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**The types and treatment outcomes of germ cell tumours of the ovary
seen at Groote Schuur Hospital, Cape Town, between 1994-2008:
a retrospective survey**

by

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DECLARATION

I, Khadiga Mohammed, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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I have entered the corrections as requested by the 2 examiners. These corrections were checked and approved by my supervisor, Dr A L van Wijk.

Signed:

signature removed

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PART A

**ABSTRACT and
STUDY
PROTOCOL**

PART A: ABSTRACT and STUDY PROTOCOL

Abstract:

Objective: This retrospective observational study aims to review patients with Malignant Ovarian Germ Cell Tumours (MOGCTs) treated at Groote Schuur Hospital over a 15 year period. The disease profiles, treatment modalities used, overall and disease free survival rates for each category were analysed. In addition, the HIV status and outcome for HIV positive patients were examined.

Method: A medical chart review of adult patients with MOGCTs treated between 1994-2008 was conducted. Data were collected in customized data sheets for transfer to an electronic spread sheet. The Kaplan-Meyer method was used to obtain 5-year survival data.

Results: Forty patients were treated for MOGCTs. Median age at the time of diagnosis was 30.2 years (range 13-63 years). Ten patients (25%) had dysgerminoma and 30 (75%) had non-dysgerminoma tumour types. The latter group comprised immature teratoma in ten, yolk sac tumour in eight, and mixed germ cell tumour in three patients, while nine patients had mature teratoma with malignant transformation. Nineteen patients were FIGO stages I-II and twenty-one were stages III –IV. Fertility sparing surgery was performed in most patients (77.5%). Twenty-eight patients received chemotherapy, mostly with a three-day platinum based chemotherapy regimen (BEP).

Excluding the group with monodermal malignant transformation in mature teratoma (MTMT), complete response to primary treatment was achieved in 24 of 31 patients (77.4%). After a median follow up of 42.5 months (range 2-60), overall five year survival rate was 69.1%, and disease free survival rate was 90.6%. Of five HIV-positive patients, three had died from MOGCT. Four of the nine patients with MMT are alive after five years.

Conclusion: The prognosis for MOGCTs is excellent if managed with standard treatment initially. Treatment of MTMT is less well defined. Patients with advanced HIV infection did poorly and should be considered for initiation of antiretroviral therapy prior to chemotherapy.

Study Protocol:

General:

This study aimed to look at the disease profiles and treatment outcomes for those patients with ovarian germ cell tumour who presented to Groote Schuur Hospital (GSH) during the 15-year period of 1994-2008. In order to perform this audit, a study proposal was prepared to guide our steps throughout this process.

A letter was submitted to the Human Research Ethics Committee of the University of Cape Town's Faculty of Health Science for approval. Permission to conduct the study was also sought from the Clinical Directorate of Groote Schuur Hospital (GSH). Permission to proceed was obtained from both (see Addendum).

Patients charts:

To perform the audit, a list of all adult patients with MOGCTs registered at GSH between 1994 and 2008 will be obtained from the Gyn-Oncology Database of the Department of Radiation Oncology. For this study, "adult" is defined as 13 years or older; this being the traditional cut-off age used at the associated tertiary hospitals of the University of Cape Town, while the Surveillance, Epidemiology, and End Results (SEER) programme in America uses 15 years (Associate Prof. A. Davidson, personal communication, 12 January 2012). As cited by Butow *et al.*, the definition used by the WHO for adolescents and young adults is an age group of 12-25 years.¹

All the patients to be included in this study were diagnosed with histologically confirmed primary germ cell tumour of the ovary, of any FIGO stage, during the chosen 15-year period of 1994-2008. There are no exclusion factors except for the extra-gonadal germ cell varieties.

Data from the medical records of these patients will be extracted and recorded on customized data sheets (see Addendum), and then transferred to an Excel spreadsheet. As a quality assurance procedure, all extracted data are to be reviewed twice from the source documents (patient charts), then cross checked with data on the Gyn-Oncology Database.

The data points to be collected include age, date of registration (defined as date of first treatment = primary surgery in all cases), FIGO stage, histological types, classified broadly into Dysgerminoma (“Dysg”) and non-Dysgerminoma (“non-Dysg”), collectively called malignant ovarian germ cell tumours (“MOGCTs”), and malignant somatic transformation in a mature teratoma, or monodermal teratoma (“MTMT”). The reason for studying the latter group separately is due to the different characteristics and clinical behaviour of the MTMT variety.

For the primary treatment(s), the type of surgery, whether fertility preserving surgery or more radical surgery, is to be documented; also, the regimen and number of cycles of chemotherapy administered, and any major side effects experienced by the patients, and/or radiotherapy details are to be recorded.

Laboratory values of HIV status (and CD4 count, if positive), and the initial levels of serum tumour markers will be noted (β -HCG, LDH, AFP, and CA125, whenever available).

Regarding the follow-up of patients, data will be recorded about response to primary treatment, date of response, and current status (alive or dead, alive with disease or disease-free, or lost) at last follow-up. In addition, the site(s), date and the treatment of confirmed disease recurrence will be recorded. For this study, follow up of living patients is truncated at five years after their registration dates.

Treatment:

Regarding the **study population and setting**, the period of review in the current study includes the time when the BEP chemotherapy regimen was already established as standard treatment in MOGCTs;² consequently, with one notable exception, all our patients received BEP as first line chemotherapy. The noticeable exception is the small group of patients with MTMT histology, where the intention was to treat according to the histological subtype which had undergone malignant transformation. These patients received a chemotherapy regimen purportedly specific to their particular subtypes.

All of the patients receiving BEP were subjected to a 3-day BEP regimen, administered as inpatients; the BEP regimen comprised cisplatinum 35mg/m² I.V, VP18/etoposide 120 mg/m² I.V, and bleomycin 15mg IV daily for three days, every

three weeks). Generally, all patients are required to have an initial audiogram and adequate renal function prior to chemotherapy (a creatinine clearance > 50 ml/minute, calculated using the Cockcroft-Gault formula).

Prehydration fluids with 1L N-Saline and two ampules MgSO₄ over two hours were administered on day 1 before each chemotherapy cycle and anti-emetics with dexamethasone 8mg and 5HT₃ antagonist I.V, day 1-2-3 were used. The cisplatin was given in 200ml N-Saline over two hours simultaneously with 500 ml Mannitol for diuresis. This was followed by bleomycin 15 IU in 1L Plasmolyte B over six hours, then 1L N-Saline 6-8 hourly x 2 as post-hydration fluids.

At GSH, carboplatinum is used if there are contraindications to cisplatin administration in an individual patient. Bleomycin was omitted if there is a contraindication, or after a cumulative dose of 300 IU, since exceeding this dose puts a patient at risk for developing pulmonary toxicity.

Since no randomised studies exist for MOGCTs to determine the optimal number of cycles, empirical practice is to use three cycles of BEP for stage I, four cycles for completely resected stage II-IV and stage IV Dysg, and up to six cycles for stage II-IV with residual disease. Where a marker is present, 1-2 cycles after normalization is advised.³ Such an approach has been the practice in our unit as well.

Statistical analysis

The patients' demographics, disease and treatment characteristics will be summarized using descriptive statistics using Excel statistical tools and expressed as numbers, with a percentage value as well. Where appropriate, a mean or median value is given.

For tumour response, the original 1981 World Health Organization response definitions are used:⁴

- Complete response (CR): The disappearance of all known disease, determined by two observations not less than four weeks apart.
- Partial response (PR): 50% or more decrease in total tumour load of the lesions that have been measured to determine the effect of therapy by two observations not less than four weeks apart.

- No response (NR): A 50% decrease in total tumour size cannot be established nor has a 25% increase in the size of one or more measurable lesions been demonstrated.
- Progressive disease (PD): 25% or more increase in the size of one or more measurable lesions or the appearance of new lesions.

The actuarial overall survival rate (OS) at five years will be determined using the Kaplan-Meier method. The initial date is that of commencement of any therapy, whilst patients will be censored at the date of death, or last follow-up.

The disease-free survival (DFS) is calculated from the date of first therapy to the date of confirmed recurrence in those patients who had achieved a complete response to primary therapy, or to the date of last follow-up, or death, where recurrence had not occurred. The 5-year OS and DFS curves will be constructed using the Kaplan-Meier method. Comparison between groups is made with the log rank method using PRISM statistical software version 5.

PART B

**LITERATURE
REVIEW**

University of Cape Town

PART B: LITERATURE REVIEW

Introduction

The objective of this review is to provide the reader with the background and justification for the research, to describe what work has been done in this field by others, then collate this information and examine, evaluate and establish its relevance. Analysis of this information and comparison with results of other researchers may allow identification of what is new, different, or confirmatory. It may identify areas where further study is needed.

The literature review is therefore an extensive search of the field of study and the theory behind it, with the aim of discovering related concepts and the potential relationship between them. Another important rationale for this review is simply to identify potential sources of information for conducting the research.

For the current project, studies conducted between 1970 and the present, addressing germ cell tumours, were searched for. The usual sources were used: PubMed, Google Scholar, reference lists in text books and journal articles. The available English language literature was scanned for any meta-analyses, randomised control trials and case series or even case reports. There are many studies of germ cell tumours in the paediatric population. However, since the focus of this research is the adolescent and adult, these paediatric studies will not be reviewed in detail and will only be referred to if necessary.

Studies of extra-gonadal germ cell tumours are excluded from this review, with the focus being on primary ovarian germ cell tumours. However, the literature on testicular germ cell tumours cannot be ignored since it includes much larger cohorts of patients and there are similarities with treatment.

In this review the focus will be on:

- a) Background and histological types.
- b) Diagnosis and staging.
- c) Tumour markers and prognostic factors.
- d) HIV and germ cell tumours.
- e) The management and outcome of the disease.

f) Conclusion.

a) **Background and histological types:**

Malignant ovarian germ cell tumours (MOGCTs) comprise a unique group of malignancies with widely varying subtypes and behaviours. Often they are highly malignant and rapidly growing tumours, but in general, they are more curable than their epithelial counterparts.^{3,5}

They are rare cancers accounting for less than 5% of all ovarian neoplasms, predominantly affecting young girls and adolescents in their reproductive age.³ The median age at diagnosis is 18 years and incidence is inversely proportional to advancing age, according to Surveillance, Epidemiology, and End Results (SEER) data of malignant germ cell tumors (1973-2002).^{5,6}

From the SEER database, the 30-year, age-adjusted incidence rate per 100,000 women-years was 0.338; the 5-year survival rate was 83.9%. Survival rates improved significantly between 1973 and 2002 and factors affecting survival included the histological subtype, race, stage of disease, and age at diagnosis.⁵ In a report from the National Cancer Institute in four member countries (Cyprus, Egypt, Israel, and Jordan) of the Middle East Cancer Consortium (MECC) the incidence of germ cell tumour between 1996-2001 was 2.2%, 3.3%, 7.2% and 10.8% in Cyprus, Israel, Egypt and Jordan, respectively, compared to 3.0% in the US SEER data.⁷

MOGCTs derive from primitive germ cells of the embryonic gonadal ridge; these primordial cells migrate into the latter at six weeks of embryonic life. Subsequently these tumours tend to have a spectrum of histological differentiation that normally assembles the primitive developing embryo. Dysgerminoma (Dysg) arises from undifferentiated tissue, and endodermal sac or yolk sac (YST) tumours show malignant tendency in extra-embryonic differentiation. Whereas immature teratomas (IT) derive from somatic differentiation from all three primitive germ cell lines,⁶ recent studies propose that Dysg may be the antecedent of some of the other germ cell tumours.⁸

Ovarian germ cell tumours are broadly classified as Dysgerminoma (Dysg), which is the most common type and the counterpart of the male seminoma, or non-

Dysgerminoma (non-Dysg) ^{3,9} The most frequently encountered types of non-dysgerminomatous tumours are immature teratomas (IT), mature teratoma with malignant transformation (MTMT), yolk sac tumour (YST), also known as endodermal sinus tumour, and mixed germ cell tumours. Less common types are embryonal carcinoma, nongestational choriocarcinoma and polyembryoma.⁹ This wide subdivision is an important distinction, as it plays an important role in the treatment and prognosis for these patients.^{10,11}

The recent WHO classification system for MOGCTs was conducted by Tavassoli and colleagues with comprehensive details regarding clinico-pathologic characteristics, as well as guidelines for the pathologist for precise diagnosis.¹² Table 1 below shows a modified version of their classification.¹³

According to the WHO system, the germ cell tumours are divided into three broad categories: primitive germ cell tumours, biphasic or triphasic teratoma, and thirdly, monodermal teratoma and somatic-type tumours associated with biphasic or triphasic teratoma (“dermoids”). This division allows for a clearer distinction between primitive germ cell tumours and the teratoma group. Moreover it allows for the accurate placement of specific subtypes which have elements of both teratoma and somatic neoplasm such as struma ovarii.^{12,13} Of 1262 cases identified by the SEER study of MOGCTs between 1973 and 2002, 32.8% had Dysg, 35.6% had IT, and 28.7% had Mixed GCTs.⁵

b) **The diagnosis, staging and tumour markers:**

Because of the relative rarity of MOGCTs it was difficult to develop clinical profiles of patients with various histological types, though over time, clinical descriptions have improved. Pain and abdominopelvic mass are the commonest presentation in young women.¹⁴ Sometimes the diagnosis is only established at the time of surgery when the presentation is one of acute abdomen. Abdominal distension and vaginal bleeding can also occur and the duration of symptoms are usually short (2-4 weeks). These tumours are usually unilateral, though they can occur bilaterally in up to 15% of cases with Dysg histology.¹⁵

The evaluation of these patients should include routine blood tests, specifically tumour markers, and chest X-ray. Ultrasound and computed tomography can play an

important role in the diagnostic imaging of these tumours, revealing solid and/or cystic components.¹²

Table 1: WHO classification of the Germ Cell Tumour (modified version, used with permission of publishers¹³)

<p>I. Primitive germ cell tumours</p> <ul style="list-style-type: none"> A. Dysgerminoma B. Yolk sac tumour C. Embryonal carcinoma D. Polyembryoma E. Nongestational choriocarcinoma F. Mixed germ cell tumour (specify components) <ul style="list-style-type: none"> 1. Diffuse embryoma variant
<p>II. Biphasic or triphasic teratoma</p> <ul style="list-style-type: none"> A. Immature teratoma B. Mature teratoma <ul style="list-style-type: none"> 1. Solid 2. Cystic (dermoid cyst) 3. Fetiform teratoma (homunculus)
<p>III. Monodermal teratoma and somatic-type tumours associated with biphasic or triphasic teratoma</p> <ul style="list-style-type: none"> A. Thyroid group B. Carcinoid group C. Central nervous system tumour group D. Carcinoma group E. Melanocytic group F. Sarcoma group G. Sebaceous tumour group H. Pituitary-type tumour group I. Retinal anlage tumour group J. Others

Table 2. FIGO staging.

Stage I	Growth limited to the ovaries.
Ia	Growth limited to one ovary: no ascites present containing malignant cells. No tumour on the external surface; capsule intact.
Ib	Growth limited to both ovaries: no ascites present containing malignant cells. No tumour on the external surfaces; capsules intact.
Ic	Tumour either Stage Ia or Ib, but with tumour on surface of one or both ovaries, or with capsule ruptured, or with ascites present containing malignant cells, or with positive peritoneal washings.
Stage II	Growth involving one or both ovaries with pelvic extension.
IIa	Extension and/or metastases to the uterus and/or tubes.
IIb	Extension to other pelvic tissues.
IIc	Tumour either Stage IIa or IIb, but with tumour on surface of one or both ovaries, or with capsule(s) ruptured, or with ascites present containing malignant cells, or with positive peritoneal washings.
Stage III	Tumour involving one or both ovaries with histologically-confirmed peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes. Superficial liver metastases equal Stage III. Tumour is limited to the true pelvis, but with histologically-proven malignant extension to small bowel or omentum.
IIIa	Tumour grossly limited to the true pelvis, with negative nodes, but with histologically-confirmed microscopic seeding of abdominal peritoneal surfaces, or histologically- proven extension to small bowel or mesentery.
IIIb	Tumour of one or both ovaries with histologically-confirmed implants, peritoneal metastasis of abdominal peritoneal surfaces, none exceeding 2 cm in diameter: nodes are negative.
IIIc	Peritoneal metastasis beyond the pelvis > 2 cm in diameter and/or positive retroperitoneal or inguinal nodes.
Stage IV	Growth involving one or both ovaries with distant metastases. If pleural effusion is present, there must be positive cytology to allocate a case to Stage IV. Parenchymal liver metastasis equals Stage IV.

These tumours are staged according to the International Federation of Gynaecology and Obstetrics (FIGO) surgico-pathological staging system for the carcinoma of the ovary (Table 2).¹⁶

On presentation, approximately 60-70% of cases of MOGCTs are FIGO stage I-II, whereas 10-20% are stage III, with stage IV being relatively rare. This is in contrast to epithelial ovarian cancer where later presentations are the norm. Spread is via the lymphatics, blood stream, or dissemination via the peritoneal surface.^{3,15}

c) Tumour markers and prognostic factors

Many MOGCTs produce the following tumour markers: Beta-human chorionic gonadotrophin (β -HCG), alpha feto-protein (AFP) and lactate dehydrogenase (LDH). These, when elevated, provide a highly sensitive and specific indicator of the presence of certain histological components. Furthermore, serial assay for these tumour markers is useful for monitoring the response to chemotherapy pre-operatively, post-operatively and for subsequent follow up.^{3,11,15}

β -HCG and AFP are specific markers for MOGCTs, the latter marker commonly being raised in YST. β -HCG can be elevated in 5% of Dysg and the combination of both markers suggests the presence of mixed GCT. LDH is a non-specific tumour marker which can be found in 88% of the germ cell tumours; however it can be of value in assessing response to therapy, or detecting a recurrence, particularly with Dysg. Similarly, even CA-125 elevation can reflect a tumour progression.^{3,9,15}

Several prognostic factors have been reported for MOGCTs: an advanced stage, specific histological types (non-Dysg/immature histology) and bulky residual disease after surgery were significantly associated with a worse overall survival.¹⁵ In a study conducted by Li *et al.*, on patients with chemo-refractory disease, it was found that an advanced stage, non-Dysg\IT histology, and residual tumour after salvage chemotherapy, were prognostic factors portending poor outcome.¹⁷ Murugaesu and co-workers reported that elevation of both AFP and β -HCG was a strong predictor of survival, compared to elevation of either marker alone.¹⁸

In a recently reported large study of 613 patients, Kumar *et al.* found that the presence of lymph node metastasis is also a poor prognostic factor.¹⁹ Other independent prognostic factors associated with relapse are non-platinum chemotherapy, very high AFP and pure YST histology.²⁰

d) HIV and germ cell tumours

Concerning the occurrence of germ cell tumours in patients with human immunodeficiency virus (HIV) infection, both these diseases target the youth in their

reproductive age. The co-existence of HIV and MOGCTs is becoming more common, especially over the last decade as the HIV pandemic has become established in some parts of the world. Since the literature for testicular germ cell tumours is more voluminous than for their ovarian counterparts, it is not surprising that guidelines exist for the management of HIV-infected men with germ cell tumours.^{21,22}

A search of the literature concerning MOGCTs and HIV has revealed a single case report for a South African patient,²³ a 16 year-old female, CD4 count of 903, with a stage IA tumour. A unilateral-salpingo-oophorectomy was done and she was able to complete four cycles of BEP chemotherapy and remain disease free and alive one year after treatment.²³ Another two cases were identified in the literature with immunosuppression and Dysg histology; since both were on immunosuppressive drugs, the authors believed that there is an association between immunosuppression and MOGCTs.²⁴

Because the literature on MOGCTs and HIV infection is sparse, it seems reasonable to extrapolate management guidelines from the testicular cancer literature for women with germ cell tumours.

e) The management and outcome of the disease

There have been no randomised trials of therapy for the MOGCTs due to their relative rarity; information on current management comes from retrospective reviews of patients' treatment outcomes and from some multi-centric prospective trials. Treatment strategies have also been adopted from prospective trials, some randomised, conducted on their more common counterparts, the male germ cell tumours.^{9,15} It is not surprising, therefore, that a recent attempt by the esteemed Cochrane group to conduct a meta-analysis of the benefits of chemotherapy in adult MOGCTs was unsuccessful.²⁵

Surgery is the initial treatment of choice: to establish the diagnosis, stage, and to completely remove, or optimally debulk the tumour. Since this disease predominantly affects young females, conservative surgery to preserve fertility is the norm.³ In general, the treatment principles for all types of MOGCTs are similar to those that guide the management of epithelial ovarian cancer (EOC), though with some exceptions. The predominant unilaterality of these adnexal tumours often

allows for the potential of fertility-sparing surgery, rather than total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO). Fertility preservation without compromising the chance of cure is feasible, even in extensive and metastatic disease. The relatively lower frequency of advanced stage disease, the excellent sensitivity to platinum-based chemotherapy, and the lower incidence of severe late effects are other differences from the EOCs.^{3,11,15}

A second-look operation (SLO) is generally unnecessary in completely resected, or tumour marker positive MOGCTs. In immature teratoma, however, whether pure or mixed with other MOGCTs, post-chemotherapy radiological assessment and second-look surgery operations are often employed. The reasons for a mainly surgical approach for all residual masses detected soon after chemotherapy, or even years later, would be diagnostic; the aim would be to exclude malignancy, prevent a “mature growing teratoma syndrome”, to relieve pressure symptoms from such a mass, and to prevent subsequent dedifferentiation of teratoma into a cancer.^{15,26}

Concerning so-called “chemotherapeutic retro-conversion”, the underlying mechanism could either be maturation of immature teratomatous elements under the influence of chemotherapy, or destruction of immature teratoma in metastases containing both mature and immature components. The latter seems the more likely, though it is uncertain why these benign masses should sometimes be enlarging (growing teratoma syndrome); perhaps this is the phenotypic outcome of the inherent growth potential of the primitive foetal tissue?^{26,27}

The recommended post-operative treatment approach for MOGCTs is chemotherapy. Historically, the evolution of the chemotherapeutic treatment of MOGCTs was the most important advance in the clinical management of these tumours. Before the 1970s and the advent of combination chemotherapy, the prognosis for patients with MOGCTs was dismal. Virtually all patients with advanced-stage disease died, and even in apparent stage I disease, only 5% to 20% of patients survived after surgery alone. Over the past 30 years, the therapeutic approach has evolved along similar lines to that used for testicular germ cell tumours. Initially, the combination of vincristine, dactinomycin, and cyclophosphamide (VAC) became the standard. However, despite high response rates, cure rates in patients with advanced MOGCT were less than 50%.^{14,28}

The introduction of cisplatin-based chemotherapy (cisplatin, vinblastine, and bleomycin - PVB) proved to be effective and improved survival in male patients with refractory testicular cancer. Subsequently, the BEP (bleomycin, etoposide and cisplatin) combination showed equal efficacy with less toxicity in this population.^{11,19,28} Therefore, while both regimens have become incorporated into the first-line treatment of patients with MOGCTs post-operatively, BEP is the current standard of care for these patients. The exceptions are stage I, grade 1 IT, and stage IA Dysg, in which adjuvant chemotherapy can be omitted.²⁸

In MOGCTs nowadays, cure rates approach 95–100% in early stage disease and 75–80% in advanced disease. Dysg has a cure rate of over 95%, even in advanced disease.^{11,19,28}

It should be noted that in the standard BEP regimen, cisplatin and etoposide are usually administered over 5 days, whereas bleomycin is administered weekly. The Gynaecologic Oncology Group (GOG) used this regimen in a study involving 93 patients with MOGCTs. While the DFS rate was an excellent 89%, acute toxicity was described as “moderate”. The reporting of treatment-related toxicities can be criticised in this paper, since most patients were reported as having “some degree of myelosuppression”. Ten patients experienced febrile neutropaenia. Muco-cutaneous toxicity is mentioned in passing as being “fairly common”. Overall, there were no drug-related deaths. The incidence of neuro- or ototoxicities is not mentioned, though pulmonary toxicity was not observed. Whether treatment delays occurred was also not described.²⁸

In testicular tumours, the EORTC/MRC have examined the BEP regimen in a large study of patients with the good prognosis subgroup. A 2 x 2 factorial design was used to compare three cycles of BEP versus 3 BEP + 1 EP, and BEP 5-day versus BEP 3-day administration. The doses of the 3-day BEP regimen were cisplatin 50 mg/m² I.V for days 1 and 2, etoposide 165mg/m² I.V for days 1-3, and bleomycin 15 mg weekly I.V x 3.²⁹ The results have subsequently been updated, confirming equivalence of three vs four cycles, as well as for the 5-day vs the 3-day regimen, although with more myelotoxicity with the latter. This did not, however, result in more dose attenuations. Non-haematological toxicity was similar. Where bleomycin is contra-indicated, four cycles of 5-day cisplatin + etoposide (PE) is equivalent to three cycles of BEP.³⁰

Various modifications to the 3-day BEP regimen have been reported in treatment for MOGCTs with the aim of “increased convenience and less toxicity”.^{31,32} The issue of equivalence of these modifications to the standard 5-day (or 3-day) BEP is of concern, and can only be established in randomised studies. There is, however, no strong evidence that these modified regimens are inferior.

In a study from Greece, Dimopoulos *et al.* evaluated the safety and activity of a 3-day modified (mBEP) regimen. These authors used BEP (cisplatin 40 mg/m² IV for days 1-3, etoposide 120 mg/m² IV on days 1-3, and bleomycin 15 mg IV on days 1-3). In a prospective study of 48 patients with MOGCTs (14 with dysg. and 34 with Non-Dysg tumours), three cycles of mBEP for stages I–III, completely resected, or four cycles for incomplete resection or stage IV, were administered on an outpatient basis. All patients with stages I/II and all with Dysg were cured, although 20 % of patients with stages III/IV Non-Dysg experienced disease progression, especially if suboptimally debulked.³¹

Interestingly, an even-shorter BEP regimen has been explored. Tay *et al.* used a 2-day BEP in a pilot study of 31 patients with MOGCT's.³³ While the overall DFS was 93%, such modifications cannot be recommended without further study. It is also tempting, for reasons of lower toxicity and ease of administration, to substitute carboplatin for cisplatinum in the chemotherapeutic management of MOGCTs. In testicular cancers, however, studies show that this approach yields inferior results.³⁴

Another important issue concerns the duration of treatment, in other words, the number of cycles to be given. With the 5-day BEP regimen, the GOG has established, and recommended, that three cycles of BEP should be a standard treatment for completely resected MOGCTs.²⁸ This study of MOGCTs notably excluded all patients with dysgerminoma. Since radiotherapy has been replaced by chemotherapy as post-operative treatment due to the fertility issues with the former, it is therefore uncertain what the appropriate number of cycles of BEP is for Dysg. There is no reason to believe, however, that Dysg would not require at least three cycles of BEP, although the reduction of chemotherapy duration, or substitution of cisplatinum by the less toxic carboplatinum requires further study.³

Risk stratification in testicular germ cell tumours generally determines the number of cycles of chemotherapy to be administered. Since neither such stratification, nor

randomised studies, exist for MOGCTs, empirical practice is to use three cycles of BEP for stage I, four cycles for completely resected stages II-IV and stage IV Dysg, and up to six cycles for stages II-IV with residual disease. Where a marker is present, one or two cycles should be given after normalization. Bleomycin should be omitted after a cumulative dose of 300 IU because exceeding this dose puts patients at risk of developing pulmonary toxicity.³

In the past, the use of radiotherapy was reserved Dysg histology. For instance, for patients with stage III disease, retroperitoneal and para-aortic lymph nodes were treated with pelvic or whole abdomen radiotherapy. This practice went out of favour due to the high sensitivity of these tumours to chemotherapy, as well as the long term toxicity of the radiation and fertility issues.⁹

Concerning the outcomes of MOGCTs, the Hellenic Cooperative Oncology Group reported on a series of 13 patients with Dysg and 40 patients with Non-Dysg. The OS at five years was 87% for the entire group, being 100% for patients with Dysg and 85% for patients with Non-Dysg tumours. Even in patients with advanced Non-Dysg tumours and residual disease after surgery, 85% remained disease free.³⁵

Lai *et al.* reviewed a larger cohort of 93 patients. The 5-year survival rate was 97% for those treated primarily at their hospital; the OS for Dysg versus Non-Dysg was 100% and 83.3%, respectively.³⁶ In another series of 113 patients with MOGCTs (stages IC to IV), it was demonstrated that long-term outcome of patients with MOGCTs is excellent, with 5, 10, and 25-year estimated survival rates of 83%, 81%, and 81%, respectively.¹⁹

Due to the relative rarity of these tumours, a degree of heterogeneity in these retrospective studies is inevitable and randomised studies are difficult to perform. Nevertheless, these case series indisputably are of value in assessing treatment outcomes, since these provide the only evidence-based information from which management guidelines for this population could be derived, apart from indirect evidence from the testicular germ cell tumour experience.

f) Conclusion

It is established that fertility preserving surgery and the BEP post-operative chemotherapy constitute the current standard of care and that the prognosis for these

patients is excellent, even in advanced disease. This latter group, however, may require further management standardization. The association between HIV and MOGCTs also requires further study.

This literature survey has been informative for this student insofar as it, to quote Marshall and Rossman (1999), built “a logical framework for research and set it within a tradition of enquiry and a context of related studies”.³⁷

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PART C

**PUBLICATION-
READY
MANUSCRIPT**

Running Head: Germ Cell Tumours of the Ovary at Groote Schuur Hospital.

**The types and treatment outcomes of Germ Cell Tumours
of the Ovary seen at Groote Schuur Hospital, Cape Town,
between 1994-2008 - a retrospective survey**

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Abstract

Objective: This retrospective observational study aims to review patients with malignant ovarian germ cell tumours (MOGCTs) treated at Groote Schuur Hospital over a 15-year period.

Method: A medical chart review of adult patients with MOGCTs treated between 1994 and 2008 was conducted. Data gathered were transferred to an electronic spreadsheet. The Kaplan-Meier method was used to obtain 5-year survival data.

Results: Forty patients were treated for MOGCTs. Median age at the time of diagnosis was 30.2 years (range 13-63 years). Ten patients (25%) had dysgerminoma and 30 (75%) had non-dysgerminomatous types. The latter group comprised immature teratoma in ten, yolk sac tumour in eight, and mixed germ cell tumour in three patients, while nine patients had mature teratoma with malignant transformation. Surgery was with fertility-sparing procedures wherever possible. Chemotherapy entailed a 3-day modified BEP regimen during the period of the study.

Excluding the group of nine with monodermal malignant transformation in mature teratoma (MTMT), complete response to primary treatment was achieved in 24 of 31 patients (77.4%). After a median follow up of 42.5 months (range 2-60), overall 5-year survival rate was 69.1%. Of five HIV-positive patients, the 5-year overall

survival rate was only 40%. Four of the nine patients with MTMT are alive after five years.

Conclusion: The prognosis of MOGCTs is excellent if managed with standard treatment initially. Treatment of MTMT is less well defined. Patients with advanced HIV infection did poorly and should be considered for initiation of antiretroviral therapy prior to chemotherapy.

Keywords:

Malignant Ovarian Germ Cell tumours, fertility-sparing surgery, chemotherapy, HIV infection.

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Introduction

Malignant ovarian germ cell tumours (MOGCTs) comprise a unique group of malignancies which derive from primitive germ cells of the embryonic gonadal ridge. They account for less than 5% of all ovarian neoplasms and have widely varying subtypes and behaviours. Although highly malignant and rapidly growing tumours, they are generally more curable than their epithelial counterparts.^{1,2,3} It is imperative that these tumours be managed from the outset with accurate diagnosis, staging and treatment.

They are broadly classified as dysgerminomas (Dysg), the most common type and the counterpart of the male seminoma, and a non-dysgerminomatous group (non-Dysg).^{2,4} This classification plays a role when it comes to the treatment and prognosis for these patients.^{5,6} A modified sub-classification of the ovarian germ cell tumours is shown in [Table 1](#).⁷

There have been no randomised trials of therapy for MOGCTs due to their relative rarity. The data on which management is based derive from retrospective reviews of patients' treatment outcomes and from some multi-centric prospective trials.

Treatment strategies have also been adopted from prospective trials, many of them randomised, conducted in their more common counterparts, the male germ cell tumours.^{4,8} It is not surprising, therefore, that a recent attempt at a meta-analysis of the benefits of chemotherapy in adult MOGCTs by the Cochrane group was unsuccessful.⁹

Table 1: WHO classification of the Germ Cell Tumours*

<p>I. Primitive germ cell tumours</p> <p>A. Dysgerminoma</p> <p>B. Yolk sac tumour</p> <p>C. Embryonal carcinoma</p> <p>D. Polyembryoma</p> <p>E. Nongestational choriocarcinoma</p> <p>F. Mixed germ cell tumour (specify components)</p> <p>1. Diffuse embryoma variant</p>
<p>II. Biphasic or triphasic teratoma</p> <p>A. Immature teratoma</p> <p>B. Mature teratoma</p> <p>1. Solid</p> <p>2. Cystic (dermoid cyst)</p> <p>3. Fetiformteratoma (homunculus)</p>
<p>III. Monodermal teratoma and somatic-type tumours associated with biphasic or triphasic teratoma</p> <p>A. Thyroid group</p> <p>B. Carcinoid group</p> <p>C. Central nervous system tumour group</p> <p>D. Carcinoma group</p> <p>E. Melanocytic group</p> <p>F. Sarcoma group</p> <p>G. Sebaceous tumour group</p> <p>H. Pituitary-type tumour group</p> <p>I. Retinal anlage tumour group</p> <p>J. Others</p>

*(modified by Roth et al⁷ – used with permission from publisher)

A survey of patients with MOGCTs treated at Groote Schuur Hospital (GSH) over a 15-year period is presented. The histological types, treatment applied, and outcomes of these patients were recorded and analyzed.

Materials and methods

Approval from both the Research Ethics Committee of the Faculty of Health Science, University of Cape Town, and the Clinical Directorate of Groote Schuur Hospital was obtained to conduct this retrospective observational study. Patients were not identified and therefore their consent was not required.

To perform the audit, a list of all adult patients with primary MOGCTs registered at GSH between 1994 and 2008 was obtained from the Gyn-Oncology database of the Department of Radiation Oncology. "Adult" was defined as 13 years or older, this being the traditional cut-off age used at the associated tertiary hospitals of the University of Cape Town. Data from the medical charts of these patients were extracted and recorded on customized data sheets, then transferred to an Excel spreadsheet. As a quality assurance procedure, all extracted data were reviewed twice from the source documents (patient charts), then cross checked with data on the Gyn-Oncology database.

The data points collected included age, date of registration (defined as date of first treatment = primary surgery in all cases), histological type, and FIGO stage. For the primary treatment(s), the type of surgery, the regimen and number of cycles of chemotherapy administered, and/or radiotherapy details were recorded. Laboratory values of HIV status (and CD4 count, if positive) and the initial levels of serum tumour markers were noted.

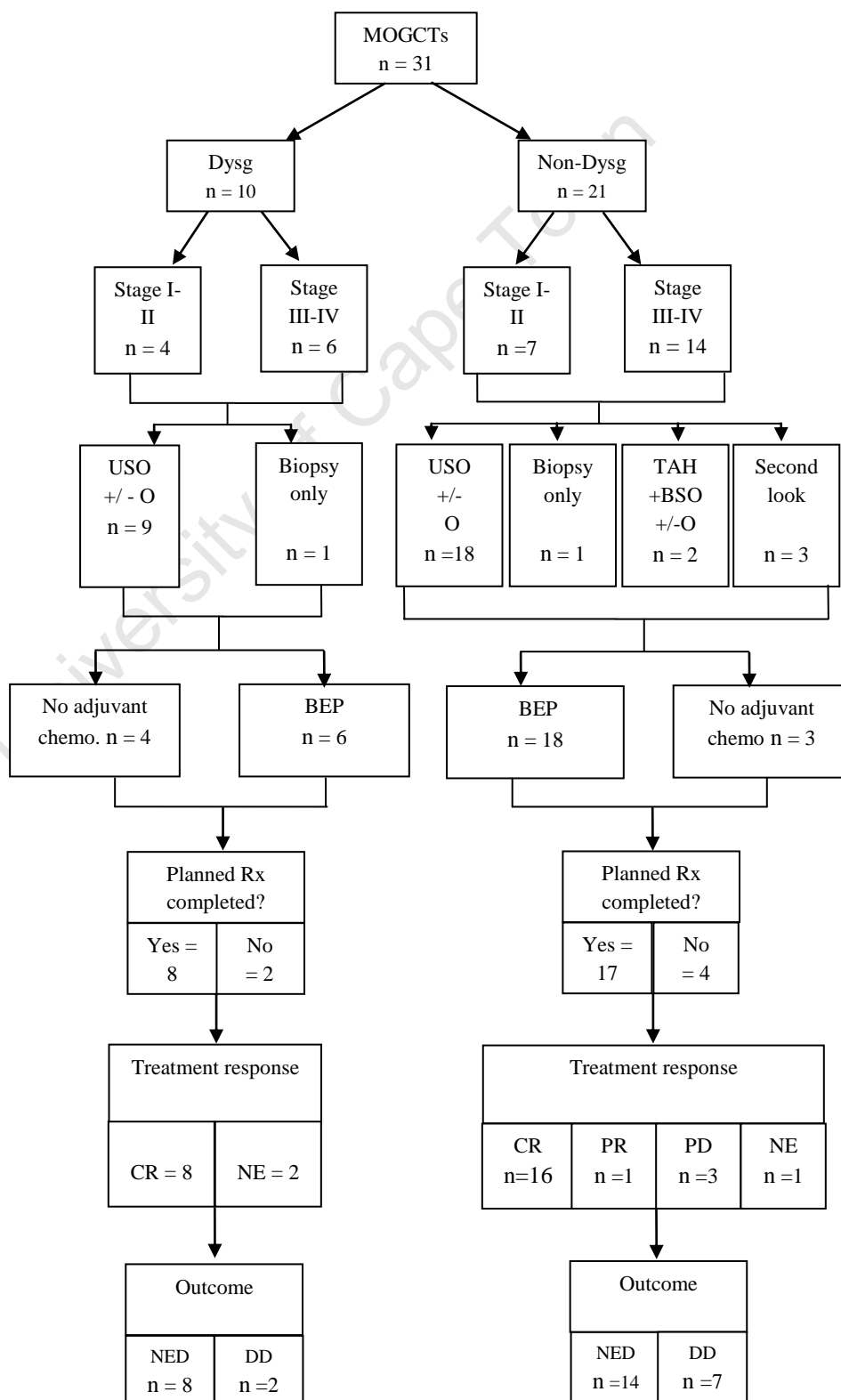
Regarding the follow-up of patients, data on response to primary treatment, date of response, and current status at last follow-up were recorded, as well as the data on site(s), date and treatment of confirmed disease recurrence. For this study, follow up of living patients was truncated five years after their registration dates. Patients' demographic, disease and treatment characteristics were summarized using descriptive statistics. The overall survival (OS) at five years was calculated from the date of registration to the date of death, or last follow-up. The 5-year OS curves were constructed using the Kaplan-Meier method. Comparison between groups was made with the log rank test. Data were analysed using PRISM^R statistical software version 5 (La Jolla, CA, USA).

Results

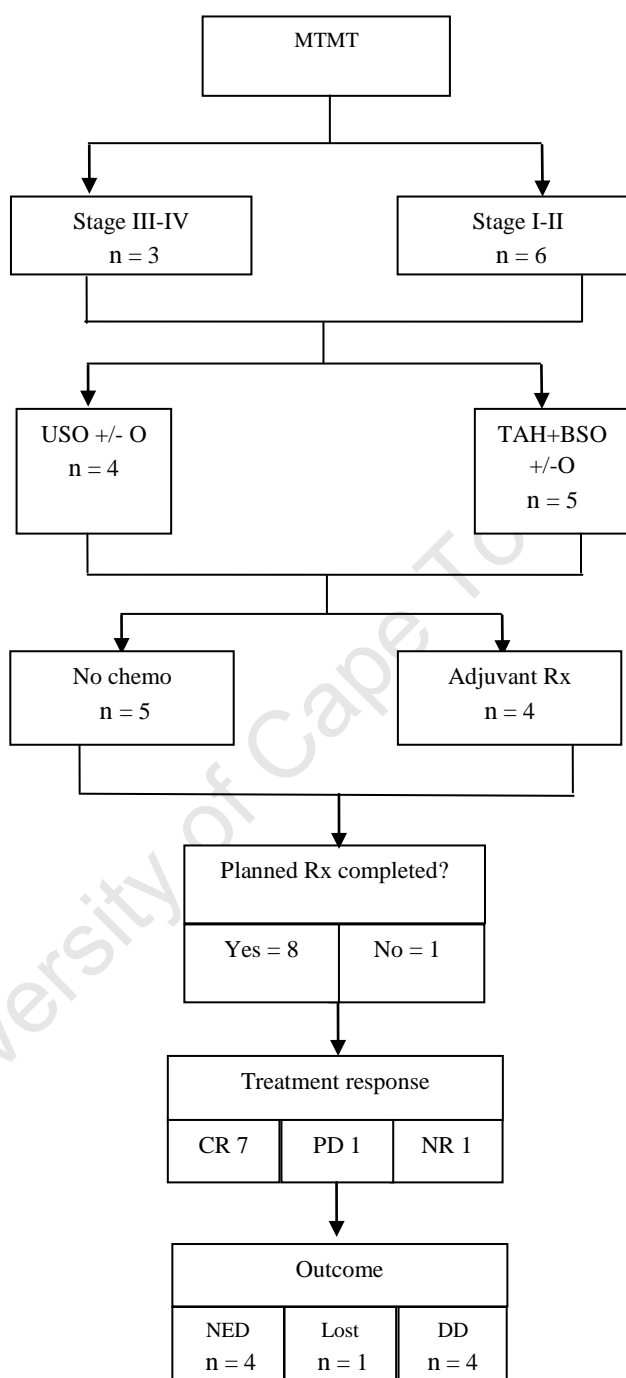
Forty patients were found on the database for the defined study period. The median age at the time of diagnosis was 30.2 years (range 13-63 years). Of the study patients, 31 had the usual types of MOGCTs, while nine had the unusual variants (see flow charts in [Figure 1](#)).

Figure 1. A) Flow chart of all the patients with MOGCTs, and B) with MTMT*.

A)



B)



Caption for Figure 1 and Table 2: Dysg.= dysgerminoma; IT= immature teratoma; YST = yolk sac tumour; Mixed GCT= mixed germ cell tumour; MTMT = mature teratoma with malignant transformation; USO +/- O =unilateral salpingo-oophorectomy +/- omentectomy; 2nd look = second look laparotomy; TAH+SO +/- O = total abdominal hysterectomy + salpingo-oophorectomy +/- omentectomy; BEP = bleomycin, etoposide and cisplatin; CR = complete response; NE = not evaluated; PR = partial response; PD = progression of the disease; NR = no response; LDH = lactate dehydrogenase; hCG = human chorionic gonadotrophin; AFP = alpha feta-protein; CA 125=cancer antigen; NED = no evidence of disease; DD = dead from disease; Planned Rx = Initial Rx recommended by multidisciplinary team – surgery with or without chemotherapy.

Table 2. Characteristics of MOGCTs according to different histology types.

Histology	Dysg.	IT	YST	Mixed GCT	MTMT
Age (median)	20.5 (range 14-63)	23.2 (range 14-37)	20.5 (range 15-32)	33 (range 22-37)	49 (range 22-62)
FIGO stage	I (40%) III (40%) IV (20%)	I (50%) II (10%) III (40%)	I (12.5%) III (50%) IV (37.5%)	III (66.6%) IV (33.3%)	I (66.6%) II (22.2%) IV (11.1%)
Type of surgery	USO +/- O 90% biopsy 10%	USO +/-O 90% biopsy 10% 2 nd look 30%	USO +/-O 87.5% biopsy 12.5%	USO +/- O 33.3% TAH+SO+/-O 66.6% 2 nd look 33.3%	USO +/- O 44.5% TAH+SO+/- O 55.5%
Adjuvant Chemotherapy	BEP used in 60% (range 1-6) cycles	BEP used in 70% (range 3-6) cycles	BEP used in 100% (range 1-7) cycles	BEP used in 100% (range 2-6) cycles	Other chemo in 44.5%
Completion of Primary treatment (%)	80%	100%	62.5%	66.6%	88.8%
Response to Treatment	CR 80% NE 20%	CR 100%	CR 50% PR 12.5% PD 25% NE 12.5%	CR 66.6% PD 33.3%	CR 77.7% PD 11.1% NR 11.1%
Tumour marker elevated	LDH 80% hCG 50%	AFP 50% CA 125 40%	AFP 75% LDH 12.5%	AFP 100% LDH 33.3% hCG 33.3%	CA125 55.5%
HIV status	30% -ve 60% NE 10% +ve	10% -ve 90% NE	25% -ve 37.5% NE 37.5% +ve	100% -ve	55.5% -ve 33.3% NE 11.1% +ve
Outcome	80% NED, 20% DD	80% NED, 20% DD	50% NED, 50% DD	66.6% NED, 33.3% DD	44.4% NED, 11.1% Lost, 44.4% DD

These variants, abbreviated as MTMT, were either a malignant somatic transformation in a mature teratoma, or monodermalteratoma. Due to the different characteristics and clinical behaviour of the MTMT group, they were analysed separately from the 31 patients with the usual varieties of MOGCTs.

The 31 patients with MOGCTs were broadly subdivided into Dysg. in 10 patients (32%) and a non-Dysg. group in 21 (68%). This latter group was made up from ten patients (32%) with immature teratoma (IT), eight patients (26%) with yolk sac tumour (YST, also known as endodermal sinus tumour), and three with mixed germ cell tumour (10%) (Table 2).

A subsequent laparotomy was performed after a variable time in five patients with IT. A “growing teratoma” situation was found in two of these patients, and both remain well following the surgical resection of these masses.

Overall, stage III (46%) was the most frequent presentation in the 31 patients with the usual types of MOGCTs, followed by stage I (32 %), stage IV (19 %), and stage II in only one patient (3%) – see Table 2. Fertility-sparing surgery was performed in most patients (93.5%).

Chemotherapy was administered to 24 of the 31 patients for a median of four cycles (range 1-7). All these patients received a 3-day BEP regimen (cisplatin 35mg/m² I.V, etoposide 120 mg/m² I.V, and bleomycin 15mg I.V, daily for three days, every three weeks). Complete response to primary treatment (surgery with or without chemotherapy) was achieved in 24 (77.4%) patients, a partial response in one (3.2%), and unresponsive or progressive disease in six (19.4%). Only two of the completely responding patients experienced disease relapse, both with IT histology. After a median follow up of 42.5 months (range 2-60 months), 71% patients were alive with no evidence of disease and 29% patients had died.

None of the 24 patients who had received chemotherapy showed any clinical features of bleomycin-induced lung toxicity. The only serious non-surgical morbidity recorded was of unexpected, severe hearing loss in one patient during her first cycle of BEP. Another died from neutropenic sepsis during salvage chemotherapy.

The 5-year overall survival (OS) rate for the 31 patients with the usual types of MOGCT was 69.1% (Figure 2): for patients with Dysg., the rate was 78.7%

compared to 65% for the non-Dysg. group. The 5-year OS for patients with stage I-II was 88.8% versus 58.3% for those with stage III-IV ($p=0.069$).

Because of the older age of the MTMT group (median age 49 years versus 22 years for the other MOGCTs), hysterectomy, oophorectomy and omentectomy were performed more commonly (five of nine patients). The histology of the transformed line was squamous cell carcinoma in six patients and one each had leiomyosarcoma, insular carcinoid and struma ovarii, respectively. The latter three patients underwent surgery alone. For the group of six patients with squamous histology, adjuvant chemotherapy of various types was given to four, and pelvic radiotherapy to the pelvis to one patient. Only two of these six patients remain alive and disease free. For the nine patients with MTMT, the 5-year OS rate was 50%.

Of the total cohort of 40 patients, the HIV status was known in only 19, of whom five were positive (Table 3). Only two patients with positive status completed planned treatment and remain in remission. Both had CD4 counts over 300, while the three patients who died from progressive disease had CD4 counts <300 , with poor physical condition and poor compliance. The 5-year overall survival was only 40% in the infected group compared to 61.5% in the negative patients and 74.7% in the untested group.

Discussion

MOGCTs are rare tumours, most of which occur at a critical point in the development of young women. Most patients can be treated successfully with fertility-preserving surgery with or without chemotherapy.^{2,5} Whilst the principles of surgical staging for ovarian neoplasms were applied in the patients reported here, there was generally less inclination to perform extensive cytoreduction due to the chemosensitivity of MOGCTs. In our study, the median age was 30.2 years, which correlates with the natural history of this disease.^{2,4,8}

Most of our patients presented with non-Dysg. histology, a quarter had Dysg., while 22.5% had a unique group of tumours, either malignant transformation within a mature teratoma, or monodermalteratoma, which is not dissimilar to the proportions in the Surveillance, Epidemiology, and End Results (SEER) study in the USA.¹⁰

Table 3. Characteristics of the five HIV-positive patients.

Age (years)	Histology type	Stage	CD4 count (initial value)	Primary treatment	Response to treatment	Overall survival (months)
32	Dysg.	IIIC	140	(USO + O) + 1 cycle of PEB	NE	37 DD
22	YST	IV	11	Bx +1 cycle of PEB	PD	4 DD
26	YST	IIIC	214	(USO +O) +1 cycle of PEB	NE	5 DD
22	YST	IV	599	(USO + O) + 5 cycles of PEB	CR	60 NED
46	MTMT	IIC	337	(TAH + BSO + O) + RT to the pelvis	CR	60 NED

The treatment of MOGCTs has been an area of great success in the field of gynaecological oncology, largely attributable to the introduction of platinum based chemotherapy since the mid 1970's.¹¹ The period of review in the current study includes the time when the BEP chemotherapy regimen was already established as standard treatment in MOGCTs,^{11,12} hence all our patients received BEP as first-line chemotherapy, albeit as modified 3-day cycles. The noticeable exception was for the small group of patients with MTMT histology where the intention was to treat according to the histological somatic subtype which had undergone malignant transformation.

It should be noted that in the standard BEP regimen, cisplatin and etoposide are usually administered over five days, whereas bleomycin is administered weekly. The Gynaecologic Oncology Group (GOG) used this regimen in a study of 93 patients with MOGCTs. While the DFS rate was an excellent 89%, the reporting of treatment-related toxicities can be criticised in this report as it is not well documented. Whether treatment delays occurred was also not described.¹³

In testicular tumours, the EORTC/MRC have examined the BEP regimen in a large study of patients within the good prognosis subgroup.¹⁴ The results have

subsequently been updated, confirming equivalence of three vs four cycles of BEP, as well as for the five day vs the three day regimen, although with more myelotoxicity with the latter. This did not, however, result in more dose attenuations. Non-haematological toxicity was similar. Where bleomycin is contra-indicated, four cycles of 5-day cisplatinium + etoposide (PE) is equivalent to three cycles of BEP.¹⁵

Various modifications to the 5-day BEP regimen have been reported in treating MOGCTs with the aim of “increased convenience and less toxicity”.^{16,17} The 3-day modified BEP regimen has been used at GSH for these reasons in both male and female germ cell tumours. The issue of equivalence of these modifications to the standard 5-day BEP is of concern, and can only be established in randomised studies. There is, however, no strong evidence that these regimens are inferior. In a study from Greece, Dimopoulos *et al.* have evaluated the safety and activity of a 3-day modified (mBEP) regimen which is similar to what has been used at GSH. In a prospective study of 48 patients with MOGCTs (14 with Dysg. and 34 with non-Dysg. tumours), all patients with stages I/II and those with Dysg. were cured, although 20 % of the patients with stages III/IV non-Dysg. experienced disease progression, especially if suboptimally debulked.¹⁶

Interestingly, an even- shorter BEP regimen has been explored. Tay *et al.* used a 2-day BEP.¹⁸ While the overall DFS was 93%, such modifications cannot be recommended without further study. It is also tempting to substitute carboplatin for cisplatinium in the chemotherapeutic management of MOGCTs. In testicular cancers, however, studies show that this approach yields inferior results.¹⁹ At GSH, carboplatinium is only used if there are definite contraindications to cisplatinium administration in an individual patient.

While Dysg. tumours are exquisitely radiosensitive, this modality is rarely used nowadays due to fertility concerns. None of the patients in the current study received radiotherapy as part of their planned primary treatments.

In the current series, the 5-year OS rate was 69.1% for the group with “pure” MOGCTs (78.7% for Dysg. and 65% for the non-Dysg. group). Comparatively, in a report on 53 patients by the Hellenic Cooperative Oncology Group, the OS at five years was 100% for patients with Dysg. and 85% for patients with non-Dysg. tumours. Even in patients with advanced non-Dysg. tumours and residual disease

after surgery, 85% remained disease free.²⁰ Lai *et al.* reviewed a larger cohort of 93 patients. The 5-year survival rate was 97% for those treated primarily at their hospital; the OS for dysg. versus Non-dysg. was 100% and 83.3%, respectively.²¹

Another large analysis of 113 patients with MOGCTs with stages IC to IV demonstrates that the long-term outcome of patients with MOGCTs is excellent, with 5, 10, and 25-year estimated survival rates of 83%, 81%, and 81% respectively.²²

Due to the relative rarity of these tumours, a degree of heterogeneity in these retrospective studies is inevitable. The current study population, however, appears to show somewhat inferior survival rates as compared to most reports. One important explanation for this finding is that six out of 31 patients (19.3%) did not complete their primary treatment due to poor compliance with the treatment programme. In addition, HIV seropositivity in three patients contributed to their inability to complete treatment, as they were too ill. Both these factors constitute an impediment to the treatment effectiveness of MOGCTs at GSH. Furthermore, the case mix in this study shows that there were relatively more patients with advanced stages than in other series, in which 60 to 70% of patients have stage I.^{2,14,20} The current study shows that 65% of the 31 patients had stage III-IV, with an OS of 58.3%, compared to 88.8% for those with early stage disease. The reason for the later stage presentations to be more common amongst our patients is the restriction of access to medical care.

There is no compelling reason to ascribe our inferior results to the 3-day BEP regimen. The relatively small numbers involved in each subgroup, however, makes detailed analysis difficult, and the limitations inherent in a retrospective study of this nature are recognized. A further limitation of the current study is that the potential consequences of chemotherapy cycle delays were not studied.

Concerning the occurrence of germ cell tumours in patients with human immunodeficiency virus (HIV) infection, the literature for testicular germ cell tumours is more voluminous than for its ovarian counterparts. Germ cell tumours are the most common solid neoplasm in men between the ages of 15 and 34 years and so it is not surprising that guidelines exist for the management of HIV-infected men with germ cell tumours.^{23,24} A search of the literature concerning MOGCTs and HIV has revealed a single case report in a South African patient,²⁵ and so it is necessary to

extrapolate management guidelines of the testicular cancer literature for women with germ cell tumours.

The poor outcome of the HIV-positive patients (OS of only 40%) was chiefly due to the three patients who presented with poor physical condition and a low CD4 count (11- 214 cells/mL). They were simply too ill to be treated effectively and all three died soon after their diagnosis. None received antiretroviral therapy (ART). The other two patients whose CD4 counts were higher (599 and 337 cells/mL respectively) were also not on ART but tolerated their adjuvant treatment well, and remain in remission. This limited experience suggests that immune status plays an important role regarding the tolerance of treatment. Close surveillance of neutrophil and CD4 cells counts, as well as the use of G-CSF and systematic anti-Pneumocystis carinii prophylaxis (PCP) are recommended during chemotherapy.²³ Clearly, the timely introduction of ART may be beneficial for some of these patients.

The subgroup of patients with MTMT in the current series had a survival rate of only 50%. Generally, these are rare tumours and occur typically in postmenopausal women.^{26,27} Most malignant transformations are squamous cell carcinomas arising from the ectoderm; the rest are carcinoid tumours or adenocarcinomas.²⁶

A review of 37 patients with squamous carcinoma showed that the 5-year survival rates for adequately staged patients were 94.7% for stage I, 80% for stage II, and 0% for patients with stage III and IV disease ($p=.0001$), all of whom died within 20 months.²⁸ A larger review of 227 cases assimilated from the literature showed that the overall 5-year survival rate for all stages was 48.4%. For Stage I, it was 75.7%, for stage II 33.8%, 20.6% for stage III, and 0% in stage IV. Patients who received adjuvant cisplatinium (plus alkylating agent) appeared to do better. The MTMT are, however, too rare and varied either for prospective studies to be performed, or for good treatment guidelines to be forthcoming from the existing literature.²⁹

A final comment is worthwhile about the interesting phenomenon of “growing teratoma syndrome,” of which two cases were encountered in the current study.^{30, 31} Both of these patients are in remission following surgical resection of these expansile masses. It is probably a phenomenon similar to another description found in the literature, the so-called “chemotherapeutic retroconversion” in immature teratoma.³⁰

In conclusion, patients with MOGCTs treated at GSH between 1994-2008 had a survival outcome perhaps slightly inferior to many reported series. The occurrence of poor compliance and HIV-related poor physical state, however, contributed to the poor outcome in some patients. Late state presentations were also more frequent in the current series. Fertility-sparing surgery and post-operative BEP chemotherapy were the standard treatments applied; the modified 3-day regimen was not obviously inferior in this small study.

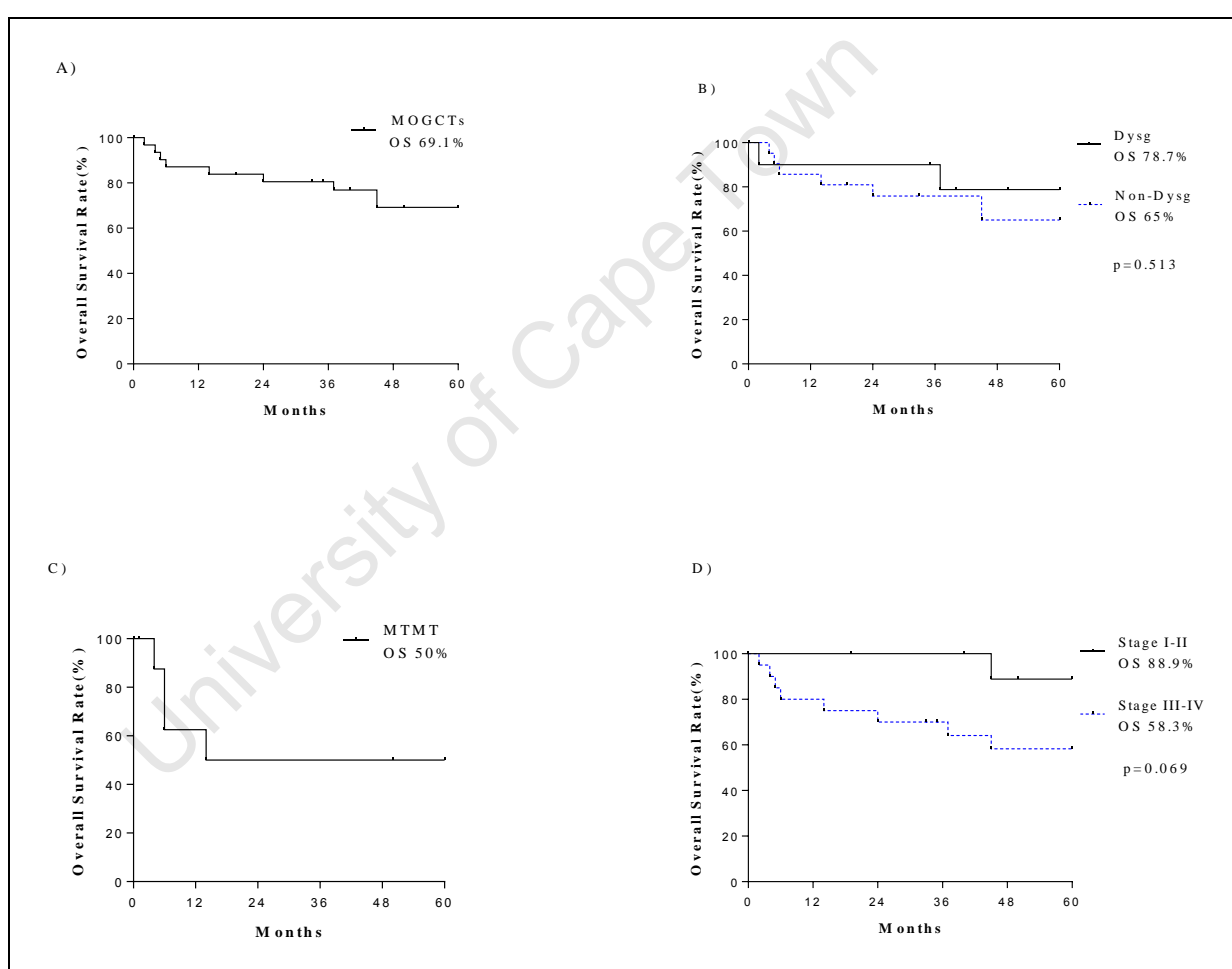


Figure 2. 5-year Overall Survival. A: all the patients with MOGCTs (excluding MTMT group). B: based on histology. C: patients with MTMT. D: stage I-II versus III-IV.

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ADDENDA

University of Cape Town

ADDENDUM A:

Author submission for SAJGO (South African Journal of Gynaecological Oncology):

How to submit your paper online:

1. Registered authors must login to submit a paper
 2. Visit www.sajgo.co.za
 3. Register on the website as an author and log in.
 4. Click on LOG IN and log in with username and password if already registered
 5. If you have forgotten your password click on [◆Forgot your password?◆](#)
 6. If you are not registered, click on [◆Not a user? Register with this site.◆](#)
 7. Select Author.
- Click on [CLICK HERE TO FOLLOW THE FIVE STEPS TO SUBMIT YOUR MANUSCRIPT.](#)
 - Follow the five steps to submit your paper.

Please submit a cover letter as a supplementary file with the following:

1. Surnames, initials and qualifications of all authors in the correct sequence
2. Full contact details of corresponding author: Title, first name, surname, e-mail address, mobile, office and fax number and postal address.
3. Declaration on copyright and originality of paper and acknowledgement of any third party sources (references and images) exempting the author(s), journal and publisher of plagiarism.
4. Declaration regarding authorship
5. Ethics committee approval
6. Conflicts of interest

Review policy and timelines

1. Immediate notification if submitted successfully
2. Notification within 3 weeks if not accepted for further review

3. Notification within 3 months if accepted for publication, if revisions are required or if rejected by both reviewers.

4. Publication within 6 months after submission.

Article section and length:

The following contributions are accepted (word counts exclude abstracts, tables and references):

- Original articles describe original investigations at an acceptable degree of completion, constituting an advance in the field. The body of the article must not exceed 3500 words of text. The abstract must either be structured and comprising no more than 250 words, or unstructured with a 200 word limit. Articles are limited to a maximum of 7 insets (tables and figures combined) and 50 references.

- Review articles that are of high quality and of relevance to the field will be published. Manuscripts of Reviews will be peer reviewed and should not exceed 2500 words and 25 references. Reviews will often be invited and unsolicited reviews are also considered.

- Brief Reports and Case Reports present complete studies that are narrower in scope than those described in Original articles. These Reports include a highly focused abstract and are limited to a total of no more than 1500 words of text, a total of 4 insets (tables or figures), and 15 references. Preferably include "Brief Report" or Case Report in the title.

- Pathologist's, Radiologist's and Surgeon's Corners intend to describe a specific issue, finding or technique that is new, of special interest or modified. This section is limited to 1000 words and up to 5 references and will be peer reviewed.

- Correspondence (Letters to the Editor) should be short and concise, commenting on a recently published article in the Journal or a controversial or topical issue of concern to the readership. Please prepare the letter in manuscript format, including a title page. The letter must not exceed 500 words, 3 authors, 1 insert (table or figure) and 5 references. A statement of potential sources of conflict of interest must accompany the letter.

- Editorials and Commentaries are generally invited by the Editor and are overviews of articles of other research or of issues of special interest to the subspeciality. Unsolicited commentaries are also considered.

Document requirements

Please include the following documents with your submission:

- *Cover letter* stating that the manuscript has not been submitted or accepted for publication elsewhere and that it is the original work contributed to and approved by all the author(s).
- *Conflict of interest and funding* statements.

- *Manuscript* which should contain a title page, abstract, text and references. It may also contain tables and figures, acknowledgements and a foot note page.

Manuscript **requirements**

Title *page*

On the title page, please supply a running head of not more than 40 characters and spaces, a title of not more than 160 characters and spaces, the names and affiliations of all the authors in the correct sequence and word counts of the abstract and text. Each author's first name, subsequent initials and surname must be used. Also supply the contact details of corresponding author.

Authorship

Authorship should be based only on a substantial contribution to conception, analysis and interpretation of data; writing the article or revising it critically and final written approval of the version to be published. The Journal uses the Uniform Requirements of Authorship for Manuscripts Submitted to Biomedical Journals as published online at www.icmje.org/index.html and all three of these conditions must be met.

Abstract

The abstract may be structured with the headings Background, Methods, Results, and Conclusions (250-word limit) or unstructured (200-word limit). Abstracts of Brief Reports should be no more than 100 words. The abstract must state the purpose of the research, the methods, results and conclusions. Include up to 10 key words, separate from the abstract.

Text

Please refer to the manuscript categories for the prescribed length of the text. The Editor reserves the right to shorten and stylise any material accepted for publication. Authors are solely responsible for the factual accuracy of their work.

The manuscript must be in English, should be in MS Word and follow the Vancouver style. Abbreviations and acronyms should be defined on first use. Pages should be numbered consecutively preferably with sections for introduction, materials and methods, results, discussion, acknowledgements followed by references.

Ethical

considerations

The Methods section must include a statement that informed consent was obtained from patients, parents or guardians when appropriate. It should also state that the human experimentation guidelines of the National Department of Health (<http://www.doh.gov.za>) or the South African Medical Research Council (MRC; <http://www.sahealthinfo.org/ethics/index.htm>) and/or those of the authors' institution(s) were followed in the conduct of clinical research or that animal experimentation guidelines (see MRC website above) were followed in animal studies. Non-South African studies should contain similar declarations relating to local guidelines where appropriate. The trial number of the approving body (bodies) should be stated when relevant.

Tables

and

Figures

Refer to the manuscript categories for prescribed number of tables and figures. Written permission from the author or copyright holder must be submitted for reprint of previously published figures or tables. Figures should be saved as high resolution (300 dpi) jpeg files. Tables should be constructed in MS Word. Graphs can be copied from MS Excel and pasted in the document. For large, intricate graphs, the coordinates and graphs must be provided as separate MS Excel files and uploaded as supplementary files.

Tables and figures can be in the text at the relevant place. Large tables (landscape A4) and photographic images are best saved as separate supplementary files. Please number them appropriately.

Figures and photographs should be of high quality with symbols, letters or numbers clear enough and large enough to remain legible after reduction. Remove all markings, such as patient identification, from radiographs before photographing. Each figure must have a separate self-explanatory legend.

Footnotes

Examples of information that can be submitted as a footnote to the manuscript include:

- Statement that authors either have or have not a potential conflict of interest.
- Statement naming sources of financial support.
- Information of previous presentation of part or all of the data.
- Current affiliations and addresses for authors whose affiliations have changed since completion of the study.
- Acknowledgements of financial support received or substantial contributions to the research or preparation of the manuscript made by persons other than the authors.

References

References should be cited in numerical order in the text, in superscript format (Format> Font> Click superscript) AFTER the full stops. (Not in brackets or as footnotes.)

References must be typed double-spaced and numbered consecutively in the order in which they are cited, not alphabetically.

The style for references should follow the format set forth in the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals* (<http://www.icmje.org>) prepared by the International Committee of Medical Journal Editors. Abbreviations for journal titles should follow *Index Medicus* format.

Authors are responsible for the accuracy of all references. Personal communications and unpublished data should only be referenced in the text.

List all authors when there are six or fewer; when there are seven or more, list the first six, then "et al." When citing URLs to web documents, place in the reference list, and use the following format: Authors of document (if available). Title of document (if available). URL. (Accessed [date]).

ADDENDUM B:**Data entry sheet for Ovarian GCT Project:****Patient demographics:**

Name	
Surname	
HN	
RTN	
Age	
Race	
Date of reg	

Histo type:

Dysgerminoma	
Non-Dysgerminoma:	
1-Immat teratoma*	
2-Yolk sac	
3-Mixed germ cell	
MTMT	
Others	

* if IMT grade?

Stage of the disease:

Ia	IIa	IIIa	VI
Ib	IIb	IIIb	
Ic	IIc	IIIc	

Tumour markers (initial value):

bHCG	LDH	AFP	CA125	other	N/S

HIV status:

Yes (if yes – enter below)	No	N/S
CD4		

Sequences of treatment

Surgery	chemo	radiotherapy
S	C	R

Type of surgery:

Biopsy only	
Uniooph	
Uniooph +OM	
TAH+BSO+OM	
TAH+BSO	
PALN removal or biopsy	
Cytoreduction	
Other	
2 nd look lap	

Chemotherapy given:

Yes	no
-----	----

If yes type of chemo:

PEB	PVB	other
-----	-----	-------

Chemo no. cycles:

Any major side effects?

Radiotherapy given:

Yes	No
-----	----

If yes, site of treatment:

PALN	
Other Mets	
Pelvis	
Pelvis +Extended field	

Primary treatment course completed:

Yes	No *
-----	------

If No: Reason (free text):.....

Relapse :

Yes			No
Locoreg	Dist	both	

Date of relapse:.....

Treatment of relapse:

Chemo	Surgery	RT	TLC	multimod

Response to primary therapy:

CR	PR	NR	PD	NE
----	----	----	----	----

Current status:

Alive NAD	Alive dis	Lost	Dead		
			dis	treat	othe

Date last seen/Died:.....

DFS:.....months

OS:.....months

Other relevant info on this patient
(text):.....

.....

University of Cape Town

ADDENDUM C:

Ethic committee approval



UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences
 Human Research Ethics Committee
 Room B52-24 Groote Schuur Hospital Old Main Building
 Observatory 7928
 Telephone (021) 423 6575 • Facsimile (021) 423 6411
 e-mail: sha.let@uct.ac.za

08 February 2011

HREC REF: 045/2011

Dr K Mohammed
 c/o Dr AL Van Wijk
 Radiation Oncology
 L7/34

Dear Dr Mohammed

PROJECT TITLE: THE TYPES AND TREATMENT OUTCOMES OF GERM CELL TUMORS OF THE OVARY SEEN AT GROOTE SCHUR HOSPITAL, BETWEEN 1994-2008- A RETROSPECTIVE SURVEY.

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the Ethics Committee has formally approved the above mentioned study.

Approval is granted for one year till the 15 February 2012.

Please submit an annual progress report (PIR016) if the research continues beyond the expiry date. Please submit a final summary of findings if you complete the study within the approval period so that we can close our file.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC REF in all your correspondence.

Yours sincerely

signature removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN ETHICS
 Federal Wide Academic Member: FW20001637.

S. Theron

ADDENDUM D:**Clinical Directorate of Groote Schuur Hospital approval**

**DEPARTMENT
of HEALTH**

Provincia Government of the Western Cape

GROOTE SCHUUR HOSPITAL

Upole@cap.gov.za
Tel: 021-404-9111 Fax: 021-404-9126
Private Bag, Observatory, 7955
www.cap.gov.za/groote_schuur

REFERENCE: Mohammed K. (Van Wijk L)
ENQUIR ES: Dr Bhavna Patel

Dr K. Mohammed
C/o Radiation Oncology
LE 33 Clinic
L-BLOCK

e-mail: thadijahammed@yahoo.com

Dear Dr Mohammed

AUDIT PROJECT: "The Types and Treatment Outcomes of Germ Cell Tumours of the Ovary Seen at Groote Schuur Hospital, Cape Town, between 1994-2008 A Retrospective Study"

Your recent letter to the hospital refers.

You are hereby granted permission to proceed with your audit project.

Please note the following:

- a) Your research may not interfere with normal patient care
- b) Hospital staff may not be asked to assist with the research.
- c) No hospital consumables and stationary may be used.
- d) No patient folders may be removed from the premises or be inaccessible.**
- e) Please introduce yourself to the person in charge of an area before commencing.
- f) Please discuss the study with the Head of Radiation Oncology before commencing.

I would like to wish you every success with this project.

Yours sincerely

signature removed

DR BHAVNA PATEL
SENIOR MANAGER: MEDICAL SERVICES
Date: 20th May 2011



Groote Schuur Hospital
Private Bag,
Observatory, 7955
Telephone : 021 404 9111

ADDENDUM E:

University of Cape Town (Dean circular approval)

Date of issue: 20/03/2011



UNIVERSITY OF CAPE TOWN
FACULTY OF HEALTH SCIENCES
DEAN'S CIRCULAR



MILDURG0011

20 March 2011

UNIVERSITY OF CAPE TOWN FACULTY OF HEALTH SCIENCES

The Dean informs the members of Section A of the Faculty of Health Sciences that the following has been approved:

Dean's Circular was presented at the meeting of the Faculty Council of Health Sciences. Should any objections to the recommendations to the TOR APPROVAL (conditions of the Dean's Circular) have been received at writing from the Dean of Health Sciences, the Dean will be taking the following action: (Regarding Faculty Meetings: Available Administration) by email on:

Friday, 31 April 2011

The recommendations will be considered at the next meeting and will be added to the

Faculty Board members who wish to receive hard copies of the Dean's Circular are kindly asked to contact Adri Windford at Tel: (021) 406 6827 or email her at Adri.Windford@uct.ac.za.

signature removed

Prof. Marshall
Dean
Faculty of Health Sciences

1

Name & student number	Degree	Area of Specialisation	Department	Qualifications	Dissertation title	Main supervisor	Co-supervisor(s)
Melvinus R. MASHOBYI	MSc MPhil	Biological Sciences	Genetics	MSc	The type and relative number of gene cell lines of the polymorphous DNA (SNPs) located between 150-1600 kb upstream of the	Dr. A. van Wyk	NA

ADDENDUM F:



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GROOTE SCHUUR HOSPITAL
DR LEON VAN WIJK
OBSERVATORY
7925 CAPE TOWN
SOUTH AFRICA

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Spec Mat: RCP ROTH LM, 2006;25:305-20, TB1

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