Ovarian germ cell malignancy: a heterogeneous tumour requiring supra-regional management

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Summary

Background: Malignant ovarian germ cell tumours (GCT) are rare tumours with clinical and histological heterogeneity. Risk adapted treatment of these tumours is advocated. *Methods:* We reviewed patients with malignant ovarian GCT managed by a single specialist during 1991-2009 at our institution. Clinicopathological features that may predict behaviour of the disease and disease outcomes were assessed. *Results:* Thirty-four patients with a median follow-up time of 5.7 years were identified. The 10-year estimated survival rates were up to 80%; 8/13 patients with Stage I disease were recommended active surveillance, of whom three relapsed and, one with an immature teratoma died. *Conclusions:* Ovarian GCT are potentially curable but appear to have a worse prognosis than their testicular counterparts. To improve expertise in the management of these complex tumours and optimise future management, a supra-regional service modeled on that used in the management of gestational trophoblastic disease is proposed.

Key words: Ovarian tumours; Germ cell malignancy.

Introduction

Ovarian germ cell tumours comprise a broad spectrum of tumours formed by cells that are believed to derive from primordial germ cells. They occur primarily in young women between the ages of ten and 30, where they represent 58-70% of ovarian tumours in this age group, with one-third classified as malignant [1]. Traditionally, it was helpful to group these tumours as dysgerminoma and non-dysgerminoma. In the modified version of the third WHO classification [2], germ cell tumours are divided into three categories: i) primitive germ cell tumours that include dysgerminomas, yolk sac tumours, embryonal carcinoma, polyembrioma, nongestational choriocarcinoma and mixed germ cell tumours, ii) biphasic or triphasic teratomas that include immature and mature teratomas, and iii) monodermal teratoma or somatic type tumours associated with biphasic and triphasic teratomas. This classification emphasises the histological heterogeneity and complexity that, along with the rarity of the disease, makes descriptions of this group of tumours and comparison between series and evidence-based treatment decisions difficult. Prior to the advent of effective chemotherapy, the survival of women with ovarian GCT was extremely poor. Since the 1970s, the therapeutic approach has evolved along similar lines to that of testicular GCT, and with the introduction of cisplatin the prognosis changed from a deadly disease to a highly curable cancer [3]. Even in patients with advanced disease, 5-year survival rates of up to 75% can be achieved [3, 4]. In general the treatment principles for all types of ovarian GCT are similar, and include a multimodality therapy approach with surgery for diagnosis and staging, eventually cytoreductive surgery if advanced disease is present, and platinum-based chemotherapy in most cases [5]. Reducing toxicity and improving quality of life without compromising efficacy is essential for these young patients. The role of adjuvant chemotherapy in patients with low risk of recurrence remains controversial; the majority of patients are cured without any additional systemic treatment and the side-effects of chemotherapy, particularly late effects, can be significant. These factors, coupled with the ability to effectively treat patients who do relapse has prompted consideration of active surveillance for this group of patients [6-10]. Unlike in testicular GCT, prognostic factors for early ovarian GCT that may help define appropriate adjuvant treatment are poorly defined due to the heterogeneity and rarity of the disease [6, 10, 11].

At present active surveillance is accepted practice for patients with Stage IA dysgerminoma or Stage IA, grade 1, unruptured immature teratoma [3]. However, several reports, particularly in paediatric patient series, suggest this strategy is appropriate for a much broader group of patients [6-10]. At the other end of the disease spectrum, in contrast to testicular GCT for whom salvage rates are higher, the outcome of patients who experience relapse or treatment failure after platinum-based combination chemotherapy remains particularly poor [6].

We have reviewed our experience within a specialist oncology centre of managing ovarian GCT, and evaluated the clinical and histological features that may predict different behaviours of the disease.

Methods

This retrospective study included all patients identified through the institutional database with a diagnosis of malignant ovarian GCT treated by a single oncologist at Weston Park Hospital, Sheffield between 1991 and 2009. Medical records were

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reviewed to obtain details regarding demographic, clinicopathological, treatment and outcome information. Histological diagnosis was defined according to the modified WHO criteria [2]. The term carcinoma associated with GCT included carcinoma associated with teratoma and yolk sac tumor with divergent differentiation of adenocarcinoma.

Staging was determined according to the guidelines of the International Federation of Gynecologists and Obstetricians (FIGO) classification system for ovarian cancer [12], based on clinical disease extent at presentation and post surgical findings. Staging was reviewed by one of the investigators. A complete response required normalisation of tumour markers and no residual masses on imaging procedures, or no viable malignant tumour found at second-look surgery.

Survival was calculated from the date of initial surgery to the date of death or last follow-up. Time to recurrence was defined as the period of time from the date of first treatment to the first observation of disease progression.

Statistical analysis: Descriptive statistics were used to characterise the patient population. Fisher's exact or Pearson's χ^2 tests were used to examine the distribution of clinical covariates between groups. Overall survival (OS) curves were plotted according to the product limit estimate of Kaplan and Meier, and the log-rank test was used to determine significance of the differences. Differences at $p \leq .05$ were considered statistically significant.

Results

Patient characteristics

A total of 34 patients with malignant ovarian GCT were referred to our institution between 1991 and 2009. The median age at diagnosis was 32 (range 13 to 65) years. The median follow-up time from the initial diagnosis was 5.7 years (range, 0.7 to 14.3 years). Patients with carcinoma associated with teratoma were older, median 54 (range 41-65) years. The commonest histologic types were immature teratomas, yolk sac tumours, and dysgerminomas. Five patients had carcinoma (3 squamous, 1 squamous plus carcinoid and 1 adenocarcinoma) associated with a teratoma. One woman with yolk sac tumour had divergent differentiation with adenocarcinoma. The characteristics of the patients at diagnosis are summarised in Table 1.

The stage of disease for each histologic subtype is shown in Table 2. At surgical staging, 13 patients (38%) had Stage I disease. One patient with yolk sac tumour had evidence of bilateral ovarian disease. Four patients with immature teratomas had mature cystic teratomas in the other ovary.

None of our patients had simultaneous elevation of either human chorionic gonadotropin beta sub-unit (b-hCG) or α-fetoprotein (AFP). Simultaneous elevation of a GCT marker (β-hCG or AFP) and an epithelial tumour marker such as CA125 or CEA was present in four patients (12%). Four of six patients with carcinoma associated with GCT expressed β-hCG or AFP.

Table 1. — *Patients characteristics*.

	No. of patients (%)
Age (years)	
Median	32.3
Range	13-65
SD	13
Histology	
Dysgerminoma	8 (24%)
Yolk sac tumour	9 (26%)
Choriocarcinoma	1 (3%)
Mixed germ cell tumour	1 (3%)
Embryonal carcinoma	1 (3%)
Immature teratoma	9 (26%)
Carcinoma associated with biphasic or triphasic teratomas	5 (15%)
Stage	
I	13 (38%)
II	7 (21%)
III	10 (29%)
IV	4 (12%)
Tumour markers at diagnosis	
hCG elevated	9 (12%)
AFP elevated	16 (35%)
CA125 or CEA elevated	5 (3%)
hCG elevated and AFP elevated	0 (0%)
hCG or AFP elevated with CA 125 or CEA elevated	4 (12%)
All tumour markers normal	8 (29%)

hCG: human chorionic gonadotropin; AFP: α-fetoprotein.

Table 2. — *Stage by histology.*

(n, % per stage)	Dysgerminoma	Yolk sac tumour	Choriocarcinoma	Mixed germ cell tumour	Embryonal carcinoma	Immature teratoma	Carcinoma associated with teratomas
I	2 (15%)	4 (31%)	0 (0%)	0 (0%)	0 (0%)	4 (31%)	3 (23%)
II	2 (29%)	1 (14%)	1 (14%)	0 (0%)	1 (14%)	1 (14%)	1 (14%)
III	4 (40%)	2 (20%)	0 (0%)	1 (10%)	0 (0%)	3 (30%)	0 (0%)
IV	0	2 (50%)	0 (0%)	0 (0%)	0 (0%)	1 (25%)	1 (25%)

Table 3. — *Primary treatment characteristics*.

	No. of patients (%)
Initial surgery	
USO	17 (50%)
BSO ± TH	14 (41%)
Resection of mass	1 (3%)
Only biopsy	2 (6%)
Extent of surgery	
Complete resection	25 (74%)
Incomplete resection	9 (26%)
Primary chemotherapy	
BEP	20 (77%)
POMB/ACE	4 (15%)
BVP	1 (4%)
Cisplatin-etoposide	1 (4%)
Radiotherapy	
Pelvic radiotherapy	1 (3%)

USO, unilateral salpingo oophorectomy; BSO, bilateral salpingo-oophorectomy; TH, Total hysterectomy.

Treatment

The primary treatments received (excluding treatment for relapse) are summarised in Table 3. Surgery was the initial treatment for the majority of the patients (n = 32, 94%). Bilateral salpingo-oophorectomy with hysterectomy was performed in 14 patients (41%); all except one had completed childbearing. Fertility preserving surgery with unilateral salpingo-oophorectomy was preferred in

Table 4. — *Summary of clinicopathological features, treatment, and outcome of those who failed primary treatment or recurred.*

	Age	Histologic subtype	FIGO Staging (grade)	Tumour markers	Primary surgery	Extent of surgery	ASvs CT	Primary CT	Response to CT	TTR (months)	Salvage treatment response	Outcome
1	43	Yolk sac tumour	IA	AFP	BSO-TH	Complete resection	AS	BEP	CR	3	NA	NED, 113 mths
2	13	Yolk sac tumour	IC	AFP	USO	Complete resection	AS	BEP	CR	3	NA	NED, 68 mths
3	46	Yolk sac tumor + adenocarcinoma	IV	AFP, CEA	Resection of mass	Incomplete resection	CT	BVP	PD	NA	NA	DOD, 1 month
4	41	Choriocarcinoma	IIC	hCG	BSO-TH	Incompleten resection	CT	BEP	PR	NA	Ifosfomide + Etoposide: CR	NED, 121 mths
5	27	Immature teratoma	IIIC (G 3)	AFP	USO	Incomplete resection	CT	POMB-ACE	PR	NA	HD-CT: CR	NED, 226 mths Thyroid cancer at 18 years
6	26	Immature teratoma	IV (G 3)	AFP, CEA	Biopsy	Incomplete resection	CT	BEP	SD	NA	NA	DOD, 2 mths
7	34	Immature teratoma	IIIA (G 3)	AFP	BSO-TH	Complete resection	CT	BEP	CR	4	Carboplatin-Paclitaxel-HD-CT: PD; Etoposide: PD	DOD, 19 mths
8	29	Immature teratoma	IA (G3)	N	USO	Complete resection	AS	BEP	SD	12	HD-CT: PD	DOD, 32 mths
9	56	Squamous carcinoma + teratoma	IIB	AFP, CA125	BSO-TH	Incomplete resection	CT	EP (+RT)	CR	35	Surgery Refuse further CT	DoD, 44 mths
10	65	Adenocarcinoma + teratoma	IA	hCG, CA125	BSO-TH	Complete resection	CT	BEP	CR	6	HD-CT: PD	DoD, 10 mths

TTR: time to relapse; CR: complete remission; PR: partial response; SD: stable disease; PD: progressive disease; AS: active surveillance; N: Normal, NED: no evidence of disease; DoD: died of disease; CT: chemotherapy; HD-CT: High dose chemotherapy, NA- not applicable. mths: months.

the other patients. Nine patients (26%) had incomplete resections. Eight patients with Stage I disease were recommended for post surgery active surveillance. Twenty-six patients received platinum-based chemotherapy that followed standardised protocols: bleomycin, cisplatin and etoposide (BEP) in 20 patients, vincristine, metotrexate, bleomycin and cisplatin/dactinomycin, etoposide and cyclophosphamide (POMB/ACE) in four, cisplatin, vinblastine and bleomycin (PVB), and cisplatin and etoposide (PE) in one each. Pelvic radiotherapy was also performed (after chemotherapy) in one patient with a squamous cell carcinoma associated with teratoma. Second-look laparotomy was performed in two patients, one with an immature teratoma incompletely resected at the first operation, and the other with only a biopsy of embyonal carcinoma at baseline. No evidence of residual disease was found in either case.

Acute toxicity of chemotherapy

Toxicities were largely as expected. Severe adverse events reported (common toxicity grade [CTC] ≥ grade 3) were neutropenic sepsis in seven patients, peripheral neuropathy in four patients, thrombotic events and acute kidney dysfunction in two patients each and non-neutropenic sepsis in one patient. There was one treatment-related death following the second cycle of chemotherapy due to neutropenic sepsis and pulmonary embolism in a patient with Stage IV immature teratomas and very poor general condition.

Disease outcome

The 10-year estimated overall survival rate was 80% (Figure 1). Six patients (18%) have died. The latest disease-related death was observed 3.8 years after diag-

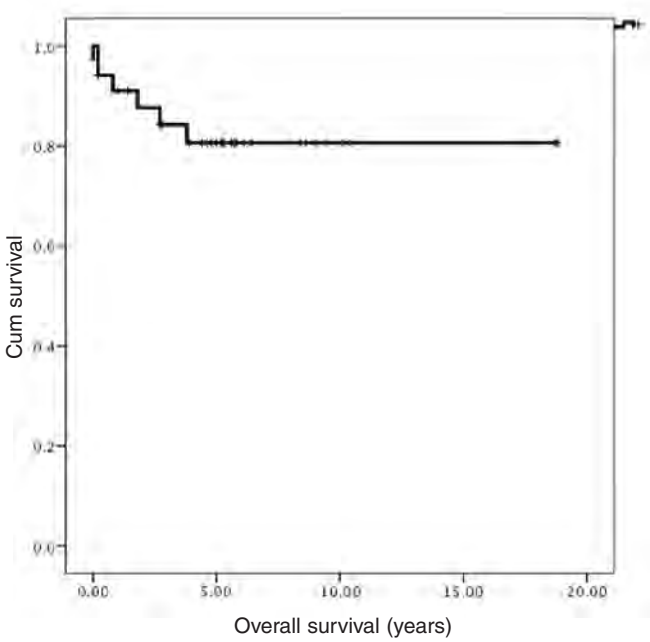

Figure 1. — Kaplan-Meier estimate of overall suvival.

Table 5. — *Summary of clinicopathological features, treatment, and outcome of Stage I patients.*

	Age	Histologic subtype	FIGO Stage	Tumour markers	Primary surgery	Extent of surgery	Surveillance vs CT	Primary CT	Response to CT	TTR (mths)	Salvage treat. response	Outcome
1	17	Dysgerminoma	IA	hHCG	USO	Complete resection	AS	NA	NA	NA	NA	NED, 12 mths.
2	19	Dysgerminoma	IC	Normal	USO	Complete resection	CT	BEP	CR	NA	NA	NED, 58 mths.
3	43	Yolk sac tumour	IA	AFP	BSO-TH	Complete resection	AS	BEP	CR	3	NA	NED, 114 mths
4	19	Yolk sac tumour	IC	AFP	USO	Complete resection	CT	BEP	CR	NA	NA	NED, 60 mths
5	25	Yolk sac tumour	IC	AFP	USO	Complete resection	CT	BEP	CR	NA	NA	NED, 38 mths
6	13	Yolk sac tumour	IC	AFP	USO	Complete resection	AS	BEP	CR	3	NA	NED, 70 mths
7	29	Immature teratoma	IA (G 3)	Normal	USO	Complete resection	AS	BEP	SD	12	HD-CT: PD	DOD, 32 mths
8	19	Immature teratoma	IA (G1)	AFP	USO	Complete resection	AS	NA	NA	NA	NA	NED, 62 mths
9	32	Immature teratoma	IC (G 3)	AFP	USO	Complete resection	CT	BEP	CR	NA	NA	NED, 53 mths
10	24	Immature teratoma	IC (G 1)	N	USO	Complete resection	AS	NA	CR	NA	NA	NED, 22 mths
11	65	Adenocarcinoma + teratoma	IA	hCG, CA125	BSO-TH	Complete resection	CT	BEP	CR	6	HD-CT: PD	DOD, 10 mths
12	55	Squamous + teratoma	IA	N	BSO-TH	Complete resection	AS	NA	NA	NA	NA	NED, 69 mths
13	52	Squamous + adenocarcinoma + teratoma	IA	hCG	BSO-TH	Complete resection	AS	NA	NA	NA	NA	NED, 10 mths

TTR: time to relapse; CR: complete remission; PR: partial response; SD: stable disease; PD: progressive disease; AS: active surveillance; CT: chemotherapy; HD-CT: High dose chemotherapy, NA- not applicable. NED: no evidence of disease; DoD: died of disease; mths: months.

nosis, and 2.9 years after relapse following primary treatment. Interestingly, all four patients with elevation of both a GCT marker and an epithelial tumour marker have died.

The 15-year estimated event-free survival rate was 69%. Two patients died during primary chemotherapy; six patients relapsed; three patients failed to achieve remission after primary chemotherapy including one patient who relapsed after active surveillance. All relapses occurred within the first four years. The median time to recurrence (TTR) was 12.6 months. Five patients received salvage treatment, four with high-dose chemotherapy and peripheral blood stem cell (PBSC) support; of these, long-term disease control was achieved in two.

To date, only patients with a diagnosis of immature teratoma or carcinoma associated with GCT have died. Ten-year estimated overall survival for this group was 58%. Two patients with pure yolk sac tumours relapsed during surveillance but were subsequently cured. All dysgerminoma cases were alive and free of disease at the last follow-up.

Two patients with initial Stage I disease have died. One was a 29-year-old woman with a Stage IA grade 3 immature teratoma, and a mature cystic teratoma in the contralateral ovary diagnosed during pregnancy. Left salpingo-oophorectomy and right cystectomy were performed. Tumour markers were normal. Twelve months later she relapsed with a 40 mm right pelvic mass and raised CA125. After four cycles of BEP the extent of disease was unchanged, and so she proceeded to high-dose chemotherapy and PBSC. Despite this she died of disease 2.7 years after the diagnosis. The other patient was aged 65 with a Stage IA adenocarcinoma associated with teratoma. Both β-hCG and CA125 were elevated. She underwent bilateral salpingo-oophorectomy and hysterectomy. After adjuvant chemotherapy with BEP (two cycles) there was no evidence of disease. The patient relapsed six months later, and despite high-dose chemotherapy and PBSC, died of disease ten months after diagnosis (Table 4).

Active surveillance as an alternative to chemotherapy

Thirteen patients were Stage I, seven Stage IA and six Stage IC. Eight patients with Stage I disease (six Stage IA) were recommended for post surgery active surveillance. Of these, three relapsed with one death. Five patients with Stage I disease (four Stage IC and one Stage IA) were recommended to receive adjuvant chemotherapy. Of these, one subsequently relapsed and died (Table 5).

Late effects of treatment

After chemotherapy nine patients of the 17 that underwent fertility preserving surgery resumed normal menstrual function; four women became pregnant, apparently

with no pregnancy complications. More than 15 years after treatment for a germ cell tumour, one patient had a squamous cell of the tongue and the other had a papillary cancer of the thyroid.

Discussion

Risk adapted management of ovarian GCT is widely advocated to minimise the exposure of patients with low risk disease to chemotherapy, while maximising survival of patients with poor prognoses. Unlike in testicular GCT, where indications for adjuvant chemotherapy or surveillance are well defined, the extreme rarity of ovarian GCT has made identifying prognostic factors a challenge [3]. The most recent studies have confirmed "old clinical impressions" that stage, residual disease, histological type and elevation of tumour markers are the most important prognostic factors [6, 11].

In a relatively recent study, non-dysgerminoma histology was associated with a significantly higher risk of treatment failure and worse overall survival [11]. Age was traditionally seen as an adverse prognostic feature; women younger than 30 seemed to have an improved three-year survival [7]. Smith *et al*. showed that during the past 30 years survival rates of malignant ovarian GCT have improved but were lower for older women [13]. However, more recently some reports have suggested that age has no prognostic significance in patients with ovarian GCT [14].

Monodermal teratomas and somatic type tumours associated with teratomas are recognised to be less sensitive to platinum-based chemotherapy than both the other ovarian GCT and testicular GCT, and are often excluded from reported series [3]. In this report, we have elected to include them since some had specific germ cell clinical characteristics including rasied GCT markers.

Sensitivity to platinum-based chemotherapy is probably one of the strongest determinants of outcome. Patients with ovarian GCT have an excellent probability of cure with aggressive primary therapy, but successful salvage may be difficult when primary treatment fails [14]. Our case series reflects this finding; only two patients responded to salvage treatment following a partial response to platinum-based chemotherapy. All the others that fail primary treatment or relapse seem to be chemoresistant patients.

Traditionally, the only patients thought to be appropriate candidates for treatment with surgery alone were those with Stage IA dysgerminoma and Stage IA, grade I immature teratoma. However, a more conservative approach and more widespread use of surveillance has been based on an emerging relatively small evidence base. In one series, 22 patients with Stage I or II were treated with surgery alone. Of these, two patients relapsed but were salvaged with repeat surgery [6]. Dark *et al*. enrolled 24 Stage IA ovarian GCT into a surveillance program. Three of these patients relapsed; two were salvaged by chemotherapy, the other became pregnant and presented with advanced disease and died following a pulmonary embolus [7]. Mitchell *et al*. reported on nine patients with ovarian GCT, with one relapse [10]. Cushing *et al*. treated 44 patients with immature teratoma (all grades). The four-year event-free and overall survival probabilities were for 97.7% and 100% respectively [8]. The worse outcome in our series may reflect the older age group of our patients, with many of the cases in the previously described series being in the paediatric rather than young adult age range.

Conservative surgery seems appropriate in women with early disease who wish to preserve fertility, with several series suggesting that oncological outcomes are not compromised by conservative surgery [15-18]. In our series, 20 women had conservative surgery. Four of our patients have subsequently had a normal uneventful pregnancy.

In advanced ovarian GCT, the benefit of cytoreductive surgery is less well established than in epithelial ovarian cancer. However, there is some evidence that patients who undergo radical debulking have a higher complete remission rate and better outcome. An early trial from the Gynaecologic Oncology Group (GOG) showed that the likelihood of disease progression after chemotherapy with vincristine, dactinomycin, cyclophosphamide (VAC) was significantly higher in patients with incompletely resected disease [19]. Optimal debulking may be particularly important for non-dysgerminoma. In a series of 33 patients with dysgerminomas, all had a complete sustained response after BEP, regardless of the size of residual disease. In contrast, only three of six patients with bulky non-dygerminomas were long-term complete responders to chemotherapy, while 14 of 16 patients with small volume residual disease achieved a durable complete response to chemotherapy [20]. Our study also showed a trend (data not shown) of improved overall survival with complete resected disease versus incomplete resection. In general, in advanced stage ovarian GCT, resection of all gross tumours seems to be an appropriate goal, tempered by safety and morbidity considerations in view of the chemosensitivity of these tumors [3]. The introduction of cisplatin-based combination chemotherapy in ovarian GCT dramatically improved outcomes. Today, around 90% of patients with early-stage disease and 75-80% with advanced disease can expect to be long-term survivors. The initial cisplatin-based combination was PVB, and in a GOG trial in 89 patients with non-dygerminomas, PVB was superior to previous regimens [21]. Subsequent trials showed long-term survival rates of 95-100% and 75-80% with surgery followed by BEP chemotherapy in early stage and advanced non-dysgerminomatous disease, respectively [22]. POMB/ACE was developed initially for the management of testicular germ cell tumours [23]. It was designated to introduce seven different cytotoxic agents as early as possible to decrease the risk of drug resistance. It has been show to be highly active and tolerated in advanced and aggressive testicular germ cell tumours and Murugaesu *et al*. have confirmed its activity in advanced ovarian GCT [5].

In previous reports, an elevated bhCG and AFP at presentation appeared to be independent adverse prognostic

factors in patients, and elevation of both tumour markers substantially increased the risk of treatment failure [6]. In our study we did not have any patient with both bhCG and AFP increased. However, patients with both an elevated GCT and epithelial tumour marker appeared to have a particularly poor outcome. This has not been reported previously and may be a chance finding in a small subset of patients. Our experience in the management of malignant ovarian GCT is probably similar to that of most other regional oncology centres. Patients present at a rate of one to two cases per year, representing about two cases per million of the female population, and each case presents a dilemma in management due to relative unfamiliarity with the disease even when referred to a single oncologist, and a limited evidence base on which to base treatment decisions.

An interesting parallel to this situation is the management of gestational trophoblastic disease (GTD) which is similarly uncommon complicating approximately 1:750 pregnancies. In the UK, all women with molar pregnancies are registered at one of three dedicated GTD centres (London, Sheffield, Dundee) for ongoing monitoring, and treatment if necessary. Our own centre in Sheffield, receives 500-600 registrations each year. Approximately 6-8% of these women subsequently require treatment, which is usually chemotherapy. The prognosis is excellent, with a cure rate in excess of 98% [24]. Similar results were obtained at the other treatment centre in the UK, and these combined national results are better than anywhere else in the world, reflecting the benefits of supra-regional specialist care for management of rare conditions. It might be expected that similar expertise, improvements in our understanding of the disease and development of more effective treatment strategies would result from centralising the management of malignant ovarian GCT. Such a strategy is currently under consideration.

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