SciMedCentral

Annals of Mens Health and Wellness

Research Article

Testicular Germ Cell Tumors in Men with Down's Syndrome: Delayed Diagnosis, Comorbidities May Contribute to the Suboptimal Outcome

Emma Weatherford[1] and Jue Wang[2,3,4]*

[1]*Baylor University, USA*
[2]*Creighton University School of Medicine at St. Joseph's Hospital and Medical Center, USA*
[3] *St. Joseph's Hospital and Medical Center, USA*
[4]*Department of Genitourinary Oncology, University of Arizona Cancer Center at Dignity Health St. Joseph's Hospital and Medical Center, USA*

***Corresponding author**
Jue Wang, Director of Genitourinary Oncology Section, University of Arizona Cancer Center at Dignity Health St. Joseph's, Phoenix, AZ, 625 N 6th Street, Phoenix, AZ 85004, Tel: 1602-406-8222; Email: jue.wang@dignityhealth.org

Submitted: 23 March 2018

Accepted: 29 March 2018

Published: 31 March 2018

Keywords

- Testicular germ cell tumor (TGCT)
- Down's syndrome (DS)
- Delayed diagnosis
- Seminoma
- Non seminomatous germ cell tumor; Orchiectomy
- Chemotherapy
- Prognosis

Abstract

Purpose: The main objective of this study was to determine the clinical features, treatment and prognosis of Down's syndrome (DS) patients with testicular germ cell tumor (TGCT).

Materials and methods: We conducted a pooled analysis of 43 Down's syndrome patients diagnosed with TGCT published in literature between January 1985 and December 2016.

Results: The median age was 30 years (range 2 – 50). A majority of tumors (67%) were seminomas. 26 (51%) patients were diagnosed as stage I, 14 (33%) and 7 (16%) as stage II and III, respectively. In the seminoma group, 18 patients (62%) were diagnosed with stage I, 9 (31%) with stage II and 2 (7%) with stage III. In the non-seminoma group, 4 patients (29%) were diagnosed with stage I, 5 (36%) with stage II and 5 (36%) with stage III. 26 out of 43 (60%) patients had documented comorbidities. The overall survival at 5 years for stage I was 100%, 76% for stage II and 68% for stage III.

Conclusion: TGCT are often diagnosed at an advanced stage in patients with DS. In addition, patients often required modifications to standard treatment regimens due to their comorbidities. Delayed diagnosis, comorbidities may contribute to the suboptimal outcome in stage II/III TGCTs in DS patients. Emphasis education on community and care provider on prevalence of TGCT, early screening and detection, are needed to improve the outcome in this population.

INTRODUCTION

Testicular cancer, although relatively rare in the general population, is the most common form of cancer among young men aged 15 to 35 [1,2]. The majority of testicular cancers are testicular germ cell tumors (TGCT) [3-5]. The incidence of TGCT has been observed to be higher among men with Down syndrome relative to the general population [6,7], despite the lower incidence of most solid tumors among the Down's syndrome (DS) population [7]. However, there is a lack of published data regarding testicular cancer among men with DS, the available information regarding clinical features, management, and treatment outcomes are limited [8-11].

In order to better understand the differences in the clinical manifestations and optimal management of testicular cancer among men with DS, we conducted a pooled analysis of 43 DS patients diagnosed with TGCT published in literature [12-31], between January 1985 and December 2016.

MATERIALS AND METHODS

Published data Search

Literature search based on PubMed search was performed using the following keywords: "Testicular germ cell tumor (TGCT)", "Testicular cancer" and "Down's syndrome". Cases were initially identified from a search of PubMed; further cases were found through references in other reports or through a search of the Baylor University library services. The full texts of reports were located when possible; when the full text was not available, the abstract or a summary published in another source was used.

Data extraction

Information regarding the patient (patient age at diagnosis, presentation, and comorbidities), the tumor (discovery, symptoms, tumor size, location, histology, and stage), examination results (tumor markers, radiologic investigation, biopsy), treatment (treatment modalities, response), and the

outcome (evidence of metastases, vital status) were recorded, when available.

Data analysis

Descriptive statistics, such as frequency counts, medians, and ranges, were used to characterize the pooled sample. Survival was calculated according to the Kaplan-Meier method and the survival curves were compared by univariate analysis with the long-rank test. Overall survival (OS) was defined as the time from the date of TGCT diagnosis to the date of death. Statistical significance was defined as a p-value<0.05. All analyses were performed using SPSS ver. 15.0 (SPSS Inc., Chicago, IL).

RESULTS

Patient and Tumor Characteristics

Forty-three DS patients with adequate clinical and pathologic data were included in final analysis. A majority (61%) of patients presented between the ages of 20 and 39; the median age was 30 years (range 2 years – 50 years). Many patients (60%) had one or more reported comorbidities. Sixteen patients (37%) had a history of cryptorchidism in one or both testes. 24(56%) involved left side testis including 4(9%) were bilateral. 20 (46%) patients presented with findings of swelling of the scrotum; 7(16%) presented with swelling of the groin; 6(14%) with abdominal or flank pain.26 out of 43 (60%) patients had documented comorbidities. Table 1 shows the demographic and tumor characteristics of these patients with TGCT published in literature.

A majority of tumors (67%) were seminomas. The remainders were nonseminomas, of which 12% were embryonic carcinomas and 16% were mixed germ cell tumors. In the seminoma group, 18 patients (62%) were diagnosed with stage I, 9 (31%) with stage II and 2 (7%) with stage III. In the non-seminoma group, 4 patients (28%) were diagnosed with stage I, 5 (36%) with stage II and 5 (36%) with stage III.

Table 1: The demographic and tumor characteristics of 43 Down's syndrome Patients with TGCT published in literature between January 1985 and June 2016.

	N (%)
Age (yr)	
<20	9 (21%)
20-29	12 (28%)
30-39	14 (33%)
>39	8 (19%)
Median Age (Range)	30 (2-50)
Comorbidities	
Yes	26 (60%)
No	17 (40%)
Crytorchidism	
Yes	16(37.2%)
No	27(62.8)
Histology	
Seminoma	29 (67%)
Embryonic carcinoma	5 (12%)
Choriocarcinoma	0 (0%)
Yolk sac tumor	1 (2%)
Teratoma	0 (0%)
Mixed	7 (16%)
Not specified	1 (2%)
Stage	
I	22 (51%)
II	14 (33%)
III	7 (16%)
AFP Levels: seminoma / nonseminoma	
Elevated	0 (0%) / 8 (57%)
Normal	15 (52%) / 2 (14%)
Unknown	14 (48%) / 4 (29%)
β-hCG Levels: seminoma / nonseminoma	
Elevated	7 (24%) / 4 (29%)
Normal	8 (28%) / 5 (36%)
Unknown	14 (48%) / 5 (36%)

Treatment and adverse effects

Treatment regimens and patient outcomes are presented in Table 2. A majority of DS patients (51%) received standard treatment. All patients underwent orchiectomy. In addition, 51% of DS patients received chemotherapy and 19% received radiotherapy. Eight reports state that the patient received modified treatment due to comorbidities (such as reduced glomerular filtration rate). Five patients (12%) experienced complications during treatment. Two of these patients died during chemotherapy, while the remainder successfully completed their therapy.

Outcome

The majority of DS patients (67%) showed no evidence of disease at the end of follow-up. Seven cases (16%) had no reported outcome. When only cases with recorded outcomes are considered, 86% of patients survived their cancer. Figure 1a presents the cancer specific survival of patients in this study. Figure 1b presents the survival by stage at presentation. The OS at 5 years for stage I was 100%, 76% for stage II and 68% for stage III. Figure 1c presents the survival by histology at presentation. There was no significant difference between seminoma and nonseminoma.

Three DS patients (7%) died due to progression of their disease. Both of these patients presented with advanced stage (two stage III and received nonstandard chemotherapy; another patient presented at stage IIB, no additional therapy or radiotherapy following orchiectomy). Two DS patients (5%) died during the period of follow-up due to causes unrelated to cancer.

DISCUSSION

Testicular cancers (TC) are rare in the general population, accounting for 1% of all human malignancy, but affect mainly young adults between the ages of 15 to 35 years [1,2]. Although TC in general shows excellent cure rates based on their chemosensitivity, multidisciplinary management, and established follow-up approach and salvage therapies [3-5], delay in diagnosis of a testicular cancer may result in an advanced stage of disease at diagnosis, which may affect disease free and overall survival [32].

Table 2: Treatment and Patient Outcome of 43 Down's syndrome Patients with TGCT published in literature between January 1985 and June 2016.

Variable	Value N (%)
Orchiectomy	
Yes	43 (100%)
No	0 (0%)
Chemotherapy	
Yes	22 (51%)
No	21 (49%)
Radiotherapy	
Yes	8 (19%)
No	35 (81%)
Outcome	
NED	29 (67%)
DOC	2 (5%)
DOD	3 (7%)
DOT	2 (5%)
NS	7 (16%)

Note: AWD, alive with disease; DOC, died due to another condition; DOD, died of disease progression; DOT, died during treatment; NA, not available; NED, no evidence of disease; NS, not specified

Emerging epideminologic and clinical evidences suggests that men with DS experience a higher frequency of testicular cancer than the general population [6-9]. The presentation of testicular cancer is similar to that of nondisabled persons: painless nodule and a swelling of the scrotum. Due to intellectual disability, indivuduals with DS may not adequately convey their symptoms and pain, often leading to delayed diagnosis and potentially worse outcome [9]. We found TC tumors in DS patients are larger and more often diagnosed at an advanced stage. In this study, 9% DS patients the symptoms was initially found by care provider, incidental discovery was noted in 12% cases. 26 (51%) patients were diagnosed as stage I, 14 (33%) as stage II and 7 (16%) as stage III. These patients may also be reluctant to reveal their symptoms because of feelings of embarrassment or fear [9]. Patients with DS may be fearful of physical examination and may therefore mask their symptoms as long as possible [8,9]. Additionally, families of these patients do not necessarily have familiar with the cancer risk in persons with DS. Delay in the diagnosis of testicular cancer is associated with greater morbidity and poorer prognosis [32].

Oncology and urology providers are confronted with challenges in the process of assessment, diagnosis, treatment and cancer follow-up in DS patients [7,8,9,11]. If the tumor is diagnosed at stage I, treatment is much easier and less toxic than if the tumor has spread to other parts of the body. Cancer treatment for stage II/III imposesvery heavy burden on daily living of patients with DS [8,9]. Furthermore, DS patients usually have multiple comorbidities which may interfere with cancer treatment. In our study, all patients underwent radical orchiectomy as an initial treatment. In addition, 51% of patients received chemotherapy and 19% received radiotherapy. More than half of the patients (60%) in our study had documented

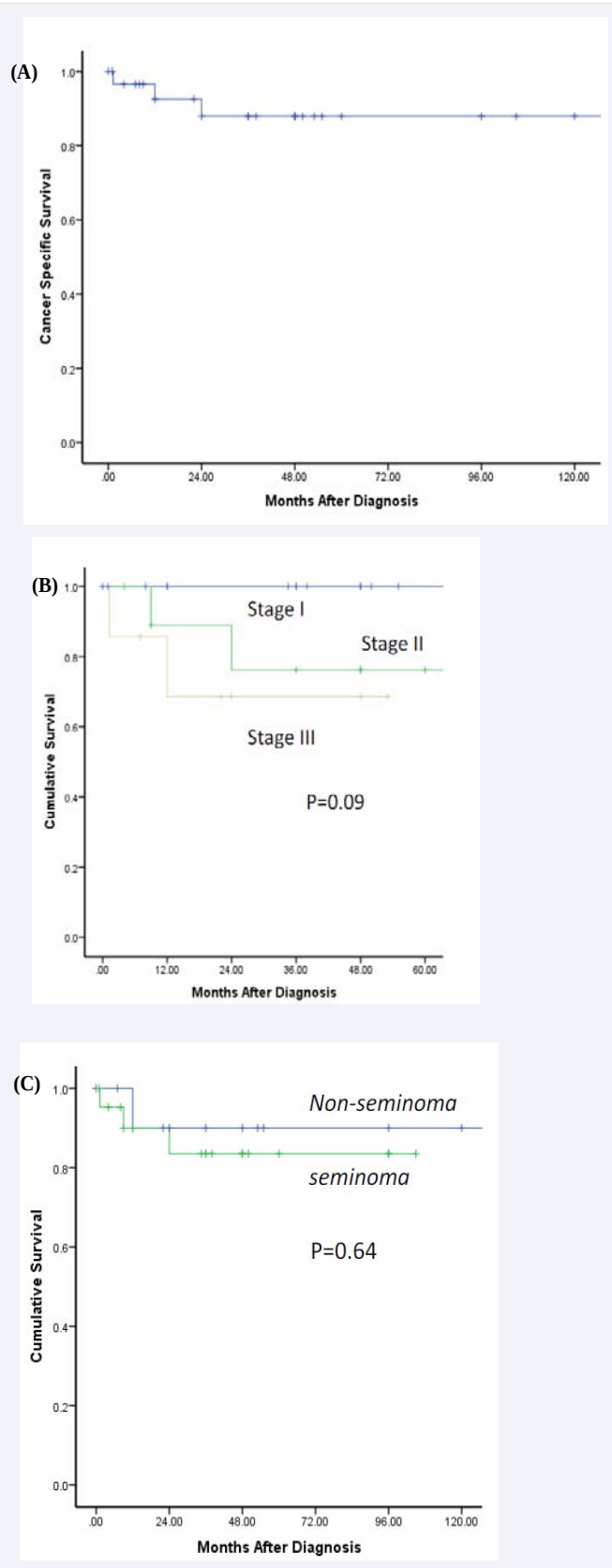

Figure 1 (a): Kaplan Meier Survival Curve of 43 Down's syndrome patients diagnosed with testicular germ cell tumors in published in literature between January 1985 and June 2016. (b): Survival distribution stratified by stage. (c): Survival distribution stratified by histology.

comorbidities. Only 51% DS patients received standard treatment. Eight reports documented that the patient received modified treatment due to comorbidities (such as reduced GFR) or mental state. Five DS patients (12%) experienced complications during treatment. Two of these patients died during chemotherapy, while the remainder successfully completed their therapy. Three DS patients (7%) died due to progression of their disease. All of them presented with advanced disease: two of these patients presented at stage III and received nonstandard chemotherapy; the third patient presented at stage IIB and his mother declined adjuvant chemotherapy or radiotherapy following orchiectomy. Two DS patients (5%) died during the period of follow-up due to causes unrelated to cancer.

There are several limitations of the present study because of the nature of retrospective design. Despite the limitations, the present study provides the most comprehensive information regarding the diagnosis and outcomes of TGCT patients with DS. The findings of this study would help improve our current understanding of the clinical features, treatment pattern and prognosis of patients with TGCT and DS and help identify optimal multidisciplinary management strategies forth is rare, but potential curable condition.

CONCLUSIONS

TGCTs are often diagnosed at an advanced stage in patients with DS. Delayed diagnosis, comorbidities likely contributed to the suboptimal outcome for stage II/III TGCTs patients in this population. Emphasis on education for both community and health care providers, early screening and detection are needed to improve the outcome for these patients. A multidisciplinary team is essential in providing high-quality, compassionate care for these patients and support for their families and caregivers.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016; 66: 7-30.
2. Hanna NH, Einhorn LH. Testicular cancer--discoveries and updates. N Engl J Med. 2014; 371: 2005-2016.
3. Masters JR, Köberle B. Curing metastatic cancer: lessons from testicular germ-cell tumours. Nat Rev Cancer. 2003; 3: 517-525.
4. Motzer RJ, Agarwal N, Beard C, Bolger GB, Boston B, Carducci MA, et al. NCCN clinical practice guidelines in oncology: testicular cancer. J Natl Compr Canc Netw. 2009; 7: 672-693.
5. Motzer RJ, Agarwal N, Beard C, Bhayani S, Bolger GB, Buyyounouski MK, et al. J Natl Compr Canc Netw. 2012; 10: 502-535.
6. Dieckmann KP, Rube C, Henke RP. Association of Down's syndrome and testicular cancer. J Urol. 1997; 157: 1701-1704.
7. Hasle H. Pattern of malignant disorders in individuals with Down's syndrome. Lancet Oncol. 2001; 2: 429-436.
8. Weatherford E, Wang J. The clinical presentation, diagnosis, treatment and long term outcome of germ cell tumor in 85 patients with Down syndrome. J Clin Oncol. 2018; 36.
9. Sharlin C, Hasan Y, Hoskin J, Weatherford E, Wang JF, Collum E, et al. Delayed in diagnosis of testicular cancer in a patient with Down syndrome: A case report and review of current literature. J Cancer Ther Sci. 2017; 1: 1-6.
10. Hafeez S, Singhera M, Huddart R. Exploration of the treatment challenges in men with intellectual difficulties and testicular cancer as seen in Down syndrome: single centre experience. BMC Med. 2015; 13: 152.
11. Hafeez S, Sharma RA, Huddart RA, Dearnaley DP, Horwich A. Challenges in Treating Patients with Down's Syndrome and Testicular Cancer with Chemotherapy and Radiotherapy: The Royal Marsden Experience. Clinical Oncology. 2007; 19: 135-142.
12. Aguilar-Ponce JL, Vidal-Millán S, Molina-Calzada C, Chilaca-Rosas F, Martínez-Cedillo J, Cruz-López JC. Treatment experiences of testicular cancer in Hispanic patients with Down's syndrome at the National Cancer Institute of Mexico. ClinTransl Oncol. 2008; 10: 768-771.
13. Braun DL, Green MD, Rausen ARl. Down's syndrome and testicular cancer: a possible association. Am J Pediatr Hematol Oncol. 1985; 7: 208-211.
14. Dada R, Kumar R, Kucheria K. A 2-year-old baby with Downs syndrome, cryptorchidism and testicular tumour. Eur J Med Genet. 2006; 49: 265-268.
15. Dieckmann KP, Rübe C, Henke RP. Association of Down's syndrome and testicular cancer. J Urol. 1997; 157: 1701-1704.
16. Hayashi T, Koike H, Katoh Y, Iguchi M, Hatanaka Y, Miyatake R, et al. A case of testicular tumor in a patient with Down's syndrome: a case report. Hinyokika Kiyo. 2000; 46: 283-286.
17. Hsiung Stripp DC, Vaughn D, Van Arsdalen K, Whittington R. Three cases of advanced seminoma and Down's syndrome: a possible association. Am J Clin Oncol. 2003; 26:197-199.
18. Ichiyanagi O, Sasagaw I. Down's Syndrome Associated with Seminoma in Undescended Testis. Scandinavian J Urol Nephrol. 1998; 32: 365-367.
19. Kamidono S, Takada K, Ishigami J, Furumoto M, Urano Y. Giant seminoma of undescended testis in Down syndrome. Urol. 1985; 25: 637-640.
20. Miki M, Ohtake N, Hasumi M, Ohi M, Moriyama S. Seminoma associated with bilateral cryptorchidism in Down's syndrome: a case report. Int J Urol. 1999; 6: 377-380.
21. Na RK, Jae-Gul C, Hyun YC. Down syndrome associated with testicular seminoma: a case report. The Korean J Pathol. 2003; 37: 442-445.
22. Sasagawa I, Kazama T, Umeda K, Kohno T, Katayama T, Miwa A. Down's syndrome associated with seminoma. Urol Int. 1986; 41: 238-240.
23. Satgé D, Jacobsen GK, Cessot F, Raffi F, Vekemans M. A Fetus with Down Syndrome and Intratubular Germ Cell Neoplasia. Pediatric Pathol Lab Med. 1996; 16: 107-112.
24. Sleijfer S, Koops HS, van der Graaf WT. Successful treatment on an out-patient basis of a patient with Down's syndrome and disseminated testicular seminoma. Neth J Med. 1996; 48: 89-91.
25. Suzuki K, Nishimi D, Yagishita T, Takanami M, Hiruta N. Testicular tumor in Down syndrome. Int J Urol. 2005; 12: 925-927.
26. Villanueva MJ, Navarro F, Sánchez A, Provencio M, Bonilla F, España P. Testicular germ cell tumor and Down syndrome. Tumori. 2000; 86: 431-433.
27. Dexeus F. Genetic abnormalities in men with germ cell tumors. J Urol. 1988; 140: 80-84.
28. Hashimoto T, Sasagawa I, Ishigooka M, Kubota Y, Nakada T, Fujita T. Down's syndrome associated with intracranial germinoma and testicular embryonal carcinoma. Urol Int. 1995; 55: 120-122.
29. Almouhissen T, Badr H, AlMatrafi B, Alessa N, Nassir A. Testicular cancer in Down syndrome with spinal cord metastases. Urol Ann. 2016; 8: 503.

30. Kuroda N, Amano S, Shiotsu T, Tamura M, Hes O, Michal M, et al. Mixed testicular germ cell tumor in an adult with cryptorchidism and Down's syndrome. APMIS. 2007; 115: 1292-1295.

31. Martin L, Rashid T, Ruston M. Bilateral orchidectomy for germ cell tumours in cryptorchid testis in Down's syndrome: a case report. J Clin Urol. 2011; 6: 322-323.

32. Huyghe E, Muller A, Mieusset R, Bujan L, Bachaud JM, Chevreau C, et al. Impact of diagnostic delay in testis cancer: results of a large population-based study. Eur Urol. 2007; 52: 1710-1716.

Cite this article

Weatherford E, Wang J (2018) Testicular Germ Cell Tumors in Men with Down's Syndrome: Delayed Diagnosis, Comorbidities May Contribute to the Suboptimal Outcome. Ann Mens Health Wellness 2(1): 1010.