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Clinical Outcomes of Local and Metastatic Testicular Sex Cord-Stromal Tumors

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Abstract

Purpose: We evaluated pathological variables of testicular sex cord-stromal tumors, management options and clinical outcomes.

Materials and Methods: We retrospectively reviewed the records of 48 patients with testicular sex cord-stromal tumors treated at Memorial Sloan-Kettering Cancer Center between 1997 and 2012. Clinical outcomes were compared based on treatment and previously described pathological factors associated with metastatic potential.

Results: Of the 48 patients 37 underwent surveillance without retroperitoneal lymph node dissection, including 34 with no high risk feature and 3 with 1. Median followup was 14.5 months (IQR 6.9–32.5). No patient experienced recurrence. Retroperitoneal lymph node dissection was performed in 11 patients, including 6 with clinical stage I disease and 2 or more high risk features who underwent early dissection, 2 with clinical stage IIa disease at diagnosis who underwent early dissection and 3 with clinical stage I disease and 2 or more high risk features who were observed elsewhere but referred to our institution due to retroperitoneal disease. Six patients with clinical stage I disease underwent early dissection, 4 had no evidence of disease at a median followup of 6.6 years and 2 experienced recurrence and died of disease. Neither of the 2 patients with IIa disease at diagnosis experienced relapse. All 3 patients with delayed dissection experienced relapse and 1 died of disease.

Conclusions: Patients with testicular sex cord-stromal tumors and 1 or no high risk feature can be safely observed without retroperitoneal lymph node dissection but longer followup is needed. Given the lack of effective alternative treatments, early retroperitoneal lymph node dissection may be beneficial in those with 2 or more high risk features, or clinical stage IIa disease.

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Study received institutional review board approval.

Keywords

testis; sex cord-gonadal stromal tumors; lymph node excision; risk; orchiectomy

Testicular sex cord-stromal tumors are a rare group of primary testicular neoplasms that arise from the hormone secreting cells of the testis. The most common subtype, accounting for 75% of these tumors, originates from Leydig cells.¹ TSCSTs also include tumors of Sertoli and granulosa cell origin as well as mixed cell types. Most commonly patients present with a painless testicular mass, although symptoms due to excessive hormonal secretion such as gynecomastia may also occur.² Together these tumors comprise approximately 4% to 5% of all testicular tumors.³

While most TSCST are indolent, approximately 10% metastasize, most commonly to the retroperitoneum in a fashion that mimics testicular germ cell tumors.⁴ Due to the lack of effective chemo-therapeutic or radiation treatment options TSCST metastasis often results in death.⁴ For this reason RPLND even in the absence of retroperitoneal disease is believed by some physicians to be critical.⁵ However, RPLND would be overtreatment in most patients with clinical stage I disease since most of them are unlikely to experience disease progression.

Kim et al challenged the notion that the only reliable criterion for malignancy is metastasis.⁵ They established 6 histopathological criteria predictive of metastatic potential for Leydig cell tumors, including tumor greater than 5 cm, necrosis, moderate or severe nuclear atypia, angiolymphatic invasion, infiltrating margins and greater than 5 mitotic features per 10 high power fields. These criteria were subsequently confirmed and applied to all TSCST subtypes.^{3,6} Kim et al advocated orchiectomy alone in patients with none of these features and RPLND when any feature was present.⁵ However, due to small cohorts with a limited number of events it remains unclear how to best treat patients with TSCST. Some investigators advocate an aggressive approach by performing RPLND in all patients with TSCST^{4,7} and others recommend observation in all patients with clinical stage I disease.⁸

We reviewed our institutional approach to these tumors. We also evaluated primary tumor pathological variables, management options and clinical outcomes in patients with TSCST.

MATERIALS AND METHODS

After receiving institutional review board approval we retrospectively reviewed the records of all patients with TSCST who received care at MSKCC between 1997 and 2012. While not all patients were initially treated at our institution, all pathological specimens were reviewed by genitourinary fellowship trained pathologists at MSKCC. Orchiectomy pathology reports were reviewed for high risk pathological features associated with metastatic potential.⁵ At MSKCC we recommend surveillance for patients with 1 or none of these high risk pathological risk features and no evidence of retroperitoneal lymphadenopathy. For patients with 2 or more high risk features, or evidence of retroperitoneal adenopathy on cross-sectional imaging we recommend RPLND. Notably not all patients underwent initial treatment at MSKCC so that not all were treated in this uniform manner.

A total of 48 patients with TSCST were referred to MSKCC for consultation or treatment between 1997 and 2012. Of the 48 patients 37 had 1 or no pathological risk feature with no evidence of retroperitoneal disease on imaging. They were classified as being at low risk and underwent routine surveillance. RPLND was performed in the remaining 11 patients, who were classified as being at high risk due to 2 or more pathological risk features, or retroperitoneal disease on imaging. Patients were characterized and compared based on risk group and indication for RPLND. All patients who underwent RPLND were treated with full bilateral template RPLND as previously described in detail.⁹ Time to RPLND was calculated as the time between orchiectomy and RPLND. Time to relapse was calculated as the time between RPLND and the date of post-RPLND relapse. Total followup was calculated as time from orchiectomy to last followup or death. All analysis was done with Stata® 12.0.

RESULTS

All 48 men in this cohort underwent partial or radical orchiectomy for TSCST. In 20 and 26 of these patients the primary tumor was on the left and right side, respectively. Two patients in this group had bilateral synchronous primary tumors. Of these tumors 65% were due to a palpable lesion but 35% were found due to other reasons. A total of 13 men had Sertoli cell tumors, 28 had Leydig cell tumors, 5 had unclassified TSCST and 2 had granulosa cell tumors.

After orchiectomy patients were stratified into 2 groups by risk (table 1). Patients with zero (34) or 1 (3) risk factor and no evidence of retroperitoneal disease on cross-sectional imaging were on surveillance for a median of 14.5 months (IQR 6.9–32.5). None of these 37 patients experienced retroperitoneal recurrence of TSCST. In this group patient age at orchiectomy was 18 to 78 years (median 37, IQR 29–52) (see figure).

The other 11 men in the cohort underwent RPLND because they had 2 or more risk factors, or retroperitoneal disease was found. With a median age at orchiectomy of 48 years (IQR 37–53) these patients were older than those with 1 or no risk factor. Ten of these patients were diagnosed with a palpable testicular mass and 1 was not. Median followup in all patients treated with RPLND was 67 months (IQR 23–112).

Six of these 11 men underwent early RPLND due to high risk features without evidence of radio-graphic disease (table 2). Metastatic nodal disease (pN2) was identified in 1 of the 6 patients, who subsequently experienced relapse in the lung, pelvis and retroperitoneum. In another patient without pathologically confirmed nodes at RPLND (N0) recurrence developed in the lung and bone. These 2 men died of progressive disease. The remaining 4 patients remained disease free at the most recent followup. Notably the 2 patients who died of disease had 5 high risk pathological features at orchiectomy while the other 4 had 4 or fewer high risk features.

The remaining 5 patients were treated with RPLND due to suspicion of nodal disease. Two patients underwent RPLND at diagnosis due to radiographic findings of retroperitoneal lesions less than 2 cm (table 2 and see figure). One of these patients had no pathological risk

factors as well as no evidence of disease at RPLND. The other patient had 3 risk factors and RPLND revealed pathologically confirmed granulosa cell tumor in the retroperitoneum. He was disease free at 61 months of followup. In the remaining 3 patients retroperitoneal disease developed during surveillance elsewhere. They were referred to MSKCC, where they underwent RPLND (table 2). After surveillance imaging in all 3 patients demonstrated retroperitoneal lesions greater than 2 cm with positive pathological findings at RPLND. After an observation period 1 of these 3 men underwent limited laparoscopic RPLND elsewhere and was referred to MSKCC after subsequent imaging revealed recurrence in the liver and retroperitoneum. At our institution he underwent repeat, open, complete template RPLND and partial hepatectomy. All 3 patients experienced subsequent relapse in the retroperitoneum and 1 of the 3 died of disease 23 months after RPLND.

DISCUSSION

After radical orchiectomy for TSCST observation in patients with 1 or no pathological risk feature for metastasis appears to be associated with little risk of disease progression or death. In this study 34 patients with no high risk feature and 3 with 1 high risk factor were observed at MSKCC following radical orchiectomy without adjuvant therapy. None of these patients experienced disease recurrence or progression.

These results are similar to those of Featherstone et al, who reviewed the records of 38 men with TSCST.⁸ At a median followup of 6.8 years after radical orchiectomy and no further intervention, no patient had metastatic disease. Similar to the portion of our cohort who underwent orchiectomy only, this was a low risk cohort and most patients had no risk factor. Each series provides strong evidence that following orchiectomy surveillance alone should be the preferred treatment in men with no risk factor for progression regardless of the TSCST histological subtype.

In patients with 1 risk factor the data are less clear. In our series all patients with a single risk factor had moderate atypia, of whom none had disease progression. However, it is unclear whether they would have fared as well if they had had extensive atypia or a different risk factor.

Also, notably these studies categorized patients only by the presence or absence of a risk factor. Biologically these risk factors exist in a continuous spectrum. For example, while 5 cm was the size criterion established by Kim et al,⁵ it is also likely that a 4.5 cm tumor has greater metastatic potential than a 1 cm tumor. While surveillance appears to be safe in patients with 1 or no risk factor, the degree of abnormality of all risk factors may warrant consideration when counseling patients.

The risk of disease progression is believed to be greatest 2 years after radical orchiectomy.⁵ As such, radiographic surveillance is most important during this period but it should be continued indefinitely. Three patients in this cohort had clinical stage I disease with 2 or more high risk features and were referred to MSKCC after an observation period elsewhere. In 1 of the 3 patients recurrence developed in the retroperitoneum within 2 years after orchiectomy, in another within 3 years and in the remaining patient more than 7 years after

orchiectomy. After an observation period and after radio-graphic evidence was found all 3 patients underwent RPLND with pathological confirmation of metastatic disease. All 3 patients subsequently experienced disease recurrence and progression. Notably they had multiple high risk features and would have been counseled to undergo RPLND at diagnosis had they been treated initially at MSKCC.

In patients with retroperitoneal disease and no evidence of distant metastasis RPLND is the preferred treatment because chemotherapy options are largely ineffective. Traditional cisplatin chemotherapy regimens have little impact on TSCST.^{2,7} In patients with TSCST and metastasis limited to the retroperitoneum full RPLND is recommended but the risk of recurrence and progression remains high. At diagnosis 2 patients had radiographic evidence of disease limited to the retroperitoneum and each underwent RPLND. One man had pathologically confirmed metastatic disease and was free of disease at more than 5 years of followup. Of the 5 men in this study with pathologically confirmed retroperitoneal TSCST he was the only patient with N1 disease and no evidence of recurrence. This indicates not only the progressive nature of the disease but also the possibility of a good outcome when the nodal burden is low.

What remains unclear is how to treat patients with high risk features who have no evidence of retroperitoneal disease. In this study 6 patients with no evidence of nodal disease and multiple high risk features underwent RPLND. One patient had pathologically confirmed retroperitoneal disease and rapidly died of disease. The remaining 5 men had pathological N0 disease, including 1 with disease recurrence outside the retroperitoneum. The others remained disease free at a median followup of 6.8 years.

Patients with multiple high risk pathological features who do not undergo RPLND are at high risk for subsequent metastasis. In the series by Mosharafa et al 17 men underwent RPLND for TSCST, including 5 with clinical N0 disease and multiple high risk features at RPLND.⁴ No patient had pathological evidence of TSCST in the retroperitoneum and none had evidence of disease at the end of the study. Two patients initially presented with clinical N0 disease and multiple high risk features. They were observed after orchiectomy and disease subsequently developed in the retroperitoneum. After RPLND these 2 men died of disease.

Farkas et al similarly identified 7 patients with Leydig cell tumors, including 2 with clinical N0 disease and multiple high risk features in the orchiectomy specimen.⁷ These 2 patients were observed and disease subsequently developed in the retroperitoneum. After RPLND each man died of disease.

Although these studies were small, similar to ours, they suggest that observation in patients with multiple high risk pathological features may provide a window of opportunity for metastatic disease to develop while RPLND may have a therapeutic benefit even when no pathological evidence of disease is found. The value of extensive nodal resection even in the absence of positive nodes was noted in various other urological diseases, including prostate,¹⁰ bladder¹¹ and germ cell testicular¹² cancer. The exact mechanism by which removing

nodes with no evidence of disease provides benefit is not altogether clear but it may be due to pathological misdiagnosis or micrometastatic lesions.

In addition to the retrospective nature of this study, there are other limitations. Followup in patients who underwent surveillance was relatively short and there may be the possibility of recurrent TSCST with longer observation. However, the finding that none of these patients experienced recurrence is encouraging, as is the finding that 35% were followed beyond 24 months, the period during which most recurrences are believed to develop.⁵ Our small sample size, particularly the small number of patients who underwent RPLND, makes it hard to reach definitive conclusions.

CONCLUSIONS

Patients with TSCST and 1 or no high risk pathological feature appear to be reasonable candidates for observation after radical orchiectomy, considering the extremely low likelihood of harboring metastatic disease in the retroperitoneum or recurrence. However, longer followup of our series and others is needed to confirm these findings. Within the limitations of our small retrospective study treating patients with 2 or more high risk pathological features remains controversial. Treatment at the time of progression appears to be associated with higher volume disease, higher relapse rates and inferior treatment outcomes compared with immediate treatment for high risk features or small volume retroperitoneal disease. Given the lack of effective alternative treatments in these patients, we favor early intervention since it appears to be associated with improved outcomes.

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Abbreviations and Acronyms

MSKCC	Memorial Sloan-Kettering Cancer Center
RPLND	retroperitoneal lymph node dissection
TSCST	testicular sex cord-stromal tumors

REFERENCES

1. Dilworth JP, Farrow GM and Oesterling JE: Non-germ cell tumors of testis. *Urology* 1991; 37: 399. [PubMed: 2024387]
2. Davis S, Di Martino NA and Schneider G: Malignant interstitial cell carcinoma of the testis: report of two cases with steroid synthetic profiles, response to therapy, and review of the literature. *Cancer* 1981; 47: 425. [PubMed: 7459829]
3. Acar C, Gurocak S and Sozen S: Current treatment of testicular sex cord-stromal tumors: critical review. *Urology* 2009; 73: 1165. [PubMed: 19362328]
4. Mosharafa AA, Foster RS, Bihrlé R et al.: Does retroperitoneal lymph node dissection have a curative role for patients with sex cord-stromal testicular tumors? *Cancer* 2003; 98: 753. [PubMed: 12910519]

5. Kim I, Young RH and Scully RE: Leydig cell tumors of the testis. A clinicopathological analysis of 40 cases and review of the literature. *Am J Surg Pathol* 1985; 9: 177. [PubMed: 3993830]
6. Cheville JC, Sebo TJ, Lager DJ et al.: Leydig cell tumor of the testis: a clinicopathologic, DNA content, and MIB-1 comparison of nonmetastasizing and metastasizing tumors. *Am J Surg Pathol* 1998; 22: 1361. [PubMed: 9808128]
7. Farkas LM, Szekeley JG, Pusztai C et al.: High frequency of metastatic Leydig cell testicular tumours. *Oncology* 2000; 59: 118. [PubMed: 10971169]
8. Featherstone JM, Fernando HS, Theaker JM et al.: Sex cord stromal testicular tumors: a clinical series-uniformly stage I disease. *J Urol* 2009; 181: 2090. [PubMed: 19286222]
9. Sheinfeld J and Bosl G: Surgery for testicular tumors In: *Campbell-Walsh Urology, 10th Edition Review*. Edited by McDougal SW, Wein AJ, Kavoussi LR et al. Philadelphia: Saunders Elsevier 2011; pp 936–964.
10. Joslyn SA and Konety BR: Impact of extent of lymphadenectomy on survival after radical prostatectomy for prostate cancer. *Urology* 2006; 68: 121. [PubMed: 16806432]
11. Herr HW, Bochner BH, Dalbagni G et al.: Impact of the number of lymph nodes retrieved on outcome in patients with muscle invasive bladder cancer. *J Urol* 2002; 167: 1295. [PubMed: 11832716]
12. Carver BS, Cronin AM, Eggener S et al.: The total number of retroperitoneal lymph nodes resected impacts clinical outcome after chemotherapy for metastatic testicular cancer. *Urology* 2010; 75: 1431. [PubMed: 20299079]

Flow diagram of patients with testicular sex-cord stromal tumors treated at MSKCC. *HRF*, high risk features. *cN0*, no radiographic evidence of nodal disease. *e/o*, evidence of. *NED*, no disease evidence. *dx*, diagnosis. *AWOR*, alive without recurrence. *OOF*, out of field high risk features, including tumor greater than 5 cm, necrosis, moderate or severe nuclear atypia, angiolymphatic invasion, infiltrating margins and more than 5 mitotic figures per 10 high power fields. *AWR*, alive with recurrence. *DOD*, died of disease.

Table 1.

Characteristics of patients with testicular sex cord-stromal tumors by risk group

	Low Risk		High Risk or Radiographic Retroperitoneal Disease Evidence	
Median age (IQR)	37	(29–52)	48	(37–53)
No. tumors:	38		12	
Lt	22		6	
Partial orchiectomy	3		2	(bilat, 1 pt)
Unilat orchiectomy	36		11	
No. presentation (%):				
Testis mass	21	(57)	10	(91)
Hormonal symptoms (decreased libido, gynecomastia)	2	(5)	0	
Infertility	7	(19)	0	
Pain	6	(16)	1	(9)
Other	1	(3)	0	
Median mos followup (IQR)	15	(3–33)	67	(49–87)
Median cm tumor size (IQR)	1.5	(0.7–2.0)	5.0	(3.8–9.0)
No. high risk features (%):				
0	34	(92)	1	(9)
1	3	(8)	0	
2	–		5	(45)
3	–		1	(9)
4	–		2	(18)
5	–		2	(18)
6	–		0	
Unspecified TSCST	2	(5)	3	(27)
Leydig cell tumor	22	(59)	6	(55)
Sertoli cell tumor	13	(35)	0	
Granulosa cell tumor	0		2	(18)

Table 2.
Clinical and pathological features, and outcomes in patients with TSCST treated with RPLND

	2 or Greater High Risk Features, No Surveillance						Retroperitoneal Disease + Surveillance			Retroperitoneal Disease, No Surveillance	
	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6	Pt 1	Pt 2	Pt 3	Pt 1	Pt 2
Stage:											
Clinical nodal*	NO	NO	NO	NO	NO	NO	N3	N2	N2	N1	N1
Pathological	T1N0M0S0	T4N2M0S0	T2N0M0S0	T1N0M0S0	T2N0M0S0	T2N0M0S0	T2N3M0S0	T1N2M1S0	T1N2M0S0	T2N0M0S0	T2N1M0S0
Histological subtype	Unclassified	Leydig	Leydig	Leydig	Leydig	Unclassified	Unclassified	Leydig	Granulosa	Leydig	Granulosa
Tumor size (cm)	4.0	12	9.0	6.2	3.8	3.5	5.4	4.1	9.0	1.0	5.0
Necrosis	No	No	Yes	No	No	Yes	No	No	No	No	Yes
Nuclear atypia	Yes	Yes	Yes	No	Yes	Yes	No	No	No	No	No
Angiolymphatic invasion	No	Yes	No	No	Yes	Yes	No	Yes	No	No	Yes
Infiltrating margin	No	No	Yes	No	Yes	No	No	No	No	No	No
Greater than 5 mitotic figures	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
No. high risk features	2	5	5	2	4	4	2	2	2	0	3
Pos lymph nodes	No	Yes	No	No	No	No	Yes	Yes	Yes	No	Yes
Time to:											
RPLND (days)	164	9	17	64	35	27	2,709	798	635	53	29
Relapse (mos)	–	8	3	–	–	–	8	17	41	–	–
Vital status	No recurrence	Died of disease	Died of disease	No recurrence	No recurrence	No recurrence	Died of disease	Recurrence	Recurrence	No recurrence	No recurrence
Followup (mos)	76	24	23	127	87	18	112	49	67	173	61

* NO-no clinical or radiographic evidence of retroperitoneal or regional lymph node metastasis, N1-metastasis with lymph node mass 2 cm or less, N2-metastasis with lymph node mass more than 2 cm but not more than 5 cm and N3-metastasis with lymph node mass more than 5 cm.