Published in final edited form as:

J Surg Oncol. 2018 June ; 117(7): 1464–1468. doi:10.1002/jso.25016.

Importance of wide re-resection in adult spermatic cord sarcomas: report on oncologic outcomes at a single institution

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Abstract

Background and objectives—We evaluated the effect of re-resection with wide margins (undertaken because initial resection performed elsewhere was incomplete) on survival in patients with spermatic cord sarcoma (SCS).

Methods—After excluding those with metastatic disease and those not undergoing surgical intervention, the records of 72 consecutive patients treated for SCS between 1981 and 2011 at Memorial Sloan Kettering Cancer Center were reviewed. Recurrence-free survival (RFS) and cancer-specific survival were calculated using the Kaplan-Meier method for compared between the 48 patients who underwent wide re-resection (WRR) within 5 months of diagnosis and the 24 who did not. The relationship of age, tumor size, tumor histology, adjuvant radiation, and wide re-resection with recurrence and death was assessed by univariate Cox regression.

Results—WRR significantly improved RFS (hazard ratio [HR] 0.16, 95% CI 0.07–0.37; $p < 0.0001$), despite the fact that patients receiving WRR had higher-grade disease. Tumor-positive margins upon WRR were strongly associated with both disease recurrence (HR 5.56; 95% CI 1.14–27.11, $p = 0.034$) and death from cancer (HR 6.16, 95% CI 1.25–30.29; $p = 0.025$).

Conclusions—A WRR with negative margins is effective in the management of patients with SCS and leads to improved RFS.

Keywords

sarcoma; spermatic cord; re-resection; negative margins

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Disclosure information: Nothing to disclose

Introduction

Soft tissue sarcomas most commonly develop in the extremities (accounting for 43% of all sarcoma cases).¹ Genitourinary sarcomas account for only 2% of all soft tissue sarcomas and 1% to 2% of malignant tumors of the genitourinary tract.[1,2] The spermatic cord and paratesticular tissue are the most common sites for sarcomas with genitourinary involvement, comprising roughly 45% of related sarcomas. The first described case of spermatic cord sarcoma (SCS) was reported in 1845, matching clinically to what is still seen today.⁴ Presenting as a firm, painless mass, this tumor is typically encountered incidentally during surgical exploration of the inguinal region for other reasons and is often mistaken for benign growths such as cord lipoma or fat-containing hernias. SCS should be considered as a diagnosis in any patient with an inguinal or scrotal mass involving the cord structures, and tissues should be evaluated by pathology.

SCSs are very rare, impeding the ability to conduct clinical trials and limiting studies to prospective registries established to help inform best practice guidelines. Such registries can provide valuable data and have been used effectively to develop treatment strategies for sarcomas in other anatomic sites.[3] Strategies proposed for optimal management of SCSs, based on the principles established for soft tissue sarcomas, rely heavily on aggressive initial surgical treatment: radical inguinal orchiectomy with a wide re-resection (WRR) to achieve negative margins (an R0 resection).[4] Risk factors for tumor recurrence and progression in adult sarcomas that may also influence outcomes in SCS include tumor grade and size, depth of invasion, surgical margin status, and use of adjuvant radiation.[5] In this study, we examined all cases of SCS in adults treated at a single tertiary referral cancer center over 30 years and evaluated the association of tumor pathology, surgical resection factors, and adjuvant radiation with recurrence-free survival (RFS) and cancer-specific survival (CSS).

Materials and Methods

Following institutional review board approval, we retrospectively reviewed the records of 81 male patients with SCS treated at Memorial Sloan Kettering Cancer Center from June 1981 through July 2011. Most of the patients in our cohort received a diagnosis elsewhere before being referred to our institution for further treatment. Nine patients were excluded from our analysis: 1 patient did not undergo any surgical intervention and 8 patients had evidence of metastatic disease at presentation. A total of 72 patients comprised the main cohort for our analysis.

Patients who presented to our institution after initial resection elsewhere were recommended for WRR because of incomplete prior resection (as indicated by a positive/indeterminate margin status or radical orchiectomy) or suspicion for residual disease based on physical examination or imaging. The goal of re-resection was to achieve negative margin status (R0) with curative intent. Treatment with WRR is defined as surgical intervention to remove the site of prior disease including all surrounding soft tissues, prior scar, including spermatic cord remnants and testis (if any), and all gross evidence of disease. Patients who underwent WRR within 5 months from initial resection were included in the WRR group. Age at first surgery, year of surgery, tumor location, tumor size, tumor grade, and histology were

compared between patients who received WRR and those who did not using Wilcoxon rank sum and Fisher's exact tests.

Prior to survival analyses, we screened subjects according to status at 5 months post-initial resection. Five patients who were not at risk for recurrence at that time point were omitted from the RFS analysis, and 3 patients who died or were lost to follow-up before 5 months were omitted from the CSS analysis.

Overall survival was estimated using the Kaplan-Meier method. The log-rank test was used to compare survival between patients who underwent WRR and those who did not. To evaluate the association between RFS and CSS and the following covariates: patient age, use of adjuvant radiation, tumor grade, location, and size, univariate Cox proportional hazards models were used.

To assess the effects of margin status after WRR among patients who had the procedure, we performed a subset analysis including only these patients. A univariate Cox proportional hazards model was used to assess the association between surgical margin status and recurrence or death from disease.

All statistical analyses were conducted using Stata 13.0 (Stata Corporation, College Station, TX).

Results

Of the 72 patients, 48 (67%) underwent WRR with curative intent to achieve complete resection with negative margins (R0). Recurrence occurred in 30/72 (42%) patients and 20/72 (28%) patients died of disease, with a median follow-up for survivors of 6.4 years after the 5-month point (interquartile range 3.5–11.5). Table I lists patient characteristics; we found no evidence of a difference in age at first surgery, tumor size, tumor location, or histology between patients who underwent WRR and those who did not. There was a higher proportion of high-grade disease among patients who underwent WRR (71 % vs 50%; $p = 0.12$), although this association was not statistically significant. The median calendar years of referral for patients who received WRR and those who did not were 2000 and 1993, respectively, suggesting that referral and/or treatment patterns have changed over time ($p = 0.001$). Liposarcoma was the most common histology. Of the 15 patients with liposarcomas that did not undergo WRR, only 3 (20%) had high-grade disease, and of those undergoing WRR, a majority (22/33 [67%]) had high-grade disease. This was statistically different between the groups ($p = 0.004$). Chemotherapy was used as adjuvant treatment in only 1 patient and as salvage therapy in 9 patients in this population.

Despite the fact that patients who underwent WRR were older and had higher-grade tumors, we found that patients who did not undergo WRR had a significantly greater likelihood of recurrence, with a difference in RFS of 30.7% (95% CI 9.8%–51.7%) and 44.1% (95% CI 19.9%–68.3%) at 2 and 5 years, respectively ($p < 0.0001$) (Figure 1).

However, as seen in Figure 2, there was no difference in CSS between those who underwent WRR and those who did not ($p = 0.3$). The differences in CSS between patients who

underwent WRR and those who did not were 1.8% (95% CI -7.4%–11.0%) at 2 years and 4.1 % (95% CI -14.3%–22.4%) at 5 years.

On univariate Cox regression, there was no evidence that age, adjuvant radiation, tumor grade, location, or size were significantly associated with RFS. Older patients were significantly more likely to die from disease in the first 10 years (hazard ratio [HR] 1.54; 95% CI 1.03–2.29; $p = 0.034$). High-grade tumors conferred a higher risk of cancer-specific death, although the association was not statistically significant (HR 2.99; 95% CI 0.92–9.77; $p = 0.069$). Tumor location, tumor size, and adjuvant radiation were not associated with death from cancer (Table II).

Since WRRs were intended to achieve negative surgical margins, we hypothesized that patients who underwent a WRR and were still found to have positive margins may have worse RFS and CSS than those for whom WRR resulted in negative surgical margins. Among the 48 patients who underwent WRR, there were 12 recurrences and 10 deaths from SCS. While this was a small sample, positive surgical margins were strongly associated with both disease recurrence (HR 5.56, 95% CI 1.14–27.11; $p = 0.034$) and cancer-specific death (HR 6.16, 95% CI 1.25–30.29; $p = 0.025$).

Notably, of the 8 patients excluded from this study because of metastatic disease at presentation, 3 survived throughout follow-up (4, 17, and 29 years after their initial surgery). Treatment included WRR with adjuvant local radiation therapy in 2 patients and local radiation therapy alone in one. The remaining 5 patients died of metastatic disease at a median of 13 months after diagnosis. Only one of these 5 patients received any form of treatment, which consisted of surgical resection alone.

Discussion

The mainstay of treatment for patients with localized soft tissue sarcoma is complete surgical resection with negative margins (R0).[6] In adult patients with SCS, surgical treatment typically includes radical orchiectomy and resection of the spermatic cord mass with both gross and microscopic negative margins. However, since SCSs arise from mesodermal-derived cord structures, including cremasteric and interstitial cells that both lie within and surround the fascial layers of the cord itself,[7] this approach may be insufficient. At our institution, WRR is performed, extending resection to the inguinal canal (and any previous scar) to include surrounding soft tissues of the cord or cord remnant to the level of the internal inguinal ring, and soft tissue deep to the internal inguinal ring.[8] A hemiscrotectomy is also performed when the tumor is invading the scrotal wall or if the tumor was removed through scrotal approach. WRR is becoming more widely utilized.

Accordingly, in our cohort of adult patients with SCS, RFS was significantly increased in patients who underwent a WRR within 5 months of initial diagnosis. This could be due to a causal effect of WRR, which reduces risk of recurrence, or selection bias. Because surgeons may select patients for WRR based on histology, tumor size, and patient age, we examined the possibility that these factors influenced our results. However, when evaluating these factors the only difference identified was that those undergoing WRR were more likely to

have high-grade disease and, therefore, a higher risk of recurrence. Despite this potential increased risk of recurrence, an RFS benefit was still evident that could not be explained by factors other than the effect of WRR.

The importance of negative margins at the time of WRR was identified in subset analyses. Margin status at initial surgery for those patients not undergoing WRR was not available; therefore, we are unable to determine how this potential selection bias and characteristic contribute to recurrence and survival. These findings reiterate the benefit of initial local control with wide surgical resection shown in previous studies in SCS and other sarcomas. [4-6,8] Surgical margin status at the time of WRR is of utmost importance for both RFS and CSS in this patient population.

Of those who did not have a WRR within 5 months of diagnosis, evidence of a local recurrence could lead to further treatment at the time of the first recurrence. This is of importance, as this early detection of a local recurrence allows appropriate treatment at that time and no increased risk of death from disease.

The role of adjuvant radiation therapy after surgical resection is still not completely defined. In an attempt to reduce high local recurrence rates (approaching 50% in some studies) of SCS in patients treated with surgery alone,[8-13] a combination of wide resection and radiation therapy has been used. In prospective randomized trials in patients with extremity sarcomas, this combination therapy was effective in reducing local recurrence rates, although no improvements in overall survival or CSS were noted.[9,14-17] Similarly, small studies and case series (3 to 15 patients) of SCS have shown low recurrence rates or no local recurrence in patients treated with adjuvant radiation therapy, but none report improvement in survival.[12,13,18,19] In our study, 27/72 (38%) patients underwent adjuvant radiation therapy after surgical resection. While we did not observe an effect on RFS or CSS, the number of patients is insufficient to adequately assess potential confounding factors, so no definitive conclusions can be drawn.

To our knowledge, we report on the largest single-center experience treating patients with SCS. Still, this analysis has several limitations. The small sample size of each treatment group may have been insufficient to detect slight differences between groups. Our results may also have been affected by bias in the selection of patients for either WRR or referral for radiation therapy. These decisions were made on an individual case basis, with input from both the treating physician and the patient. As noted above, there were not enough patients to determine the benefit of adjuvant radiation therapy. Though our data seem to suggest that proper surgical control and negative margin status is the key factor influencing outcomes, at our institution, appropriately selected patients will still be counseled on the potential benefits of adjuvant radiation therapy.

The rarity of SCS precludes the conduct of a randomized controlled trial to determine the best treatment paradigm, leaving outcomes from large-center experiences as the best guide to effective treatment. In turn, this approach has its own limitations, including the potential inapplicability of surgical and oncologic outcomes achieved at high-volume centers to other centers or institutions.

Conclusions

Sarcoma of the spermatic cord is rare, but once diagnosed, proper management is crucial to patient outcome. Our study shows that the most effective strategy for increasing RFS is a complete WRR after diagnosis to achieve R0 status. A complete WRR should consist of radical orchiectomy and removal of the cord remnant and surrounding tissue and scar to the level of the internal inguinal ring with a negative surgical margin and hemiscrotectomy when necessary.

Acknowledgments

Funding: This study was supported by the Sidney Kimmel Center for Prostate and Urologic Cancers and the National Institutes of Health/National Cancer Institute Cancer Center Support Grant (P30 CA008748).

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Acronyms

SCS	spermatic cord sarcoma
RFS	recurrence-free survival
WRR	wide re-resection
HR	hazard ratio
CI	confidence interval
CSS	cancer-specific survival

Figure 1. Kaplan-Meier estimates of recurrence-free survival for patients who had wide re-resection within 5 months of diagnosis (red line) and those who did not (blue line), $p < 0.0001$.

Figure 2. Kaplan-Meier estimates of cancer-specific survival for patients who had wide re-resection within 5 months of diagnosis (red line) and those who did not (blue line), $p = 0.3$.

Table I
Patient Characteristics for all Patients By Wide Re-Resection Status*

	No WRR (n = 24)	WRR (n = 48)	p Value
Age at first surgery (years)	53 (46–66)	61 (52–68)	0.2
Size of tumor (n=63) (cm)	4.3 (3.0–7.0)	5.0 (3.2–8.0)	0.7
Tumor location (n=71):			
Left	9 (39%)	24 (50%)	0.5
Right	14 (61%)	24 (50%)	
Histology:			
Liposarcoma	15 (63%)	33 (69%)	0.3
Leiomyosarcoma	4 (17%)	9 (19%)	
Malignant fibrous histiocytoma	2 (8.3%)	2 (4.2%)	
Myosarcoma and other	0 (0%)	3 (6.3%)	
Spindle cell	1 (4.2%)	1 (2.1%)	
Embryonal rhabdomyosarcoma	2 (8.3%)	0 (0%)	
High-grade tumor	12 (50%)	34 (71%)	0.12
Margin status at WRR:			
Positive		23 (48%)	
Negative		25 (52%)	
Adjuvant radiation	11 (46%)	16 (33%)	0.3
Year of surgery	1993 (1985–1996)	2000 (1997–2005)	0.001

* Data are reported as median (interquartile range) or frequency (%).

WRR, wide re-resection

Univariate Cox Regression Models for Recurrence-Free Survival and Cancer-Specific Survival

Table II

	Recurrence-Free Survival			Cancer-Specific Survival		
	HR	95% CI	p Value	HR	95% CI	p Value
Wide re-resection	0.16	0.07–0.37	<0.0001	0.59	0.23–1.51	0.3
Age at first surgery(per 10 years)	0.96	0.72–1.27	0.8	1.54	1.03–2.29	0.034
Adjuvant radiation	1.35	0.63–2.88	0.4	1.09	0.43–2.76	0.9
High grade	1.29	0.58–2.86	0.5	2.99	0.92–9.77	0.069
Right-sided tumor	1.63	0.75–3.54	0.2	1.19	0.47–3.03	0.7
Size of tumor (cm)	0.96	0.84–1.09	0.5	0.81	0.62–1.07	0.13