

# The types and treatment outcomes of germ cell tumours of the ovary seen at Groote Schuur Hospital, Cape Town, between 1994 and 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. Gathered data were transferred to an electronic spreadsheet. The Kaplan-Meier method was used to obtain five-year survival data.

**Results:** Forty patients were treated for MOGCTs. Median age at the time of diagnosis was 30.2 years (a range of 13-63 years). Ten patients (25%) had dysgerminoma and 30 (75%) had non-dysgerminomatous types. The latter group comprised immature teratoma (10 patients), yolk sac tumour (8), mixed germ cell tumour (3), and mature teratoma with malignant transformation (MTMT) (9). Standard staging surgery was performed with fertility-sparing procedures wherever possible. Chemotherapy entailed a three-day modified bleomycin/etoposide/cisplatin (BEP) regimen during the study period. Excluding the group of nine with monodermal malignant transformation in mature teratoma, complete response to primary treatment was achieved in 24 of 31 patients (77.4%). After a median follow-up of 42.5 months (a range of 2-60), the overall five-year survival rate was 69.1%. The overall five-year survival rate was only 40% in five human immunodeficiency virus (HIV)-positive patients. Four of the nine patients with MTMT were 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.

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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 the tumours are highly malignant and grow rapidly, they are generally more curable than their epithelial counterparts.<sup>1-3</sup> It is imperative that these tumours are managed from the outset with accurate diagnosis, staging and treatment.

They are broadly classified as dysgerminomas, the most common type and the counterpart of the male seminoma and a non-dysgerminomatous group.<sup>2,4</sup> This classification plays a role in the treatment of and prognosis for these patients.<sup>5,6</sup> A modified

subclassification of the ovarian germ cell tumours is shown in Table I.<sup>7</sup>

There have been no randomised trials of therapy for MOGCTs because of their relative rarity. The data on which management is based derive from retrospective reviews of patients' treatment outcomes and from multicentric prospective trials. Treatment strategies have also been adopted from prospective trials, many of them randomised, and conducted in their more common counterparts, the male germ cell tumours.<sup>4,8</sup> Therefore, it is not surprising that a recent attempt at a meta-analysis of the benefits of chemotherapy in adult MOGCTs by the Cochrane group was unsuccessful.<sup>9</sup>

A survey of patients with MOGCTs treated at Groote Schuur Hospital over a 15-year period is presented. The

**Table I:** World Health Organization classification of the germ cell tumours (used with permission)<sup>7</sup>

<p><b>I. Primitive germ cell tumours</b></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><b>II. Biphasic or triphasic teratoma</b></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><b>III. Monodermal teratoma and somatic-type tumours associated with biphasic or triphasic teratoma</b></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>

histological types, applied treatment and outcomes of these patients were recorded and analysed.

## Method

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, therefore, their consent was not required.

To perform the audit, a list of all adult patients with primary MOGCTs, registered at Groote Schuur Hospital between 1994 and 2008, was obtained from the gynaecology-oncology database of the Department of Radiation Oncology. "Adult" was defined as a patient aged 13 years or older. This is 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 customised 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 gynaecology-oncology database.

The collected data points included age, date of

registration (date of first treatment is defined as the primary surgery in all cases), histological type, and International Federation of Gynaecology and Obstetrics (FIGO) stage. The type of surgery, the regimen and number of cycles of administered chemotherapy, and/or radiotherapy details were recorded, or the primary treatments. Laboratory values of human immunodeficiency virus (HIV) status (and CD4 count, if positive) and the initial levels of serum tumour markers were noted.

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

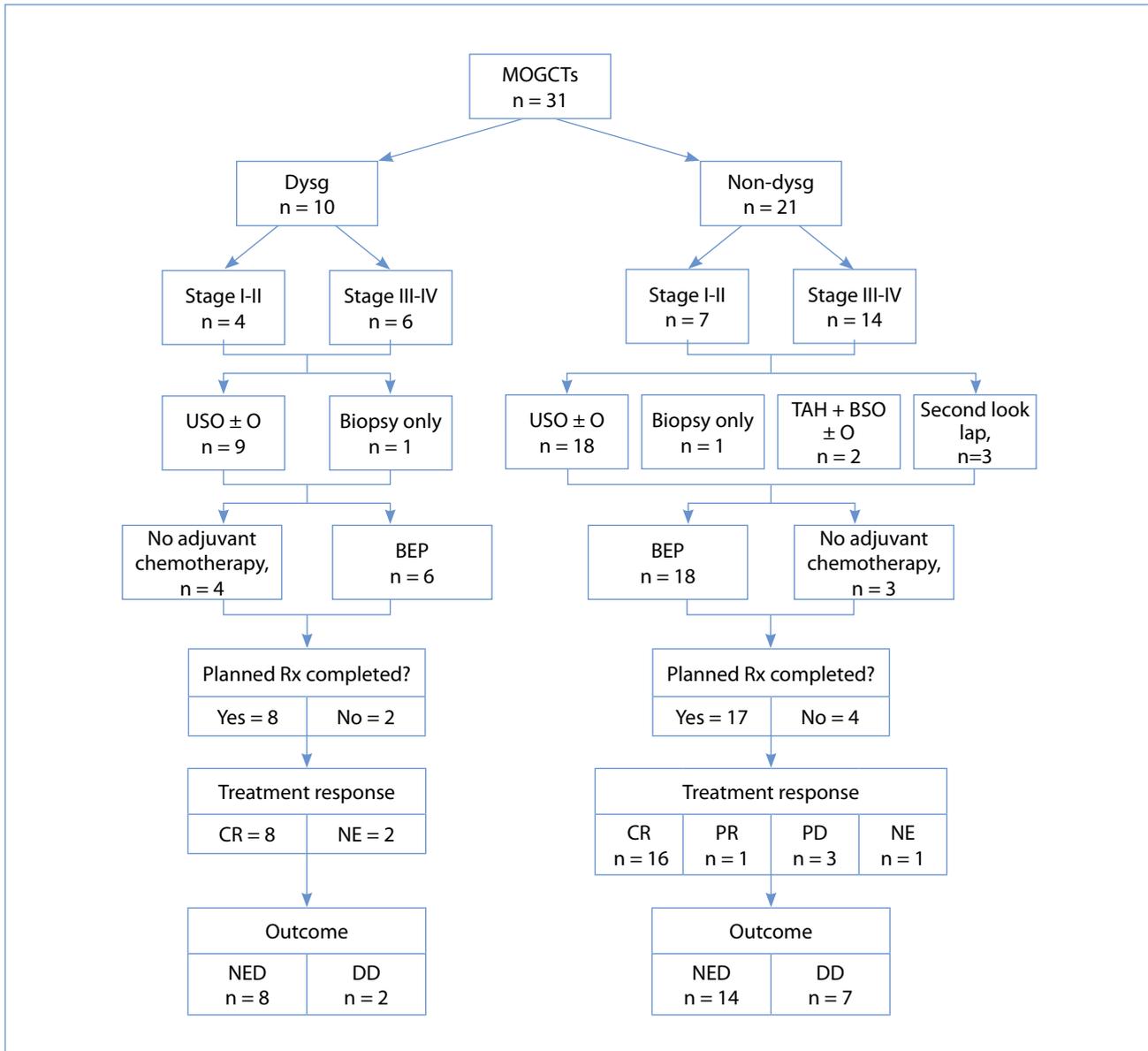
## Results

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

These variants, abbreviated as MTMT, were either a malignant somatic transformation in a mature teratoma or monodermal teratoma. Because of 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 dysgerminoma (10 patients, 32%) and non-dysgerminoma (21 patients, 68%). This latter group was made up of 10 patients (32%) with immature teratoma (IT), eight patients (26%) with yolk sac tumour, (also known as endodermal sinus tumour), and three with mixed germ cell tumour (10%) (Table II).

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%), (Table II). Fertility-sparing surgery was performed in most patients (93.5%). Cytoreductive surgery was carried out for some patients who presented with advanced disease (III and IV). A second look laparotomy was performed



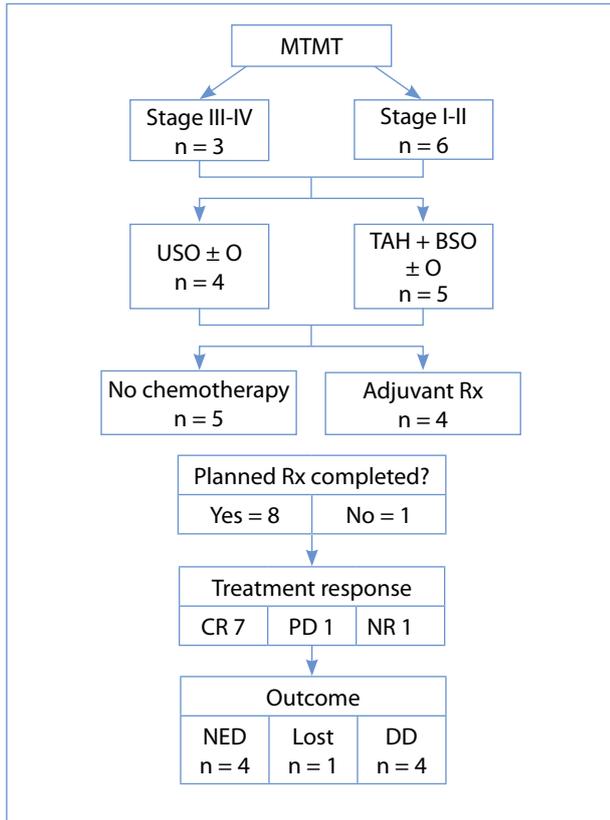
BEP: bleomycin, etoposide and cisplatin, CR: complete response, DD: dead from disease, Dysg: dysgerminoma, MOGCTs: malignant ovarian germ cell tumours, NE: not evaluated, NED: no evidence of disease, Non-dysg: Non-dysgerminoma, PD: progression of the disease, PR: partial response, second look lap: second look laparotomy, TAH + BSO ± O: total abdominal hysterectomy + salpingo-oophorectomy ± omentectomy, USO ± O: unilateral salpingo-oophorectomy ± omentectomy

**Figure 1a:** Flow chart of all the patients with malignant ovarian germ cell tumours

following postoperative chemotherapy for radiological masses in two patients who had early-stage, high-grade IT. Mature teratoma (“growing teratoma”) was excised, which required no further treatment. The third patient with grade I IT with mature glial peritoneal implants was found to have recurrent masses three years after initial surgery. A relaparotomy revealed widespread neuroblastomatous recurrence.

Chemotherapy was administered to 24 of the 31 patients for a median of four cycles (a range between 1 and 7). All these patients received a modified three-

day bleomycin, etoposide and cisplatin (BEP) regimen (cisplatin 35 mg/m<sup>2</sup> intravenously, etoposide 120 mg/m<sup>2</sup> intravenously and bleomycin 15 mg intravenously, daily for three days, every three weeks). Four patients with dysgerminoma did not receive adjuvant chemotherapy: three had stage IA, and one, stage IV disease, who demised immediately after her surgery. Of the non-dysgerminomatous group, three patients did not receive chemotherapy. One had an early-stage tumour, while two with low-grade IT had mature peritoneal implants (labelled stage III). It was felt that they did not require chemotherapy.



CR: complete response, DD: dead from disease, MTMT: mature teratoma with malignant transformation, NED: no evidence of disease, NR: no response, PD: progression of the disease, TAH + BSO ± O: total abdominal hysterectomy + salpingo-oophorectomy ± omentectomy, USO ± O: unilateral salpingo-oophorectomy ± omentectomy

**Figure 1b:** Flow chart of all the patients with mature teratoma with malignant transformation

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 6 (19.4%). Only two of the completely responding patients experienced disease relapse, both with IT histology. One received salvage chemotherapy, although both died from progressive disease. After a median follow-up of 42.5 months (a range of 2-60 months), 71% patients were alive with no evidence of disease. Twenty-nine per cent of patients had died.

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

The overall five-year survival rate for the 31 patients with the usual types of MOGCT was 69.1% (Figure 2). For patients with dysgerminoma, the rate was 78.7%,

compared to 65% for the non-dysgerminomatous group. The overall five-year survival for patients with stage I-II was 88.8% vs. 58.3% for those with stage III-IV (p-value = 0.069).

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

Of the total cohort of 40 patients, the HIV status was known in only 19, of whom five were positive (Table III). Only two patients with positive status completed planned treatment and remained 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 overall five-year survival was only 40% in the infected group, compared to 61.5% in the HIV-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. Generally, patients can be treated successfully with fertility-preserving surgery, with or without chemotherapy, with preservation of reproductive function as a secondary objective.<sup>2,5</sup> In our study, the median age was 30.2 years, which correlates with the natural history of this disease.<sup>2,4,8</sup>

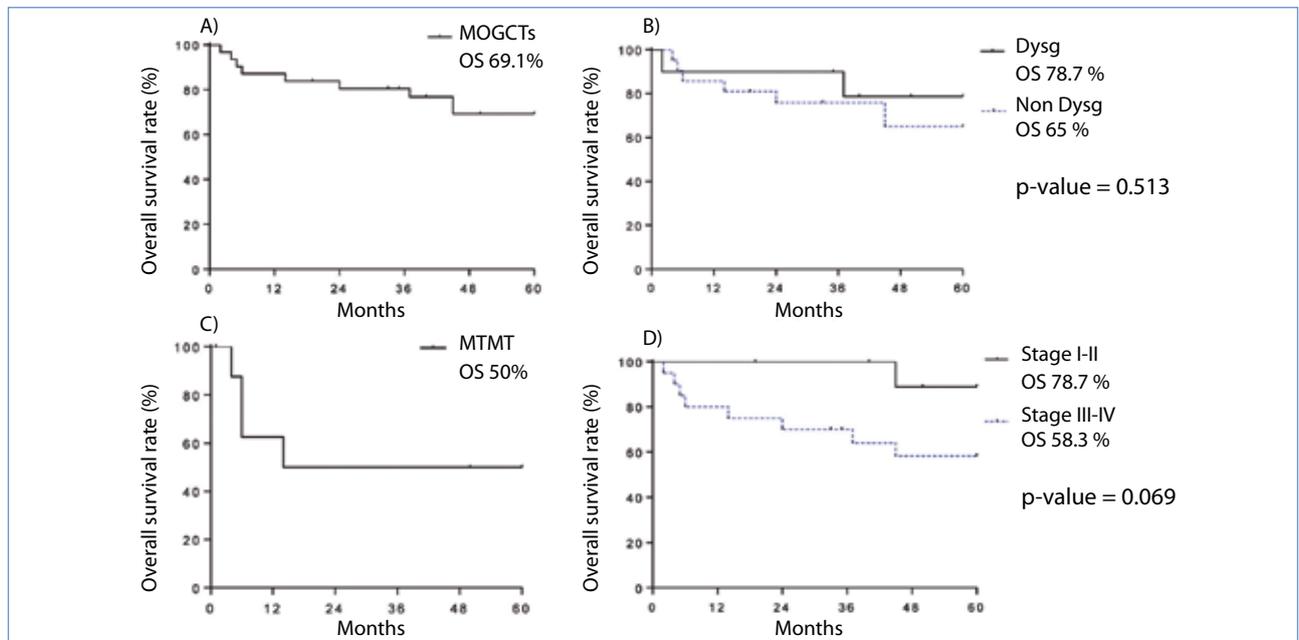
Most of our patients presented with non-dysgerminomatous histology, a quarter had dysgerminoma, while 22.5% had a unique group of tumours, either malignant transformation within a mature teratoma or monodermal teratoma, which is not dissimilar to the proportions in the Surveillance, Epidemiology and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

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-1970s.<sup>11</sup> The period of review in the current study includes the time when the BEP chemotherapy regimen was already established as standard treatment in MOGCTs,<sup>11,12</sup> hence all of

**Table II:** Characteristics of malignant ovarian germ cell tumours 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%, second look laparotomy: 30%	USO ± O: 87.5%, biopsy: 12.5%	USO ± O: 33.3%, TAH + SO ± O: 66.6%, second look laparotomy: 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 chemotherapy in 44.5%
Completion of planned 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% negative 60% NE 10% positive	10% negative 90% NE	25% negative 37.5% NE 37.5% positive	100% negative	55.5% negative 33.3% NE 11.1% positive
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

AFP: alpha feta-protein, BEP: bleomycin, etoposide and cisplatin, CA 125: cancer antigen, CR: complete response, DD: dead from disease, Dysg: dysgerminoma, FIGO: International Federation of Gynaecology and Obstetrics, hCG: human chorionic gonadotrophin, HIV: human immunodeficiency virus, IT: immature teratoma, LDH: lactate dehydrogenase, mixed GCT: mixed germ cell tumour, MTMT: mature teratoma with malignant transformation, NE: not evaluated, NED: no evidence of disease, NR: no response, PD: progression of the disease, PR: partial response, TAH + BSO ± O: total abdominal hysterectomy + salpingo-oophorectomy ± omentectomy, USO ± O: unilateral salpingo-oophorectomy ± omentectomy, YST: yolk sac tumour



Dysg: dysgerminoma, Non-Dysg: Non-dysgerminoma, MOGCTs: malignant ovarian germ cell tumours, MTMT: mature teratoma with malignant transformation, OS: overall survival

**Figure 2:** Overall five-year survival. A): All the patients with malignant ovarian germ cell tumours (excluding mature teratoma with malignant transformation group). B): based on histology. C): patients with mature teratoma with malignant transformation. D): stage I-II versus III-IV

**Table III:** Characteristics of the five human immunodeficiency virus-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 BEP	NE	37 DD
22	YST	IV	11	Bx + 1 cycle of BEP	PD	4 DD
26	YST	IIIC	214	(USO + O) + 1 cycle of BEP	NE	5 DD
22	YST	IV	599	(USO + O) + 5 cycles of BEP	CR	60 NED
46	MTMT	IIC	337	(TAH + BSO + O) + RT to the pelvis	CR	60 NED

Bx: biopsy CD4: cluster of differentiation 4, BEP: bleomycin, etoposide and cisplatin, CR: complete response, DD: dead from disease, Dysg: dysgerminoma, MTMT: mature teratoma with malignant transformation, NE: not evaluated, NED: no evidence of disease, PEB: PD: progression of the disease, RT: radiotherapy, TAH + BSO ± O: total abdominal hysterectomy + salpingo-oophorectomy ± omentectomy, USO ± O: unilateral salpingo-oophorectomy ± omentectomy, YST: yolk sac tumour

our patients received BEP as first-line chemotherapy, albeit as a modified three-day regimen. The noticeable exception was 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 used this regimen in a study of 93 patients with MOGCTs. While the disease-free survival rate was an excellent 89%, the reporting of treatment-related toxicities can be criticised in this report as it was not well documented. It was also not stated whether or not treatment delays occurred.<sup>13</sup>

With regard to testicular tumours, the European Organisation for Research and Treatment of Cancer (EORTC)/Medical Research Council (MRC) have examined the BEP regimen in a large study of patients within the good prognosis subgroup.<sup>14</sup> The results have subsequently been updated, confirming equivalence of three versus four cycles of BEP, as well as for the five-day versus the three-day regimen, although with more myelotoxicity with the latter. However, this did not result in more dose attenuations. Nonhaematological toxicity was similar. Where bleomycin was contraindicated, four cycles of five-day cisplatin and etoposide (PE) was considered to be equivalent to three cycles of BEP.<sup>15</sup>

Various modifications to the five-day BEP regimen have been reported in treating MOGCTs with the aim of "increased convenience and less toxicity".<sup>16,17</sup> The issue of equivalence of these modifications to the standard five-day BEP is of concern, and can only be established in randomised studies. However, there is no strong evidence that these regimens are inferior. In a study from Greece, Dimopoulos et al evaluated

the safety and activity of a three-day modified regimen which was similar to that used at Groote Schuur Hospital. In a prospective study of 48 patients with MOGCTs (14 with dysgerminoma and 34 with non-dysgerminomatous tumours), all patients with stages I/II and those with dysgerminoma were cured, although 20% of the patients with stages III/IV non-dysgerminoma experienced disease progression, especially if suboptimally debulked.<sup>16</sup>

Interestingly, an even shorter BEP regimen has been explored. Tay et al used a two-day BEP.<sup>18</sup> While the overall disease-free survival was 93%, such modifications cannot be recommended without further study. It is also tempting to substitute carboplatin for cisplatin in the chemotherapeutic management of MOGCTs. However, in testicular cancers, studies show that this approach yields inferior results.<sup>19</sup> At Groote Schuur Hospital, carboplatin is only used if there are definite contraindications to cisplatin administration in an individual patient.

In the current series, the overall five-year survival rate was 69.1% for the group with "pure" MOGCTs (78.7% for dysgerminoma and 65% for the non-dysgerminomatous group). Comparatively, in a report on 53 patients by the Hellenic Cooperative Oncology Group, the overall survival at five years was 100% for patients with dysgerminoma and 85% for patients with non-dysgerminomatous tumours. Even in patients with advanced non-dysgerminomatous tumours and residual disease after surgery, 85% remained disease free.<sup>20</sup> Lai et al reviewed a larger cohort of 93 patients. The five-year survival rate was 97% for those treated primarily at their hospital. The overall survival was 100% and 83.3% for dysgerminoma and non-dysgerminoma, respectively.<sup>21</sup>

Another large analysis of 113 patients with MOGCTs with stages IC to IV demonstrates that the long-term

outcome of patients with MOGCTs was excellent, with 5-, 10-, and 25-year estimated survival rates of 83%, 81% and 81% respectively.<sup>22</sup>

Because of the relative rarity of these tumours, a degree of heterogeneity in these retrospective studies is inevitable. However, the current study population appears to show somewhat inferior survival rates than those in most reports. One important explanation for this finding is that six out of 31 patients (19.3%) did not complete their primary treatment because of 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 Groote Schuur Hospital. Furthermore, the case mix in this study shows that there were relatively more patients with advanced stages than those in other series, in which 60-70% of patients had stage I.<sup>2,14,20</sup> The current study shows that 65% of the 31 patients had stage III-IV, with an overall survival of 58.3%, compared to 88.8% for those with early-stage disease.

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

The literature for testicular germ cell tumours is more voluminous than that for its ovarian counterparts with regard to the occurrence of germ cell tumours in patients with HIV infection. Germ cell tumours are the most common solid neoplasm in men between the ages of 15 and 34 years. So it is not surprising that guidelines exist for the management of HIV-infected men with germ cell tumours.<sup>23,24</sup> A search of the literature on MOGCTs and HIV has revealed a single case report in a South African patient.<sup>25</sup> Therefore, 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 (an overall survival of only 40%) was chiefly because of the three patients who presented with a 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 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 remained in remission. This limited experience suggests that immune status plays an important role

with regard to the tolerance of treatment. Close surveillance of neutrophil and CD4 cells counts, as well as the use of granulocyte-colony stimulating factor and systematic anti-*Pneumocystis carinii* prophylaxis are recommended during chemotherapy.<sup>23</sup> 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.<sup>26,27</sup> Most malignant transformations are squamous cell carcinomas arising from the ectoderm. The rest are carcinoid tumours or adenocarcinomas.<sup>26</sup>

A review of 37 patients with squamous carcinoma showed that the five-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-value = 0.0001), all of whom died within 20 months.<sup>28</sup> A larger review of 227 cases assimilated from the literature showed that the overall five-year survival rate for all stages was 48.4%. It was 75.7% for stage I, 33.8% for stage II, 20.6% for stage III and 0% for stage IV. Patients who received adjuvant cisplatin (plus alkylating agent) appeared to do better. However, the MTMT are too rare and varied, either for prospective studies to be performed, or for good treatment guidelines to be forthcoming from the existing literature.<sup>29</sup>

A final comment is worthwhile on the interesting phenomenon of "growing teratoma syndrome," of which two cases were encountered in the current study.<sup>30,31</sup> Both of these patients were in remission following surgical resection of these expansile masses. It is probably a phenomenon similar to that described in the literature, the so-called "chemotherapeutic retroconversion" in immature teratoma.<sup>30</sup>

## Conclusion

Patients with MOGCTs treated at Groote Schuur Hospital between 1994-2008 had a survival outcome perhaps slightly inferior to many reported series. However, the occurrence of poor compliance and a HIV-related compromised physical state contributed to the poor outcome in some patients. Late-stage presentations were also more frequent in the current series. Fertility-sparing surgery and postoperative BEP chemotherapy were the standard applied treatments. The modified three-day regimen was not obviously inferior in this small study.

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