A contemporary population-based study of testicular sex cord stromal tumours: Presentation, treatment patterns, and predictors of outcome

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Abstract

Introduction: We aimed to characterize demographic distribution, patient outcomes, and prognostic features of testicular sex cord stromal tumours (SCST) using a large statewide database.

Methods: Adult male patients diagnosed with SCST between 1988 and 2010 were identified within the California Cancer Registry (CCR). Baseline demographic variables and disease characteristics were reported. Primary outcome measures were cancer-specific survival (CSS) and overall survival (OS). Bivariate and multivariate Cox proportional hazards models were employed to identify predictors of survival.

Results: A total of 67 patients with SCST were identified, of which 45 (67%) had Leydig cell and 19 (28%) had Sertoli cell tumours. Median age was 40 years and the majority of patients (84%) presented with localized disease. Following orchiectomy, nine patients (15%) underwent retroperitoneal lymph node dissection (RPLND), whereas 54 patients (80%) had no further treatment. With a median followup of 75 months, two-year OS and CSS was 91% and 95%, respectively, for those presenting with stage I disease. For those presenting with stage II disease, two-year OS and CSS was 30%. Predictors of worse OS included age >60 (hazard ratio [HR] 5.64; p<0.01) and metastatic disease (HR 8.56; p<0.01). Presentation with metastatic disease was the only variable associated with worse CSS (HR 13.36; p<0.01). Histology was not found to be a significant predictor of either CSS or OS.

Conclusions: We present the largest reported series to date for this rare tumour and provide contemporary epidemiological and treatment data. The primary driver of prognosis in patients with SCST is disease stage, emphasizing the importance of early detection and intervention.

Introduction

Testicular sex cord stromal tumours (SCST) comprise a rare disease and are reported to represent only 3–5% of all testicular tumours. These tumours arise from gonadal sex cords (Sertoli and granulosa cells) and from the stroma (Leydig cells). The most common histological variant of SCST is Leydig cell, comprising 75–80% of all SCSTs.[1] The majority of these tumours occur between the ages of 20–60 years and most commonly present with painless testicular enlargement or a palpable mass.[2] Though uncommon, patients can present symptomatically. Symptoms from excessive hormone secretion, such as gynecomastia, can be seen in up to 15% of adults with Leydig cell tumours, though Sertoli cell tumours are rarely symptomatic.[1]

Due to the rarity of this malignancy, there is an absence of prospective randomized studies addressing this disease. Little is known about the overall prognosis and no evidence-based guidelines currently exist for the treatment and surveillance of these tumours. Current knowledge is derived from single-institution experiences and small retrospective case series. Individual case reports have suggested that SCSTs exhibit a benign course and rarely recur, indicating that surgical treatment with orchiectomy alone will cure majority of these tumours;[3-6] however, in a minority of cases, metastatic disease is found at the time of diagnosis. The prognosis for these individuals is poor.[7,8] Prior published series have reported the incidence of metastatic disease to be approximately 10%. The most common site of metastasis is to the retroperitoneum — similar to testicular germ cell tumours.[1,9] Other studies have reported higher rates of metastatic disease, with Bertram et al reporting a 20% rate of metastatic disease at the time of diagnosis and a 40% risk of metastatic involvement within two years of diagnosis.[10]

Furthermore, malignant SCSTs have been reported to respond poorly to conventional radiotherapy and cytotoxic

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chemotherapy. Controversy remains as to the recommended treatment due to a lack of evidence-based data. Some "centres of excellence" support testes-sparing surgery in small tumours, while other centres routinely perform prophylactic retroperitoneal lymph node dissection (RPLND) after the initial radical orchiectomy.[4-7,11] Some centres have employed high-risk histological features in the orchiectomy specimen to risk-stratify patients and identify those who may benefit most from RPLND, although none of these findings have been well validated.[8,11-14] In addition, no data have been published to date regarding population-level characteristics of this malignancy. Therefore, the objective of this current study is to describe population-level characteristics of SCSTs, ascertain current practice patterns regarding treatment, and assess predictors of overall survival (OS) and cancer-specific survival (CSS).

Methods

Population

We performed a population-based, retrospective cohort study with data derived from the California Cancer Registry (CCR). We reviewed all patients over the age of 18 diagnosed with SCST in California between 1988 and 2010. By statute, the CCR captures data throughout the state and represents the California subset of the Surveillance, Epidemiology, and End Results (SEER) database. Using International Classification of Disease (ICD) 9th edition (prior to 2002) and ICD-10 (starting in 2002) diagnostic codes, all patients with confirmed testicular cancer between the years 1988 and 2010 were identified. Patients with unspecified histology or testicular malignancy other than SCST (Leydig cell, Sertoli cell, mixed) were excluded. The final cohort consisted of 67 individuals.

Cause of death and last followup were clearly identified in the registry, providing us information on OS and CSS. TNM staging of all patients at presentation was extrapolated from staging data routinely collected within the database. Staging data in the CCR is not collected in standard TNM staging format, but identifies staging categories that are readily converted into an equivalent TNM stage. A separate staging variable was created to distinguish patients presenting with localized vs. metastatic disease. All patients having undergone initial treatment with either chemotherapy or radiotherapy were distinctly coded in the registry. All patients with lymph nodes from a surgical specimen were identified as having undergone RPLND. Patients who did not meet criteria for having undergone chemotherapy, radiotherapy, or RPLND were defined as treated with active surveillance. Other covariables included in the analysis included patient age, race, and socioeconomic status.

Statistical analysis

General descriptive statistics were calculated for the overall cohort and also based upon individual histology. Predictors of OS and CSS were analyzed using bivariate and multivariate Cox proportional hazards models. Potential covariables were analyzed initially in a univariable analysis and subsequently included in a multivariate model. Selection of covariables for the multivariate model was based on clinical relevance and/or statistical significance in the univariable analysis. Hazard ratios (HR), 95% confidence intervals (CI), and p values were provided for variables in each analysis. Significance was defined as a p value less than 0.05. Kaplan-Meier curves were created for OS and CSS and stratified based on disease stage and histology. Differences between groups in the Kaplan-Meier curves were assessed using a log-rank test. All analysis was performed with SAS (version 9.3).

Results

Overall characteristics of the study cohort are presented in Table 1. A total of 67 patients with SCST were identified in

Table 1. Patient characteristics for the overall cohort and stratified by histology

	Sertoli	Leydig	Mixed	Overall
Total patients	19 (28%)	45 (67%)	3 (4%)	67
T stage				
T1/2	16 (89%)	29 (81%)	3 (100%)	48 (72%)
T3/4	2 (11%)	7 (19%)	0 (0%)	9 (13%)
N stage				
N0/Nx	12 (75%)	33 (94%)	2 (100%)	47 (70%)
N+	4 (25%)	2 (6%)	0 (0%)	6 (9%)
M stage				
M0/Mx	16 (84%)	40 (95%)	2 (67%)	58 (87%)
M+	3 (16%)	2 (5%)	1 (33%)	6 (9%)
Stage				
Localized	12 (63%)	42 (93%)	2 (67%)	56 (84%)
Metastatic	7 (37%)	3 (7%)	1 (33%)	11 (16%)
Initial treatment				
RPLND	5 (26%)	4 (9%)	0 (0%)	9 (13%)
Chemotherapy	1 (5%)	3 (7%)	0 (0%)	4 (6%)
Radiotherapy	1 (5%)	0 (0%)	0 (0%)	1 (1%)
Surveillance	12 (63%)	38 (84%)	3 (100%)	53 (79%)
Age				
Median (IQR)	36 (28–49)	42 (31–54)	61 (32–89)	42 (28–89)
Race				
Caucasian	8 (42%)	23 (51%)	2 (67%)	33 (50%)
Black	3 (16%)	4 (9%)	0 (0%)	7 (10%)
Hispanic	7 (37%)	12 (27%)	1 (33%)	20 (30%)
Asian	1 (5%)	4 (9%)	0 (0%)	5 (7%)
American-Indian	0 (0%)	2 (4%)	0 (0%)	2 (3%)

IQR: interquartile range; RPLND: retroperitoneal lymph node dissection.

California between 1988 and 2010. Among these patients, 45 (67%) had Leydig cell and 19 (28%) had Sertoli cell tumours. The median followup was 75 months and the median age at presentation was 42 years old (interquartile range [IQR] 28–89). The majority of the patients were Caucasian (49%), whereas the remainder of patients was identified as Hispanic (30%), African American (10%), Asian (7%), and American Indian (3%). The majority of patients presented with localized disease (84%), while 16% of patients presented with either lymph node-positive or metastatic disease. The most common therapeutic approach following orchiectomy was surveillance (79%), followed by RPLND (13%). Only 9% of patients presenting with localized disease underwent RPLND, compared 36% among those with metastatic disease. None of the five patients undergoing RPLND for localized disease died after a median followup of 15 years.

The two-year CSS for patients presenting with localized SCST disease was 95%, compared to 30% among those with metastatic disease. Kaplan-Meier curves for CSS, stratified by disease stage are presented in Fig. 1A. The impact of patient and disease characteristics on CSS is presented in Table 2. Predictors of CSS on univariate analysis included metastatic disease at presentation (HR 8.5; p<0.01) and T3/T4 disease (HR 3.95; p<0.05). Metastatic disease at presentation was the only independent predictor of decreased CSS on multivariate analysis.

OS in patients with localized disease was 91% at two years. OS in the metastatic population was 30%, which was identical to CSS at two years. Kaplan-Meier curves for OS stratified by extent of disease at presentation are demonstrated in Fig. 1B. The impact of patient characteristics on OS is presented in Table 3. Significant predictors of worse OS on univariable analysis included age >60 (HR 7.16; p<0.05), stage T3/4 tumours (HR 6.11; p<0.05), and metastatic disease (HR 6.11; p<0.05). On multivariate analysis, age >60 was no longer a significant predictor of OS; however, metastatic disease remained a predictor of worse OS (HR 8.56; p<0.01). Histological subtype was not found to be a significant predictor of OS in either univariable (p=0.71) or multivariable analysis (p=0.16). Kaplan-Meier curves for OS stratified by histological subtype are presented in Fig. 1C.

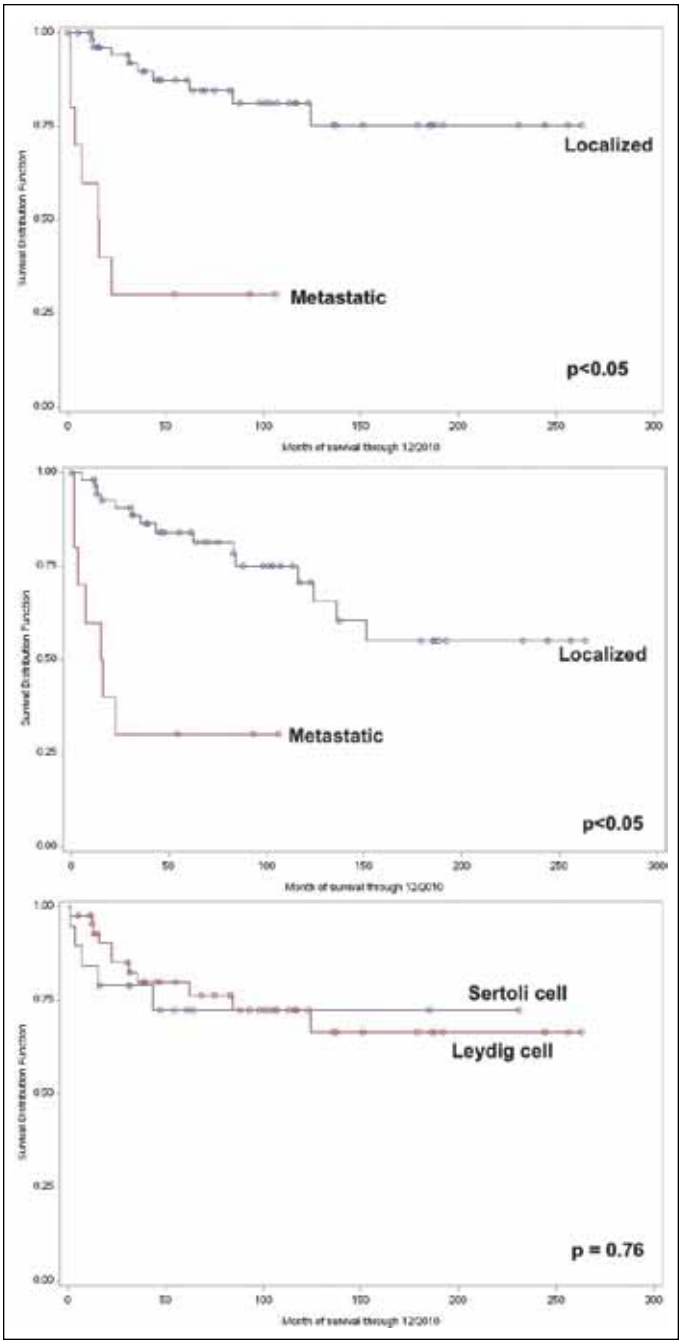

Fig. 1. (A) Cancer-specific survival stratified by extent of disease at presentation; ***(B)*** overall survival stratified by extent of disease at presentation; and ***(C)*** overall survival stratified by tumour histology.

Discussion

Although SCST patients with localized disease have a very good overall prognosis, individuals presenting with advanced and metastatic tumours drive the mortality in this disease. Consistent with prior published series, the majority (84%) of patients in our study presented with localized disease, whereas 16% had metastatic or clinical stage II disease at presentation.[15] Prior single institution experiences suggest the majority of SCST are benign and rarely progress.[3,16] Conversely, the minority of patients that do present with metastatic disease have a poor prognosis.[7,8,17] In our series, patients with metastatic SCST at presentation have a two-year CSS of 30%, compared to a two-year CSS of 95% in those presenting with stage I disease. We present the first population-based analysis and largest published series to date characterizing this malignancy. Furthermore, we emphasize the importance of early diagnosis and prompt management in this patient population.

Table 2. Univariable and multivariable analysis for predictors of cancer-specific survival

	Univariable		Multivariable	
Age group	Hazard ratio (CI)	p	Hazard ratio (CI)	p
<30	Ref		Ref	
30–39	2.09 (0.34–12.78)	0.42	1.20 (0.18–8.00)	0.84
40–49	2.69 (0.52–13.96)	0.23	0.31 (0.44–12.88)	0.31
50–59	1.49 (0.21–10.61)	0.68	1.64 (0.22–12.23)	0.62
60+	5.18 (0.91–29.47)	0.63	4.07 (0.69–23.81)	0.11
Race				
Caucasian	Ref			
Other	0.58 (0.21–1.60)	0.29		
Stage				
Localized	Ref		Ref	
Metastatic (LN or M)	8.50 (3.04–23.75)	<0.01	13.36 (3.57–50.04)	<0.01
T stage				
T1/T2	Ref			
T3/T4	3.95 (1.30–11.97)	0.01		
LN status				
N0	Ref			
N+	5.50 (1.29–23.42)	0.02		
Nx	2.63 (0.61–11.24)	0.18		
Metastasis				
M0	Ref			
M1	28.21 (7.27–109.5)	<0.01		
Histology				
Sertoli	Ref		Ref	
Leydig	0.85 (0.29–2.45)	0.76	2.32 (0.58–9.20)	0.22
SES (quintile)				
1 (lowest)	Ref			
2	1.19 (0.26–5.35)	0.81		
3	-	0.99		
4	1.24 (0.31–4.96)	0.75		
5 (highest)	1.58 (0.31–7.96)	0.57		

CI: confidence interval; SES: socioeconomic status.

Table 3. Univavariable and multivariable analysis for predictors of overall survival

	Univariable		Multivariable	
Age group	Hazard ratio (CI)	p	Hazard ratio (CI)	p
<30	Ref		Ref	
30–39	2.31 (0.50–10.63)	0.28	1.48 (0.30–7.10)	0.62
40–49	2.01 (0.47–8.51)	0.34	1.74 (0.41–7.34)	0.45
50–59	1.96 (0.44–8.77)	0.38	1.78 (0.39–8.16)	0.45
60+	7.16 (1.65–31.08)	0.01	5.64 (1.26–25.21)	0.02
Race				
Caucasian	Ref			
Other	0.69 (0.29–1.62)	0.39		
Stage				
Localized	Ref		Ref	
Metastatic (LN or M)	6.11 (2.34–15.93)	<0.01	8.56 (2.68–27.37)	<0.01
T stage				
T1/T2	Ref			
T3/T4	3.49 (1.26–9.63)	0.02		
LN status				
N0	Ref			
N+	4.57 (1.14–18.30)	0.03		
Nx	2.33 (0.66–8.13)	0.18		
Metastasis				
M0	Ref			
M1	18.33 (5.42–61.90)	<0.01		
Histology				
Sertoli	Ref		Ref	
Leydig	1.20 (0.44–3.29)	0.71	2.37 (0.71–7.93)	0.16
SES (quintile)				
1 (lowest)	Ref			
2	1.77 (0.51–6.13)	0.36		
3	0.47 (0.08–2.60)	0.38		
4	0.96 (0.27–3.48)	0.97		
5 (highest)	1.38 (0.30–6.29)	0.67		

CI: confidence interval; SES: socioeconomic status.

The findings in this study suggest that there may be a role for earlier intervention to identify and treat patients prior to the progression of metastatic disease. Given that metastatic SCST responds very poorly to radiation therapy and chemotherapy, RPLND remains the mainstay of management beyond radical orchiectomy. The timing and utility for RPLND after initial orchiectomy is still debated. Featherstone and colleagues reviewed records of 38 men with SCST, of which 37 were clinical stage I. After a median followup time of 6.8 years following radical orchiectomy and without further intervention, no patients developed metastatic disease.[18] These findings suggest that stage I disease rarely progresses.

Conversely, Mosharafa et al report their series of 17 patients undergoing RPNLD after radical orchiectomy for SCST.[11] Of these, four patients (31%) with clinical stage I disease were reclassified as pathological stage II following RPLND. None of the nine patients with pathologic stage I disease had recurrence after 4.5 years, but 6/8 patients with stage II or III disease died of disease progression, with a mean survival of 2.4 years. Furthermore, 4/8 patients diagnosed with stage I disease and managed initially with surveillance subsequently developed retroperitoneal disease. This represents a cohort of patients that may have benefited from early RPLND.

Di Tonno et al report their series of five patients (out of a total of 51 patients) with SCST and undergoing RPLND for either stage II disease or unfavourable histology. There were no relapses among these five patients.[8] RPLND was performed on a select group of high-risk patients, resulting in favourable outcomes. Indications for RPNLD, particularly in stage I disease, remain unclear. Our current data suggest that patients with stage I disease undergoing RPLND achieve long-

term disease control, as none of the five patients undergoing RPLND for stage I disease died with a median followup of 15 years. This remains a primarily surgically treated disease, and early intervention with RPLND may benefit those with minimal or unrecognized lymph node disease; however, disease control and long-term survival can still be achieved without RPLND in a majority of stage I patients. Identifying high-risk groups that benefit from early RPLND is one of the remaining important questions in treating this disease.

Surveillance in stage I SCSTs is still the preferred treatment for men with no risk factors for progression; however, for those with more than one risk factor, the data remains unclear. Herein lies a cohort of patients that may benefit the most from aggressive, early intervention. Kim et al was one of the first to identify histological features on orchiectomy specimen that were suggestive of a potential for malignant progression.[15] Most recently, Silberstein et al used similar high-risk histological features to help stratify patients and identify those who may benefit most from RPLND.[12] The six high-risk features included in their risk-stratification model include tumour size greater than 5 cm, necrosis, moderate or severe nuclear atypia, angiolymphatic invasion, infiltrating margins, and greater than five mitotic features per 10 high-power fields. In their cohort of 48 patients with SCST, the majority was observed, while 11 patients underwent RPNLD for either stage I disease with >2 high-risk features or stage IIa disease. Of the patients with stage I disease who received post-orchiectomy RPLND, four demonstrated no evidence of disease at 6.6 years followup; however, two patients recurred and died of disease. The two patients who had stage IIa disease who underwent immediate RPNLD did not relapse. This study suggests that the timing of RPLND is important; those with stage I disease with concerning histological features and patients who underwent immediate RPLND after diagnosis of stage II disease fared well. Those that underwent a period of surveillance prior to RPLND all relapsed. Many presenting with metastatic disease may have missed a window for cure with RPLND, while surgical intervention to treat unrecognized or micro-metastatic spread may benefit certain patients. Perhaps closer surveillance in those with minimal risk factors and early intervention in those demonstrating non-localized disease could improve survival outcomes.

Although we provide a population-level analysis and report a comparatively large series for this rare tumour, several limitations of the study must be considered when interpreting these results. First, we are limited by the availability of information and variables within the large registry database. Of importance is the lack of specific pathological and histological data. These details would include previously identified high-risk factors, such as necrosis, nuclear atypia, angiolymphatic invasion, and mitotic features. Such detail will play an increasing role in stratifying patients as we assess risk and determine treatment, but will likely only be available from institutional databases. While we lack this information, we believe that we provide a unique perspective of a large series of patients evaluated from a population level. This allows us to present outcomes of patients across various disease stages and treatment approaches.

Although the role of RPLND in managing patients with SCST remains unclear, our data highlight the importance of early diagnosis and prompt management, as a significant shift in prognosis occurs as the disease progresses beyond a localized stage. Future studies to identify which patients will benefit the most from early intervention will further clarify the role for RPLND in the treatment algorithm of these patients.

Conclusion

We present the largest series to date reporting outcomes on patients with SCSTs. The primary driver of prognosis in patients with SCST is disease stage, emphasizing the importance of early detection and intervention. Further work is warranted to investigate the role and timing of surgical intervention, as well as the best surveillance strategies for this rare group of tumours.

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