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ORIGINAL REPORT

Malignant Ovarian Germ Cell Tumors: Identification of Novel Prognostic Markers and Long-Term Outcome After Multimodality Treatment

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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ABSTRACT

Purpose
Malignant ovarian germ cell tumors are rare and knowledge about prognostic parameters currently is limited. This study was undertaken to evaluate long-term outcome of patients with malignant ovarian germ cell tumors (MOGCTs) after chemotherapy and to assess prognostic parameters.

Patients and Methods
A total of 113 patients with stage IC to IV MOGCTs were included into this retrospective study. Patients were treated at two large regional cancer centers between 1977 and 2003.

Results
Ten-year recurrence-free and overall survival rates were 82% and 81%, respectively. A total of 20 patients experienced relapse, all within the first 8 years. Outcome after relapse was poor, with only 10% of patients achieving long-term survival. Univariate and multivariate analyses demonstrated that initial stage of disease (relative risk [RR], 5.96; 95% CI, 3.47 to 10.22; $P = .03$) and elevation of serum markers β-human chorionic gonadotropin and alpha-fetoprotein (RR, 3.90; 95% CI, 1.40 to 10.9; $P = .009$) were significant predictors of overall survival, whereas age at diagnosis was of no prognostic value.

Conclusion
This is the first study to identify stage and tumor markers as prognostic parameters for patients with MOGCTs. This might help to select patients for risk-adapted treatment. There is need for improvement of therapeutic strategies after relapse.

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INTRODUCTION

Malignant ovarian germ cell tumors (MOGCTs) are rare but aggressive tumors, accounting for approximately 1% to 2% of all ovarian malignancies.[1] The peak incidence is in young women or adolescent girls, and germ cell tumors (GCTs) account for 58% of all ovarian tumors in women younger than age 20 years; one third of these tumors are malignant.[2] Apart from stage IA disease, multimodality therapy with initial surgery and platinum-based combination chemotherapy generally is regarded as the standard of care and has improved the prognosis significantly. Even patients with advanced disease are curable and should be treated with this intent.[3]

Despite many similarities, previous reports have suggested that prognostic factors might differ for ovarian and testicular GCTs. Whereas for advanced testicular GCTs a number of prognostic classification systems are in use[4-6] (most of them incorporating stage, histology, and serum markers β-human chorionic gonadotropin [β-hCG], alpha-fetoprotein [AFP], and lactate dehydrogenase), prognostic parameters for MOGCTs currently are not well characterized. Previous studies have been unable to demonstrate a clear correlation between outcome and stage or serum markers, but suggested that age could be of prognostic relevance; women younger than age 30 years have an improved 3-year survival. However, the significance of these findings is limited by the small number of patients included in the analyses.[7]

The purpose of this study was to evaluate long-term outcome with MOGCTs in a larger series of patients and to define prognostic parameters for relapse and survival. This study focuses on patients with stage IC to IV disease or stage I disease with persisting or increasing tumor markers (stage IM), given that these patients received multimodality treatment including chemotherapy as part of their initial management. Patients with stage IA/B disease

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and postoperative normalization of tumor markers underwent a surveillance program, were excluded from this analysis, and are reviewed in a parallel publication (in preparation).

PATIENTS AND METHODS

Patient Population

This retrospective study included all patients with a diagnosis of a MOGCT who were evaluated and treated at Charing Cross Hospital (London, United Kingdom) or Mount Vernon Hospital (Northwood, United Kingdom) between 1977 and 2003. The study was conducted in accordance with local regulations and with the approval of the local institutional review boards.

Patients were identified through the institutional databases, which provided demographic, clinicopathologic, treatment, and outcome information. In addition, medical records were reviewed to obtain details regarding patient characteristics, surgical treatment, and chemotherapy.

A total of 148 patients with MOGCTs were identified and 113 patients with stage IC to IV or stage IM disease who received chemotherapy as part of their initial treatment were selected for this analysis. Thirty-five patients with stage IA/B disease and postoperative normalization of tumor markers were excluded from the analysis; they underwent surveillance after surgery. They will be reviewed in a separate publication (in preparation).

Histologic diagnosis was established after surgical resection or biopsy. The histologic type was defined according to the WHO classification.[8] Pathologic specimens were reviewed centrally, with the exception of 13 patients in whom mixed MOGCTs were diagnosed at referring hospitals but material was unavailable or insufficient for central review.

Serum tumor markers β-hCG were centrally assessed, and in 94 patients (83%) at least one of the markers was found to be above the upper limit of normal (4 U/L for β-hCG; 13 ng/mL for AFP; Table 1). Serum lactate dehydrogenase levels were not measured routinely during the first years of the observational period and were therefore not available for the majority of patients.

Tumors were classified and staged according to clinical and pathologic information. Stage at diagnosis based on the revised Federation International de Gynecologie et d'Obstetrique criteria for ovarian tumors[9] was IC/M, II, III, and IV in 20%, 22%, 24%, and 20%, respectively. In 16 patients, the initial clinical stage could not be assessed accurately due to limited surgery and/or initiation of medical treatment before computed tomography scanning. However, all of these patients had at least stage II disease.

Table 1. Patient Characteristics

Characteristic	No. of Patients	%
Age, years		
Median	24	
Range	4-60	
Stage at presentation		
IC/M	23	20.4
II	25	22.1
III	27	23.9
IV	22	19.5
> IC/M (uncertain exact stage)	16	14.2
Histologic subtype		
Dysgerminoma	14	12.4
Teratoma	17	15.0
Yolk sac tumor	30	26.5
Mixed	36	31.9
Embryonal	2	1.8
Choriocarcinoma	1	0.9
Unclassified	13	11.5
Baseline tumor marker levels		
hCG elevated	39	34.5
AFP elevated	72	63.7
hCG and AFP elevated	17	15.0
hCG and AFP normal	19	16.8
Surgery		
No initial surgery	7	6.2
Oophorectomy (unilateral or bilateral)	63	55.8
Debulking surgery (including BSOH)	43	38.1

Abbreviations: hCG, human chorionic gonadotropin; AFP, alpha-fetoprotein; BSOH, bilateral salpingo-oophorectomy and hysterectomy.

Treatment

Surgery was the initial treatment for the majority of patients (94%), consisting of complete resection by unilateral or bilateral salpingo-oophorectomy in 56% of patients or debulking surgery with bilateral salpingo-oophorectomy in the remaining 38% of patients. The goals of surgery were to achieve complete resection or optimal tumor debulking with removal of as much gross tumor as could be done safely, while preserving fertility. Surgery followed institutional guidelines, which recommend open laparotomy, paracolic gutter washings and/or collection of ascites for cytology, surgical staging, fertility-conserving procedure with removal of the affected ovary and other gross tumor manifestations, omental biopsy, and biopsy of the contralateral ovary if dysgerminoma was suspected in the primary site. After chemotherapy, all residual masses were resected.

Treatment followed standardized protocols and most patients received platinum-based combination chemotherapy according to one regimen (89 patients; vincristine 1 mg/m^2 day 1, methotrexate 100 mg/m^2 intravenous bolus followed by methotrexate 200 mg/m^2 during 12 hours on day 1, bleomycin 30 mg day 2, and cisplatin 120 mg/m^2 day 3 [POMB]; dactinomycin 0.5 mg days 1 to 3, etoposide 100 mg/m^2 days 1 to 3, and cyclophosphamide 500 mg/m^2 day 3 [ACE]), or according to another regimen (17 patients; cisplatin 20 mg/m^2 days 1 to 5, etoposide 100 mg/m^2 days 1 to 5, and bleomycin 100 mg/m^2 days 1, 8, and 15 [BEP]). BEP chemotherapy was offered to patients with stage IC/M or stage II disease and low tumor markers, whereas POMB/ACE generally was used in patients with more advanced disease. Fifteen patients had commenced chemotherapy at other centers and seven patients were treated subsequently with alternative regimens.

Follow-up was carried out according to the institutional standard. Between 3 and 6 weeks after surgery, full staging was carried out including physical examination, assessment of serum markers, and a computed tomography scan of chest, abdomen, and pelvis. During follow-up, clinical assessments and measurement of serum markers were performed monthly for the first year, at 2- and 3-month intervals for the second and third year, respectively, every 6 months for the fourth and fifth year, and once a year thereafter.

Statistical Methods

Descriptive statistics were used to characterize the patient population (Table 1). The primary end point for this analysis, overall survival (OS), was defined as the time from the date of first treatment to the date of death as a result of any cause. Time to recurrence (TTR), only for patients who experienced relapse, was defined as the period of time from the date of first treatment to the first observation of disease progression. OS and TTR were estimated using the method of Kaplan and Meier. The univariate log-rank test was used to evaluate possible associations between survival and patient or disease covariates. Cox regression multivariate analysis was performed to test the significance of various prognostic factors. Variables with $P \leq .05$ on univariate analysis were selected for multivariate analysis. Receiver operating characteristic curve analysis was used to define specific marker values of prognostic significance for OS. All analyses were performed using the Statistical Package for the Social Sciences software program (version 12.0; SPSS Inc, Chicago, IL). All P values were two sided. Differences at $P \leq .05$ were considered statistically significant.

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RESULTS

Patient Characteristics

The characteristics of the patients at diagnosis are summarized in Table 1. The median patient age was 25.8 years (range, 4 to 60 years). The median follow-up time was 8 years.

Outcome

All patients responded initially to the treatment but 20 patients experienced recurrence of disease (17.7%). All relapses occurred within the first 8 years. Five- and 10-year actuarial recurrence-free rates were 83% and 82%, respectively. The median TTR for patients who experienced relapse was 7 months. Relapse rates were similar in patients treated with POMB/ACE (14.6%) or BEP (17.7%) regimens.

All patients who experienced relapse received salvage chemotherapy but long-term disease control was only achieved in two patients (10%). Four patients underwent salvage high-dose therapy after failure of conventional salvage regimens but only one patient achieved long-term remission. The remaining 18 patients (90%) experienced progression while receiving salvage therapy and eventually died as a result of their disease.

Five, 10-, and 25-year estimated survival rates were 83%, 81%, and 81%, respectively (Fig 1). The latest disease-related death was observed at 8 years after the initial diagnosis, after relapse at 7.6 years from diagnosis. There were no treatment-related deaths among patients receiving POMB/ACE or BEP chemotherapy. However, one patient who had received POMB/ACE-treatment for stage III dysgerminoma, including a cumulative etoposide dose of 1,300 mg/m^2, died as a result of an acute myeloid leukemia 7 months after completing chemotherapy for the MOGCT.

Prognostic Parameters

Univariate and multivariate regression analyses were performed to evaluate the influence of age, histology, stage of disease, and tumor markers on recurrence and OS. Only initial stage of disease (relative risk, 5.96; 95% CI, 3.47 to 10.22; $P = .03$) and elevation of both β-hCG and AFP (relative risk, 3.90; 95% CI, 1.40 to 10.9; $P = .009$) were of significant predictive value in both univariate and multivariate analysis (Table 2).

Whereas pretreatment AFP- or β-hCG levels when taken alone failed to predict survival or were of borderline significance only, elevation of both tumor markers proved to be a strong predictor of survival on univariate and multivariate analysis. One-year survival for patients with normal initial β-hCG and/or AFP was 89.6% compared with 50.4% for patients with elevation of β-hCG and AFP (Fig 2). Receiver operating characteristic curve analysis was applied to evaluate further the relevance of the level of β-hCG and AFP elevation, but there were insufficient data to define different cutoff values (data not shown).

Univariate and multivariate analysis also confirmed that advanced stage of disease at presentation was an independent poor prognostic indicator (Fig 3). Five-years OS rates were 100%, 85%, 79%, and 71%, for patients with stage IC/M, II, III, or IV disease, respectively.

In contrast to previous findings, age at diagnosis was of no significant prognostic value on both univariate and multivariate analysis.

Table 2. Univariate and Multivariate Analysis

	Univariate Analysis			Multivariate Analysis		
Parameter	*P*	HR	95% CI	*P*	HR	95% CI
Stage	.0085	1.88	1.14 to 3.12	.03	5.96	3.47 to 10.2
Elevated hCG and AFP	.001	4.93	1.97 to 12.4	.009	3.90	1.40 to 10.9
Elevated hCG	.05	2.41	1.00 to 5.83			
Elevated AFP	.69					
Age > 30 years	.13					

Abbreviations: HR, hazard ratio; hCG, human chorionic gonadotropin; AFP, alpha-fetoprotein.

DISCUSSION

MOGCTs are rare and highly aggressive malignancies that are most often seen in young women. Before the introduction of combination chemotherapy, the outcome of advanced MOGCTs was almost invariably fatal, but the majority of patients can now be cured with multimodality therapy including platinum-based chemotherapy. Our findings confirm that long-term outcome of patients with MOGCTs is excellent, with 10- and 25-year survival rates of 81% and 81%, respectively.

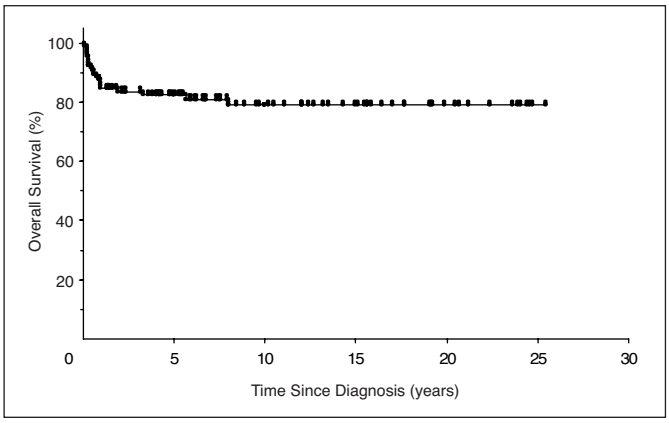

Fig 1. Kaplan-Meier estimate of overall survival.

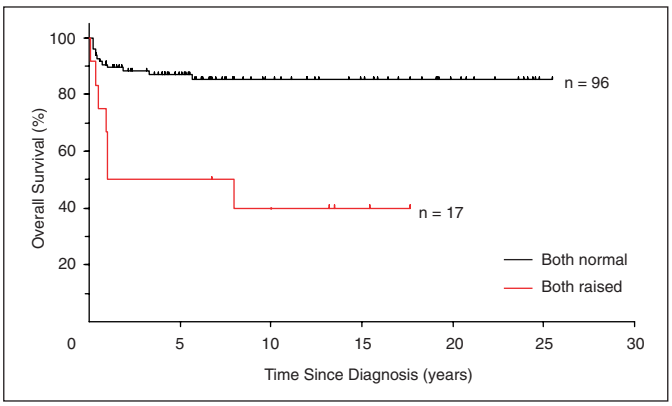

Fig 2. Kaplan-Meier estimate of overall survival by serum markers (alpha-fetoprotein [AFP] and human chorionic gonadotropin [hCG] elevated *v* AFP and/or hCG within normal range).

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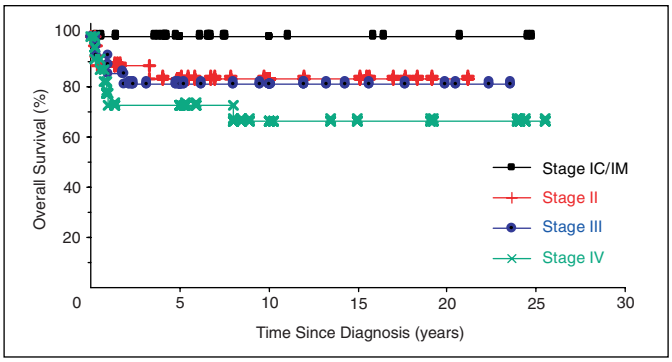

Fig 3. Kaplan-Meier estimate of overall survival by initial stage of disease.

Most patients underwent initial surgery according to institutional guidelines, and complete resection was achieved in 56% of patients. In the remaining patients, debulking surgery was performed to remove as much gross tumor as possible, while trying to preserve fertility. However, the role and the extent of debulking surgery remain controversial despite its routine application. With the introduction of effective platinum-based chemotherapy, a shift away from radical surgery toward fertility-conserving approaches seems to produce favorable results. Nonetheless, randomized data proving that platinum-based therapy alone is no worse than radical surgery followed by chemotherapy is lacking and indeed unlikely to be generated given the rarity of this disease. Consequently, for the present, given that the disease is chemotherapy sensitive and the results of fertility conserving surgery seem reasonable, we still feel comfortable recommending this approach. All residual masses postchemotherapy should be excised for three reasons: to exclude active residual tumor, to prevent a mature growing teratoma syndrome, or to prevent subsequent dedifferentiation of teratoma back into active cancer.

Several platinum-based chemotherapy regimens such as BEP; cisplatin, etoposide, and bleomycin; and vincristine, dactinomycin, and cyclophosphamide have been used successfully for the treatment of MOGCTs but the optimal regimen remains to be determined. The POMB/ACE regimen was developed initially for the management of testicular GCTs.[10] It was designed to introduce seven different cytotoxic agents as early as possible to decrease the patient's risk of developing drug resistance. By alternating the myelosuppressive ACE regimen with the less myelotoxic POMB regimen, treatment cycles can be administered at 2-weeks interval. The regimen is generally well tolerated, with few long-term adverse effects, and fertility can be preserved in most patients.[11,12] POMB/ACE has been shown to be highly active in advanced and aggressive testicular GCTs[11]; this study confirms its high antitumor activity in patients with advanced MOGCTs. Randomized trials would be indicated to define further the role of POMB/ACE and other platinum-based regimens, but are unlikely to be realized in view of the rarity of the disease.

Only a few, relatively small studies have reported long-term results of patients with MOGCTs.[13-18] Comparison among these trials is difficult because of substantial heterogeneity in relevant clinicopathologic and therapeutic features, such as stage distribution, histologic subtypes, surgical management, indication for the use of chemotherapy, and chemotherapy regimens (Table 3).

In contrast to most other studies, patients with stage IA/B disease were excluded from our study because they did not receive systemic therapy. The role of adjuvant chemotherapy in these patients remains controversial; the majority of patients are cured without additional systemic treatment and remaining patients can be treated effectively at relapse. Charing Cross and Mount Vernon groups have therefore adopted a surveillance policy for all stage IA/B MOGCTs that demonstrated a 5-year survival rate of 95%.[19]

The exclusion of patients with stage IA/B disease from the analysis led to a shift in stage distribution toward more advanced stages compared with other studies. Thus, only 20% of patients were stage IC/M, and more than 43% of patients had stage III or IV disease at presentation in our study. In contrast, in other studies stage I patients accounted for up to 71%,[13-18] whereas the numbers of patients with stage III or IV disease were low. Considering these differences in stage distribution, our results compare favorably to other series, with a 5-year survival of 81% for all patients and 100% for stage IC/M patients.

Although a number of series of MOGCTs had been described before this study, prognostic factors for relapse or survival were poorly defined. Previous studies suggested age older than 30 years as an indicator of poor outcome, but failed to establish any other prognostic

Table 3. Treatment and Outcome of Patients With MOGCT

Study	No. of Patients	Stage*	Stage I†		Indication for Chemotherapy	Patients With Chemotherapy		Chemotherapy Regimen	5-Year Overall Survival (%)
			No.	%		No.	%		
Lai et al[16]	93	IA-IV	64	69	Stage IA-IV	93	100	BEP	97 (IA-II) 88 (III-IV)
Billmire et al[18]	131	IA-IV	41	31	Stage IA-IV	131	100	BEP, HD-BEP	97
Zanetta et al[17]	169	IA-IV	98	58	Stage IA-IV‡	105	62	AC, PVB, BEP	95
Zanagnolo et al[15]	55	IA-IV	39	71	Stage > 1A	40	73	AC, VAC, PVB, POMB/ACE	91
Williams et al[13]	93	I-III	60	65	Stage I-III	93	100	BEP	96
Skof et al[14]	23	IA-IV	11	48	Stage IA-IV	21	91	Cisplatin based	87

Abbreviations: MOGCT, malignant ovarian germ cell tumor; FIGO, Federation International de Gynecologie et d'Obstetrique; BEP, cisplatin, etoposide, and bleomycin; PVB, cisplatin, etoposide, and bleomycin; AC, doxorubicin, cyclophosphamide; VAC, vincristine, dactinomycin, and cyclophosphamide; POMB/ACE, vincristine, methotrexate, bleomycin, cisplatin, dactinomycin, etoposide, and cyclophosphamide.
*Initial stage of MOGCT according to FIGO.
†Patients with stage I disease at presentation.
‡Stage IA patients with dysgerminoma were excluded because they received no chemotherapy.

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factor. However, these studies were limited because they were based on relatively small numbers of patients.

In this larger series of MOGCTs, we were able to show for the first time that stage and elevated tumor markers are independent poor prognostic indicators. Attempts to define risk categories for different levels of β-hCG and/or AFP elevation were unsuccessful; this might be related to the size of the study. Larger series are required to assess the relevance of the level of marker elevation.

In contrast to previous findings, our study indicated that age has no prognostic significance in patients with MOGCTs. These findings are important because they identify similar prognostic factors for MOGCT as those described previously in testicular GCTs. This is in accordance with the clinical observation that testicular and ovarian GCTs behave similarly.

Despite the fact that most patients can be cured with multimodality treatment, some patients eventually experience relapse. This study revealed that the outcome of patients who experience relapse after platinum-based combination chemotherapy is particularly poor; only 10% are long-term survivors. This is in contrast with the findings in testicular GCT, in which the salvage rates with second-line therapy are considerably higher.[20] At present, it is unclear why relapsed MOGCTs seem to behave so differently than relapsed testicular GCTs, and additional investigation certainly is warranted. There is a clear need for improvement of therapeutic strategies after relapse. Potential options for salvage therapy include high-dose chemotherapy, which has been used successfully in patients with relapsed testicular GCTs. Within our study, four patients underwent salvage high-dose therapy but only one patient achieved long-term remission. Given that all patients had received prior conventional salvage chemotherapy, it is unclear if these results could have been improved with earlier introduction of high-dose chemotherapy. Additional work is required to define the role of high-dose chemotherapy as well as other salvage treatments in the management of relapsed MOGCTs.

In summary, this study showed for the first time that increasing stage and elevated hCG and AFP at presentation are independent adverse prognostic factors in patients with MOGCTs. In addition, elevation of both hCG and AFP substantially increases the risk of treatment failure. This is relevant for the management of MOGCTs because it helps to identify which patients may require more intensive therapeutic strategies.

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Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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