Print ISSN: 2321-6379
Online ISSN: 2321-595X
DOI: 10.17354/ijss/2017/361

Original Article

Profile of Testicular Germ Cell Tumors in Kashmir: A Retrospective Analysis

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Abstract

Background: Testicular tumors are the most common solid neoplasm in young men. Germ cell tumors (GCT) constitute over 90% of all the malignant testicular neoplasms. The incidence of testicular tumors shows a significant geographic variation with the highest number of cases being reported in Scandinavia, Germany and Switzerland and lowest in Asian and African nations. Presently, there are only a few well-established risk factors for this disease, notably cryptorchidism and age. However, for the most part, the etiology of testicular cancer remains unknown.

Aim and Objective: To analyze the profile of testicular GCT at a tertiary cancer center in Kashmir.

Materials and Methods: This retrospective analysis of testicular germ cell tumor cases was performed in the year 2017 on 40 patients enrolled in the Department of Radiation Oncology, Government Medical College, Srinagar, from 2012 to 2017.

Results: Of the 40 patients analyzed, majority had seminomatous histology. Most of them presented with unilateral disease with laterality toward the right side. Bilateral tumors presented at an earlier age than unilateral disease. Most of the patients enrolled belonged to rural areas. Tumor markers such as lactate dehydrogenase and beta-human chorionic gonadotropin had statistically significant association with the overall stage of disease.

Key words: Germ cell, Kashmir, Testicular tumor

INTRODUCTION

Testicular cancer is a rare neoplasm, accounting for only 1% of all male cancers. It is, however, the most common solid malignancy in young men.[1] Globally, there has been an increase in the incidence of testicular cancer, with studies reporting almost doubling of its incidence in the past 40 years,[2] with western nations reporting a decrease in the mortality over the years.[1] Age-standardized incidence rates are highest in New Zealand (7.8), UK (6.3), Australia (6.1), Sweden (5.6), USA (5.2), Poland (4.9), and Spain (3.8) per 100,000 men. India, China, and Colombia have the lowest incidence (0.5, 1.3, and 2.2, respectively) per 100,000 men. India has the lowest overall testicular cancer incidence −1.7% (−2.5; −0.8).[1] Cryptorchidism or maldescended testis (MDT) is the most established factor associated with testicular cancer, with a 2-4 fold increase in the risk of testicular cancer.[3] Several studies undertaken to correlate any association between testicular cancer and various possible risk factors have shown mixed results, with current literature on the causes of testicular cancer being limited only to a few established risk factors including age, race, and MDT.[4] Seminoma and nonseminoma do not seem to have substantial difference in etiological risk factors because of similar incidence trends and nearly half of all tumors being composed of both "seminoma" and "nonseminoma" elements.[5] While as western nations report early stage at diagnosis,[6] Indian literature reports a locally advanced stage at presentation.[7] Kashmir valley is ethnically, topographically and climatically distinct from rest of India, hence this study was undertaken to analyze the profile of testicular cancer patients in Kashmir Valley

Access this article online

www.ijss-sn.com

Month of Submission : 05-2017
Month of Peer Review : 06-2017
Month of Acceptance : 07-2017
Month of Publishing : 07-2017

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with regard to various parameters and their corroboration with world literature.

MATERIAL AND METHODS

This study was conducted in the Department of Radiation Oncology, Government Medical College, Srinagar, from 2012 to 2017. It was a retrospective analysis conducted on 40 patients with histological documentation of germ cell tumor. Patients with histologies other than germ cell tumor were not included in the analysis. Data were analyzed with respect to demographic and clinical profile of patients such as age, residence, socioeconomic status, birth order, presenting sign and symptom, history of smoking, and history of trauma. Patients who were operated were staged radiologically, surgically, and with tumor markers, while as patients not subjected to surgery were staged radiologically and with tumor markers.

RESULTS

In our study, a total of 40 cases of testicular germ cell tumors were enrolled, of which 65% were seminomatous tumors and the rest nonseminomatous. The patients presented at a mean age of 37.0 years with a standard error of 2.00 years; the minimum and maximum age of presentation was 16 and 65, respectively.

Testicular swelling was the most common presenting symptom in 65% of the patients with tender testicular mass being the most common sign. 60% of the patients did not have any identifiable risk factor, while in the rest cryptorchidism was the major risk factor identified. Over 67% of the patients were subjected to high inguinal orchiectomy, which was the most common surgical procedure undertaken (Figure 1).

Patients with bilateral disease presented earlier with a mean age at of presentation of 24.2 years in contrast to 38.9 years for unilateral disease (d = −14.7 95% confidence interval −3.23 to −26.14, $t = 2.595$, $P = 0.013$), although unilateral disease was more common representing 87.5% of all the cases ($\chi^2 = 22.5$, $P = 0.00001$). In unilateral testicular tumors right sided tumors were more common (55% of total) but the difference as compared to left was not statistically significant ($\chi^2 = 2.314$, $P = 0.175$).

Coming to the sociodemographic profile of the patients, 82.5% of patients belonged to the rural areas and rest from urban areas, the difference being statistically significant ($\chi^2 = 16.9$, $P = 0.00004$). 72% patients were employed ($\chi^2 = 8.1$, $P = 0.006$).

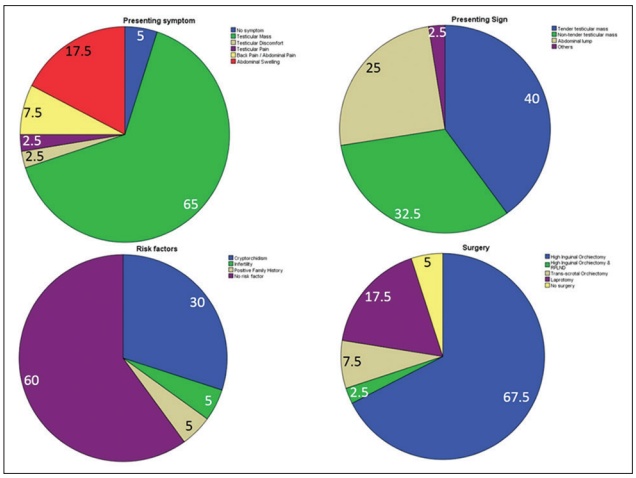

Figure 1: Clinico-demographic parameters of testicular tumor

The median overall stage of disease at presentation for the cases was "II-C" (35% of all cases and maximum among all stages). Various variables, like risk factors, age at presentation, prognostic group, socioeconomic profile, smoking habits, history of trauma, biochemical markers, among others, were tested for association with the overall stage of disease using the "Kruskal-Wallis" test. Only lactate dehydrogenase (LDH), beta-human chorionic gonadotropin (β-HCG) and prognostic group had statistically significant association with the overall stage of disease. Higher levels of LDH > S1 ($\chi^2 = 9.806$, $P = 0.003$, $\eta^2 = 0.2514$), β-HCG > S2 ($\chi^2 = 8.415$, $P = 0.019$, $\eta^2 = 0.2158$) and poorer prognostic group ($\chi^2 = 8.111$, $P = 0.005$, $\eta^2 = 0.2078$) predicted a higher overall stage of the disease.

Statistical analysis for the data was performed using the SPSS software (v20, IBM Corporation).

DISCUSSION

Over 95% of all primary testicular tumors are of germ cell origin. Less frequent tumors include Leydig cell, Sertoli cell, and other rare or poorly defined histological types. Approximately, half of the testicular GCT (TGCT) is classical seminomas and the rest nonseminomatous, including subtypes like embryonal carcinoma, yolk cell tumor, teratoma, choriocarcinoma, and spermatocytic seminoma.[5] Our study revealed 65% of the tumors to be seminomatous and rest nonseminomatous. Intra tubular germ cell neoplasia also known as carcinoma *in situ*, reported to be precursor for all TGCT in adolescents and young adults[8] was not seen in any of our cases.

More than 80% of TGCT in men are seen in second to fourth decade of life whereas 15-20% is seen in men aged 45 years or older.[4]

Our study revealed mean age at disease presentation to be 37 years with the patients having bilateral disease presenting at an earlier age. Our findings are corroborated by other studies reporting bilateral TGCT's to present at an earlier age.[9]

Retrospective studies have shown the prevalence of bilateral TGCT tumors to be around 1-2%,[10] with majority (80-85%) occurring metachronously.[11] Whereas the association of bilateral disease with earlier presentation was significant in our study, we could not elicit any association between bilateral disease with undescended testis, as reported in various studies.[9]

Studies as early as the beginning of the 19th century has shown MDT to be strongly associated with testicular neoplasia[12] with some reports showing the relative risk of association to be 5-10 fold.[13] Our analysis showed 30% of the patients having MDT.

Rural preponderance of testicular neoplasms was reported as early as in 1974, where agricultural based rural areas were shown to have a higher incidence than urban populations.[14] No big analysis has been carried in India comparing rural versus urban demography of testicular cancer. Of late many studies have shown mixed results with some analyses showing no association with rural/urban dwelling,[15] while some studies showing urban habitation to be at higher risk than general population.[2] Overall, if at all any association, its reported to be nonsignificant.[16] Our study showed over 80% of the patients to be from rural areas, possibly due to more agricultural activities like use of carcinogenic pesticides in rural areas.[14] Differences in the incidence of testicular tumors with regard to different ethnicity as reported in studies[17] could not be elicited in our analysis.

Association with smoking was nonsignificant in our study. Retrospective studies too have not shown any significant association of testicular tumors with maternal smoking.[18]

Testicular trauma though proposed by some authors as a risk factor for testicular tumors, was not a significant finding in our analysis.[19]

Data on testicular GCT have shown Stage I to be the most common stage at presentation,[20] however, our study revealed most common stage at presentation to be Stage II C, the cause of which could not be verified.

Three relatively specific and sensitive serum biomarkers are used in the diagnosis, prognosis, and surveillance of testicular cancer and include alpha-fetoprotein (α-FP), beta subunit of β-HCG, and LDH.[21] These tumor markers, along with other prognostic factors, help in stratifying patients into good, intermediate, and poor prognosis categories.[22]

Increased levels of α-FP are typically found in nonseminomatous tumors[23] α-FP levels are typically not elevated in seminomas; however, if increased levels of α-FP are found in pure seminoma, it must be considered and treated as a nonseminomatous germ cell tumor. Elevated serum β-HCG levels are typically present in both seminomas and nonseminomas. Increased levels of serum β-HCG following orchiectomy is an indication of persistent disease, whereas rising levels of β-HCG after treatment completion and disease remission indicates disease relapse.[21] Increased levels of serum LDH have been seen to be associated with advanced testicular tumors in approximately 80% seminomas and 60% of nonseminomas.[23] Our analysis revealed a significant association of LDH and β-HCG with overall disease stage, where by higher levels of these markers were seen in higher stage disease. These markers coupled with other poor prognostic factors such as positive family history and infertility are indirect predictors of survival.

High inguinal orchiectomy has been the standard surgical procedure for a suspected testicular cancer. Procedural deviations such as trans-scrotal orchiectomy, open testicular biopsy, and fine needle aspiration have been historically negated in view of prognostic implications.[24]

Whereas some studies have revealed statistically significant differences in the local recurrence rate among patients undergoing scrotal violation versus the inguinal approach,[25] some authors report that the effect of higher local recurrence in trans-scrotal approach was not statistically significant to impact the survival rates or distant recurrence in all groups analyzed.[24]

In our analysis, apart from the 70% patients who were subjected to orchiectomy and orchiectomy plus retroperitoneal lymph node dissection, rest were subjected to either laparotomy (17.5%) or trans-scrotal orchiectomy (7.5%). Laparotomy was performed in patients who presented with abdominal disease whereas trans-scrotal surgery was inadvertently carried out at peripheral health service hospitals.

CONCLUSION

Testicular germ cell tumor continues to be a disease of young adults with a slight predominance of seminomatous histology. Testicular swelling is the most common symptom for which consultation is sought, with bilateral testicular tumor patients presenting at a significantly earlier age. Over

one-third patient had associated cryptorchidism while the majority did not have an identifiable risk factor. Majority of the patients came from rural areas the cause of which needs to be ascertained with further studies. Although majority of patients had undergone high inguinal orchiectomy over 7% patients had undergone nonstandard surgical procedures which underscores the importance of timely referral and intervention at a dedicated oncological center.

As against earlier disease presentation in rest of the world, patients in our analysis reported at a locally advanced stage. LDH and β-HCG had a significant implication with overall disease stage.

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How to cite this article: Mustafa SA, Mitla V, Banday SZ, Kuchay S. Profile of Testicular Germ Cell Tumors in Kashmir: A Retrospective Analysis. Int J Sci Stud 2017;5(4):183-186.

Source of Support: Nil, **Conflict of Interest:** None declared.