REVIEW OF TESTICULAR CANCER FROM 2000 UNTIL 2015 IN HUSM

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ABSTRACT

Background

Testicular cancer is a rare malignancy worldwide, especially among Asians. Even though it is associated with 98% survival, it is mainly a disease of young adults and the incidence is increasing worldwide. There is no reported survival outcome among testicular cancer patients who are treated in Hospital Universiti Sains Malaysia (HUSM), Kubang Kerian. This study aims to analyze the 5-years OS and PFS and associated predictive factor for survival among testicular cancer patients treated in HUSM.

Methodology

This is a retrospective cohort study performed in HUSM. All histopathology confirmed cases of testicular cancer are included. Patient demographics, histopathological findings of the surgical specimen, serum tumor markers, relevant radiological findings, treatment modalities received and patient survival status until 31st July 2017 were reviewed. Kaplan-Meier plot was used to calculate 5-years OS and PFS. Log-rank test and Pairwise comparison were used to calculate the survival difference between two or more groups. Univariate Cox regression analysis was used to analyze the association between predictive factors and survival outcome.

Results

Sixty-two (62) patients were included in the study with a median follow-up of 20.5 months. Median age at diagnosis is 33 years and 95% of patients are from Malay ethnic group. Non-seminomatous Germ-cell tumor (NSGCT) is the most common tumor subgroup comprising 66.1%. More than 65% of patients presented with metastatic disease at presentation. Five-year OS is 68.4%, 64.2% and 33.3% for NSGCT, seminoma and non-germ cell tumor (NGCT)

respectively. Five-year PFS is 51.0%, 41.0% and 26.7% for NSGCT, seminoma and NGCT respectively. Co-existing Diabetes/ hypertension (HR= 3.72, 95% CI: 1.52 – 9.11; p= 0.004), Non-germ cell histology (HR= 4.11, 95% CI: 1.52 – 11.14; p= 0.005) and presence of spermatic cord invasion (HR= 3.30, 95% CI: 1.12 – 9.77; p=0.031) are associated with poor OS. Age group 51 to 60 years is the only predictive factor for poorer OS (HR= 9.65, 95% CI: 2.05 – 45.5; p= 0.004) and PFS (HR= 10.25, 95% CI: 2.29 – 45.9; p= 0.002).

Conclusion

Testicular cancer is a rare disease which mainly affects young Malay males. NSGCT is the commonest subtype encountered and is associated with the highest OS and PFS. Age 51 to 60 is associated with worse OS and PFS. Meanwhile, co-existing Diabetes or hypertension, non-Germ cell histology, and presence of spermatic cord invasion are predictors of poor OS.

ABSTRAK

Latar Belakang

Kanser testis adalah kanser yang jarang berlaku terutamanya dalam kalangan penduduk Asia. Kanser tersebut dikaitkan dengan kelangsungan hidup yang tinggi tetapi kerap berlaku dalam golongan muda. Insiden kanser testis juga kian meningkat di seluruh dunia. Tidak ada kajian yang melaporkan berkaitan kelangsungan hidup pesakit-pesakit kanser testis yang dirawat di Hospital Universiti Sains Malaysia (HUSM), Kubang Kerian. Kajian ini bertujuan untuk menganalisa "Kadar Kelangsungan Hidup (OS)" dan "Kadar Kelangsungan Hidup Bebas Penyakit (PFS)" bagi tempoh 5 tahun serta faktor-faktor yang meramal kelangsungan hidup dalam kalangan pesakit kanser testis.

Metodologi

Kajian kohort secara retrospektif ini dijalankan di HUSM dan telah mengkaji semua kes kanser testis yang telah disahkan melaui pemeriksaan histo-patologi. Maklumat yang diteliti adalah termasuk demografi pesakit, penemuan histopatologi spesimen pembedahan, aras serum penanda tumor, penemuan radiologi yang relevan, modaliti rawatan yang diterima dan status kelangsungan pesakit sehingga 31 Julai 2017. Plot Kaplan-Meier digunakan untuk menghitung OS dan PFS 5-tahun. Ujian "Log-rank" dan "Pairwise comparison" diguna pakai untuk menganggar perbezaan kelangsungan di antara dua atau lebih kumpulan. Kaedah regresi Cox digunakan untuk menganalisa hubungan antara faktor peramal dan kelangsungan hidup.

Keputusan

Enam puluh dua (62) pesakit telah dikaji dan menerima rawatan susulan bagi tempoh median 20.5 bulan. Umur median pesakit ketika didiagnosa kanser adalah 33 tahun. 95% daripada pesakit merupakan daripada kumpulan etnik Melayu. Tumor "Non-seminomatous Germ cell" (NSGCT) adalah jenis tumor yang paling kerap dihadapi. Manakala 65% daripada pesakit telah didiagnosa dengan penyakit peringkat metastatik. Kadar OS 5-tahun adalah 68.4%, 64.2% dan 33.3% untuk tumor NSGCT, seminoma dan tumor "non-germ cell" (NGCT). PFS 5 tahun pula adalah 51.0% untuk NSGCT, 41.0% untuk seminoma dan 26.7% untuk NGCT. Penyakit Diabetes mellitus/ darah tinggi (HR = 3.72, 95% CI: 1.52 - 9.11; p= 0.004), histologi "Non-germ cell" (HR= 4.11, 95% CI: 1.52 – 11.14; p= 0.005), dan penglibatan salur spermatik (HR = 3.30, 95% CI: 1.12 - 9.77: p= 0.031) dikaitkan dengan OS yang rendah. Kumpulan umur 51 hingga 60 tahun adalah satu-satunya faktor ramalan bagi kedua-dua OS (HR = 9.65, 95% CI: 2.05 - 45.5; p= 0.004) dan PFS yang rendah (HR= 10.25, 95% CI: 2.29 – 45.9; p= 0.002).

Kesimpulan

Kanser testis adalah penyakit yang jarang dihadapi tetapi memberi kesan terutamanya kepada lelaki Melayu muda. NSGCT adalah jenis yang paling kerap yang dihadapi dan menunjukkan kadar kelangsungan paling tinggi dalam kalangan penghidap kanser testis. Pesakit berumur 51 hingga 60 dikaitkan dengan kedua-dua OS and PFS yang lebih rendah. Sementara itu, pesakit Diabetes atau darah tinggi, histologi jenis "Non-germ cell" dan penglibatan salur spermatik akan meramal OS yang lebih rendah.

1.1 INTRODUCTION

Testicular cancer is a rare urology malignancy that affects 0.4% of all men (National Cancer Institute, 2016) and comprises 1% of all newly diagnosed malignancy in adults. Incidence of testicular cancer in Asians are reported 0.7 to 1.3 per 100,000 population. Incidence of testicular cancer is highest among Scandinavian which is reported around 2.9 to 10.3 per 100,000 population (Garner *et al*., 2005; Manecksha & Fitzpatrick, 2009). Interestingly, most of testicular cancers are diagnosed in patients in the prime age of 35 years old or younger. 5-year Overall Survival is excellent ranging from 95 to 98% and mortality from testicular cancers are rare (Garner *et al*., 2005; Omar & Tamin, 2011; Australian Institute of Health and Welfare, 2014; Cancer Research UK, 2016; National Cancer Institute, 2016).

1.1 LITERATURE REVIEW

1.1.1 Histopathological Types: Primary testicular cancers are classified according to World Health Organization classification into Germ Cell (GCT) and Non – Germ Cell Tumor (NGCT). GCTs are more common with a frequency of 80%. It can further be sub-divided to seminoma and non-seminoma. On the other hand, NGCTs includes sex cord cells tumors, carcinoid tumors, tumors of ovarian epithelial type, hematopoietic tumors, and mesenchymal tumors of spermatic cord or para-testicular tissues. Testicular cancers may present as pure single histology type or mixed histology subtypes (Sesterhann & Davis, 2004; Eble *et al.*, 2004; Chalya *et al*., 2014).

1.1.2 Presenting Symptoms: Patient commonly presents with the complaint of unilateral painless testicular swelling. Other common symptoms at presentation include scrotal heaviness, testicular pain, abdominal swelling and primary infertility. (Thornhill *et al.*, 1986; Khan & Protheroe, 2007; Chalya *et al.*, 2014).

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1.1.3 Risk Factors: Previous observational studies have identified certain risk factors for the development of testicular cancer:

1) Cryptorchidism/ mal-descent testis: Patients with cryptorchidism are 7 to 9 times more likely to be diagnosed with testicular cancer (Pinczowski *et al*., 1991; Moller & Skakkebæk, 1996; Swerdlow *et al*., 1997)
2) Testicular carcinoma in-situ: Skakkebæk *et al*. (1972) observed patients with atypical germ cell neoplasia during testicular biopsy for infertility and who was later diagnosed with testicular carcinoma
3) Sub-fertility: A man with children is 40% less likely to be diagnosed with testicular cancer compared to a man without child (Møller & Skakkebaek, 1999; Jacobsen *et al*., 2000)
4) Previous history of testicular malignancy: Patients with testicular cancer are 22 to 27 times more likely to develop a second primary testicular cancer in the contralateral testis (Osterlind *et al*., 1991; Colls *et al*., 1996; Che *et al*., 2002)
5) Paternal or siblings with testicular cancer: Twins to a patient with testicular cancer is 37 times more likely to be diagnosed with testicular cancer. The increase in incidence also observed among non-twin brothers (8 to 9 times increased in relative risk) and an offspring to a father with testicular cancer (4 times increase risk) (Forman *et al*., 1992; Swerdlow *et al*., 1999; Chalya *et al*., 2014).

1.1.4 Prognostic Factors: Factors which are identified contributing to poor patient outcome include presence of tumor larger than 4 cm, tumor invasion of rete testis (Warde *et al*., 2002), presence of lympho-vascular invasion, embryonal histology and trans-scrotal involvement

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(Nicolai & Pizzocaro, 1995; Colls *et al.*, 1999; International Prognostic Factors Study Group, 2010).

1.1.5 Role of Ultrasonography of Testis: Ultrasonography of both testes is the first choice of imaging modality in suspected testicular cancer. Ultrasonography is safe, radiation-free and is widely available. It is a relatively inexpensive modality to accurately differentiate between intra- and extra-testicular mass, vascularity, synchronous tumor of the contralateral testis and identify different tumor subtypes (Lung & Sidhu, 2011; Kreydin *et al*., 2013).

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1.1.6 Role of Tumor Markers: Tumor markers for testicular cancers are readily available and proven for diagnosis and management of GCTs since the 1980s (Light, 1985). Tumor markers are used to diagnose, stage, prognosticate, decide adjuvant therapy, monitor response to treatment and monitor for recurrence (Light, 1985; Leman & Gonzalgo, 2010; Milose *et al*., 2012; Fizazi *et al*., 2015). Baseline tumor markers should be obtained prior to orchidectomy and repeated until tumor markers normalize. Elevated tumor markers are directly proportionate to tumor burden (Milose *et al.*, 2012). Persistently elevated tumor markers after surgery suggest the presence of residual disease or metastases.

1) Alpha-fetoprotein (AFP): AFP is a glycoprotein molecule which is synthesized in the fetal yolk sac, liver and intestine. Half-life of AFP is 5 to 7 days. It is raised in embryonal, teratoma and yolk sac tumors. AFP is not produced in pure seminoma or choriocarcinoma (Light, 1985; Milose *et al*., 2012).
2) β-Human Chorionic Gonadotrophin (β-HCG): β-HCG is a glycoprotein molecule composed of an α and a β-subunit. β-HCG is produced by syncytiotrophoblast giant cells. Half-life of β-HCG is 24 to 36 hours. This tumor marker is raised in seminoma, choriocarcinoma and embryonal tumors (Light, 1985; Milose *et al.*, 2012)

3) Lactate dehydrogenase (LDH): LDH is a cellular enzyme normally produced in muscle cells, kidney, brain and liver. There are multiple LDH iso-enzymes with variable half-life. LDH is elevated in up to 40-60% of testicular GCTs and levels more than 2000 U/L is suggestive of bulky disease (Milose *et al.*, 2012).

1.1.7 Disease Staging: The American Joint Committee on Cancer (AJCC) TNM staging is used to define the extent and spread testicular cancer to lymph nodes and distant organs. Staging of cancer helps to decide appropriate treatment based on collective outcomes of similar groups (AJCC, 2010). The International Germ Cell Cancer Collaborative Group (IGCCCG) prognosis system is used to classify metastatic GCTs (Mead, 1997). Newer prognosticating models has been developed to identify specific poor prognosis groups which may not respond to standard chemotherapy (Bhala *et al*., 2004; Fizazi *et al.*, 2004; Sammler *et al*., 2008; International Prognostic Factors Study Group, 2010; Kojima *et al*., 2015).

TNM staging for testicular cancer adapted from AJCC TNM 7th Edition

Primary Tumor	
pTx	Primary tumor cannot be assessed.
pT0	No evidence of primary tumor.
pTis	Intratubular germ cell neoplasia (testicular intraepithelial neoplasia).
pT1	Tumor limited to testis and epididymis without vascular/ lymphatic invasion. Tumor may invade tunica albuginea but not tunica vaginalis.
pT2	Tumor limited to testis with vascular/ lymphatic invasion. OR tumor extending through tunica albuginea with involvement of tunica vaginalis.
pT3	Tumor invades spermatic cord with/ without vascular invasion.
pT4	Tumor invades scrotum with/ without vascular invasion.

<table>
<tr><td>Regional lymph nodes</td><td></td></tr>
<tr><td>Nx</td><td>Regional lymph nodes cannot be assessed</td></tr>
<tr><td>N0</td><td>No regional lymph nodes metastases</td></tr>
<tr><td>N1</td><td>Metastases with a lymph node mass 2 cm or less in greatest diameter, OR multiple lymph nodes, none more than 2cm in diameter</td></tr>
<tr><td>N2</td><td>Metastases with a lymph node mass more than 2cm but not more than 5cm in diameter, Or multiple lymph nodes, any one mass more than 2 cm but not more than 5 cm in diameter.</td></tr>
<tr><td>N3</td><td>Metastases with a lymph node larger than 5 cm in diameter.</td></tr>
<tr><td>Distant metastases</td><td></td></tr>
<tr><td>Mx</td><td>Distant metastases cannot be assessed</td></tr>
<tr><td>M0</td><td>No distant metastases</td></tr>
<tr><td>M1a</td><td>Distant metastases to non-regional lymph node or lungs</td></tr>
<tr><td>M1b</td><td>Distant metastases to other site(s)</td></tr>
<tr><td>Serum tumor markers</td><td></td></tr>
<tr><td>Sx</td><td>Serum tumor markers not available/ not performed</td></tr>
<tr><td>S0</td><td>Serum tumor marker within normal limits</td></tr>
<tr><td></td><td>
<table>
<tr><th>AFP (ng/ml)</th><th>B-HCG (mIU/ml)</th><th>LDH (U/L)</th></tr>
<tr><td>S1</td><td><1000</td><td><5000</td><td><1.5 x Normal</td></tr>
<tr><td>S2</td><td>1000 - 10000</td><td>5000 - 50000</td><td>1.5 – 10 x Normal</td></tr>
<tr><td>S3</td><td>>10000</td><td>>50000</td><td>>10 x Normal</td></tr>
</table>
</td></tr>
<tr><td>Stage</td><td></td></tr>
<tr><td>Stage I</td><td>Any pT N0 M0 Sx</td></tr>
<tr><td>IA</td><td>pT1 N0 M0 S0</td></tr>
<tr><td>IB</td><td>pT2-4 N0 M0 S0</td></tr>
<tr><td>IS</td><td>Any pT N0 M0 S1-3</td></tr>
<tr><td>Stage II</td><td>Any pT N1-3 M0 Sx</td></tr>
</table>

IIA	Any pT N1 M0 S0 OR Any pT N1 M0 S1
IIB	Any pT N2 M0 S0 OR Any pT N2 M0 S1
IIC	Any pT N3 M0 S0 OR Any pT N3 M0 S1
Stage III	Any pT Any N M1 Sx
IIIA	Any pT Any N M1a S0 OR Any pT Any N M1a S1
IIIB	Any pT N1-3 M0 S2 OR Any pT Any N M1a S2
IIIC	Any pT N1-3 M0 S3 OR Any pT Any N M1a S3 OR Any pT Any N M1b Any S

1.1.8 Treatment options

1.1.8.1 High orchidectomy: All patient with suspected testicular cancer should undergo radical high orchidectomy via an inguinal exploration. A skin incision is made in the inguinal region 3 cm above the inguinal skin fold and the subcutaneous fascia divided. The spermatic cord is isolated at the external inguinal ring using blunt dissection, the testis within the tunica is separated from the scrotum. The testis is free to be examined after division of the gubernaculum. After the surgeon confirms the presence of testicular tumor, the external oblique aponeurosis is divided until exposing the internal inguinal ring. The spermatic cord is clamped as high as possible and the spermatic cord structures are individually ligated. After the cord is divided, care is taken to avoid tumor spillage. The wound is washed with distilled water for irrigation and the surgical layers are closed in layers (Pizzocaro & Guarneri, 2009). Testis-sparing surgery is a safe alternative and may be considered in patients with synchronous bilateral tumor, metachronous contralateral tumor or tumor smaller than 30% of the testicular volume (Weissbach, 1995; Brunocilla *et al*., 2013). Intraoperative frozen section is also an option if there is doubt regarding the testicular mass prior to radical orchidectomy. Trans- scrotal biopsy is contraindicated in suspected testicular cancer.

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1.1.8.2 Retroperitoneal Lymph Node Dissection (RPLND): RPLND was classically indicated in all testicular cancers patient for staging lymph node metastases and surgical cure of retroperitoneal disease. Nerve sparing techniques was introduced to improve the morbidity of RPLND complications including erectile dysfunction. Current techniques involve the use of laparoscopic or robotic nerve sparing RPLND and is indicated for residual retroperitoneal tumor post chemotherapy (Ranieri *et al.*, 1994; Klein, 2000; Nonomura *et al.*, 2002; Mitsinikos *et al.*, 2012; Hillelsohn *et al.*, 2012; Hugen *et al.*, 2016).

1.1.8.3 Chemotherapy: Platinum-containing chemotherapy has played an important role in the management of testicular GCTs. Einhorn (1977) reported 85% cure rate in treating metastatic testicular cancer with Cisplatin-Vinblastine-Bleomycin (PVB) regime. Substitution of Vinblastine with Etoposide shows improved survival with a better toxicity profile. This has led to the Bleomycin-Etoposide-Cisplatin (BEP) regime which is the standard first line chemotherapy regime in the management of Stage II and III testicular GCTs (Peckham *et al.*, 1983; Williams *et al.*, 1987). Patients who receive BEP chemotherapy has shown complete cure rates up to 95% and 90% 5-year survival (Mead, 1997).

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Study by Einhorn et al (1989) found that among metastatic testicular cancers with IGCCCG favorable prognosis group, 3 cycles of BEP chemotherapy is the optimum duration. Intermediate and poor prognosis metastatic GCTs are given an extra cycle of BEP regime (Einhorn *et al.*, 1989; Einhorn, 2006). Cisplatin-based chemotherapy has been associated with severe oto-, neuro- and nephro-toxicity. A study in Germany showed that substituting cisplatin for Carboplatin (JEB) regime having comparable response rate to BEP (Pinkerton *et al.*, 1990; Bokemeyer *et al.*, 1996). However, there is a significant risk of late relapse (32% vs 13%, p= 0.03). Another identified complication of Bleomycin is the risk of pulmonary toxicity. A study

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by de Wit *et al.* (1997) has shown that patients who receive Etoposide-Cisplatin (EP) regime are less likely to achieve complete pathological response compared to patients who receive BEP (87% vs 95%, p= 0.0075). However, both groups show similar Overall Survival and Disease Free Progression (de Wit *et al.*, 1997). Attempts to improve the standard chemotherapy regime was largely unsuccessful. The addition of Paclitaxel to BEP (BEP-T) shows higher complications but did not show survival benefit (de Wit *et al.*, 2012). Substitution of Bleomycin with Ifosfamide in Cisplatin-Ifosfamide-Etoposide (VIP) had higher rates of toxic complications compared to BEP. VIP and other regimes containing Ifosfamide and/ or Paclitaxel are used as second and third-line chemotherapy or for salvage chemotherapy in recurrent metastatic testicular cancers (Loehrer *et al*., 1986; Nichols *et al*., 1998; Motzer *et al*., 2000; Kondagunta *et al*., 2005). High-dose chemotherapy (HDCT) with autologous stem cell rescue offers up to 27% cure among patients with metastatic testicular GCTs refractory to second or third line chemotherapy (Einhorn *et al.*, 2007). However, HDCT is associated with high toxicity rates and morbidities. Fizazi *et al.* (2015) studied into intensification of chemotherapy dosage among patient who did not show immediate response by monitoring serial tumor marker decline rates. Patient who were subjected to dose intense chemotherapy shows improved PFS and is more likely to avoid HDCT compared to patients who receive standard dose chemotherapy (Fizazi *et al.*, 2015).

1.1.8.4 Radiotherapy (RT): Adjuvant RT reduces the relapse rate for Stage I seminomatous GCT from 14% to 4% compared to patients undergoing active surveillance alone. However, patients who received adjuvant RT are 2 times more likely to have a second malignancy in the contralateral testis compared with patients who undergo orchidectomy alone (Travis *et al*., 2005). Alternatively, Carboplatin 7 Area Under the Curve (AUC) achieved similar reduction in

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risk of testicular cancer relapse in Stage I seminoma and 80% less likely of developing a second malignancy in the contralateral testis (Oliver *et al*., 2011).

1.1.9 Local Studies: In Malaysia, an average of 19000 newly diagnosed cancer cases was reported annually in 2006 and 2007 with men comprising 45% of the cases. Testicular cancers make up 1% of all newly diagnosed malignancies in Malaysian men. In 2006, 104 new cases of testicular cancer were reported and another 74 new cases were reported the following year. The commonest ethnic group diagnosed with testicular cancer is the Malay ethnic group (n=99), followed by Chinese (n=46) and Indian (n=11). 75% of testicular cancer cases were diagnosed among 15 to 50-years of age. Seminoma (35%) was the commonest single histology tumor subtype in 2007 (National Cancer Registry, 2006; Omar & Tamin, 2011).

Tan *et al*. (2011) reported similar Malay ethnic predominance from their 10-years retrospective study based in a tertiary center in the national capital of Kuala Lumpur. The author reported 33 cases of testicular cancers treated in the study period with 87% comprised of GCTs. However, in their series, they encountered more NSGCTs (n=21) compared to seminomas (n=6). NSGCTs were diagnosed with a mean age of 28.7 years where as seminoma was diagnosed at a mean age of 31.3 years. Cases of primary testicular lymphomas were diagnosed among older patients with mean age of 69.7 years. Seventy percent of GCTs presented with raised serum tumor markers either AFP, β-HCG or LDH. All cases of testicular lymphoma presented with raised LDH. The single case of rhabdomyosarcoma of testis was negative for all three serum tumor markers. All of the patients had high radical orchidectomy and majority of them received adjuvant chemotherapy. The authors reported 5-year OS of 83.9% in their series. However, the authors did not elaborate regarding patient stage at diagnosis, prognostic factors, chemotherapy

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regimes used, the response of the tumor to the chemotherapy, salvage treatment offered, complications after treatment and duration of follow up (Tan *et al*., 2011).

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1.2 RATIONALE OF STUDY

This study aims to bridge the lack of local data on the testicular cancer cohort. This retrospective cohort study intends to identify patients' demographics, common presenting symptoms, clinical-pathological characteristics, 5-year OS and PFS. This study was planned to identify whether factors such as age at presentation, co-existing morbidities, site of primary tumor, histology subtype, presence of lympho-vascular invasion, presence of spermatic cord invasion, site of tumor metastases and disease staging at diagnosis are associated with patient outcome (OS and PFS). This study was also designed to study the types of treatment modalities given and to identify common complications of treatment. This study may identify specific target population factors which may contribute to the local testicular cancer patient survival and act as a reference for future audits.

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2. STUDY PROTOCOL

2.1 DOCUMENTS SUBMITTED FOR ETHICAL APPROVAL

STUDY PROTOCOL PROPOSAL

REVIEW OF TESTICULAR CANCER FROM 2000 TO 2015 IN HUSM

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MPM 37639

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INTRODUCTION

Testicular cancer is a rare malignancy that affects approximately 0.4% of all men (National Cancer Institute, 2016) with a reported incidence of 1% of newly diagnosed malignancy in adults. Most testicular cancers are diagnosed in patients younger than 35 years old. 5-year Overall Survival has been reported excellent ranging from 95 to 98% and mortality from the disease is rare (Garner et al., 2005; Omar & Tamin, 2011; Australian Institute of Health and Welfare, 2014; Cancer Research UK, 2016; National Cancer Institute, 2016).

Testicular cancer can be classified according to Germ Cell (GCT) and Non – Germ Cell Tumor (NGCT). GCTs are the commoner of the two with a frequency of 80%. GCTs as the name implies originates from germ cell and can be sub-classified to seminoma and non-seminoma. On the other hand, NGCT may arise from sex cord cells, hematological, epithelial or mesenchymal origin. Testicular cancer also presents with mixed histology subtypes (Eble et al., 2004; Sesterhenn & Davis, 2004; Chalya et al., 2014).

Patient most commonly presents with a complaint of unilateral painless testicular swelling. Other common symptom at presentation includes scrotal heaviness and testicular pain (Thornhill et al., 1986; Khan & Protheroe, 2007; Chalya et al., 2014).

Previous studies have identified certain risk factors for developing testicular cancer: cryptorchidism (Pinczowski et al., 1991; Moller & Skakkebæk, 1996; Swerdlow et al., 1997), testicular carcinoma in-situ (Skakkebæk, 1972; Moller & Skakkebæk, 1996; Rørth et al., 2000), sub-fertile men (Møller & Skakkebaek, 1999; Jacobsen et al., 2000), previous history of testicular malignancy (Osterlind et al., 1991; Colls et al., 1996; Che et al., 2002), paternal or siblings with testicular cancer (Forman et al., 1992; Chalya et al., 2014). Factors which are

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identified as poor prognostic factors include presence of tumor sized more than 4 cm, invasion of rete testis (Warde et al., 2002), presence of lymphovascular invasion, embryonal histology and trans-scrotal involvement (Nicolai & Pizzocaro, 1995; Colls et al., 1999; International Prognostic Factors Study Group, 2010).

Once testicular cancer is clinically suspected, ultrasonography of both testes will be done along with serum tumor markers (α-Fetoprotein, β-Human Chorionic Gonadotrophin, and Lactate dehydrogenase). Ultrasonography of the testes is widely available and it is a relatively inexpensive modality to accurately differentiate between intra- and extra-testicular mass, vascularity, a synchronous tumor of the contralateral testis and differentiate tumor subtypes (Lung & Sidhu, 2011; Kreydin et al., 2013).

Testicular cancers are surgically approached via an inguinal incision, the testis is exteriorized within its intact tunica layer and the spermatic cord ligated and transected at the deep inguinal ring. A prosthesis may be placed into the scrotum in the same surgical setting. Once the histopathological diagnosis is confirmed, patients will undergo further imaging studies to complete clinical staging. The American Joint Committee on Cancer (AJCC) TNM staging is commonly used to define the extent and spread of the tumor to lymph nodes and distant organs. Staging of cancer helps in decision making on appropriate treatment based on collective outcomes of similar groups (AJCC, 2010). The International Germ Cell Cancer Collaborative Group (IGCCCG) is also a widely used prognostic system specifically for metastatic GCTs (Mead, 1997). Newer prognosticating models has been developed and proposed by multiple researchers to identify poor prognosis groups which may not respond to standard therapy (Bhala et al., 2004; Fizazi et al., 2004; Sammler et al., 2008; International Prognostic Factors Study Group, 2010; Kojima et al., 2015).

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Platinum-containing chemotherapy played a tremendous role in the management of metastatic testicular GCTs. Einhorn reported 85% cure rate in treating metastatic testicular cancer with Cisplatin-Vinblastine-Bleomycin (PVB) regime (Einhorn, 1977). Substitution of Vinblastine with Etoposide has shown improved survival with a better toxicity profile. This leads to the Bleomycin-Etoposide-Cisplatin (BEP) regime which is even currently used as first line chemotherapy (Peckham et al., 1983; Williams et al., 1987). Among metastatic GCTs, the patient achieved up to 90% cure rate and survival (Mead, 1997). The chemotherapy duration was optimized to 3 cycles for good prognosis in metastatic testicular cancer to reduce toxic complications (Einhorn et al., 1989; Einhorn, 2006).

Bleomycin carries the risk of pulmonary toxicity. However, chemotherapy regimes which attempted to exclude Bleomycin shows less favorable outcome (de Wit et al., 1997). Attempts to improve the standard chemotherapy regime was largely unsuccessful. The addition of Paclitaxel to BEP (BEP-T) do not show any survival benefit (de Wit et al., 2012). Meanwhile, substitution of Bleomycin with Ifosfamide in Cisplatin-Ifosfamide-Etoposide (VIP) has higher toxic complications compared to BEP. VIP and other regimes containing Ifosfamide and/ or Paclitaxel are used as second-line chemotherapy or for salvage therapy in recurrent metastatic testicular cancers (Loehrer et al., 1986; Nichols et al., 1998; Motzer et al., 2000; Kondagunta et al., 2005). High-dose chemotherapy (HDCT) with autologous stem cell rescue offers up to 27% cure among patients not responsive to second or third line chemotherapy (Einhorn et al., 2007). However, HDCT is recommended for refractive metastatic testicular GCTs is due to higher toxicity and morbidities. The latest study into chemotherapy agent intensification may avoid poor prognosis patients undergo HDCT. A patient who received dose-dense chemotherapy has better PFS and

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lower risk for requiring salvage HDCT compared to patients on standard dose chemotherapy (Fizazi et al., 2015).

In Malaysia, an average of 19000 newly diagnosed cancer cases was reported annually in 2006 and 2007 with men comprising 45% of the cases. The incidence of testicular cancer among Malaysian men comprises 1% of all newly diagnosed cases. 104 new cases of testicular cancer were reported in 2006 and another 74 new cases were reported the following year.

The commonest ethnic group diagnosed with testicular cancer is the Malay ethnic group (n=99), followed by Chinese (n=46) and Indian (n=11). Almost 75% of cases are diagnosed among 15 to 50-years of age. The commonest single histology tumor subtype reported in 2007 was seminoma (35%). (National Cancer Registry, 2006; Omar & Tamin, 2011).

Tan *et al.* (2011) reported similar Malay ethnic predominance and relatively young mean age at diagnosis. However, in their series, they encountered more NSGCTs compared to seminomas. The authors reported 5-year OS of 83.9% which is lower compared to larger published series. However, they did not elaborate regarding patient stage at diagnosis, prognostic factors, chemotherapy regimes used, the response of the patient to the treatment and whether any salvage treatment was offered (Tan *et al.*, 2011).

This study aims to bridge this lack of local data on the local testicular cancer cohort. This retrospective review intends to identify local patients' demographics, the proportions of different histological testicular cancer subtypes and 5-year OS. We also plan to identify individual risk factors and prognostic factors which may contribute to a patient's outcome. The study is also designed to collect the frequency of different treatment modalities offered to patients and the frequency of complications. This study may identify specific target population factors which

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may contribute to these patients' outcome and act as a reference for future audits.

RESEARCH QUESTIONS

1. What is the prevalence of testicular cancer in HUSM from 2000 until 2015?
2. What are the demographics and commonest presentation of testicular cancer?
3. What is the most common histological subtype of testicular cancer encountered in HUSM?
4. What is the most common stage at diagnosis of testicular cancer presented in HUSM?
5. What is the Overall Survival and Progression Free Survival for these patients?
6. Is there an association between prognostic factors (age, duration of symptoms, site of cancer, histological subtype, lymphovascular invasion, the size of primary tumor, spermatic cord involvement, site of metastases, staging of the primary tumor and co-morbids) with Overall Survival and Progression-Free Survival?
7. What is the commonest chemotherapy regime used in HUSM for the treatment of testicular cancer?
8. What is the frequency of complications of chemotherapy?

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OBJECTIVE

- **General objective**
    - To study the prevalence, outcome and possible prognostic factors among patients diagnosed with testicular cancer in HUSM
- **Specific objectives**
    - To describe the demographics of testicular cancer patients treated in HUSM from 2000 until 2015
    - To identify the commonest presentation of patients diagnosed with testicular cancer in HUSM
    - To describe the proportions of different histology subtypes and staging at diagnosis of testicular cancer patients presented in HUSM
    - To calculate the Overall Survival and Progression Free Survival for testicular cancer patients in HUSM
    - To identify the association between prognostic factors and patients' outcome (Progression Free Survival and Overall Survival)
    - To describe the proportions of chemotherapy regimes in the management of testicular cancer in HUSM
    - To describe the proportions of complications of chemotherapy

METHODOLOGY

Research Design

This study is a retrospective cohort study involving patients diagnosed with testicular cancer in HUSM.

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Study Area

Data collection will be done in HUSM.

Source Population

- **Reference population**
    - Testicular cancer patients attended in HUSM
- **Target population**
    - Testicular cancer patients treated in HUSM from 1st January 2000 until 31st December 2015
- **Sampling frame**
    - HUSM admission register for testicular cancer

Subject Criteria

- **Inclusion criteria**
    - Patients with histopathological (HPE) confirmed diagnosis of testicular cancer
    - Patients treated in HUSM during the study period
- **Exclusion criteria**
    - Incomplete or missing case notes

- Patients diagnosed with testicular cancer and other concomitant malignancy

Sampling Method

Convenience sampling. Case folders will be traced from HUSM record unit until the calculated sample size is achieved.

Sample Size

Median survival time in control group formula (m1)

m1= t log e (1/2)/ log e (p)

p = probability of subject survives until time (t)

Tan GH et al (2011) reported 84% 5-years survival. Thus,

m1 = 60 log e (1/2)/ log e (0.84) = 36 months

Median survival time in experimental group (m2)

de Wit et al (1997) reported 89% 3-years survival

m2 = 36 log e (1/2)/ log e (0.89) = 20 months

Sample size calculations via PS Power and Sample Size Calculation Software Version 3.0.

Parameters	Value
α	0.05
Power	0.8
Median survival time 1 (m1)	36
Median survival time 2 (m2)	20

Accrual time in which patients are recruited (months)	180
Additional follow up time after end of recruitment (months)	60
Ratio of control to experiment	1

Sample size required with 10% drop out is 60 patients.

Data Collection

Information collected from case notes will be filled in written or electronic data collection sheet.

Definition of Terms Employed in this Study

- "Overall Survival" is defined as the length of time from the start of treatment or the date of diagnosis for a disease, such as cancer, that patients diagnosed with the disease are still alive. Usually expressed as 5-year Overall Survival. The date of starting primary chemotherapy is taken as the date of starting treatment (National Cancer Institute).
- "Progression Free Survival" is defined as the length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse. Measured from the start of primary chemotherapy until the onset of disease progression (biochemical/ radiological relapse, disease progression or death) (National Cancer Institute).

Data Analysis

Data will be entered and analyzed using SPSS version 22. Descriptive statistics will be used to summarize the socio-demographic characteristics of subjects. Numerical data will be presented as mean (Standard Deviation) or median (Inter-Quartile Range) based on their normality distribution. Categorical data will be presented as frequency and percentage.

Kaplan-Meier plot or Life Table Method will be used to calculate mean and median Overall Survival and Progression Free Survival.

Association between prognostic factors and survival will be analyzed with Simple Cox Regression.

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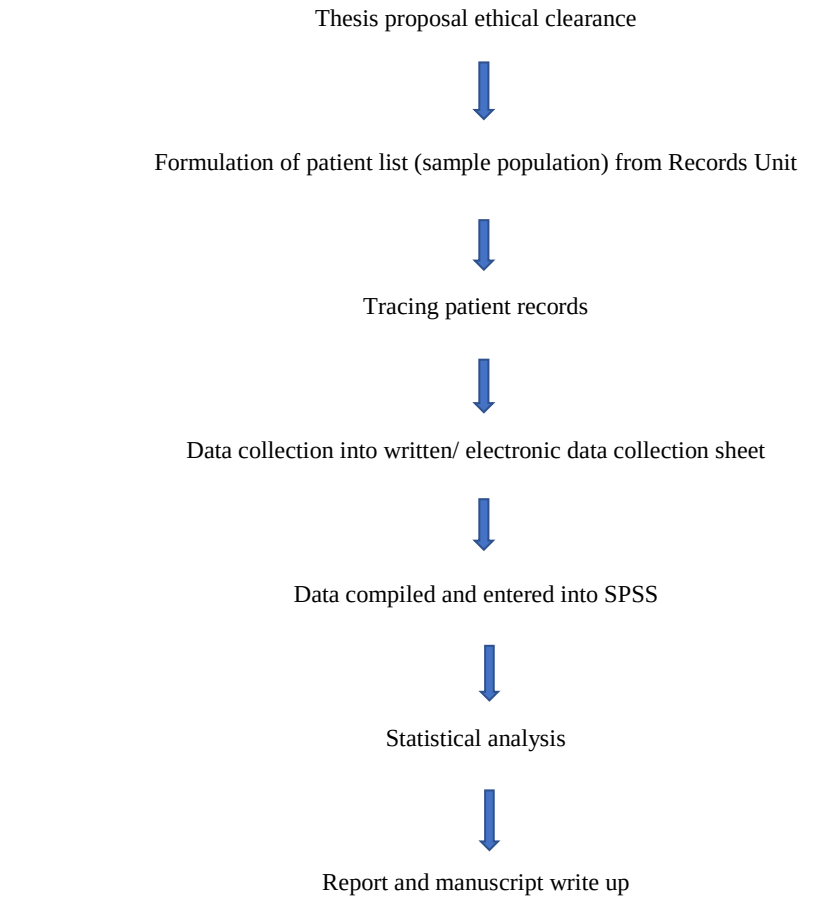
Flow Chart


Thesis proposal ethical clearance
Formulation of patient list (sample population) from Records Unit
Tracing patient records
Data collection into written/ electronic data collection sheet
Data compiled and entered into SPSS
Statistical analysis
Report and manuscript write up

Gantt's Chart

	2016							2017						
Action	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul
Literature review														
Proposal preparation														
Proposal presentation					**12/10**									
Ethical approval														
Data collection														
Data analysis														
Thesis writing														
Submission														

Milestones

- Ethical approval by 31 March 2017
- Data collection by 31 May 2017

Data analysis and manuscript writing by 31 Jun 2017