RESEARCH COMMUNICATION

# Clinicopathological Features and Survival of Testicular Tumours in a Southeast Asian University Hospital: A Ten-year Review

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## Abstract

**Introduction: Testicular cancer mainly affects young men worldwide. There is lack of published data on patients with this malignant condition from the Southeast Asian region. The aim of this study was therefore to determine the clinicopathologic features of testicular cancer patients treated in a Southeast Asian university hospital and their overall survival rate. Materials and methods: This was a retrospective study of testicular cancer patients treated between January 2001 and February 2011. Their epidemiological data, clinical presentation, pathologic diagnosis, stage of disease and treatment were gathered and the overall survival rate of this cohort was analyzed. Results: Thirty-one patients were included in this study. The majority of them were of Malay ethnicity. The average age at presentation was 33.7 years. The commonest testicular cancer was non-seminomatous germ cell tumour, followed by seminoma, lymphoma and rhabdomyosarcoma. More than half of all testicular germ cell tumour (GCT) patients had some form of metastasis at diagnosis. All the patients were treated with radical orchidectomy. Adjuvant chemotherapy was given to those with metastatic disease. Four seminoma patients received radiotherapy to the para-aortic lymph nodes. The 5-year survival rate for all testicular cancers in this cohort was 83.9%. The survival rate was 88.9% in 5 years when GCT were analyzed separately. Conclusion: GCT affects patients in their third and fourth decades of life while lymphoma patients are generally older. Most of the patients treated for GCT are of Malay ethnicity. The majority have late presentation for treatment. The survival rate of GCT patients treated here is comparable to other published series in other parts of the world.**

**Keywords:** Asian - testicular cancer - seminoma - nonseminomatous germ cell tumour - lymphoma, rhabdomyosarcoma

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## Introduction

Cancer is becoming a greater healthcare burden in Malaysia, with an estimated incidence rate of 150 per 100,000 (Lim, 2002). Urological cancers rank highly in this country, with cancers of the urinary bladder and prostate being in the top 10 leading malignancies in males (Hong et al., 2010; Kong et al., 2010). Testicular cancer is a disease of young men (Manecksha, 2009). Although it is not as common as other urological cancers, the economic impact of this disease that afflict men in their most productive years is potentially significant.

There is a lack of published data regarding testicular cancer among men from Malaysia and the Southeast Asian region. Testicular cancer is known to vary in its incidence among different ethnic groups (Bosl, 1997; Gilligan et al., 2010; Purdue et al., 2005). This variation was found even in men from different ethnic backgrounds living in the same region according to one European study (Jack, 2007). The incidence in Asian countries is notably lower than those in Europe (Chia et al., 2010). The multiracial background of Malaysia offers an opportunity to study the variations among men from different ethnicities. It is also essential to understand the disease presentation, pathologic and survival data in this part of the world. This study was conducted to determine the clinicopathologic features and overall survival of testicular cancers treated in a Southeast Asian university hospital.

## Materials and Methods

This was a retrospective study of patients treated for testicular tumours in Universiti Kebangsaan Malaysia Medical Centre (UKMMC) between January 2001 and February 2011. Approval was obtained from the ethics committee of UKMMC. The patients were identified from the admission and operative records of the Urology Unit and Oncology Department of UKMMC. These patients' information and treatment history were traced from the hospital's case notes and computerized information system. Patients who had complete records were included while those with grossly incomplete data were excluded.

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**Table 1. Epidemiological Characteristics According to Histological Type**

| Variables | Non-seminomatous germ cell tumour | Seminoma | Lymphoma | Rhabdomyo-sarcoma |
|---|---|---|---|---|
| Mean (range) age, years | 28.7(18-47) | 31.3(23-39) | 69.7(66-76) | 30.0(30) |
| Ethnicity, N (%): | | | | |
| Malay | 17 (81.0) | 5 (83.3) | 1 (33.3) | 0 (0.0) |
| Chinese | 2 (9.5) | 1 (16.7) | 2 (66.7) | 0 (0.0) |
| Indian | 2 (9.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Myanmarese | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (100.0) |
| Laterality, N (%): | | | | |
| Right | 15 (71.4) | 0 (0.0) | 1 (33.3) | 1 (100.0) |
| Left | 6 (28.6) | 6 (100.0) | 2 (66.7) | 0 (0.0) |

This cohort's epidemiological data such as age and ethnic background were recorded. The clinicopathologic information including presenting symptoms, duration of symptoms, side of tumour, pathologic diagnosis, stage of cancer at presentation and treatment details were gathered. The histopathology results of these tumours were classified according to the 2004 version of the World Health Organization (WHO) histologic classification of testis tumours (Eble et al., 2004) The tumour staging was based on the 7th edition of the American Joint Committee on Cancer's (AJCC) TNM classification of testicular cancer (Edge et al., 2010) It was also noted whether these patient were still being followed up in UKMMC. Those who were no longer being seen in UKMMC were called via telephone to determine the status of their wellbeing. The data were analyzed using IBM SPSS software version 19. The Kaplan-Meier survival analysis was used to calculate survival.

## Results

Thirty-three cases of testicular cancers were treated in UKMMC within the study period. Thirty-one cases were included in this study and 2 cases were excluded due to inadequate data. The majority of patients were of Malay ethnicity while those from Chinese, Indian and Myanmarese ethnic backgrounds made up the rest of this cohort. The average age at which these patients presented was 33.7 years (Table 1).

All the patients presented with the chief complaint of testicular swelling. Seven (22.6%) of them had associated scrotal pain while 1 (3.2%) patient complained of dyspnea from lung metastasis. Just over half of them had right-sided testicular cancer (Table 1). One patient presented to this hospital with a contralateral testicular cancer, having been treated for a right-sided cancer 2 years earlier. The median duration within which they sought treatment after first noticing the testicular swelling was 7 months (range, 1-60 months). Twenty-six (83.9%) patients had gone to see a doctor within 1 year of developing the symptoms. On clinical examination, the mean size of the testicular swellings was 9.5 cm (range, 4.0-18.0 cm) in its largest dimension.

The commonest testicular cancer treated in UKMMC within this period was non-seminomatous germ cell tumours (NSGCT). This was followed by pure seminomas, lymphomas and a single case of rhabdomyosarcoma (Table 2). Histologically, all the testicular lymphomas were diffuse large B-cell lymphomas. On average, NSGCT presented in the third decade of life, while seminomas and rhabdomyosarcoma were diagnosed in the early fourth decade of life. All 3 patients with testicular lymphoma were above 65 years old.

There was a predominance of Malay patients who accounted for more than 80% of all testicular germ cell tumours (GCT) in this cohort. There were more Chinese patients with testicular lymphoma than the other ethnic groups. All the Indian patients in this cohort had NSGCT. The only case of rhabdomyosarcoma was a patient of Myanmarese descent. There appeared to be a tendency for NSGCT to develop in the right testis with a 2.5:1 proportion, whereas seminomas were predominantly seen in the left testis (Table 2).

More than half of all testicular GCT had some form of metastasis at diagnosis. Only 38.1% of NSGCT and 50.0% of seminoma patients came with stage 1 disease, and they were all T1 or T2 diseases. The T3 and T4 cases already had either lymph node or distant metastasis upon diagnosis. Almost half of all NSGCT cases already had metastases beyond the regional lymph nodes at presentation. In contrast, although there was a high percentage of malignant regional lymphadenopathy in seminoma patients, none had distant metastasis (Table 3). Of the 3 lymphoma patients, 2 had stage 1EA disease, and 1 had stage 4 disease. The patient with rhabdomyosarcoma had inguinal lymphadenopathy but no other evidence of metastasis elsewhere.

In this study, the majority of NSGCT patients had elevation of either serum alpha-fetoprotein (AFP) or human chorionic gonadotropin (hCG) at presentation. Only 1 (4.8%) NSGCT patient, who incidentally also had metastatic disease upon diagnosis, did not have any raised tumour markers. Half of seminoma cases had elevated hCG levels and none had raised AFP. Notably, 2 testicular lymphoma cases had elevated levels of AFP (Table 4).

All the patients had radical orchidectomy. Twenty-three patients received post-operative chemotherapy, of which 18 had the bleomycin, etoposide and cisplatin (BEP) regimen for metastatic germ cell tumours. Three patients had a single dose carboplatin (AUC 7) for seminomas. Four seminoma patients received radiotherapy to the para-aortic

**Table 2.The Number of Patients with Raised Serum Tumour Markers According to Histological Type**

| Number of cases (%) with raised tumour markers at presentation | Non-seminomatous germ cell tumour N = 21 (%) | Seminoma N = 6 (%) | Lymphoma N = 3 (%) | Rhabdomyo-sarcoma N = 1 (%) |
|---|---|---|---|---|
| Alpha-fetoprotein | 16 (76.2) | 0 (0.0) | 2 (66.7) | 0 (0.0) |
| Human chorionic gonadotropin | 15 (71.4) | 3 (50.0) | 0 (0.0) | 0 (0.0) |
| Lactate dehydrogenase | 9 (42.9) | 3 (50.0) | 3 (100.0) | 0 (0.0) |

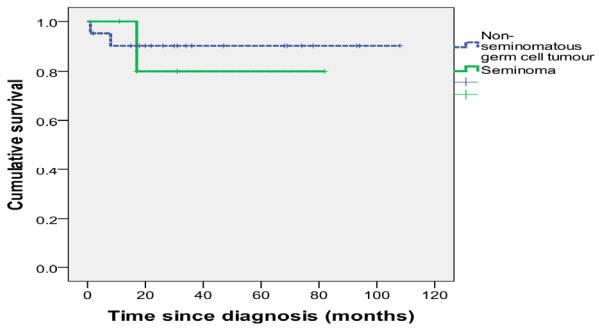


**Figure 1. Survival Rates of Germ Cell Tumours According to Histological Type**

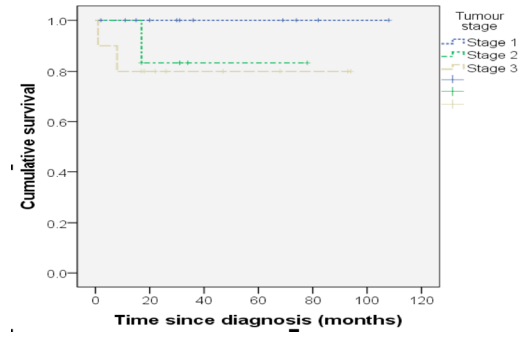


**Figure 2. Survival Rates of Germ Cell Tumours According to the Stage at Presentation**

lymph nodes. One lymphoma patient had the rituximab, dexamethasone, cytarabine and cisplatin (R-DHAP) chemotherapy regimen. The only rhabdomyosarcoma patient in this series had the ifosfomide, mesna, vincristine and actinomycin regimen.

The overall 5-year survival rate of all testicular cancers in this cohort was 83.9%. When testicular GCT were analyzed separately, the overall survival rate was 88.9% in 5 years. NSGCT had a better 5-year survival rate of 90.5% compared to seminomas, which had 83.3% survival in 5 years (Figure 1). All testicular GCT that presented with stage 1 disease survived. Stage 2 and 3 testicular GCT had 5-year survival rates of 83.3% and 80.0% respectively (Figure 2). Only 1 of the 3 testicular lymphoma patients survived the disease. The patient with rhabdomyosarcoma was lost to follow-up soon after chemotherapy.

## Discussion

The results of this study show that testicular cancer is indeed a disease of young men. With the exception of the 3 cases of testicular lymphomas, which unsurprisingly affected older men, the rest of the patients were in the third and fourth decade of life. This trend is similar to studies from other parts of the world (Manecksha, 2009; Park et al., 2008). The age distribution of testicular germ cell tumours also mimic worldwide data where NSGCT and pure seminoma patients present in their twenties and thirties respectively (Bosl, 1997; Manecksha, 2009; Park et al., 2008).

The relatively small number of patients in this cohort reflects the low incidence of this disease in the Asian population. In another Asian study that also covered a 10-year period yielded a similar average of about 24 testicular germ cell tumours from each of the 20 participating hospitals (Park et al., 2008). It is well known that there is a higher incidence of testicular cancer among Caucasian men as compared to Asian or African men (Bosl, 1997; Gilligan et al., 2010; Jack, 2007; Purdue et al., 2005). The present study recruited only Asian men. Interestingly, there seems to be a greater tendency for Malay men to develop testicular GCT than men of other Asian ethnicities. Although the Malays are the predominant ethnic group in this country, they do not account for more than 80% of the population or patients in this hospital. Therefore the large proportion of Malay men with testicular GCT in this cohort is definitely a point to note. A larger sample size might be required to confirm this observation.

In most populations that were studied, there tended to be more seminomas than NSGCT (Park et al., 2008; Purdue et al., 2005). The reverse is true here, where NSGCT accounted for 77.8% of all testicular GCT and 67.8% of all testicular cancers. Seminomas only made up 22.2% of testicular GCT. In this cohort, NSGCT is more likely to present in the right testis while seminomas on the left. This observation could be attributed to the small sample population. Nevertheless, it is remarkable that all 6 seminomas presented in the left testis.

It appears that most patients present rather late for medical treatment in this country. On average they delayed seeking medical treatment until 7 months after the onset of symptoms and when the mean clinical size of the testes was 9.5 cm. This trend contributed to the large proportion of metastatic cases. One of the possible reasons for this phenomenon could be the vast array of alternative medicine available in this region. Traditional healers are readily available in both rural and urban areas. These patients who had to choose between losing a testis to surgery versus non-surgical traditional methods could understandably be swayed towards the latter. Another reason might simply be the lack of knowledge about this disease. Creating awareness amongst the public and teaching them self-testicular examination is the key to early detection and diagnosis.

Serum tumour markers are used as an adjunctive tool for staging, prognosis and monitoring in testicular GCT (Klein, 1993; Gilligan et al., 2010). Their role in other testicular tumours like lymphomas and rhabdomyosarcomas are not defined. AFP and hCG have been recommended as tumour markers for NSGCT (Gilligan et al., 2010). Either 1 or both these tumour markers are reported to be elevated in about 90% of NSGCT (Albers et al., 2005). This pattern holds true in this cohort where 95.2% of NSGCT had either raised AFP or hCG, or both. Remarkably, the only NSGCT patient who did not have raised tumour markers already had metastatic disease. Therefore, tumour markers alone may not be able to predict the stage of the tumour. Seminomas can have raised hCG levels and this was observed in 50% of cases in the current study. None of the seminoma patients here had raised AFP. This is consistent with the fact that seminomas do not produce AFP (Gilligan et al., 2010). LDH is less specific and can be elevated when there is tissue destruction. Nevertheless, it is used to assist in staging and prognosis of testicular GCT (Albers et al., 2005; Gilligan et al., 2010). It was not routinely tested in this study cohort. This shortcoming will be fed back to

the hospital staff to improve our services in the future.

Incidentally, 2 of the 3 testicular lymphoma cases here had raised AFP. This tumour marker can be elevated in conditions such as hepatocellular carcinoma, certain benign liver diseases and various other gastrointestinal cancers. In rare instances, hereditary elevated AFP have been reported (Gilligan et al., 2010). One of these patients was infected with the hepatitis B virus. An ultrasound scan of the liver also showed a small liver nodule in segment VI. However, he passed away before further tests could be performed to ascertain the nature of that nodule. The other patient with raised AFP was found to have fatty liver on computed tomography (CT) scan of the abdomen. There were no other investigative findings to suggest the source of this elevated tumour marker in his case.

There is paucity of survival data on testicular cancers from Asian countries. Most of the data regarding Asian patients were from Western studies that included a small proportion of Asian naturalized citizens. In one American study that looked into survival of testicular GCT, Asian-Americans were noted to have a 5-year overall survival rate of about 88% (Nguyen, 2005). Another study on the American population that included all testicular cancer histology found that the Asians within that population had a survival rate between 92-99% (Biggs, 2004). The 88.9% survival rate of GCT in the present study is similar to the result of the former article.

NSGCT here has a better 5-year survival rate of than seminomas (90.5% vs 83.3%). This is despite the fact that more NSGCT patients presented with metastatic disease than seminomas. Given that nearly all stage 1 GCT patient should survive up to 5 years, the difference in this observation is based on the survival numbers of the metastatic patients (Krege et al., 2008). The survival rate of metastatic NSGCT is between 48-92%. This depends on the prognostic category the patient falls into as defined by the International Germ Cell Cancer Collaborative Group. The survival rates of metastatic seminomas range between 72-86% (IGCCCG, 1997). Perhaps more of the metastatic NSGCT cases in this cohort were in the good prognosis category, therefore giving it a better overall survival rate. Although the sample population of this cohort is too small to verify this difference, it represents one of the very few published survival data from Asian countries.

As expected, there was 100% survival in stage 1 testicular GCT patients. Stage 2 and 3 patients both achieved 80% or more survival rates. It is expected that stage 2 survival rate would be closer to 95% but the result of this study fell short of that mark. However, stage 3 patients seem to do better than the 75% survival rate quoted in previous studies (Ward et al., 2005). It is difficult to pinpoint the reasons for this result but it is likely that they are multifactorial. Genetics, treatment strategies and response to treatment probably interplay.

In conclusion, testicular GCT is a disease of the third and fourth decade of life. Testicular lymphomas affect patients above the age of 65 years. Patients of Malay ethnicity have the most number of testicular GCT compared to other ethnic groups living in this country. A larger sample population is needed to determine if this difference is significant. Most of the patients present rather late for treatment, thus leading to larger proportions of the more advanced stages seen in this study. The survival rates of testicular GCT are comparable to other published series despite having more patients presenting with metastatic disease.

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