1. BACKGROUND

1.1 The setting

Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) provides paediatric oncology services for a wide catchment area which includes a large part of Gauteng Province, as well as Limpopo, North West and Kwazulu Natal Provinces. In recent years, ongoing conflict and economic instability in other African countries have led to an increase in foreign patients receiving treatment at this hospital. The unit treats both state-funded patients and those funded privately or by medical insurance.

Patients under the age of 18 years with malignancies including germ cell tumours are treated in the paediatric haematology and oncology unit of the CMJAH, although there some of the older teenage patients are seen by adult oncology and gynaecology services. Patients are referred either from various referral centres or from the surgical departments of the hospital.

1.2 Brief overview of germ cell tumours

Germ cell tumours (GCTs) occur in both children and adults. They are thought to arise from primordial germ cells or from somatic cells which have evaded the influence of organisers and inducers[1]. They present in a heterogeneous fashion, including both malignant and non-malignant forms. In addition, tumours which initially presented as benign masses may later progress to malignant forms[2]. These tumours can arise in gonads of both male and female patients, and in midline structures such as the brain and mediastinum. Despite the devastating consequences that mass lesions can have in these organs, the outcome is usually excellent with fertility and function preserved as these tumours are very sensitive to available treatment.

1.3 Relevance of this group of tumours

Germ cell tumours may incorporate mature tissues from all three primitive cell lines and have been known to form whole organs or tissues, such as hair or bone. They can occur in various parts of the body, from the brain to the gonads. Diagnosis may be difficult, especially in intracranial GCTs, but current treatment is generally highly effective[2].

Malignant germ cell tumours represented only 3.4% of new paediatric oncology cases at CMJAH over the 28 year period studied. Despite this relatively low percentage, it is worthwhile to audit this group as the diagnosis may be challenging, the treatment is multidisciplinary and the side effect profile significant.

1.4 Purpose of auditing this cohort of patients

The overall management regimen used (surgery and adjuvant chemotherapy, with or without neo-adjuvant chemotherapy) is based on internationally recognised and proven protocols[3,4.5], but the outcome in patients seen at CMJAH has not yet been analysed. In addition, this audit offers the opportunity to devise strategies to decrease toxicity without affecting the survival rate.

One of the challenges in the management of childhood malignancies is that these conditions occur infrequently, making standardisation of treatment based on randomised clinical trials difficult. The comparison of the treatment of rare conditions such as germ cell tumours is even more difficult due to small numbers, thus clinicians have to rely on case series rather than the more optimal randomised controlled trials. There is a paucity of such published series in Africa[6] and particularly South Africa[7.8.9], and thus a retrospective analysis of this reasonably large group of patients is justified.

Many reported series concentrate on one specific tumour type, e.g. testicular germ cell tumours[10]. However, it is appropriate to evaluate these tumours as one group as they are sufficiently similar in histiogenesis, patterns of spread and response to treatment.

Significant improvements in the survival rates of childhood cancers in high income countries (HIC) were made in the era beginning in the late 1970s with the introduction of combinations of potent chemotherapeutic agents[11,12]. Any improvements since then have been incremental and achieved with great difficulty. It is now widely accepted that the current challenge is to shift from improving survival to minimising toxicity by decreasing the intensity of chemotherapy and radiotherapy regimens[13], even in low resource settings[14,15]. The attempt to identify risk groups has aided this goal in paediatric oncology centres in the US[16] and UK[11], but has not yet been replicated in South Africa or other African countries.

It has been postulated that South African children with solid tumours present later than their counterparts in HIC, and that this may affect their outcome[17]. However, long delays have been documented in series from both the USA[18] and Britain[19], with no subsequent decrease in survival rates. In an American series of central nervous system germ cell tumours, it was noted that many patients present after a prolonged duration of symptoms, but that the event free survival rate was unaffected by such delays in presentation[18]. Nevertheless, morbidity is worsened by delays, as complications such as blindness may be irreversible

Uniformity of care in malignant teratomas has been documented to contribute to improved survival rates, and adoption of standardised treatment protocols has accounted for improvements in survival rates over time[19]. Worldwide, in various specialist centres, clinicians modify their practice according to latest research and attempt to standardise protocols. As an example, standard of care for intracranial GCTs used to be craniospinal irradiation, which led to severe long-term sequelae[20]. In the

current era, chemotherapy is given to decrease the radiation dose and field and improve quality of life[20],[21,22].

1.5 Classification system

The five major histological subtypes are germinoma (seminoma, dysgerminoma), teratoma, embryonal carcinoma, yolk sac tumour and choriocarcinoma, in order of increasing malignant potential[16]. Teratoma and yolk sac tumour are the most common types in children, but complexity arises when we consider that, for example, yolk sac tumours occurring at any age are malignant, but teratomas may be benign in the prepubescent testis, and malignant in the older patient[2].

The heterogeneity of this group of tumours has led to a variety of terminologies. Different studies use different terminology and classification systems, making comparisons difficult. Examples include benign or malignant GCT[23], intra- and extracranial GCT's, gonadal and nongonadal tumours, germinoma/seminoma and nongerminoma/ nonseminoma[10,24].

The following histological-anatomical classification system has been used, for the relative simplicity:

Table 1 : Modified Dehner classification of germ cell tumours[2]

GONADAL GERM CELL TUMOURS

Ovarian

- Teratoma
  - Mature (solid, cystic)
  - Immature
  - Teratoma with associated malignant germ cell tumour component
  - Teratoma with associated malignant somatic component
- Germinoma
- Yolk sac tumour (endodermal sinus tumour)
- Embryonal carcinoma
- Mixed malignant germ cell tumour
- Choriocarcinoma
- Gonadoblastoma
- Polyembryoma

Testicular

- Teratoma
- Yolk sac tumour (endodermal sinus tumour)
- Embryonal carcinoma
- Teratocarcinoma
- Gonadoblastoma
- Other (seminoma/germinoma, choriocarcinoma, mixed germ cell)

EXTRAGONADAL GERM CELL TUMOURS

- Teratoma (pineal, mediastinal, retroperitoneal, sacral, other)
- Yolk sac tumour (endodermal sinus tumour)
- Embryonal carcinoma

This classification system does not correlate simply with prognosis, but it does incorporate all major histological subtypes and indicate the site of the tumour.

1.6 Epidemiology

Worldwide, the overall incidence of malignant germ cell tumours is approximately 3% of all childhood cancers[2]. The annual incidence of malignant germ cell tumours in South Africa is reported to be 3.3% of all paediatric malignancies[25]. GCTs present differently at different ages, in terms of both tumour site and histological subtype[20].

No significant geographical differences in incidence have been reported for extracranial tumours, but the incidence of intracranial GCTs is reported to be higher in Japan[18] and other Asian countries[20]. An overall male predominance is observed in CNS GCTs[20].

Conditions known to affect gonadal development and sex hormone production and regulation have been implicated in the pathogenesis of paediatric germ cell tumours. Known associations include cryptorchidism[10], gonadal dysgenesis/ sex chromosome abnormalities[26], androgen insensitivity syndromes[27] and Li-Fraumeni syndrome[26]. In addition, there are documented cases of familial germ cell tumours[28,29].

The incidence of particular germ cell tumours has been noted to be different in different race groups[29]. For example, in American studies, Caucasian males under age 20 are about 7 times more likely to develop a germ cell tumour in the testis compared to African American males[30].

1.7 Known prognostic factors

In chemo-sensitive tumours such as GCTs, the current challenge is to shift from improving survival to minimising toxicity. This can be achieved by decreasing the intensity of chemotherapy and radiotherapy regimens. The stratification into risk groups has aided this goal in paediatric oncology centres in the other centres[23] but has not yet been validated or replicated in South Africa or other African countries.

Parameters which have been found to correlate individually with poorer prognosis include:

- extragonadal primary tumour[11], mediastinal tumour[5,31]
- metastatic disease at time of diagnosis[11]
- raised levels of lactate dehydrogenase[10] and the tumour markers alpha-fetoprotein[5,31] and beta-human chorionic gonadotrophin[5] at diagnosis

Many of these factors are considered individually to have prognostic significance, but the predictive value was noted to be markedly increased when they were used in combination with other parameters[24]. In addition, various papers document conflicting reports[11,32].

Because germ cell tumours have so many variants, it may not be possible to identify a fixed set of prognostic indicators for the entire group. Different histological subtypes have different prognoses and prognostic indicators. For example, testicular seminomas secreting β-hCG do not have a worse prognosis than those with low serum levels, while intracranial germinomas with high levels of tumour markers fare worse and require more aggressive treatment[22].

1.7.1 Lactate dehydrogenase (LDH)

LDH is an enzyme found in many cell types including myocardium, white cells, bone, lung and many tumours. A high LDH level has been shown to correlate with poor prognosis in many variants of GCT[33].

1.7.2 Specific tumour markers

The level of alpha-fetoprotein (α-FP), a glycoprotein synthesised by the fetal liver and fetal yolk sac, is raised in various conditions including certain germ cell tumours and hepatoblastoma. Levels are high in yolk sac tumour, as well as immature teratoma, possibly due to occult microscopic foci of yolk sac tumour (YST). Higher levels have been

found to correlate with poorer prognosis in certain variants[33]. Levels are only moderately raised in embryonal carcinoma and some seminomas and dysgerminomas[34].

Beta human chorionic gonadotrophin (β-hCG) is a peptide hormone synthesised by the embryo early after conception, and later by the syncytiotrophoblast (part of the placenta). Levels of this substance are high in tumours that originate in the extraembryonic tissues, such as choriocarcinoma, and are moderately raised in seminoma and dysgerminoma[2].

It is considered essential to measure levels of these markers in the diagnostic evaluation, to aid in making the diagnosis, as a baseline before initiating definitive treatment and to allow monitoring upon completion of therapy[35].

1.7.3 The example of sacrococcygeal teratoma (SCT)

Certain prognostic factors are specific to this tumour type. The most important prognostic factor in SCT is age at diagnosis. Antenatal diagnosis at less than 30 weeks gestation is associated with a higher risk of fetal demise and peripartum morbidity. In all sacrococcygeal teratomas, the risk of malignancy is approximately 15-20%[34]. Presentation close to birth is associated with a lower incidence of malignant elements, while diagnosis at more than two months of age is associated with poorer outcome, related to the higher incidence of malignancy. The outcome in sacrococcygeal tumours is also affected by surgical skill. The risk of local recurrence is 4-11%, but rises to 37% in patients in whom the coccyx was not removed at the time of primary surgery[34].

1.8 Risk group stratification

Traditional staging systems have been found to be insufficient to prognosticate accurately for adult patients in the era of aggressive and effective chemotherapy. In GCTs, which now have a good overall prognosis, schemes which range from stage 1 (localised) to stage 4 (metastatic) are being superseded by more sophisticated risk stratification systems which incorporate multiple variables and correlate more closely with survival rates[33]. These studies relate to adults only and the corresponding literature about the paediatric population is lacking.

The International Germ Cell Consensus Classification (IGCCC) staging system was devised to include multiple factors such as tumour markers to determine the aggressiveness of the tumour, allowing clinicians to tailor treatment regimens more closely to the individual adult patient[33]. As many of the chemotherapy regimens have side effects now considered unacceptable, decreasing the dose and/or duration of chemotherapy in patients with low risk tumours is considered mandatory in regions with adequate resources to monitor patients closely.

Paediatric GCTs have traditionally been divided into risk groups according to stage: Children's Oncology Group Stage III and IV have been considered high risk, regardless of site[36]. The most recent intergroup paediatric studies showed that site of the primary tumour (which correlates with age) was an important factor in outcome[5,13,37]. Gonadal tumours had excellent overall survival even if late stage, whereas all extragonadal tumours had a poorer outcome[5].

Various studies have been conducted to identify prognostic factors in children: In a study of malignant nonseminomatous tumours, elevations of α-FP > 10 000 ng/mL predicted worse outcome, and the combination of site, stage and α-FP were found to identify three risk groups with significantly different outcomes[31] (100% vs 81% vs 43%).

A UKCCSG study found only that α-FP > 10 000 ng/mL was helpful in prognostication in malignant extracranial germ cell tumours[38], while a German study showed no correlation in malignant sacrococcygeal tumours[32].

Frazier et al performed a study specifically to address the question of whether the risk stratification of the IGCCC could also apply to paediatric germ cell tumours. The original IGCCC system was designed to study metastatic testicular germ cell tumours in adults. The authors concluded that this system performed well in other subgroups, namely children, females and non-metastatic patients[36]. Certain of the factors used in the adult system, namely α-FP, LDH and mediastinal primary site, were found to be good predictors of outcome in paediatric patients, but that the β-hCG level was not useful. However, the cut-off level was thought to be too high to be used in children. In addition, age > 15 years was found to predict poorer outcome and children younger than 6 months were excluded as α-FP levels below this age are so variable[36]. A recommendation was put forward to develop a *de novo* paediatric prognostic classification system, though this has not yet been achieved.

Studies that have examined which prognostic classification system to use have noted a lack of uniformity in assigning patients to a specific risk category[24]. Certain patients were considered good risk by one set of criteria and poor risk when applying a different system. This has treatment implications, as patients assigned to the good risk group will be exposed to less intense chemotherapy.

1.9 Modalities of treatment

Effective treatment of germ cell tumours involves complete resection of the primary tumour, in combination with chemotherapy. With the exception of patients with intracranial tumours, few patients will require radiation. In some patients, it may be possible to remove the primary tumour at the start of therapy, but a large proportion of

patients will require neo-adjuvant (preoperative) chemotherapy, as well as adjuvant chemotherapy[2].

Before the use of standardised combination chemotherapy, survival rates were low, rarely exceeding 20%[5]. Germ cell tumours are extremely sensitive to a number of agents, and the implementation of combination chemotherapy based on a platinum "backbone" contributed most to improved survival rates[10]. First line chemotherapy for all GCTs, both intra- and extracranial, is thus based on platinum compounds, namely cisplatin or carboplatin. Other agents that are effective in intracranial tumours include ifosfamide and etoposide[39], while etoposide, bleomycin and vinblastine are effective in extracranial tumours[12,38].

Current protocols in academic centres stratify patients according to risk groups and give two agent combinations in lower risk tumours[13]. At CMJAH, during the period studied, all patients were treated with three-to-four agent combinations for six cycles. As failure to complete cancer treatment is a documented problem in children in low income countries[40] and the available options for salvage therapy in case of relapse are few, a decision was taken to treat all patients as high risk with maximum therapy. In addition, challenges to close monitoring and follow-up have been documented in other African series[17,41,42].

The two main protocols used in paediatric germ cell tumours are modified BEP (bleomycin, etoposide and cisplatin, modified by the addition of vinblastine) and JEB (carboplatin, etoposide and bleomycin). The main difference between these two protocols is the platinum agent, i.e. cisplatin or carboplatin. Earlier reports indicated that JEB was less effective than BEP[43], but JEB using high (now standard) dose carboplatin has been shown to be equally effective with more tolerable late effects[3]. The UKCCSG group showed that JEB and BEP were equally effective, but that BEP was

more toxic in the long term[38,44]. The United States Children's Oncology Group followed suit and abandoned the use of high dose cisplatin because of unacceptable nephro- and ototoxicity[5].

In high-income countries, most children with cancer are enrolled into clinical trials and are said to have better outcomes than those who are treated "off protocol"[10,41]. Children with more common conditions, such as leukaemia and lymphoma, have been shown to have favourable outcomes when treated in this manner[14] while outcomes in adult males with malignant teratomas in the UK have been found to be significantly better in academic specialist units with experience in treating these tumours[19]. Due to various factors, most notably financial and infrastructural constraints, most paediatric oncology patients in South Africa are not enrolled into trials but are treated in centralised specialist centres, according to protocols that have been proven to be successful in other settings.

1.10 Early effects of treatment

Early toxic effects include myelosuppression and renal dysfunction[2]. In general, most of these effects are transient and resolve spontaneously. However, late effects may be devastating.

1.11 Late effects of treatment according to site of tumour

Late effects are related to the site of the tumour and the type of treatment. Chemotherapy, surgery and radiation all have significant side effects. These will be discussed according to site of tumour, as well as specific agents. As most patients with germ cell tumours can be expected to survive and have a normal lifespan, it is now considered essential to minimise adverse effects of therapy to preserve quality of life[22].

1.11.1 Brain tumours

Children who survive brain tumours are known to experience cognitive deficits, often from the radiation, but also from the effects of the tumour. Visual deficits range from small visual field deficits to complete blindness. Effects on the pituitary gland range from isolated diabetes insipidus to panhypopituitarism[2].

1.11.2 Mediastinal tumours

Radiation to this area can cause pulmonary fibrosis which is exacerbated by the use of bleomycin. Radiation adjacent to or involving the heart may later contribute to the development of cardiomyopathy and cardiac failure[2].

1.11.3 Abdominal tumours

Generally, few late sequelae of treatment are experienced by patients with abdominal germ cell tumours. Surgery may leave the patient with adhesions, which can cause a range of problems, including intestinal obstruction and infertility in females. However, these are usually rare. Radiation to this area may also affect adjacent organs but is usually only given in relapsed or high risk tumours[2].

1.11.4 Gonadal tumours

Gonadal germ cell tumours typically have excellent overall survival rates, and should thus be treated as conservatively as possible to minimise side effects. Surgical excision is always required. Removal of one or both gonads may lead to hormonal deficiencies, with abnormalities of pubertal development and infertility. A small percentage of females with ovarian tumours have bilateral disease, leading to removal of both ovaries. These patients will require hormone replacement therapy and will be infertile[2].

1.12 Late effects of different treatment modalities

1.12.1 Chemotherapy

While highly effective, cisplatin is a notoriously toxic agent. Known side effects include deafness and renal failure[5,38].

Etoposide has been associated with the development of acute myeloid leukaemia in a small number of patients, and many modern protocols try to avoid the use of this agent in lower risk tumours. This late effect may occur even decades after the completion of treatment[47].

Vinblastine has few late side effects, but has been shown to cause deafness in rare instances[48].

The most important late effect of bleomycin is pulmonary fibrosis, which may occur in up to 50% of children treated with this agent, but is often not clinically relevant[12].

1.12.2 Radiation

In any site, the use of conventional radiotherapy is associated with damage to adjacent organs, causing effects such as hypothyroidism and other organ dysfunction[2]. The development of second malignant neoplasms is associated with radiation in about 4.2% of children with GCTs[11].

It may be difficult to assign responsibility to a specific modality for the development of second malignant neoplasms (SMN). Men who survive testicular GCTs have demonstrated increased risk of developing a host of malignancies up to 20 years from the primary diagnosis. These include acute leukaemia, melanoma, non-Hodgkin lymphoma, cancers of the stomach, colon, rectum, pancreas, prostate, kidney, bladder,

thyroid and connective tissue[49]. Many in this cohort received radiation and these patients were thus more likely to develop SMNs.

1.13 Long term follow-up

Children who have been successfully treated for malignancies are followed up by the treating unit for at least five years. This is to ensure that any side effects of treatment are managed appropriately and that relapse is detected as early as possible to maximise the effect of retreatment. Late effects of the tumour may also require management. Patients are referred for management of endocrine abnormalities such as panhypopituitarism after the treatment of intracranial tumours, and to paediatric endocrinologists or gynaecologists if there is female hormone dysfunction.

In HIC, with higher doctor-patient ratios, most of these children would be seen in a dedicated late effects clinic. However, in countries with fewer resources, such as South Africa, it remains the responsibility of the paediatrician or paediatric oncologist to monitor these patients, often well into adulthood. Some patients are lost to follow up as they reach adulthood, and certain problems such as infertility and second malignant neoplasms may not be detected.

1.14 Relapse

The predicted risk of relapse is related to initial determination of risk factors at presentation. Nearly all tumours will recur in two years following completion of treatment, though late relapses are possible but rare[43]. Unlike many other solid neoplasms, many relapsed GCTs can be salvaged with available chemotherapy[43]. Some may require more intensive measures such as stem cell transplants, which are not as available in South Africa as in many high income countries.

2. AIMS OF THE STUDY

The primary aims were to

- describe the patient population and the characteristics of the tumours,
- determine overall survival rates, rates of relapse and causes of death and to
- compare these parameters with those documented in series from both high and low income countries.

The secondary aims were to

- determine if any of the known prognostic factors were relevant in this cohort,
- record rates of treatment-related toxicity and
- to determine which staging system would be best suited to our patients.

3. MATERIALS AND METHODS

3.1 Study design

A retrospective, cross-sectional descriptive study of paediatric patients with germ cell tumours treated at CMJAH during the study period.

3.2 Study site

The Paediatric Haematology/ Oncology Unit of the Charlotte Maxeke Johannesburg Academic Hospital.

2.3 Study period

The study was conducted by retrospective case-file review covering the 28 year period from 1st January 1983 to 30th November 2011. This period was chosen as the chemotherapy protocols remained relatively unchanged during this interval, and a new protocol was adopted in December 2011.

3.4 Study sample

Seventy five patient records were identified that met the inclusion criteria. Patient records were identified with the clinic database.

3.5 Study method and data collection

Inclusion criteria for entry into the study were the following:

- All children (0-18 years) with a proven diagnosis of germ cell tumour treated at CMJAH during the study period.

Exclusion criteria:

- Patient files which had substantively incomplete records, most notably no histology result.

The files were reviewed to obtain the following information:

- Demographics: age, sex, race
- Duration of presenting symptoms
- Predisposing factors (dysmorphism, cryptorchidism and familial cancer syndromes)
- Diagnosis: histological subtype, anatomical site of primary tumour, stage at presentation, level of tumour markers
- Treatment: details of chemotherapy, surgery and radiation
- Early and late effects of treatment
- Details of relapse
- Date and cause of death

3.6 Data analysis

Data was manually collected on a separate data collection sheet (see Appendix A)
The data was analysed using the Stata Statistical software package version 10.1 in conjunction with a biostatistician. Cox regression analysis tests, a Cox proportional hazard model, and log rank regression tests were employed. Univariate analyses were performed which identified predictors of disease outcome using Kaplan Meier estimates. A p value of less than 0.05 was used to indicate statistical significance.

3.7 Ethics

Access to patient files was restricted to the investigator and study supervisor. It was not necessary to reveal any patient identifiers in the final paper and adherence to strict levels of confidentiality was adhered to at all times. Permission to conduct retrospective analysis was obtained from the Human Research Ethics Committee of the University of the Witwatersrand. (Reference number: M060215)

4. RESULTS

4.1 Study population

From 1 January 1983 to 31 November 2011, there were 75 documented cases of germ cell tumours seen in the unit. This included 56 malignant tumours, 17 benign tumours and 2 tumours in which the presence or absence of malignant elements was not recorded. Malignant germ cell tumours represent 3.2% of all paediatric malignancies (total 2300) seen over this period at CMJAH.

4.1.1 Age

The age range of patients at presentation was one day to 14 years 9 months, with a mean of 5.3 years. All the patients who presented at one day of age had sacrococcygeal tumours. (Patients older than 15 years may have been treated in the adult oncology or gynaecology service, but our database does not contain details of these patients.)

4.1.2 HIV status

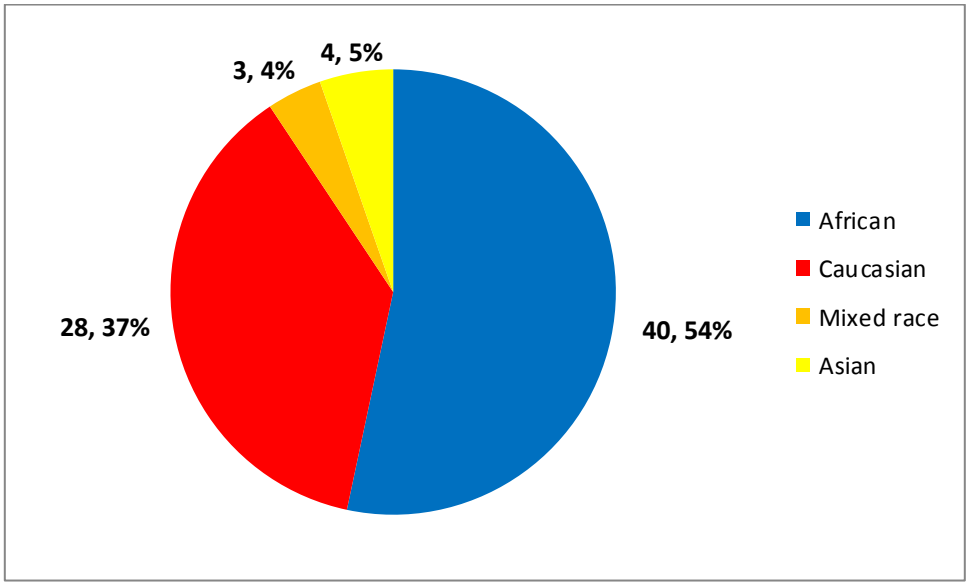
There were 45 HIV negative patients, one HIV positive patient, and 29 in whom HIV status was unknown. Routine testing was introduced in the 1990s, and all patients in whom consent was obtained were tested.

4.1.3 Sex

In the total cohort, there were 46 females and 29 males. A female predominance is shown, with a female-to-male ratio of 1.6:1. There was a male predominance in central nervous system tumours: male to female ration 1.5:1.

4.1.4 Race

Figure 1: Race of paediatric patients with GCTs at CMJAH, 1983 to 2011.



4.1.5 Predisposing conditions

There were two documented cases of cryptorchidism, and three cases of possible familial cancer syndromes.

4.2 Duration of symptoms

The duration from onset of disease-specific symptoms to presentation to our unit ranged from 1 day to 1095 days. The median duration of presenting symptoms was 90 days. As patients with sacrococcygeal tumours most commonly present in the neonatal period, and thus there is no delay in presentation, the duration of symptoms was calculated again excluding this group of tumours. Once these tumours were excluded, the median duration of symptoms was 120.5 days but the difference between these two medians was statistically insignificant. In seven patients (9.2%) the records did not contain details of duration of symptoms.

4.3 Distribution of tumours

As germ cell tumours are a heterogeneous group, it is necessary to classify them according to various parameters:

4.3.1 Table 2: Distribution of tumours by malignant elements

Type of tumour	Number	Percentage of total
Malignant germ cell tumours	56	74.7%
Benign germ cell tumours	17	22.7%
Unknown	2	2.6%
Total	75	100 %

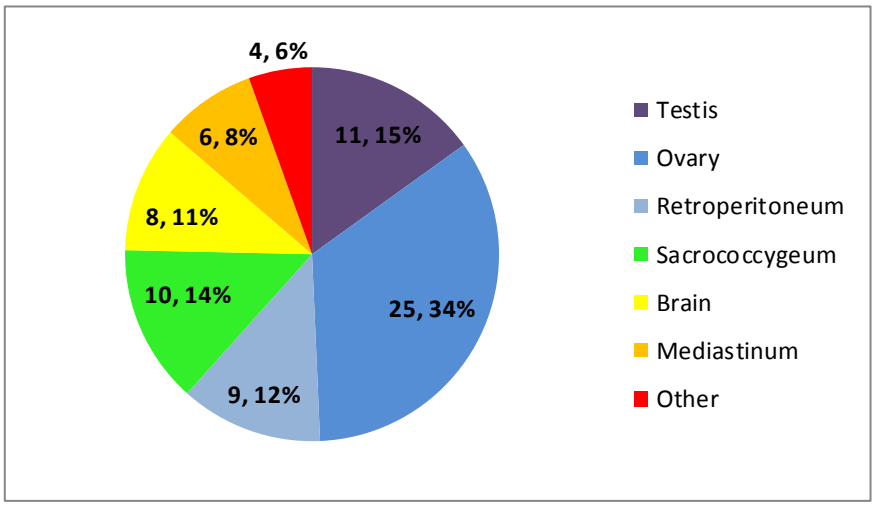
4.3.2 Table 3: Distribution of tumours by anatomy and histological elements

GONADAL GERM CELL TUMOURS		
Ovarian		**Number**
	Teratoma	
	Mature (solid, cystic)	2
	Immature	5
	Teratoma with associated malignant GCT component	2
	Germinoma	12
	Embryonal carcinoma	2
	Mixed malignant germ cell tumour	1
	GCT NOS	1
Testicular		
	Teratoma	3
	Yolk sac tumour (endodermal sinus tumour)	4
	Other (seminoma, choriocarcinoma, mixed germ cell)	4
EXTRAGONADAL GERM CELL TUMOURS		
	Teratoma (pineal, mediastinal, retroperitoneal, sacral, other)	26
	Yolk sac tumour (endodermal sinus tumour)	9
	Other	4

4.3.3 Distribution of tumours by primary site

Gonadal tumours comprised 48% of the total, while extragonadal tumours made up the remaining 52% of these malignancies.

Figure 2: Distribution of tumours by anatomical site.



4.4 Treatment

Of the 75 patients, seventeen patients had benign tumours and required no further treatment after surgery. Four patients with malignant tumours received no curative therapy:

- one patient died of septicaemia before treatment was initiated,
- one patient defaulted before treatment was initiated,
- two patients died from complications of their malignancies before treatment was initiated.

4.4.1 Chemotherapy

Of the nine patients with brain tumours

- three received no chemotherapy (one died, two treated with surgery and of these two, one had radiation)
- 5 received ICE
- 1 received ICE and VEC

See Appendix B for details of treatment protocols

Of the patients with extracranial malignant germ cell tumours:

48 received chemotherapy

- 41 received BEP (2 received other chemotherapy in addition to BEP)
- 6 received ICE (1 with other chemotherapy)
- 1 received a combination of other chemotherapeutic agents

4.4.2 Radiation therapy

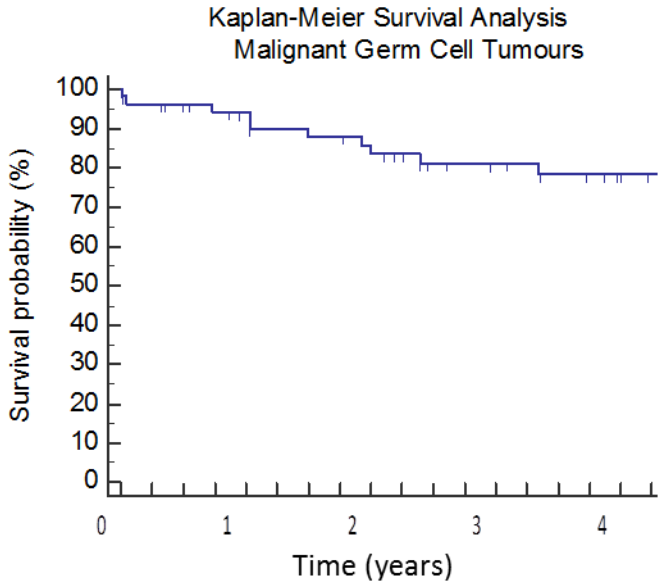
Sixteen patients required radiation, eight as part of standard therapy for brain tumours and eight received radiotherapy for disseminated or refractory disease.

4.5 Survival rate

For the 28 year period under study, the three year overall survival rate for patients with malignant GCTs was 73.7 %. All patients with benign tumours survived. Of the eight patients treated for brain tumours, five survived, while three of the eight patients who received radiotherapy for disseminated or refractory disease survived.

When patients who died before treatment could be initiated were excluded from the analysis, the survival rate for patients with malignant tumours was 77.8%. Two patients (2.6 %) were lost to follow up upon completion of therapy. All other patients were followed up for at least three years.

Figure 3: Kaplan-Meier survival analysis curve for malignant germ cell tumours



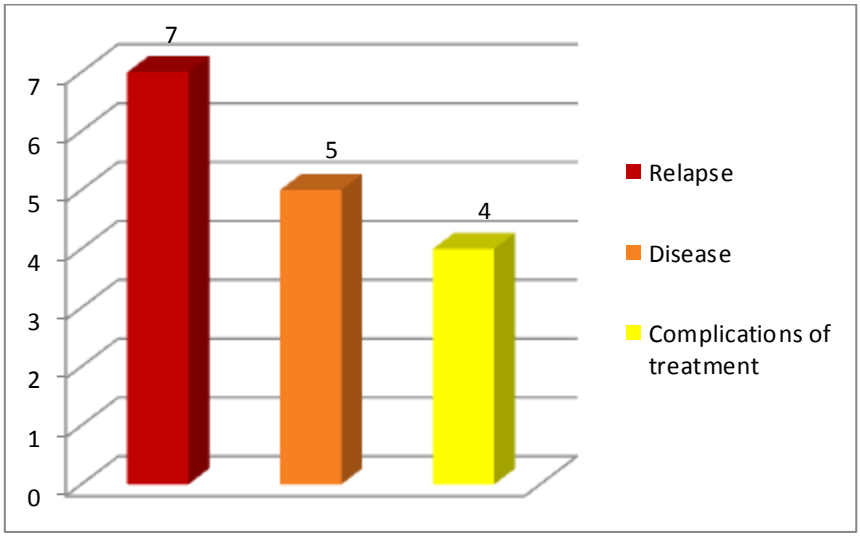
4.6 Causes of death

Causes of death include the following:

- Relapse 7 (43.8%)
- Disease 5 (31.3%)
    - Two patients abandoned curative treatment.
    - Two patients were terminal on presentation.
    - One died of septicaemia before treatment initiated
- Complications of treatment 4 (25%)

Fatal complications of treatment included immediate post-operative complications such as intracerebral haemorrhage as well as neutropaenic sepsis after the administration of chemotherapy.

Figure 4: Causes of death



4.7 Relapse

All patients who relapsed did so within 26 months from diagnosis. Of the 54 patients who received treatment for malignant germ cell tumours, 15 relapsed and of these, 10 died. Five of these patients did not receive definitive treatment as first-line therapy and this contributed to the high relapse rate. Thus, 33% were treated successfully with relapse therapy.

4.8 Early toxicity rates

Fifty four patients received chemotherapy, of whom 16 did not develop myelosuppression as a consequence.

4.8.1 Myelotoxicity

Myelotoxicity is represented by either a combination of or one of the following: leukopaenia, anaemia and thrombocytopaenia. 32 out of 48 patients who received chemotherapy (67%) experienced significant (Grades III and IV) but transient myelotoxicity.

Table 4: Myelotoxicity associated with the different chemotherapy regimens

Chemotherapy regimen	Total number of patients	Number patients with myelotoxicity	WCC grade III and IV	Hb grade III and IV	Platelets grade III and IV
BEP	41	25	20	7	11
ICE	6	6	6	1	5
Other	1	1	1	0	1
Total (%)	48	32 (67%)	27 (56.3%)	7 (14.6%)	17 (35.4%)

(See Appendix C for grading of myelosuppression)

Of the 41 patients treated with BEP, 25 (61%) experienced significant myelotoxicity, in contrast with 6/6 patients treated with ICE.

As a consequence of this myelotoxicity, one patient died of neutropaenic sepsis (following chemotherapy for relapse) and the remaining cases resolved spontaneously. No patients were given granulocyte colony stimulating factor (filgrastim, Neupogen®). There were only two documented cases of patients in whom dose reductions were made due to toxicity, and all but one patient completed six cycles of chemotherapy.

4.8.2 Hearing loss

Of the 41 patients treated with regimens containing cisplatin, 14 (34%) developed clinically significant hearing impairment, considered to be related to the use of cisplatin. In some of these patients, ototoxic antibiotics were administered, either concurrently or very soon after chemotherapy was given. Available records are incomplete as to how many patients were given more than one ototoxic agent.

4.8.3 Renal dysfunction

5 (10.4%) of the 48 patients who received chemotherapy developed renal tubular acidosis and 2 (4.9%) developed chronic renal failure.

4.8.4 Other adverse events

One patient developed a small pulmonary embolus. The exact details of this case are not recorded.

4.9 Late toxicity rates

4.9.1 Second malignant neoplasms

There were no documented instances of second malignant neoplasms in the follow up period.

4.9.2 Effect on fertility

There have been no documented instances of infertility due to chemotherapy, however most patients are not followed up in a late effects clinic. Two patients had bilateral ovarian tumours and underwent bilateral oophorectomies and are thus infertile following surgery.

4.10 Long term follow-up

Three patients were lost to follow-up (4%) and of these, only one was considered to be high risk according to both IGCCC and traditional staging system. The average duration of follow up was 1528 days with a range of 1 to 8149 days.

4.11 Prognostic factors

Available staging systems and prognostic factors apply only to extracranial malignant tumours[37,50,51], thus intracranial tumours are not assessed here. There were 48 patients available for assessment.

Assigning patients according to the traditional staging system results in the following stage distribution:

Table 5 : Malignant extracranial germ cell tumours. Conventional staging.

Stage	Number of patients	Number alive	% survival at 3 years
1	12	12	100
2	13	10	76.9
3	14	9	64.3
4	9	6	66.7

See Appendices D, E and F for staging systems

Assigning patients according to the **IGCCC system** (See Appendix E) results in the following risk group distribution:

Table 6: Malignant extracranial germ cell tumours. Staging according to the International Germ Cell Consensus Classification.

Risk group	Number of patients	Number alive	% survival at 3 years
Good	18	16	88.9
Intermediate	8	6	75
Poor	17	10	58.8
Unclassifiable	5	5	100

4.11.1 Univariate analysis/ validation of potential prognostic factors

Table 7: Log Rank (Mantell-Cox) analysis of significance of various parameters in prognostication

Variable	Chi-Square	Degrees of freedom	Significance (p value)
Sex	0.493	1	0.483
Race	3.400	3	0.334
Duration of symptoms	3.613	4	0.461
Surgical excision	**13.466**	**2**	**0.001**
LDH level	2.078	3	0.556
αFP level	1.296	3	0.730
β-hCG level	1.602	2	0.449
Site of primary tumour	7.119	4	0.130
Histological subtype	3.842	5	0.572
Stage (I-IV)	6.732	4	0.151
IGCCC prognostic stage	5.478	4	0.242

Three year survival rates were analysed for a number of variables. The only variable that was found to have a significant impact on survival was completeness of surgical excision ($p = 0.001$). All others were found not to achieve statistical significance. In particular, race and prolonged duration of symptoms did not impact on survival in this analysis.

5. DISCUSSION

In settings with adequate resources and support, treatment of malignancies is moving towards specific treatment tailored to the individual patient. In its most sophisticated form, this treatment is extremely expensive in diseases such as leukaemia[52]. The aim of this strategy is to treat the malignancy effectively while minimising toxicity. While it may not yet be possible to adapt this strategy to the South African setting, certain principles can be applied to treatment in this environment. The first step towards tailored therapy is to ensure that low risk malignancies are treated with low intensity chemotherapy which still preserves a good survival rate, while higher risk tumours receive more aggressive therapy.

Many researchers have attempted to devise a risk stratification system for paediatric germ cell tumours[16,31,32], and yet no single system has found favour with a majority of clinicians and researchers. The patients in this cohort had overall good survival rates, but unacceptably high rates of permanent toxicity. The aim of this audit was to characterise the patient population, determine which of two different staging systems correlated better with survival, and scrutinise survival and treatment toxicity rates.

5.1 Demographics

In this simple retrospective audit, the incidence of germ cell tumours presenting to our unit was similar to that reported elsewhere[16]. Of the total number of malignancies reported during this period in this unit, 3% were GCTs. This parallels incidence rates in other centres, both nationally[25] and internationally[4,53]. In addition, the sex ratios and ages of patients at presentation were similar to those reported in other series.

The racial demographics of patients in this study do not accurately reflect the demographics of the country. The hospital was opened to patients of all races only in 1994 and thus patients of African ethnicity appear relatively under-represented.

5.2 HIV infection rates

The low rate of HIV infection may appear unusual in a South African population, but the high proportion of patients in whom HIV status was unknown reflects the long period over which patients were seen. HIV was not routinely tested for until the 1990's and many patients presented before this time. Only one HIV positive patient was documented, which may reflect the fact that germ cell tumour incidence is not increased in the HIV positive population[54].

5.3 Predisposing conditions

Only two patients were documented as having a condition known to predispose to the development of germ cell tumours (cryptorchidism) and three came from families with possible familial cancer syndromes. It has been stated that 5-10% of female patients with GCTs have sex chromosomal abnormalities[26,55], but as we do not routinely test for these, they most likely remain undetected.

5.4 Tumour site and histology

The breakdown of tumours by site appears to correlate well with other series in a similar time period[56], as does the breakdown by histological subtypes. Nearly three quarters (74.7%) of the cohort had malignant GCTs, which is higher than in many other series[56,57]. Anecdotal reports suggest that this is because many patients with benign tumours were treated in the paediatric surgery department and not referred to our unit.

In both American[56] and British series[57], approximately 50% of the GCTs were extragonadal, and 50% were gonadal. In this series, 50.7 % are gonadal and 49.3 % extragonadal. In this group, 12% of the patients had intracranial tumours, more than that reported in most other large series[16,56,57] but similar to Japanese series, known to have higher rates[18] than other countries.

5.5 Staging and prognostic classification systems

In older studies, only conventional disease staging (Stage I to IV) was shown to be a prognostic factor in childhood GCT's[56,16,31]. Subsequently, intensive platinum-based therapy was shown to improve survival in all patients requiring chemotherapy, narrowing the gaps between the traditional stages[3,4].

In adults, the conventional staging system in use for many decades is no longer considered to be adequate for prognostication in malignant germ cell tumours. The increased efficacy of modern chemotherapy, as well as the multitude of other factors found to have prognostic significance in adult tumours, led to the development of more complex staging systems. Among these, the system devised by the International Germ Cell Consensus Classification (IGCCC)[33] group has attained fairly widespread use in staging tumours in adults[51]. Despite the supposed standardisation offered by the IGCCC , this system still does not apply to all GCTs and may not be applicable to the paediatric population as tumours develop in different sites and may show different patterns of spread[31] although some correlations have been shown[36].

There remain a variety of prognostic staging systems in use, for example, for nonseminomatous GCTS, metastatic testicular GCTs, ovarian tumours, etc. Prognostic factors are less clearly defined in children, as the rarity of childhood cancers and GCTs specifically, means that most series are too small and lack heterogeneity[31].

Despite on-going clinical research, a widely applicable staging system has yet to be devised for the paediatric population and clinicians in different centres use different systems. Certainly the conventional staging system (Stage I to IV[56]) is easier to apply and all of our patients could be staged using this system, while 5/48 were defined as "unclassifiable" according to the IGCCC system. The IGCCC system requires multiple parameters, and some patients referred to our unit did not have initial tests performed before definitive surgery and could thus not be classified.

In this series, the only prognostic factor shown to have statistical significance was completeness of surgical excision. All other factors analysed were not shown to have statistical significance. These include sex, race, duration of presenting symptoms, levels of LDH, alpha-fetoprotein and beta human chorionic gonadotrophin, tumour site and histological subtype as well as classification according the IGCCC. These individual factors have shown to be prognostic in series of adult patients, but not overwhelmingly so in paediatric series[12]. Most paediatric GCTs which secrete tumour markers, excluding sacrococcygeal tumours in neonates, secrete them in much lower levels than those in adults, which is one of the reasons the adult system is not directly applicable in childhood GCTs[36].

As all of the patients in this study could be assigned a stage on the traditional staging system, thus implying that this system should be used rather than the IGCCC scheme.

5.6 Delays in diagnosis

Patients in Africa are often thought to have poorer outcomes than their counterparts in better resourced settings due in part to delays in diagnosis[17,58]. However, there is little published data to support this assertion. The reasons for diagnostic delays were not

analysed in this retrospective audit. In both a South African[58] and a Nicaraguan study[59], diagnostic delays were more likely to be due to physicians than caregivers, in contrast with work done in high income countries[60] where patient/caregiver factors were more important. In our patients, diagnostic delays were not shown to influence survival negatively. The median duration of presenting symptoms in this cohort was 120 days, higher than to that reported in British[19] and American[18] germ cell tumour studies, which concluded that delay was not an independent prognostic variable. Despite the markedly longer duration of symptoms in this study, delay was not shown to impact negatively on survival.

5.7 Survival rate

The three year survival rate was chosen rather than a five year survival rate so that more patients could be analysed, and as no relapses occurred later than 26 months from completion of therapy. The three year survival rate of 73.7% is on a par with documented figures from other, better resourced centres. When patients who died before treatment could be initiated were excluded from the analysis, the survival rate for patients with malignant tumours was 77.8%. This is a satisfactory survival rate, which adds strength to the argument that we should move from more to less toxic regimens while preserving the survival benefit. In addition, the survival rate of 33% of children treated for relapse compares favourably with other series[43]. It should be noted, however, that 15/54 patients relapsed and only a third of these were salvageable so reduction of treatment intensity should be done cautiously bearing in mind that no prognostic variables were identified apart from completeness of surgical excision.

5.8 Causes of death

Of the 16 patients in this cohort who died, the main cause of death was relapse (7, or 43.7%), followed by disease (5, or 31.3%, of which 4 did not receive any treatment).

Four patients died from complications of treatment, which represents 8.3% of the total number of patients who received treatment. Complications of treatment may be unavoidable, but the high rate of deaths caused by treatment would indicate that caution should be exercised when calculating a risk-benefit analysis and deciding whether to treat a patient aggressively or more conservatively.

5.9 Toxicity rates

In well-renowned research centres such as St Jude Children's Research Hospital, patients are treated with surgery alone if low risk, three courses of chemotherapy if intermediate risk and four courses if high risk with good survival rates[56]. Using the conventional staging system, nine out of 48 (19%) of our patients were classified as Stage IV and 14 were stage III. Using the IGCCC system, 17/48 (35.4%) of patients with malignant GCTs were classified as poor prognosis, but all patients who required chemotherapy were treated with maximal therapy. According to international guidelines, only high risk patients should receive maximal therapy to minimise exposure to toxic agents in those who do not require it[13,38].

In this cohort, nearly all patients who received chemotherapy were treated with six cycles of chemotherapy as a matter of course. Reasons for this include the perception that our patients present late, we have higher rates of loss-to-follow-up than better resourced countries and the fact that we have less access to aggressive salvage therapy in cases of relapse. In addition, risk-adapted therapy is a relatively new approach to treatment.

It is evident that patients in this study presented with a longer duration of symptoms than those in high-income countries, and it must be noted that the diagnostic lag time is different for different malignancies[61]. In addition, this study shows that increased duration of presenting symptoms does not correlate with poor outcome in germ cell

tumours. The assumption that there are high rates of loss-to-follow up was not proven as the rate of LTFU was 3% in this cohort. Accordingly, consideration should be paid to the option of stratifying all patients according to an accepted system and tailoring treatment according to risk group. In the light of the high rates of treatment toxicity, it is imperative that exposure to toxic agents be decreased while preserving the good survival rate. However, such modifications are time-consuming and might require a higher doctor-patient ratio than the current one.

The rate of clinically significant short term myelotoxicity in patients who received BEP (61%) is considered acceptable for high dose chemotherapy. Two patients are documented as having died from neutropaenic sepsis following the administration of chemotherapy; one during first treatment and one during salvage chemotherapy (see causes of death table). In the remainder of the patients, all cases of myelotoxicity resolved shortly after completion of therapy. It was not found necessary to dose-reduce the treatment in this group of patients.

In contrast, the rates of permanent toxicities such as hearing impairment (34.1%) and renal complications (15.3% = 10.4% renal failure and 4.9% renal tubular acidosis) are unusually high. Large German studies using the same protocol documented approximately 6 to 11% of patients who were treated with BEP developed hearing loss[12,32,62] while a head-to-head study of BEP versus JEB[43] showed equivalent rates at 10%. However patients in these studies did not receive six courses as a matter of routine, as our patients have in the past, nor did they receive vinblastine, also known to be ototoxic. Patients on chemotherapy are at risk for nephrotoxicity as a result of dehydration from poor oral intake and vomiting, as well as being treated for neutropaenic sepsis with nephrotoxic agents such as amikacin and vancomycin. Decreased renal clearance of these agents may lead to increased rates of ototoxicity with subsequent deafness.

Two of the agents used in the modified BEP protocol (cisplatin and vinblastine) are known to be ototoxic (cisplatin more commonly than vinblastine) and this protocol has been phased out since this audit was completed. As a result of the association with oto- and nephrotoxicity, the use of cisplatin has largely been abandoned in high income countries, despite its lower cost. High dose carboplatin is now considered equally effective, although it is more myelotoxic. COG studies concluded that there is no real survival benefit with high dose cisplatin, but a marked increase in toxicity[5]. UKCCSG studies showed decreased permanent toxicity when carboplatin was substituted for cisplatin[3]. Since this audit, more intensive screening has been instituted to detect subclinical ototoxicity in all patients receiving chemotherapy in this unit.

No second malignant neoplasms were detected, though these may occur decades after the primary diagnosis and may not be reported to our unit.

5.10 Follow up

Very few patients were lost to follow up. Apart from the permanent toxicities mentioned previously, there were few other serious concerns. It must be noted that many patients are followed up by other clinicians or in other centres once they reach adulthood, thus second malignancies or fertility problems, for example, may not be reported to us.

5.11 Limitations of the study

As this a retrospective study, data collection relied on adequacy of clinical notes and completeness of data in the clinic database. While most file notes are fairly comprehensive, it is usual to find some of the necessary data has not been recorded. In particular, details such as syndromic features (e.g. Klinefelter syndrome) may not have

been recorded, possibly due to the subtlety of diagnostic features in the prepubertal period.

Many patients are referred to our unit once the diagnosis has been made, often after definitive surgery. These patients are often not investigated adequately in the pre-operative period as the diagnosis is not suspected. Baseline tumour markers and LDH are not tested and this constitutes missing data, making it impossible to stratify according to the IGCCC system.

For an accurate estimation of the prognostic value of certain parameters, it is necessary to accrue large numbers of patients. Paediatric cancers are rare, and germ cell tumours are particularly rare. It is thus difficult to gather enough data to draw firm conclusions about these factors. However, it is reasonable to compare our data to larger datasets to assess correlation.

Bleomycin-induced respiratory compromise may be sub-clinical and, as patients are not routinely tested for this, it may be underdiagnosed. Similarly, other long term side effects may occur but may not be reported to us, as they may occur decades after completion of treatment. Infertility and development of second malignancies are examples of adverse events that may not come to our attention.

While all reasonable attempts are made by clinic staff to ensure regular, on-going monitoring, a few patients have been lost to follow up. For the same reason, the development of long term side effects may not be recorded in these notes.

An important finding of this study is that duration of disease-specific symptoms was not found to be a predictor of prognosis; a prospective study would be far better designed to assess this with greater accuracy.

6. RECOMMENDATIONS

Patients should be treated according to an accepted risk stratification system and managed with a risk-adapted approach to treatment if at all possible. In general, low risk patients should be treated with surgery alone, medium risk patients with the minimum effective chemotherapy and high risk patients only with maximal effective therapy. The number of cycles of chemotherapy should be tailored to the individual patient, and should be based on a carboplatin "backbone".

Until referring clinicians are better educated about investigating solid tumours and appropriate referrals, the traditional staging system should remain the mainstay of prognostication. Patients should be followed up closely, though detection of relapse is unlikely after three years from completion of effective therapy. Once considered cured, all patients should be followed up for as long as possible to detect development of second malignancies, as well as side effects of therapy. Patients and caregivers should receive detailed oral and written instructions regarding follow up. Ideally, these cancer survivors should be seen in a multi-disciplinary late effects clinic to ensure continuity of care in a comprehensive manner.

Paediatric oncologists who are engaged in clinical research should devise a multicentre, prospective trial of therapy to assess whether JEB does indeed offer the best cure rate with the least toxicity, and whether the IGCCC system has applicability in a South African setting. Such trials are among the important activities of the South African Children's Cancer Study Group, and would ensure standardisation of care with centralisation of expertise.

7. CONCLUSION

Despite the inherent limitations of treating malignancies in a relatively resource-poor setting, the patients in this cohort had good survival rates. Permanent toxicity rates were, however, unexpectedly high. Efforts should be made to preserve the survival benefit while decreasing toxicity. Cost savings could be made by treating low risk patients with surgery alone, and treating moderate and high risk patients with fewer courses of high dose chemotherapy. Of course, every effort must then be made to monitor these patients very closely to detect and treat relapses early. As the treatment protocol in our unit has now changed to a less toxic regimen, patients on the new protocol should be followed up and a similar audit performed to document survival rates and toxicity rates.

As with many such series, and indeed with this one, the numbers are small and conclusions often equivocal. The two main findings were that complete surgical excision is a good prognostic factor and that duration of disease-specific symptoms does not contribute to decreased survival.

The search for an inclusive paediatric system should continue, to allow comparisons between centres and to this end clinicians and researchers are encouraged to contribute to large multicentre studies. A single system that could be used in all malignant GCTs would be ideal, but the heterogeneity of this group of tumours makes this an ambitious quest.

Appendix A

Germ cell tumours data capture sheet

Name _____ GT _____ Old _____
Date of birth ____/____/____
Date of Δ ____/____/____ **Age of pres to 294** _____ yrs ____ months
Sex Male □ Female □
Race African □ Asian □ Mixed □ White □ Other □
HIV Pos □ Neg □ Unknown □
Height _____ cm **Weight** _____ kg
Duration of presenting symptoms _____ years _____ months
Dysmorphism Yes □ No □ Unknown □
Specify _____
Cryptorchidism Yes □ No □ Unknown □ N/A □
Diagnosis

Teratoma	Mature	□	Which elements are
	Immature	□	immature on histology?
	Malignant	□	_____
Germinoma	Seminoma	□	_____
	Dysgerminoma	□	_____
	Germinoma	□	_____
Embryonal carcinoma		□	_____
Yolk sac tumour		□	_____
Choriocarcinoma		□	_____
Gonadoblastoma		□	_____
Polyembryoma		□	_____

1° Site

Brain	□
Coccyx	□
Mediastinum	□
Ovary	□
Retroperitoneum	□
Testis	□
Vagina	□
Unknown	□

Stage _____ Unknown □
Tumour markers
AFP _____ range _____ Days post op _____
B-HCG _____ range _____ Days post op _____
LDH _____ range _____ Days post op _____
Other _____ range _____ Days post op _____
Size of tumour _____ Unknown □
Complete excision? Yes □ No □ Unknown □

LN involvement Yes □ No □ Unknown □
Based on CT □ Sonar □ Histo □
Distant parenchymal inv. at Δ Yes □ No □ Unknown □
Based on X-ray □ CT □ Sonar □ Histo □

Neo-adjuvant chemo Yes □ No □ Unknown □
Adjuvant chemo given Yes □ No □ Unknown □
Chemo regimen BEP □ Other □ Specify_____
Number of cycles _____Unknown □
Chemo-related toxicity Yes □ No □ Unknown □
If yes, specify_____
Short term □ Long term □

Relapse Yes □ No □ Unknown □
Local □ Distant□ Combination □ N/A □
Date of relapse post Δ 1 yr □ 2 yrs □ Other □ _____N/A □
2nd surgery Yes □ No □ Unknown □ N/A □
2nd chemo regimen _____N/A □

Radiotherapy Yes □ No □ Unknown □
Dose _____Gray N/A □

Death Yes □ No □ Unknown □
Date of death_____
Cause of death _____N/A □

Period of follow up post diagnosis_____years_____months
Outcome

	1 yr	2 yr	2-5 yr	5 - 10 yr	> 10 yr
On Rx					
Alive + well					
Died					
LTFU					

2° malignancies Yes □ No □ Unknown □
Specify_____
(Leukaemia, GI malignancies, sarcomas, melanoma, genitourinary carcinoma)

Appendix B

ICE Protocol
Intracranial germ cell tumours

Day 1	Ifosfamide	2 g/ m^2 IVI over 6 hours
	Etoposide	150 mg/m^2 IVI
	Mesna	600 mg/m^2 prior to ifosfamide, followed by 3 hourly doses X 6
Day 2	Ifosfamide	2 g/ m^2 IVI over 6 hours
	Etoposide	150 mg/m^2 IVI
	Mesna	600 mg/m^2 prior to ifosfamide, followed by 3 hourly doses X 6
Day 3	Carboplatin	500 mg/m^2 IVI over 2 hours

VEC Protocol
Intracranial tumours

Day 1	Vincristine	1.5 mg/m^2 IVI
	Etoposide	100 mg/m^2 IVI over 1 hour
	Carboplatin	200 mg/m^2 IVI over 2 hours
Day 2	Etoposide	100 mg/m^2 IVI over 1 hour
	Carboplatin	200 mg/m^2 IVI over 2 hours
Day 3	Etoposide	100 mg/m^2 IVI over 1 hour
	Carboplatin	200 mg/m^2 IVI over 2 hours

BEP Protocol
Germ cell tumours in all locations other than intracranial

Day 1	Vinblastine	0.2 mg/kg IVI
	Cisplatin	100 mg/m^2 over 6 hours with mannitol
Day 2	Bleomycin	15 mg/m^2 IVI
	Etoposide	120 mg/m^2 IVI
Day 3	Etoposide	120 mg/m^2 IVI

Appendix C

Grades of myelotoxicity

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Leukocytes	LLN to $3x10^9$	2-3 $x10^9$	1-2 $x10^9$	< 1 $x10^9$
Hb	LLN to 10 g/dL	8-10 g/dL	6.5-8 g/dL	< 6.5 g/dL
Platelets	LLN to 75 $x10^9$	50-75 $x10^9$	10-50 $x10^9$	< 10 $x10^9$
Neutrophils	1.5–2 $x10^9$	1–1.5 $x10^9$	0.5-1 $x10^9$	< 0.5 $x10^9$

NCI Guidelines: Adverse Event Reporting Requirements

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf

Appendix D

St Jude Children's Research Hospital staging system for germ cell tumours

Stage I	Tumour totally resected, with negative margins, negative lymph nodes, and negative tumour markers 1 month postoperatively
Stage II	Tumour totally resected, with positive margins, microscopic lymph node involvement, negative peritoneal fluid and negative tumour markers
Stage III	Gross residual disease or gross lymph node involvement ± peritoneal fluid ± tumour markers
Stage IV	Visceral abdominal involvement or distant metastasis ± tumour markers

Marina N, Fontanesi J, Kun L, Rao B, Jenkins JJ, Thompson EI, Etcubanas E. Treatment of childhood germ cell tumors. Review of the St. Jude experience from 1979 to 1988. Cancer. 1992 Nov 15;70(10):2568-75.

Appendix E

Staging system used by Children's Oncology Group GCT trials

Testicular

I Limited to testis, completely resected by high inguinal orchiectomy; no clinical, radiographic, or histologic evidence of disease beyond the testis; tumor markers normal after appropriate half-life decline; patients with normal or unknown markers at diagnosis must have negative ipsilateral retroperitoneal lymph node sampling to confirm stage I disease

II Transcrotal orchiectomy; microscopic disease in scrotum or high in spermatic cord (<5 cm from proximal end); retroperitoneal lymph node involvement (<2 cm) and/or increased tumor markers after appropriate half-life decline

III Tumor-positive retroperitoneal lymph node(s) >2 cm in diameter; no visceral or extra-abdominal involvement

IV: Distant metastases that may include liver

Ovarian

I Limited to ovary, peritoneal washings negative for malignant cells; no clinical, radiologic, or histologic evidence of disease beyond the ovaries (gliomatosis peritonei did not result in upstaging); tumor markers negative after appropriate half-life decline

II Microscopic residual or positive lymph nodes (<2 cm); peritoneal washings negative for malignant cells (gliomatosis peritonei did not result in upstaging); tumor markers positive or negative

III Gross residual or biopsy only, tumor-positive lymph node(s) >2 cm in diameter; contiguous visceral involvement (omentum, intestine, bladder); peritoneal washings positive for malignant cells

IV Distant metastases that may include liver

Extragonadal

I Complete resection at any site, coccygectomy included as management for sacrococcygeal site, negative tumor margins

II Microscopic residual; lymph nodes negative

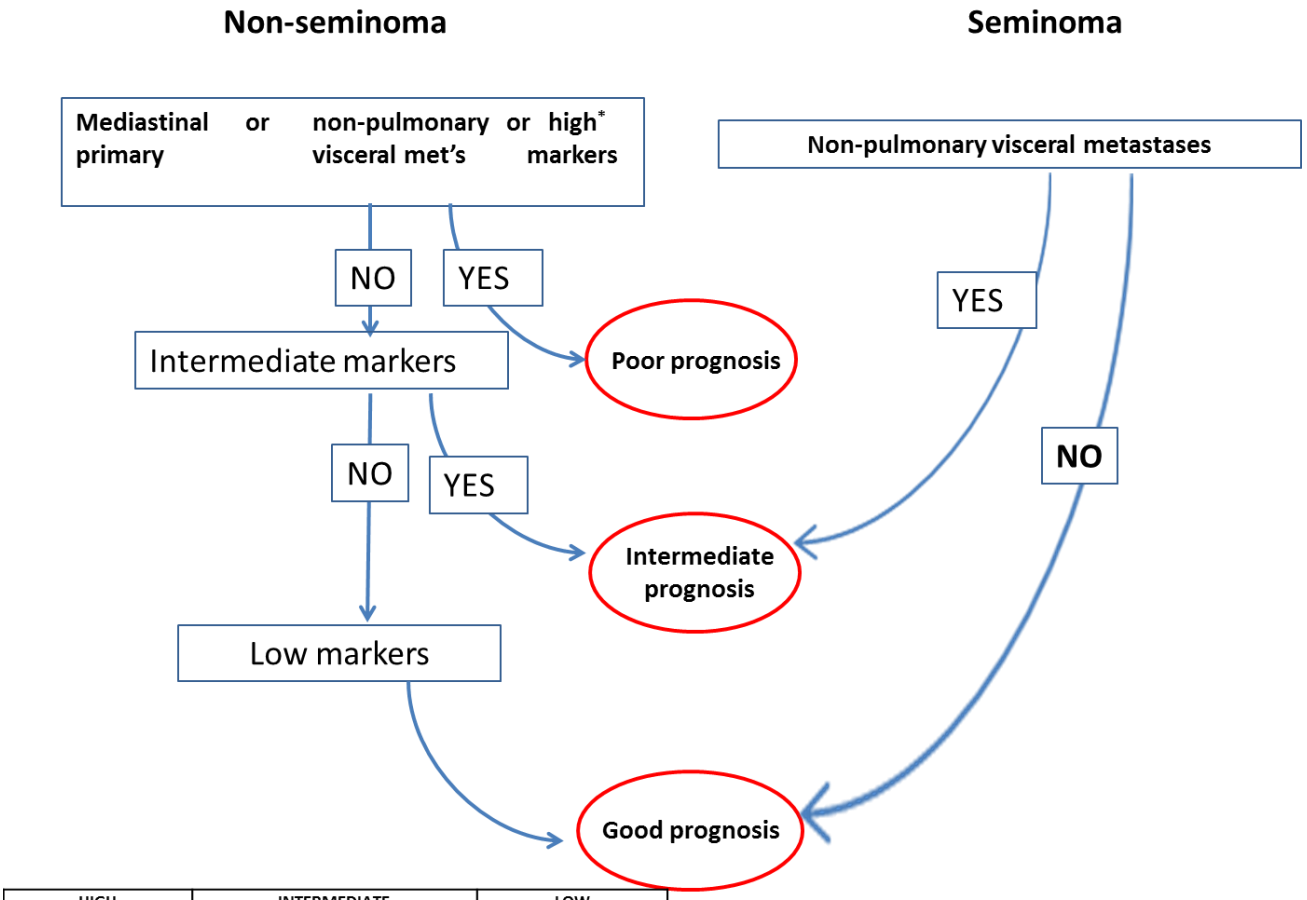
III Gross residual or biopsy only; regional lymph nodes negative or positive

IV Distant metastases that may include liver

Cushing B, Giller R, Cullen JW, et al. Randomized comparison of combination chemotherapy with etoposide, bleomycin, and either high-dose or standard-dose cisplatin in children and adolescents with high-risk malignant germ cell tumors: a pediatric intergroup study—Pediatric Oncology Group 9049 and Children's Cancer Group 8882. J Clin Oncol. 2004;22:2691-2700

Appendix F

International Germ Cell Consensus Classification



HIGH	INTERMEDIATE	LOW
AFP > 10 000 ng/mL	AFP > 1000 and < 10 000ng/mL	AFP < 1000 ng/mL
hCG > 50 000 IU/L	hCG > 5000 and < 50 000 IU/L	hCG < 5000 IU/L
LDH > 10 X N	LDH >1.5 X N and < 10 X N	LDH < 1.5 X N

International Germ Cell Cancer Collaborative Group. International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. J Clin Oncol. 1997;15:594-603.

Appendix G

Plagiarism report

Appendix H

PHOTOCOPY
ORIGINAL WITH
DR POOLE

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Poole

CLEARANCE CERTIFICATE	PROTOCOL NUMBER M060215
PROJECT	Paediatric Haematology and Oncology Database
INVESTIGATORS	Dr J Poole
DEPARTMENT	Paediatric Haematology & Oncology
DATE CONSIDERED	06.02.24
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 06.02.27 CHAIRPERSON .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor :

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10005, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

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