RESEARCH ARTICLE

# Clinical Profile, Treatment and Survival Outcome of Testicular Tumors: A Pakistani Perspective

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## Abstract

**Background: Testicular cancer management is considered a marvel of modern science with excellent treatment results. Pakistan has a distinct ethnic variation and geographic distribution but data regarding clinical presentation of testicular tumors and their management is under reported. The objective of this study was to determine clinical profile, treatment modalities and survival outcome of testicular tumors in the Pakistani population. Materials and Methods: A retrospective review of patients who received treatment for testicular cancer at Shaukat Khanum Cancer Hospital from January 2009 to December 2012 was performed. Patient demographics, clinical features at presentation and treatment modalities were assessed. For categorical variables chi square test was used. Survival was calculated using Kaplan Meier survival curves and Log rank test was employed to determine significance. Results: The most common tumor was mixed germ cell tumor in 49% patients. For all tumor variants except seminoma, stage III was the most common clinical stage at presentation. Majority of patients with non seminomatous germ cell tumors presented in the15-30 year age group as compared to seminoma which was most prevalent in the 30-40 year age group. Orchiectomy followed by chemotherapy was the most common treatment modality in 80% patients. Expected 5 year survival for seminomas and non-seminomatous germ cell tumors was 96% and 90% respectively which was not significantly different (p=0.2). Conclusions: Despite a distinct clinical profile of testicular tumors in Pakistani population, survival is comparable with published reports.**

**Keywords:** Testicular neoplasms - survival - seminoma - germ cell tumor

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## Introduction

Testicular cancer represents a rare entity on population based analysis (Chia et al., 2010). This tumor predominantly affects younger males and affects the most active and functional years of their life (Tan et al., 2011; Cost et al., 2013). There is high variability in incidence of testicular cancer with respect to ethnicity and geographic location. Incidence might be as high as 11.5 per 100,000 in white men compared with 1 to 2 per 100,000 in Blacks and Asian men (Purdue, 2005) (Bray et al., 2006). Across Europe and United states there has been a definite increase in the incidence of this malignancy (Bray et al., 2006; Shah et al., 2007; Walschaerts et al., 2008; Stang et al., 2009). Despite this variability 5 year survival in excess of 90% has been reported in Asian population irrespective of their geographical location (Biggs and Schwartz, 2004; Chia et al., 2010; Nguyen and Ellison, 2005).With this perspective of ethnic variation and gradual increase in incidence of testicular cancer, recent data from South East Asia and in particular Pakistan regarding the profile of testicular tumors at presentation and their treatment is limited. The objective of current study was to determine clinical presentation, management and survival outcome of testicular cancer from a tertiary care cancer hospital in Pakistan.

## Materials and Methods

Data of patients who received treatment for histology proven testicular cancer at Shaukat Khanum Cancer Hospital from January 2009 to December 2012 was retrospectively reviewed. Patients under the age of 16 years were excluded. A total of 247 patients were included in the study. All patients with suspected diagnosis of testicular cancer underwent standard clinical exam, imaging and lab investigations including tumor marker levels. Patients were discussed in multi-disciplinary meeting and appropriate management was initiated. After orchiectomy, standard treatment options included chemotherapy, retroperitoneal lymph node dissection (RPLND) and surveillance. Radiation therapy was used for palliative management of isolated metastatic deposits. Excision of retroperitoneal nodal masses was performed in patients with resectable residual masses after chemotherapy. All patients were kept under long term surveillance. In the present study patient's age, clinicopathological characteristics and treatment

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modalities were assessed. Tumor marker levels were assessed only for patients who had orchiectomy in Shaukat Khanum Cancer Hospital. Patients were stratified on basis of age, clinical stage and type of tumor. All tumors were staged according to American Joint Committee on Cancer 7th edition recommendations. For categorical variables chi square test was used. Overall survival was calculated by subtracting date of last follow up from date of first presentation to hospital. Kaplan Meier curves were used to determine estimated overall survival and Log rank test was used to determine significance. All analysis was performed on SPSS version 20.

## Results

*Pattern of presentation*

Around 60 new patients received treatment for testicular cancer in each year of study period and these numbers stayed constant over four years of study. Figure 1 represent various treatments provided to patients for each year of study. Orchiectomy followed by chemotherapy was the most common treatment modality. Median age at presentation was 33 years with range of 17 to 78 years. Mixed germ cell tumor (MGCT) (48%) and seminoma (28%) were the most common types of tumor (Table 1). About 80% of patients underwent orchiectomy elsewhere before they were referred to Shaukat Khanum for further management. Majority of these patients (70%) presented within 4 weeks of orchiectomy. Amongst 44 patients who had orchiectomy at Shaukat Khanum, Alpha fetoprotein (AFP) was raised in 41% and human Chorionic Gonadotropin (hCG) in 27% patients. Of 31 patients with non seminomatous germ cell tumors (NSGCT), AFP was raised in 18 while hCG in 8 patients. Overall 20 patients out of 31 (64%) with NSGCT had elevation of one or both tumor markers. Table 1 demonstrates patient characteristics at presentation.

Table 2 represents the clinical stage and age wise distribution of testicular tumors. Stage 3 was the most common clinical stage at presentation for all tumor types except seminomas. Patients with seminomatous tumors presented in stage 1 in 50% cases and more than 40% patients were in 30-40 year age group. For all other tumors 15-30 year age group was the most common age at presentation. This difference in age group distribution was statistically significant (p=0.002).

*Treatment*

Orchiectomy followed by chemotherapy was the most common treatment modality for both seminoma and NSGCT i.e. 81% and 79%. The second most common treatment modality was orchiectomy alone which was performed in 30 patients. Orchiectomy followed by RPLND was performed in 4 patients with non-seminomatous tumors on basis of patient preference. Excision of residual abdominal masses post chemotherapy was performed in 4 patients with intra-abdominal tumors irresectable at the time of presentation. Table 3 represents treatment modalities with respect to stage and tumor types.

*Survival*

The expected 5 year survival for stage 1, 2 and 3 tumors

**Table 1. Patient Characteristics at Presentation**

| | | No. | % |
|---|---|---|---|
| Primary diagnosis | Mixed germ cell tumor | 120 | 48.6 |
| | Seminoma | 70 | 28.3 |
| | Yolk sac tumors | 13 | 5.3 |
| | Choriocarcinoma | 3 | 1.2 |
| | Embryonal Carcinoma | 14 | 5.7 |
| | Teratoma | 14 | 5.7 |
| | Others | 13 | 5.3 |
| Laterality* | Right | 134 | 54.3 |
| | Left | 103 | 41.7 |
| Presented post orchiectomy | Outside | 203 | 82.2 |
| Time lapse | <4 weeks | 169 | 68.4 |
| | >4 weeks | 78 | 31.6 |
| Pre orchiectomy raised tumor markers | | | |
| | Alpha fetoprotein | 18 | 40.9 |
| | B-HCG | 12 | 27.2 |
| Clinical stage at presentation | I | 92 | 37.2 |
| | II | 31 | 12.6 |
| | III | 124 | 50.2 |

*variables with missing data

**Table 3. Treatment Modalities with Respect to Stage and Tumor Type**

| | | Stage I | Stage II | Stage III | Total No. | % |
|---|---|---|---|---|---|---|
| Orchiectomy+chemotherapy | Seminoma | 27 | 10 | 20 | 57 | 28.9 |
| | NSGCT* | 36 | 17 | 87 | 140 | 71.1 |
| Orchiectomy alone | Seminoma | 7 | 1 | 0 | 8 | 26.6 |
| | NSGCT | 17 | 2 | 3 | 22 | 73.4 |
| Orchiectomy+chemotherapy+Palliative radiation | | | | | | |
| | Seminoma | - | 0 | 1 | 1 | 12.5 |
| | NSGCT | - | 1 | 6 | 7 | 87.5 |
| Orchiectomy+Retroperitoneal lymph node dissection | | | | | | |
| | Seminoma | 0 | - | - | 0 | 0 |
| | NSGCT | 4 | - | - | 4 | 100 |
| Chemotherapy+Excision of residual abdominal masses | | | | | | |
| | Seminoma | - | - | 2 | 2 | 50 |
| | NSGCT | - | - | 2 | 2 | 50 |
| Others | Seminoma | 1 | - | 1 | 2 | 50 |
| | NSGCT | - | - | 2 | 2 | 50 |

*NSGCT Non seminomatous germ cell tumor

**Table 2. Age and Stage Wise Distribution of Various Testicular Germ Cell Tumors**

| | | Mixed GCT* | Seminoma | Yolk sac tumor | Embryonal Carcinoma | Teratoma | Chorio carcinoma | Others | Total | Percent % | P value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Stage wise presentation | Stage I | 40 | 35 | 4 | 3 | 6 | 0 | 4 | 92 | 37.2 | NS |
| | Stage II | 14 | 11 | 2 | 0 | 1 | 0 | 3 | 31 | 12.6 | |
| | Stage III | 66 | 24 | 7 | 11 | 7 | 3 | 6 | 124 | 50.2 | |
| Age Groups (Years) | 15-30 | 67 | 13 | 5 | 8 | 9 | 3 | 7 | 112 | 45.3 | 0.002 |
| | 31-40 | 38 | 30 | 5 | 4 | 3 | 0 | 5 | 85 | 34.4 | |
| | 41-50 | 10 | 19 | 2 | 1 | 2 | 0 | 0 | 34 | 13.7 | |
| | >50 | 5 | 8 | 1 | 1 | 0 | 0 | 1 | 16 | 6.4 | |
| Total | | 120 | 70 | 13 | 14 | 14 | 3 | 13 | 247 | 100 | |

*GCT Germ cell tumor

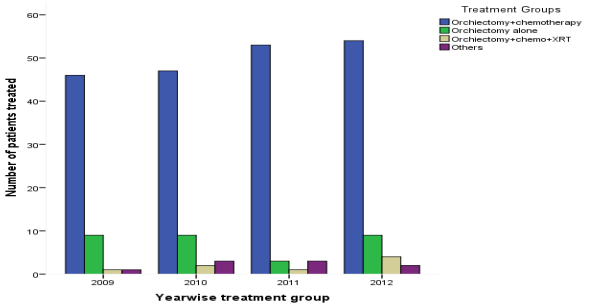


**Figure 1. Year Wise Distribution of Patients and Various Treatments Received**

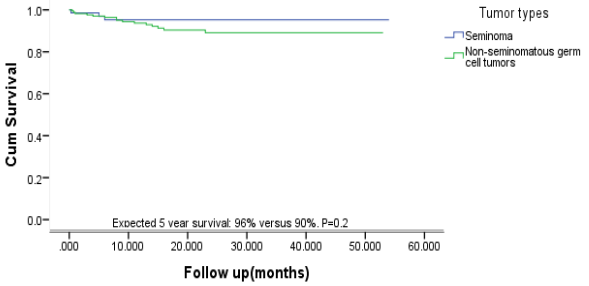


**Figure 2. Expected 5 year Survival for Seminomatous Versus Non Seminomatous Germ Cell Tumors**

was 98%, 94% and 88% respectively. Although there was an inverse relationship between stage at presentation and survival, it did not reach statistical significance (p=0.06). No significant difference in survival was observed between non-seminomatous and seminomatous germ cell tumors with expected 5 year survival of 90% and 96% (p=0.2) respectively as shown in Figure 2.

## Discussion

The present study highlights significant differences in testicular tumor profile of Pakistani population when compared with other parts of the world. The age distribution however was comparable with young men affected more frequently (Bhutani et al., 2002; Mushtaq et al., 2007). Short term follow up results were also comparable to published reports.

Mixed germ cell tumor (MGCT) was the most common tumor encountered in the present study. This is in contrast to the worldwide distribution of germ cell tumors where seminomas more frequent. Chia et al (2010) in there study on epidemiology of germ cell tumors showed that seminoma was the most common testicular cancer in majority of countries with tumor registries. Only 37% patients in the present study presented in stage 1. Stage 3 was the most common stage at presentation for all tumor variants except seminomas. Conflicting results have been reported from different parts of the world. Shah et al (2007) looked at trends of incidence of testicular cancer utilizing Surveillance, Epidemiology and End Result registries (USA) and found increasing incidence of localized testicular cancer from 1999-2003 in white men (73%). A decrease in localized testicular cancer was observed in the same time period in Blacks and it was near 50%. It was shown by Biggs and Schwartz (2004) that the percentage of localized testicular cancer was high in Asian American population reaching up to 70% in Chinese, Japanese and Filipino men. Bhutani et al (2002) in their study on germ cell tumors in 71 patients in India reported metastatic disease in 27 patients at presentation. They also reported high prevalence of non seminomatous tumors in their study. Mushtaq et al (2007) in their study involving 107 patients in Pakistan determined pathological distribution of testicular cancer and reported non seminomatous tumors to be more prevalent than seminomas. While no clear explanation exists as to why there are geographic and ethnic differences with respect to stage at presentation for testicular germ cell cancers, several factors are thought to be responsible. These include but are not limited to differences in time periods when studies were conducted, racial disparities in access to health care and dissimilarities in educational level of certain ethnicities (Franks et al., 2005; Ward et al., 2005).

Serum tumor markers have a prognostic role and are used for staging testicular cancers. Measurement of tumor markers like AFP and hCG is recommended for NSGCT (Klein, 1993; Gilligan et al., 2010). Raised tumor markers can be found in germ cell tumors in up to 50% patients (Wanderas, 1995). AFP may be raised in 50-70% and hCG in 40-90% patients with NSGCT (Albers, 2005) (Tan et al., 2011) (Shin and Kim, 2013). In the present study elevated tumor markers were found in 64% patients with NSGCT and 31% patients with seminomas. This finding cannot be generalized for the whole population as tumor markers were only assessed in patients who had orchiectomy in Shaukat Khanum Hospital.

A variety of treatment options exist for testicular cancer after orchiectomy. Surveillance, chemotherapy, RPLND and radiation therapy all have their benefits and side effects. In recent years, role of radiation therapy has become limited in seminomas due to risk of second non germ cell malignancies and cardiovascular side effects (Zagars, 2004) (Travis, 2005) (Van den Belt-Dusebout et al., 2007). Although, it has been shown recently that radiotherapy does not increase cardiovascular morbidity (Beard et al., 2013). For seminomas, excision of residual nodal masses is recommended in patients with PET avid resectable disease. All patients with NSGCT with residual masses after chemotherapy require resection. In the present study radiation therapy was used to treat isolated metastatic deposits in palliative setting. Surveillance is a feasible option for both and 10 year relapse free survival of 93.4 and 75% has been shown for stage I seminomas and non-seminomas respectively (Kobayashi et al., 2013). Surveillance was used with caution in the current study because follow up was difficult in majority cases where patients had to travel long distance for check-up. Excision of residual masses was reserved for patients with resectable residual disease on imaging after normalization of tumor markers post chemotherapy and occasionally it was performed in patients with stage I disease that preferred surgery over chemotherapy and surveillance. Chemotherapy has been advocated for localized NSGCT's (Ondrus et al., 1992; Pont et al., 1996). In the present study patients received 2 cycles of carboplatin based chemotherapy for localized NSGCT. The standard treatment for advanced germ cell tumors is three cycles of Bleomycin, Etoposide and Cisplatinum (BEPX3) in good prognosis and BEPX4 for intermediate or poor prognosis patients. This yielded impressive survival outcomes in many reported studies (Elinhorn et al., 1989;

Bookmeyer et al., 1996; Horwich et al., 1997). The same regimen was used in the present study and 5 year survival of 88% was reported for stage III tumors.

There are several limitations of the present study. These include short follow up of patients and thus long term survival for the study population remains to be answered. There was incomplete pre-operative clinical information since majority of patients presented after orchiectomy elsewhere. In patients who presented after orchiectomy, tumor marker levels were not available or could not be relied upon. To overcome this we assessed tumor markers only for patients who presented to the hospital before undergoing any surgical intervention.

Incidence of testicular cancer is very low. Over a period of 20 years, only 41 patients with testicular cancer were treated in a university hospital in Tunisia (Sataa et al., 2012). The present study involved a significantly large sample size considering the low incidence of testicular cancer. To our knowledge, this is the first study of this type reported from Pakistan. MGCT were the most common type of testicular malignancy and a high percentage of patients presented with metastatic disease. Many a time patients presented post orchiectomy with limited clinical and tumor marker information posing challenges regarding treatment decisions. Despite these variations, survival comparable to published reports was achieved. There is a dire need to educate general population and medical staff in developing countries regarding signs and symptoms of testicular cancer and the importance of referring these patients to appropriate centers in a timely manner.

## References


Albers P, Albrecht W, Algaba F, et al (2005). Guidelines on testicular cancer. *Eur Urol*, **48**, 885-94.

Bokemeyer C, Kohrmann O, Tischler J, et al (1996). A randomized trial of cisplatin, etoposide and bleomycin (PEB) versus carboplatin, etoposide and bleomycin (CEB) for patients with 'good-risk' metastatic non-seminomatous germ cell tumors. *Ann Oncol*, **7**, 1015-21.

Bhutani M, Kumar L, Seth A, et al (2002).Germ cell tumours of the testis: clinical features, treatment outcome and prognostic factors. *Natl Med J India*, **15**, 18-21.

Biggs ML, Schwartz SM (2004). Differences in testis cancer survival by race and ethnicity: a population-based study, 1973-1999 (United States). *Cancer Causes Control*, **15**, 437-44.

Bray F, Ferlay J, Devesa SS, McGlynn KA, Moller H (2006). Interpreting the international trends in testicular seminoma and non seminoma incidence. *Nat Clin Pract Urol*, **3**, 532-43.

Bray F, Richiardi L, Ekbom A, et al (2006). Do testicular seminoma and nonseminoma share the same etiology? Evidence from an age period- cohort analysis of incidence trends in eight European countries. *Cancer Epidemiol Biomarkers Prev*, **15**, 652-8.

Beard CJ, Travis LB, Chen MH, et al (2013). Outcomes in stage I testicular seminoma: a population-based study of 9193 patients. *Cancer*, **119**, 2771-7.

Chia VM, Quraishi SM, Devesa SS, et al (2010). International trends in the incidence of testicular cancer, 1973-2002. *Cancer Epidemiol Biomarkers Prev*, **19**, 1151-9.

Cost NG (2013). Testicular germ cell tumors Current concepts and management strategies. *Minerva Urol Nefrol*, **65**, 133-55.

Einhorn LH, Williams SD, Loehrer PJ, et al (1989). Evaluation of optimal duration of chemotherapy in favorable-prognosis disseminated germ cell tumors: a Southeastern Cancer Study Group protocol. *J Clin Oncol*, **7**, 387-91.

Franks P, Fiscella, K, Meldrum S (2005). Racial disparities in the content of primary care office visits. *J Gen Intern Med*, **20**, 599-603.

Gilligan TD, Seidenfeld J, Basch EM, et al (2010). American Society of Clinical Oncology Clinical Practice Guideline on uses of serum tumor markers in adult males with germ cell tumors. *J Clin Oncol*, **28**, 3388-404.

Horwich A, Sleijfer DT, Fossa SD, et al (1997). Randomized trial of bleomycin, etoposide, and cisplatin compared with bleomycin, etoposide, and carboplatin in good-prognosis metastatic nonseminomatous germ cell cancer: a Multi institutional Medical Research Council/European Organization for Research and Treatment of Cancer Trial. *J Clin Oncol*, **15**, 1844-52.

Klein EA (1993). Tumour markers in testis cancer. *Urol Clin North Am*, **20**, 67-73.

Kobayashi K, Saito T, Kitamura Y, et al (2013). Oncological outcomes in patients with stage I testicular seminoma and nonseminoma: pathological risk factors for relapse and feasibility of surveillance after orchiectomy. *Diagn Pathol*, **8**, 57.

Mushtaq S, Jamal S, Mamoon N, Akbar N, Khadim T (2007). The pathological spectrum of malignant testicular tumours in northern Pakistan. *J Pak Med Assoc*, **57**, 499-501.

Nguyen MM, Ellison LM (2005). Testicular cancer patterns in Asian-American males: an opportunity for public health education to impact outcomes. *Urol*, **66**, 606-9.

Ondrus D, Hornak M, Matoska J, Kausitz J, Belan V (1992). Primary chemotherapy in the management of low stage (IIA and IIB) non-seminomatous germ cell testicular tumours. *Int Urol Nephrol*, **24**, 299-304.

Pont J, Albrecht W, Postner G, et al (1996). Adjuvant chemotherapy for high-risk clinical stage I nonseminomatous testicular germ cell cancer: long-term results of a prospective trial. *J Clin Oncol*, **14**, 441-8.

Purdue MP, Devesa SS, Sigurdson AJ, McGlynn KA (2005). International patterns and trends in testis cancer incidence. *Int J Cancer*, **115**, 822-7.

Shah MN, Devesa SS, Zhu K, McGlynn KA (2007). Trends in testicular germ cell tumours by ethnic group in the United States. *Int J Androl*, **30**, 206-13.

Stang A, Rusner C, Eisinger B, Stegmaier C, Kaatsch P (2009). Subtype specific incidence of testicular cancer in Germany: a pooled analysis of nine population-based cancer registries. *Int J Androl*, **32**, 306-16.

Sataa S, Nfoussi H, Abaza H, et al (2012). Testicular cancer patterns in Tunisian men: diagnosis problems, pathological types and prognosis. About 41 patients. *Tunis Med*, **90**, 613-8.

Shin YS, Kim HJ (2013).Current management of testicular cancer. *Korean J Urol*, **54**, 2-10.

Travis LB, Fossa SD, Schonfeld SJ, et al (2005). Second cancers among 40,576 testicular cancer patients: focus on long-term survivors. *J Natl Cancer Inst*, **97**, 1354-65.

Tan GH, Azrif M, Shamsul AS, et al (2011). Clinicopathological features and survival of testicular tumours in a Southeast Asian university hospital: a ten-year review. *Asian Pac J Cancer Prev*, **12**, 2727-30.

Van den Belt-Dusebout AW, de Wit R, Gietema JA, et al (2007). Treatment-specific risks of second malignancies and cardiovascular disease in 5-year survivors of testicular cancer. *J Clin Oncol*, **25**, 4370-8.

Wanderas EH, Tretli S, Fossa SD (1995). Trends in incidence of testicular cancer in Norway 1955-1992. *Eur J Cancer*, **31**, 2044-8.

Ward KD, Vander Weg MW, Read MC, Sell MA, Beech BM (2005). Testicular cancer awareness and self-examination among adolescent males in a community-based youth organization. *Prev Med*, **41**, 386-98.

Walschaerts M, Huyghe E, Muller A, et al (2008). Doubling of testicular cancer incidence rate over the last 20 years in southern France. *Cancer Causes Control*, **19**, 155-61.

Zagars GK, Ballo MT, Lee AK, Strom SS (2004). Mortality after cure of testicular seminoma. *J Clin Oncol*, **22**, 640-7.