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Bilateral Testicular Germ Cell Tumors in the Era of Multimodal Therapy

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Abstract

Objectives—To characterize the incidence, presentation, management, and relapse of a large population of bilateral testicular germ cell tumors (TGCT) from a single institution.

Methods—We identified bilateral TGCT diagnosed between 1/1989 and 2/2014. We categorized synchronous and metachronous TGCT, noting time between 1st and 2nd TGCT, histology [seminoma vs. nonseminoma (NSGCT)], stage and treatments. Kaplan Meier survival estimates characterized relapse.

Results—Of 5,132 TGCT patients, 128 (2.5%) had bilateral TGCT. Bilateral TGCT increased over time--1.7% in 1989-1994 up to 3.8% in 2010-2/2014. The 35 (27%) synchronous TGCT had 20 (57%) concordant seminoma, 5 (14%) concordant NSGCT, and 10 (29%) discordant. The 93 (73%) metachronous cases had median time interval to 2nd TGCT of 73 months (range 5 months to 28.6 years). Compared to 1st TGCT, 39 (42%) had discordant histology, 29 (31%) concordant seminoma, and 25 (27%) concordant NSGCT. Stage at 1st tumor was statistically similar to second TGCT (2nd stage I/II/III in 69%/22%/10%). Increasing duration between 1st and 2nd TGCT was not associated with higher stage (II/III) at second TGCT (p=0.09). Treatment at 1st tumor was not associated with stage at 2nd tumor. Relapse following bilateral diagnosis was 16.8% (95%CI 10.5-26.2%) at 5 years.

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Conclusions—Incidence of bilateral TGCT increased with >25% of metachronous TGCT presenting 10 years after 1st TGCT; possible causes include increased survivorship and/or referral bias. Stage was statistically similar at 1st and 2nd tumor; stage at 2nd tumor was not associated with time interval between tumors or prior treatment modality at 1st tumor.

Keywords

Bilateral; Testicular Germ Cell Tumor; Testicular Cancer; Incidence; Metachronous; Survivorship

Introduction

Bilateral testicular germ cell tumor (TGCT) is a rare event; reported incidence is roughly 1-3% of all TGCT cases.¹⁻⁶ However, the lifetime risk may be underestimated because of limited follow up in many series. Metachronous TGCT are diagnosed on average 5 years after initial diagnosis in the United States,² with more than 20% presenting at least 10 years after initial diagnosis.¹ The cumulative risk of metachronous TGCT may be substantially greater at 20-25 years after initial diagnosis compared to series with only 5-10 years of follow up.^{5, 7}

Most men with TGCT experience lengthy survival due to advances in multimodal treatment. Durable survival results in longer time at risk for detection of a second TGCT and long-term morbidity from prior treatments. Initial population-based studies have suggested that platinum based chemotherapy might reduce the risk of metachronous bilateral TGCT,^{7, 8} although growing evidence in TGCT patients associates platinum based chemotherapy with long-term cardiac toxicity and radiation or chemotherapy with risk of secondary malignancies.⁸⁻¹³ There is no consensus on factors associated with the risk of bilateral disease and comprehensive data is lacking. Perhaps more importantly, it is unclear how prior treatments (chemotherapy, radiotherapy, lymph node dissection) affect stage and management of metachronous bilateral TGCT, or risk of relapse following diagnosis of bilateral TGCT. Herein we characterize a large population of bilateral TGCT cases from a single institution and determine the patterns of presentation for synchronous and metachronous tumors; among patients with metachronous disease we determined if clinical, pathological, and treatment variables at first TGCT are associated with risk of advanced disease at second TGCT and risk of relapse following diagnosis of bilateral TGCT.

Patients and Methods

Study population

This IRB approved cohort study identified men within the Memorial Sloan Kettering Cancer Center (MSKCC) prospectively maintained TGCT database that were diagnosed with bilateral TGCT. This included men with synchronous tumors or a metachronous second TGCT occurring during the interval from January 1989 to February 2014. Physicians verified data on the diagnosis of each TGCT, treatment, and outcomes. To determine the incidence of bilateral disease we queried the total number of TGCT diagnoses in the database within the same time period, including date of diagnosis and last follow up. The

length of follow up for unilateral cases was used to define the time at-risk for development of metachronous TGCT among survivors.

Clinical and pathological variables

We gathered data on the presentation of disease, including age, family history (1st degree relative), history of cryptorchidism, prior inguinal surgery, year of second TGCT, time interval to second tumor, and presence of testicular microcalcifications on imaging reports. Histology was grouped as seminoma (pure) or nonseminoma. Concordant histology was defined as the same histologic grouping between first and second TGCT; discordant histology was defined as pure seminoma in one testis and nonseminoma in one testis. All pathologic specimens from outside institutions were internally reviewed at MSKCC at the time of initial clinical consultation. Synchronous cases included concurrent bilateral orchiectomies and staged orchiectomies if both TGCTs were present at initial diagnosis. Pathologic staging is according to the AJCC 7th edition classification system.¹⁴

Treatment and Outcomes

Disease management after initial staging was categorized by surveillance, radiation, chemotherapy or RPLND (primary). Post-chemotherapy RPLND and adjuvant chemotherapy following RPLND were noted when applicable. We noted International Germ Cell Consensus Classification (IGCCC) risk group¹⁵ when data was available. Chemotherapy only included platinum based regimens. Specific information on radiotherapy and chemotherapy dosing regimens was not analyzed as separate categories in order to keep groups large enough for statistical analysis; similarly, RPLND was not broken down by template or full bilateral dissection in order to prevent categorical sizes that would be too small for analysis. Primary RPLND for stage I disease is offered at our institution based on risk factors including pT2 (lymphovascular invasion), predominant embryonal histology, suspicious adenopathy in the primary anatomic landing zone, and patient preferences. Surveillance was defined as clinical decision to monitor a patient with stage I disease with serial follow up, imaging, and serum tumor markers. We defined relapse of TGCT as definitive radiographic recurrence, biopsy confirmation, or new elevation of serum tumor markers following an initial period post-orchiectomy without evidence of disease. Contralateral TGCT was defined as metachronous disease and was not considered relapse. For simplification we only analyzed outcomes of relapse following treatment of bilateral disease (synchronous or 2nd metachronous TGCT), not relapses that developed between 1st and 2nd TGCT (n=5).

Statistical Analysis

Treatments for synchronous and metachronous tumors were analyzed separately and stratified by AJCC stage and seminoma vs. nonseminoma histology. Metachronous tumors included treatments per stage at first tumor and second tumor individually. For metachronous tumor we used univariate logistic regression to analyze possible associations between variables at first TGCT for the outcome of advanced disease (clinical stage II/III) at the second TGCT. The *a priori* selection of variables at first tumor included age, stage, exposure to treatments (includes initial and relapse treatments prior to 2nd TGCT), and time interval to diagnosis of second TGCT. Multivariable logistic regression was performed to

analyze treatments while adjusting for clinical stage and histology. Survival analysis for endpoint of relapse following the diagnosis of bilateral TGCT was carried out with Kaplan Meier survival estimates and univariable Cox regression; significant variables on univariate analysis would be added into a multivariable model. Statistics were performed with Stata v12.0.

Results

Of 5,132 patients with a TGCT diagnosed between 1989 and 2/2014, 128 (2.5%) had bilateral TGCT. During this time period the incidence of bilateral testis cases at MSKCC steadily increased; from 1989-1994 only 13 of 747 (1.7%) had bilateral disease, while in 2010-2/2014, bilateral disease represented 39 of 1035 (3.8%) of TGCT patients. Incidence of bilateral disease is illustrated in Table 1a. Patients with unilateral TGCT had substantially shorter follow up (length of time at risk for metachronous TGCT) of a median 26 months (mean 49 months), compared to median 73 months (mean 96 months) that was required to develop metachronous bilateral TGCT.

The 128 patients with bilateral disease (Table 1b) included 35 (27%) synchronous cases with median age at diagnosis of 33 years (IQR 28, 37) and 93 (73%) metachronous cases with age at first tumor of 29 years (IQR 24, 33). Only 3 (2%) patients had a family history of TGCT while 10 (8%) had history of cryptorchidism, 18(14%) prior inguinal surgery (9 synchronous, 9 metachronous); 65 (64%) had testicular microcalcifications on ultrasound [contralateral calcification in metachronous 43 (60%), bilateral calcification in synchronous 22 (73%)]. Median follow up was 44 months (IQR 12, 109) from the onset of bilateral TGCT. For those with metachronous disease the median time to diagnosis from first to second TGCT was 73 months/6.1 years with a range of 5-344 months (IQR 39, 140), or a maximum of 28.6 years from initial TGCT. Among those with metachronous disease there was no statistical association between increasing time interval between first to second orchiectomy and later year of diagnosis; although a number of patients with long intervals presented in later years, the proportion with long time interval to development of metachronous disease stayed relatively stable over time (Figure 1).

Synchronous disease histology and treatment is stratified by stage in Table 2a. The 35 cases included 20 (57%) concordant seminoma, 5 (14%) concordant nonseminoma, and 10 (29%) discordant. Stage distribution for synchronous TGCT was stage I in 20 (57%), stage II in 9 (26%), and stage III in 6 (17%). Synchronous cases treated with chemotherapy were IGCCC good risk (8), intermediate risk (3), and poor risk (1).

The 93 metachronous cases are summarized in Table 2b. First TGCT was seminoma in 47 (51%) and NSGCT in 46 (49%). Stage at 1st TGCT was stage I in 70 (75%), stage II in 17 (18%), and stage III in 6 (6%); stages were slightly higher at second TGCT (not significant) with stage I in 64 (69%), stage II in 20 (22%) and stage III in 9 (10%). Histology at 2nd TGCT was seminoma 50 (54%) and 43 (46%) NSGCT; compared to 1st TGCT histology, 39 (42%) had discordant histology, 29 (31%) concordant seminoma, and 25 (27%) concordant NSGCT. IGCCC risk group among metachronous patients who underwent primary chemotherapy at 1st TGCT was good (19), intermediate (1), and poor (0). Metachronous

cases treated with primary chemotherapy at 2nd TGCT were IGCCC good risk (23), intermediate risk (2), and poor risk (2).

Logistic regression was performed for metachronous cases to determine if any clinical, pathologic, or treatment variables were associated with advanced disease (clinical stage II/III) at second tumor. Longer time interval between 1st and 2nd TGCT was not statistically associated with higher stage (II/III) at second TGCT (logistic regression $p=0.09$). There were no other statistically significant associations with advance stage at second TGCT, including type of prior treatments (chemotherapy, radiotherapy, or RPLND). Prior chemotherapy exposure was noted in 22 of 93 (24%) metachronous patients at the time they were diagnosed with the second TGCT. Among these 22 metachronous patients with prior chemotherapy, 8 (36%) required additional chemotherapy at 2nd TGCT (1 adjuvant), RPLND was performed in 7 cases (2 primary RPLND), and radiotherapy in 3 cases.

A total of 17 (13.3%) patients experienced a relapse following diagnosis of bilateral TGCT (3 synchronous, 14 metachronous). Cumulative probability of relapse (Figure 2) was 9.3% (95% CI 5.1-16.6%) at 1 year, 10.4% (95% CI 5.9-18.1%) at 2 years, and 16.8% (95% CI 10.5-26.2%) at 5 years. Cox proportional hazard models did not identify any clinical, pathological, or treatment variables associated with relapse following bilateral TGCT. There were two deaths from TGCT, including 1 synchronous case of NSGCT that was treated with primary RPLND prior to referral to our center; he then underwent salvage chemotherapy and RPLND with pathology that included teratoma, rhabdomyosarcoma, primitive neuroectodermal tumor, osteosarcoma, chondrosarcoma, and glioneuronal differentiation. He followed up at an outside institution and died of disease approximately 14 months after salvage RPLND. The second death was a metachronous TGCT patient with autism and mental retardation who suffered severe chemotherapy related complications during treatment for 1st TGCT; he had bulky retroperitoneal disease at 2nd TGCT, however was deemed too high risk for chemotherapy. He underwent RPLND, relapsed shortly after surgery and was treated with palliative oral etoposide.

Comment

This is the largest single institution experience with bilateral testicular germ cell tumor to date and we demonstrate an increasing incidence at a major referral center. Although we cannot determine the impact of referral bias, this data supports that the proportion of metachronous TGCT is increasing relative to synchronous TGCT. Perhaps most importantly, greater than 50% of metachronous TGCT cases presented at least 5 years after first tumor and 25% presented 12 years or more after first tumor, ranging up to 28 years. The proportion and time interval of metachronous disease with late presentation of second TGCT is slightly increased compared to the previous MSKCC series.¹ Furthermore, we highlight that treatments at first TGCT did not affect stage of second TGCT or the potential need for further regional or systemic treatment. This has implications both for treatment or surveillance of the second TGCT.

We identified an expanding time interval to diagnosis of 2nd TGCT when compared to a previous study from our institution. The current interval for metachronous diagnosis is also

longer than previously reported in a series where 16 of 445 Stage I TGCT followed without chemotherapy developed metachronous TGCT.¹⁶ Patients were discharged from routine follow-up after a 10-year disease free interval; median interval between TGCT was 4.7 years, but 3 of 16 developed metachronous tumors after 10 years and up to a maximum of 18 years. Fossa and colleagues analyzed SEER data including roughly 29,000 patients with TGCT between 1973 and 2001 and determined 1% had metachronous TGCT at a median interval of 63 months (range 3-223).² A systematic review published in 2012 of roughly 50,000 men noted that 1.3% developed metachronous TGCT at a mean interval of 65.6 months. These intervals are shorter than our reported median interval of 73 months/6.1 years (range 5-344 months); the discrepancy could be related to more current data in this study, since the incidence at MSKCC accelerated over the last decade. Patients treated in the modern era experience lengthy survivorship and continue to be at risk for metachronous disease over a much longer period of time. These time intervals highlight that long-term follow-up of TGCT is essential to identify potentially curable metachronous TGCT.

The overall percentage of bilateral cases in our series was 2.5%; however the incidence rose from 1.7% to 3.8% since 2010. Synchronous disease represented a small and relatively stable portion of TGCT (0.7% averaged across the study), but the metachronous cases gradually increase over time (1.2% up to 2.7% since 2010). Zequi et al reported the prevalence of bilateral TGCT was 1.82% from 19 pooled studies, however they could not comment on incidence over time; within the pooled analysis synchronous cases represented 0.6% of all TGCT.¹⁷ United States population-based data published by Fossa et al demonstrated a 0.6% overall proportion of synchronous cases across 30 years, but did not describe synchronous changes over time. The number of metachronous TGCT included 287 of 29515 (1%) cases; they estimated a 15-year cumulative incidence of 1.9% for metachronous TGCT. However, a later Norwegian population based study demonstrated cumulative risk of metachronous TGCT increased in the era of platinum based chemotherapy; the study grouped TGCT before 1980 versus TGCT between 1980-2007. The 10- and 20-year cumulative incidence of metachronous TGCT before 1980 was 1.3% and 1.9%; from 1980 onwards the 10- and 20-year cumulative incidence was 2.7% and 3.9% (95% CI 3.3-4.7%).⁷ This supports that incidence of bilateral disease may be rising although TGCT incidence is much higher in Norway compared to the US.¹⁸

We cannot conclude causality of survivorship duration or referral bias on the rising incidence at MSKCC, however both are likely contributors. We noted a shorter median follow up of 26 months for unilateral TGCT (a relatively short time at-risk for development of bilateral TGCT) compared to the median interval of 73 months required to diagnosis metachronous bilateral TGCT. This could be a sign of referral bias, however as noted in Figure 1, the latency to 2nd TGCT was stable over time. We did not highlight cumulative incidence estimates for this study because differences in follow up for unilateral and bilateral TGCT would lead to over-estimated incidence over time— for example, the 5 year cumulative incidence estimate is 1.58% (95 CI 1.13-2.20%) and 20 year estimate is 11.9% (95 CI 8.4-16.7%), data not shown. The true incidence of bilateral TGCT in the US is likely somewhere between this current report and the SEER study of Fossa et al; although cumulative incidence estimates from SEER might have less follow-up bias, the state/regional

registries included within the SEER study omitted several states with large referral centers for TGCT, including New York, Indiana, Oregon, Minnesota, and Texas.²

Another important finding of this study is that the clinical stage at the metachronous 2nd TGCT was not lower than at 1st TGCT. This contradicts some previous reports that suggest surveillance after 1st tumor leads to earlier diagnosis of 2nd tumor, with stage I representing roughly 70-75% of metachronous cases in pooled analysis,¹⁷ and closer to 90% in smaller studies.¹⁶ We noted a slightly higher prevalence of Stage II and Stage III disease at 2nd TGCT; however this was not statistically significant. We postulated that a late presentation of metachronous TGCT might be associated with advanced disease; although stages II/III tended to present later in our series, this was not a statistically significant relationship (logistic regression $p=0.09$).

Currently there are no clear criteria to determine who is at risk of developing a second TGCT, whether it presents early versus late, and whether it will be advanced stage at diagnosis. Although some have proposed that chemotherapy would be protective against second tumor,^{7, 8} there were roughly one fourth (22 of 93; 24%) of metachronous patients with prior chemotherapy at second TGCT. We did not identify any variables associated with advanced stage at metachronous diagnosis, including year of diagnosis, time interval between or stage at second tumor, in addition to exposures such as prior TGCT treatments, microlithiasis or prior inguinal surgery. Furthermore, a number of patients with prior chemotherapy presented with stage II or III disease and required additional treatments-- among 22 metachronous patients with prior chemotherapy, 8 (36%) required additional chemotherapy at 2nd TGCT (1 adjuvant), RPLND was performed in 7 cases (2 primary RPLND), and radiotherapy in 3 cases. Although previous data suggests no decrease in overall survival for metachronous TGCT, these patients with multiple treatments have additive risk of long term morbidity.¹³ Multiple treatments did not preclude the risk of relapse after 2nd TGCT, which occurred in 3 metachronous cases who had chemotherapy at 1st diagnosis. This data has implications both for surveillance and treatment after metachronous TGCT diagnosis.

We have limited accounting for possible variation in treatment or surveillance outside MSKCC; however patients with late presentation of 2nd TGCT (possibly poor surveillance) had no significant difference in clinical stage at presentation or disease outcomes. Furthermore, chemotherapy and radiotherapy follow standard regimens. Surgeon experience and templates may influence RPLND; after 1999 all RPLND at MSKCC included bilateral templates and year of treatments was used to adjust for variability over time. We also note that fertility and hormonal status pre- and post-treatment is a topic of interest but is beyond the scope of this study.

Conclusions

Incidence of bilateral TGCT at MSKCC increased with >25% of metachronous TGCT presenting 10 years after 1st TGCT; causes could be increased survivorship and/or referral bias. Stage was statistically similar at 1st and 2nd tumor; stage at 2nd tumor was not associated with time interval between tumors or prior treatment modality at 1st tumor.

Regional or systemic treatments at first tumor do not preclude the need for further regional or systemic treatments at 2nd TGCT. These findings highlight that long term follow-up is essential to identify cases of metachronous TGCT that may present with potentially curable advanced disease.

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Figure 1.
Relationship between year of diagnosis and time interval to 2nd TGCT.

Figure 2. Risk of relapse following treatment of bilateral TGCT

*dashed line represents 95% CI

Table 1a**Incidence of bilateral TGCT at MSKCC**

Date range	Bilateral diagnoses (n=128)	All TGCT diagnoses (n=5132)	Bilateral % of total TGCT	Synchronous (n=35)	% total TGCT	Metachronous (n=93)	% total TGCT
1989 - 1994	13	747	1.7%	4	0.5%	9	1.2%
1995 - 1999	12	769	1.6%	4	0.5%	8	1.0%
2000 - 2004	27	1209	2.2%	10	0.8%	17	1.4%
2005 - 2009	37	1372	2.7%	6	0.4%	31	2.3%
2010 - 2/2014	39	1035	3.8%	11	1.1%	28	2.7%

Table 1b
Patient characteristics

Bilateral testis cancer at MSKCC 1989-2014		
Number of cases	128	
Presentation of 2nd TGCT		
Synchronous	35	27%
Metachronous	93	73%
Median Age Synchronous TGCT (yr, IQR)	33	(28, 37)
Median Age Metachronous 1st TGCT (yr, IQR)	29	(24, 33)
Median Time to Metachronous 2nd TGCT (mo, IQR)	73	(39, 140)
Family history testis cancer	3	2%
History of cryptorchidism	10	8%
Prior inguinal surgery	18	14%
Testicular Microcalcifications (n=102)	65	64%
Contralateral calcification (metachronous)	43	60%
Bilateral calcification (synchronous)	22	73%
Median follow up after bilateral diagnosis (mo)	44	(12, 109)

Table 2a
Synchronous bilateral TGCT histology and treatment

	Number	Stage I	Stage II	Stage III
All Synchronous	35	20 (57%)	9 (26%)	6 (17%)
Seminoma, concordant	20 (57%)	13	3	4
Treatments				
Surveillance	6	6		
Radiation	9	7	2	
Chemotherapy	5		1	4
Post-Chemo RPLND	3		1	2
RPLND	0			
Adjuvant Chemotherapy	-			
Nonseminoma, concordant	5 (14%)	3	1	1
Treatments				
Surveillance	1	1		
Radiation	1			1 (Brain)
Chemotherapy	2		1	1
Post-Chemo RPLND	2		1	1
RPLND	2	2		
Adjuvant Chemotherapy	0			
Discordant histology	10 (29%)	4	5	1
Treatments				
Surveillance	1	1		
Radiation	0			
Chemotherapy	5		4	1
Post-Chemo RPLND	4		3	1
RPLND	4	3	1	
Adjuvant Chemotherapy	0			

Table 2b
Metachronous bilateral TGCT histology and treatment

	Number			
Variable	93			
Combined histology				
Concordant seminoma	29 (31%)			
Concordant nonseminoma	25 (27%)			
Discordant sem/nonsem	39 (42%)			
First tumor	Number	Stage I	Stage II	Stage III
Histology and Treatment	93	70 (75%)	17 (18%)	6 (6%)
Pure Seminoma	47 (51%)	43	4	0
Treatments				
Surveillance	6	6		
Radiation	39	36	3	
Chemotherapy	1	0	1	
Post-Chemo RPLND	1		1	
RPLND	1	1		
Adjuvant Chemotherapy	0			
Mixed/Nonseminoma	46(49%)	27	13	6
Treatments				
Surveillance	9	9		
Radiation	1	1		
Chemotherapy	18	2	10	6
Post-Chemo RPLND	7		5	2
RPLND	18	15	3	
Adjuvant Chemotherapy	3	1	2	
Second tumor	Number	Stage I	Stage II	Stage III
Histology and Treatment	93	64 (69%)	20 (22%)	9 (10%)
Pure Seminoma	50 (54%)	43	6	1
Treatments				
Surveillance	35	35		
Radiation	6	6		
Chemotherapy	6	1	4	1
Post-Chemo RPLND	1		1	
RPLND	3	1	2	
Adjuvant Chemotherapy	2	1	1	

Variable	Number			
	93			
Mixed/Nonseminoma	43(46%)	21	14	8
Treatments				
Surveillance	15	15		
Radiation	0	0		
Chemotherapy	22	3	11	8
Post-Chemo RPLND	11		7	4
RPLND	6	3	3	
Adjuvant Chemotherapy	3	1	2	