and 2 (11%) underwent incomplete resection with gross residual disease (R2 resection).

Surgical resection margin status was not determined in 3 patients (16%) (Rx resection). All 11 patients of R0 and Rx resection did not undergo postoperative adjuvant therapy. Four of 8 R0 resection patients had recurrence and 3 patients underwent treatment after recurrence as follows; re-operation of tumor resection, chemotherapy (CT), embolization followed by radiofrequency ablation. All 3 Rx patients had recurrence and underwent treatment after recurrence as follows; radiation therapy (RT), CT with RT (2 patients). Two of 6 R1 resection patients underwent postoperative adjuvant therapy of CT and CT with RT. Five of 6 R1 resection patients, including 2 patients who underwent postoperative adjuvant therapy, had recurrence and underwent treatment after recurrence as follows; CT with RT, immunotherapy, re-operation of tumor resection (2 patients), re-operation of tumor resection followed by CT. One of 4 R2 resection patients underwent CT with RT after surgical resection. Median recurrence interval of R0, R1 and Rx resection was 41.5 months (range 14-69 months), 4 months (range 2-53 months) and 41 months (range 7-77 months), respectively. Two of R0 resection patients had distant recurrence sites, one had multiple bone metastases and the other had liver and thighbone metastases. Other patients had local recurrences. Four of 10 local recurrence patients underwent re-operation with curative intent and the number of the patient of R0, R1 and Rx was 2, 1 and 1, respectively. All of 4 patients who did not

undergo surgical resection underwent CT, RT (2 patients), and CT with RT.

Overall survival

At the end of the study follow-up period, 15 of the 25 patients were alive. Overall survival rate at 5 years was 54.2% and median survival time was 63 months (fig. 1a). Overall survival rate of inoperable, R2 resection, and recurrent cases at 5 years was 28.1% and median survival time was 25 months (fig. 1b). The distribution of 25 STS according to histological characteristics is shown in table 2. On univariate analysis, unfavorable prognostic variables for overall survival were presence of metastasis at diagnosis (*P*=0.0005; overall survival at 5 years, 0% *vs.* 73.2%), absence of surgical resection (*P*=0.0003; overall survival at 5 years, 0% *vs.* 66.8%), histological subtype of rhabdomyosarcoma (*P*=0.0068; overall survival at 5 years, 21.4% *vs.* 67.7%), and primary organs other than retroperitoneum (*P*=0.0410; overall survival at 5 years, 38.2% *vs.* 69.3%) (fig. 1c–f). There were no significant differences in survival according to age (*P*=0.1687), sex (*P*=0.1722), tumor size (largest dimension classified by less than 10 cm *vs.* greater than 10 cm, less than 15 cm *vs.* greater than 15 cm, and less than 20 cm *vs.* greater than 20 cm; *P*=0.1464, 0.4503, and 0.5958, respectively). There were also no significant differences between R0 and R1 resection (*P*=0.2385), or

between R0 and R1+2 resection (*P*=0.0722). There were no significant differences in survival according to whether undergoing CT or not (*P*=0.7084) and undergoing RT or not (*P*=0.3721). On multivariate analysis, absence of surgical resection remained a significant predictor of unfavorable prognosis (HR 2.67, 95% CI 1.03–7.76, *P*=0.044) (table 3).

Discussion

As adult urological STS is very rare, clinical research regarding this disease is difficult. To our knowledge, this is the first case series study of adult urological STS performed in Japan. There have been 3 previous clinical studies of adult urological STS. Mondaini *et al.* reported a series including 22 adult patients with genitourinary sarcomas of different histological types who were identified and reviewed in a multicenter study performed in 8 different hospitals in Tuscany, central Italy [5]. The MSKCC group reported two consecutive series, one including 43 patients treated between 1982 and 1989 [6] and another including 131 patients between performed between 1977 and 2003. The latter study extended the former with prolonged follow-up, and allowed the use of multiple variables for determining local recurrence-free and disease-specific survival [3]. Less than 5% of STS arise in the genitourinary tract and only 15% of STS arise within the retroperitoneum [2,7]. All retroperitoneal STS are considered deep lesions with a generally poor prognosis [8,9].

Overall survival rate at 5 years was 54.2% and median survival time was 63 months. These results were consistent with those of the previous study by Coindre *et al.* in which the 5-year survival rate of STS was 50–60% [10]. On univariate analysis, the

presence of metastasis, rhabdomyosarcoma, primary organs other than the retroperitoneum, and absence of surgical resection were unfavorable prognostic variables for overall survival. The presence of metastasis and rhabdomyosarcoma were reported previously to be unfavorable prognostic variables [3]. Prognosis of genitourinary STS may be more unfavorable than that of retroperitoneal STS. On multivariate analysis, the absence of surgical resection remained as an unfavorable prognostic variable for overall survival. Lewis *et al.* reported the presence of unresectable disease and incomplete surgical resection as the most significant factors predictive of disease-specific death [11]. In a study by van Dalen *et al.* in 143 patients treated in the Netherlands, complete tumor resection was correlated with better overall survival on multivariate analysis [12]. However, Dotan *et al.* reported that complete resection was not a significant factor predictive of disease-specific survival on univariate and multivariate analysis in 102 patients with primary tumors only [3]. Interestingly, in the present study there were no significant differences between R0 and R1 resection or between R0 and R1+2 resection. These results suggest that any type of surgical resection can provide the best chance of survival in patients presenting with primary disease or with primary and metastatic disease.

Size of STS is an important prognostic variable. According to the American Joint

Committee on Cancer staging criteria for STS, sarcomas have classically been stratified into two groups on the basis of size: T1 lesions are 5 cm or smaller, and T2 lesions are larger than 5 cm [13]. In the present study, all sarcomas were greater than 5 cm in the largest dimension. This may have been because STS arising from retroperitoneum can achieve a large size due to the flexibility of the retroperitoneum and the large volume of space available for organ displacement. There were no significant differences in size of tumors in the present study. However, Ramanathan *et al.* suggested that further stratification of tumors larger than 5 cm would provide more accurate prognostic information. When 316 patients with STS were grouped into four subgroups on the basis of tumor size (less than 5 cm, 5 to less than 10 cm, 10 to 15 cm, and greater than 15 cm), each subgroup had a different prognosis, as shown by the 5-year survival rates of 84%, 70%, 50%, and 33%, respectively [14]. R0 resection may be an important prognostic factor in the early phase of STS with small tumors of less than 5 cm. However, any type of surgical resection can be a prognostic factor in the advanced phase with large tumors greater than 5 cm or with metastases as in the present cases.

As to metastatic or advanced STS except for specific types of sarcomas such as gastrointestinal stromal tumor, the effect of CT or RT is not established. In the present study, R1 and R2 resection patients could be comparable with R0 resection patients in

respect to postoperative adjuvant therapy, because only 2 R1 resection patients underwent postoperative adjuvant therapy of CT or CT with RT. It may be improper to assess the efficacy of CT and RT, because the sample size was small and various treatments were metachronously performed. However, we tried to analyze the efficacy of CT and RT on univariate analysis about inoperable, R2 resection, and recurrent cases. We could not clarify that surgical resection improved the efficacy of CT and RT.

The present study had a number of limitations. Small sample size may have prevented determination of the precise statistical significance. Histological grade was not considered as a prognostic variable in the present study because it was not clear in some older specimens. Moreover, all patients were Japanese, so the distribution of STS according to histological subtype or primary organ may differ in patients from other ethnic backgrounds.

Finally, this study provided evidence that surgical resection, regardless of the status of the surgical margins, may contribute to a favorable prognosis in adult patients with urological STS. Larger prospective studies with longer follow-up periods are needed to confirm these findings.

Conclusions

In the present study, although sample size was small, it was confirmed that surgical resection, regardless of status of surgical margins, may contribute to a favorable prognosis in adult patients with locally advanced or metastatic urological STS.

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Figure legends

Fig. 1. Kaplan-Meier analysis of overall survival (a) in overall cases, (b) in inoperable, palliatively resected or recurrent cases, (c) according to presence *vs.* absence of metastasis at diagnosis, (d) according to presence *vs.* absence of surgical resection, (e) according to histological subtype of rhabdomyosarcoma *vs.* other, and (f) according primary organ of retroperitoneum *vs.* other.

Table 1 Characteristics in patients with urological STS

Variable	n
No. patients	25
Median age at diagnosis (range)	54 (16-77)
No. men/women (%)	21 (84) / 4 (16)
Median months followup (range)	25 (1-182)
No. primary organ (%)	
Retroperitoneum	14 (56)
Bladder	3 (12)
Kidney	3 (12)
Paratesticular	3 (12)
Prostate	2 (8)
No. histological subtype (%)	
Rhabdomyosarcoma	7 (28)
Liposarcoma	5 (20)
MFH	4 (16)
Leiomyosarcoma	4 (16)
Other	5 (20)
No. metastasis at diagnosis (%)	
Yes	5 (20)
No	20 (80)
No. underwent resection (%)	
Yes	21 (84)
No	4 (16)
No. complete resection (%)	
Yes (negative margin, R0 resection)	8 (38)
No positive margin, R1 resection	6 (29)
gross residue, R2 resection	4 (19)
unknown, Rx resection	3 (14)
No. tumor size (largest dimension) (%)	
< 10 cm	8 (32)
10-15 cm	5 (20)
15-20 cm	4 (16)
> 20 cm	4 (16)

unknown	4 (20)
No. adjuvant therapy (%)	
Chemotherapy	9 (36)
Radiotherapy	9 (36)
Other or none	7 (28)
No. last follow-up status (%)	
No evidence of disease	5 (20)
Disease	10 (40)
Dead of disease	10 (40)

MFH, malignant fibrous histiocytoma

Table 2 Distribution of 25 urological sarcomas according to histological characteristics

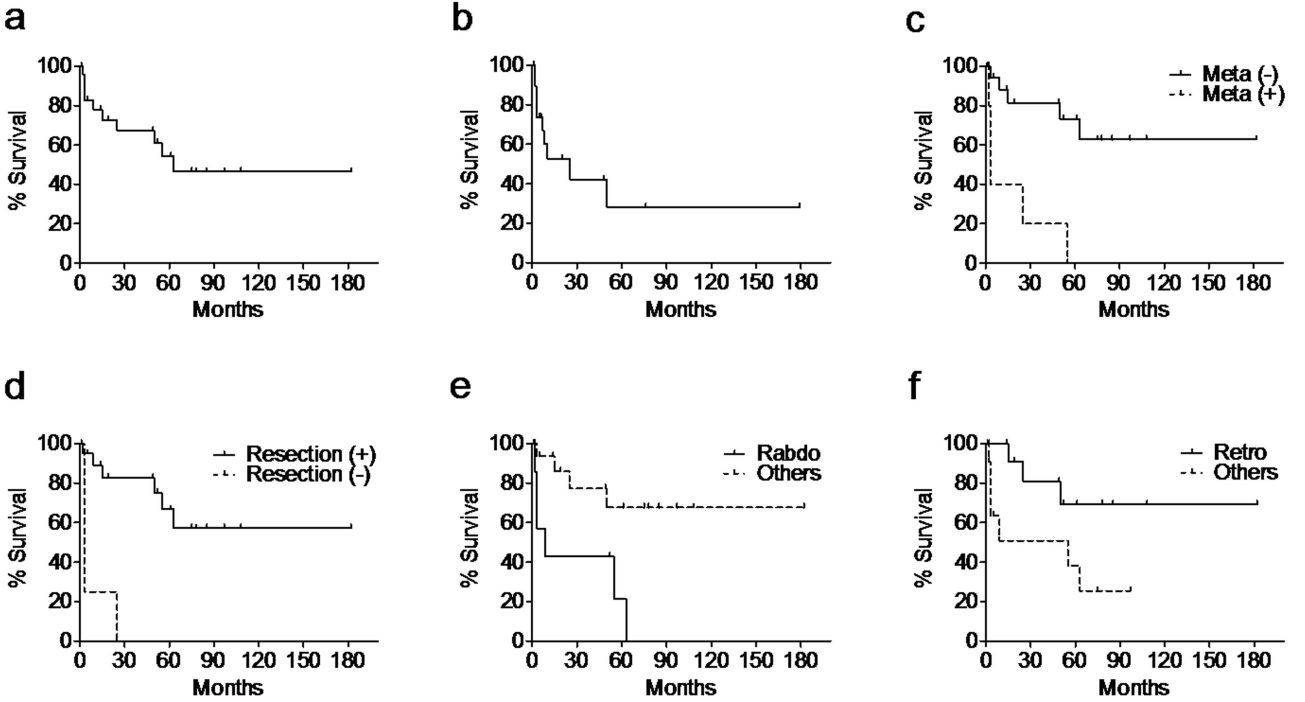
Histological subtype	n	Met.	Res.	Primary organ				
				Retro.	Bladder	Kidney	Parates.	Prostate
Rhabdomyosarcoma	7	3	5	1	1	2	1	2
Liposarcoma	5		5	4			1	
MFH	4	1	3	3	1			
Leiomyosarcoma	4		4	3		1		
Other	5	1	4	3	1		1	
Total	25	5	21	14	3	3	3	2

Met., metastasis; Res., resection; Retro., retroperitoneum; Parates., paratesticular; MFH, malignant fibrous histiocytoma

Table 3 Multivariate analysis of variables and overall survival in 25 patients

Variables	HR (95% CI)	*P* value
Primary organ (other vs retro.)	1.32	0.562
Histological subtype (rhabdo. vs other)	1.78	0.154
Metastasis at diagnosis (yes vs no)	1.41	0.374
Underwent resection (no vs yes)	2.67 (1.03-7.76)	0.044

Retro., retroperitoneum; Rhabdo., rhabdomyosarcoma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Resection (+)
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Rabdo
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Retro
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