Malignant Ovarian Germ Cell Tumours

A Survival and Prognostic Analysis

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The medical records and histopathology of all ovarian germ cell tumours (OGCT) in a tertiary centre between 1980 and 1996 were reviewed. Response, overall survival (OS), relapse-free survival (RFS) and prognostic factors were analysed. Sixty-seven patients with OGCT were identified and treated, including 33 dysgerminomas, 18 immature teratomas, 10 endodermal sinus tumours, and 6 mixed tumours. Fifty-three patients (79%) received conservative surgery, 24 (36%) had residual disease post-primary surgery, and 43 (64%) had chemotherapy. Complete response was achieved in 62 patients (93%), 4 out of 5 patients who relapsed were successfully salvaged; OS and RFS at 5 years were 89% and 76%, respectively. Advancing stage of disease was the only significant adverse prognostic factor ($p = 0.0001$ for OS, and 0.0003 for RFS at 5 years). Out of 44 women with the potential to conceive following treatment, there were 16 successful pregnancies. None of the children born subsequent to the chemotherapy were reported to have any congenital abnormalities. The review indicates a high cure rate in OGCT with combined surgery and chemotherapy and that conservative surgery and preservation of fertility are feasible.

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Malignant ovarian germ cell tumours (OGCT) represent less than 10% of all malignant ovarian tumours and predominantly affect young women of childbearing age. OGCT are among the few adult solid tumours where appropriate management impacts significantly on outcome (1). Given the rarity of these tumours, there are no prospective trials, and all reported literature is retrospective and non-controlled. In this review, we report our experience with these tumours, at King Faisal Specialist Hospital and Research Centre (KFSH & RC), a tertiary referral centre, focusing on management, outcome, prognosis, and fertility issues.

PATIENTS AND METHODS

All women with OGCT referred to the Section of Medical Oncology at KFSH & RC between the years 1980 and 1996 were retrospectively identified. The medical records of all patients were reviewed for clinico-pathologic findings, laboratory and radiologic investigation results, management, outcome, and follow-up details. The histopathologies of all the patients were classified as per the World Health Organization (WHO) system.

All patients underwent some form of surgical procedure at presentation. Surgery was defined as conservative if limited to unilateral oophorectomy or salpingo-oophorectomy, with or without biopsies from other sites including the contralateral ovary. Surgery was termed as radical if hysterectomy and/or bilateral salpingo-oophorectomy was carried out. Initial work-up for all patients included a complete medical and obstetric history, physical examination, complete blood count including differential cell count, renal and hepatic biochemical profile, alpha feto protein (αFP) and beta subunit of human chorionic gonadotrophin (βHCG). Imaging studies included chest x-ray, computerized tomographic (CT) scan and/or ultrasound (US) of the abdomen and pelvis. Staging was assigned as per the FIGO (Fédération Internationale de Gynécologie et d'Obstétrique) system. Given the number of patients, patients were assigned to Stages I–IV without further subcategorization. Residual disease following surgery was assessed by either radiologic imaging (CT scan), tumour marker assessment (αFB, βHCG), or both. Second-look laparotomy was performed in some patients after completion of systemic treatment.

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Forty-three (64%) patients received chemotherapy following initial surgery. This was almost always platinum-based combination chemotherapy. Standard PVB (cisplatin, vinblastine, bleomycin) or PEB (cisplatin, etoposide, bleomycin) was the most frequently used regimen. Other treatments included VIP (etoposide, ifosfamide, cisplatin), and CAP (cyclophosphamide, doxorubicin, cisplatin). Chemotherapy was administered every three weeks with monitoring of blood counts, tumour markers, and renal/hepatic function. Only three patients received radiation therapy.

Responses were assessed using WHO criteria. Complete response (CR) was defined as complete resolution of all clinically and radiologically measurable disease; partial response (PR) as greater than 50% resolution of sum of perpendicular diameters of all measurable disease; stable disease (SD) as resolution of less than 50%, or less than 25% increase in total disease measurement. Progressive disease (PD) was any increase in disease measurement greater than 25%. Toxicity of chemotherapy was graded using WHO criteria. Patients were followed up with clinical, tumour marker, and radiologic assessment. In premenopausal women who had conservative surgery, subsequent successful pregnancies were documented.

STATISTICS

The proportion of patients with a given characteristic was compared by χ^2 test. Prognostic factors associated with response to treatment were analysed using a logistic regression model. Overall survival (OS) was measured from diagnosis to death censored by end of follow-up, and relapse-free survival (RFS) was measured from time of CR to relapse or death censored by end of follow-up. The distribution of survival duration was estimated by the Kaplan and Meier method (2).

Ninety-five percent confidence intervals (95% CI) for these probabilities and the median survival times were obtained using the method of Simon & Lee (3). Levels of statistical significance for differences between these curves were obtained by the logrank statistic (4). Median follow-up time was estimated by reversing the codes for the censoring indicator in a Kaplan–Meier analysis. Features independently associated with OS and RFS were identified in a multivariate analysis by proportional hazards regression (5, 6). For the regression analysis, all variables that attained a univariate p-value of 0.20 or less were considered in the variable selection process. All reported p-values are nominal two-sided values, unless otherwise stated. After termination of model-building, adjusted covariates with significance levels of less than 5% in the models were regarded as significant only if they were included by the forward selection process and likewise were not removed by the backward selection process.

RESULTS

Sixty-seven women (median age 20, range 12–64 years) with OGCT, of whom 61 were of Saudi nationality, were seen between 1980 and 1996. All except two were premenopausal. Site of involvement was unilateral in 62 (39 on the right, and 23 on the left), bilateral in 3, and not known in 2 patients. There were 33 (49%) dysgerminomas, 18 (27%) immature teratomas, 10 (15%) endodermal sinus tumours, and 6 (9%) mixed tumours. In the majority of patients, 55 (82%) presented with abdominal mass, while pain was the presenting complaint in 48 (72%). Other non-specific symptoms were mainly of a gastrointestinal or genitourinary nature. Duration of presenting symptoms ranged from 1 to 48 months, with a median of 3 months. Only 9 patients had symptoms with duration greater than 10 months. Four women were pregnant at diagnosis.

Information on tumour markers was available in 38 patients for αFP of whom 31 were normal, and 7 elevated. βHCG was available in 37 patients of whom 28 were normal, and 9 elevated. Staging and management are summarized in the Table.

Table 1

Comparison of outcome with other series

	D	ND	Stage			Total	Median FU (months)	Alive, no active disease
			I/II	III	IV			
Gershenson D.M.	14	12	13	9	0	26	22	25 (96%)
Schwartz P.E.*	26	55	57	22	2	81	68	75 (92%)
Cheung M.M.C.**	13	24	21	10	2	37	48	35 (94%)
Williams S.	0	93	70	23	0	93	38	91 (97%)
Ezzat A.***	33	34	44	14	3	67	62	60 (89%)

Abbreviations: D = dysgerminoma; ND = non dysgerminoma.
* Includes 28 consultations only, treated elsewhere.
** Includes 4 patients with recurrent disease.
*** 6 patients (not shown) could not be staged.

Dysgerminoma

With a total of 33 patients, this formed the biggest single subgroup. All were pre-menopausal, and the ages ranged from 12 to 45 years (median 20). All 33 patients underwent initial surgery, 27 of these being conservative. Tumour maximum dimensions were < 10 cm in 4, 10–20 cm in 19, > 20 cm in 5, and unknown in 5 patients. The pathologic stages were: I = 20, II = 3, III = 8, and IV = 2. After initial surgery, 10 patients had residual disease.

Fifteen patients (all with Stage I disease) had surgery alone, 2 had surgery and radiation therapy, 1 had surgery, radiation and chemotherapy. The other 15 had chemotherapy following surgery, PEB in 12 and PVB in 3. Six patients received 3 cycles of chemotherapy, 6 received 4 cycles, 2 received 5 cycles, and 1 had 6 cycles. Chemotherapy was chosen over radiotherapy in almost all cases because of fertility considerations.

All 33 patients were rendered disease-free at the end of initial treatment. Three patients subsequently suffered relapse, 2 in the pelvis and 1 with lung and liver metastases, but all 3 were successfully salvaged with chemotherapy. All patients with Stage II and beyond received chemotherapy initially, while only 4 out of 20 Stage I patients had chemotherapy, one patient received radiation therapy and remained disease free while one patient who only had surgery relapsed but was salvaged successfully with chemotherapy. Likewise the one patient with Stage II disease was initially treated with surgery and radiation therapy, but she relapsed and was salvaged successfully with chemotherapy. At the time of analysis, 2 patients died in CR of unrelated causes, while the remaining 31 remain in CR. Of 25 women with potential for pregnancy, 12 had successful pregnancies after treatment.

Immature teratoma

All but 1 of the 18 patients in this group were pre-menopausal, and 14 out of 18 patients had conservative surgery. Tumour size was < 10 cm in 4, 10–20 cm in 7, > 20 cm in 4, and size unknown in 3 patients. Stage distribution was I = 7, II = 5, III = 3, and unknown in 3 patients. Five patients had surgery alone as treatment, while the other 13 had chemotherapy following surgery, but none had radiation therapy. Seven patients had PEB, and 3 had PVB regimes, while the other 3 had other platinum combinations. Three patients had 3 cycles and 5 had 4 cycles, while another 4 patients had 2, 5, 6, and 12 cycles, respectively. The number of cycles given was not documented for one patient.

Of the 18 patients, 16 were rendered disease-free with initial treatment. Of the other 2 patients, 1 was successfully converted to CR with second-line chemotherapy, while 1 succumbed to PD. Of the 16 who achieved initial CR, 1 patient who initially had surgery alone relapsed in the pelvis, but was salvaged with chemotherapy. At the time of analysis, 17/18 patients remain disease-free, and 1 died of PD. Of 10 eligible patients, 2 had successful pregnancies.

Endodermal sinus tumour

Nine of 10 women in this subgroup were pre-menopausal, and 8 out of 10 had conservative surgery. Tumour size was < 10 cm in 3, 10–20 cm in 3, > 20 cm in 2, and unknown in 2. Stage distribution revealed: I = 5, II = 3, III = 2. Six women had residual disease post-surgery. Chemotherapy was given to 9 of 10 patients, PEB in 7, PVB in 1 and the other platinum combination in 1. Three patients received 3 cycles, four patients received 4 cycles, and the other two patients received 5 and 7 cycles, respectively.

Of the 10 patients, 9 were rendered disease-free, while 1 patient could not be salvaged and is now terminally ill. Of the 9 patients with CR, 1 relapsed, could not achieve remission with further chemotherapy, and remains alive with disease. At the time of analysis, 8 patients remain in CR, and 2 patients are terminal. Of 7 eligible patients, 1 conceived successfully.

Mixed tumours

All six patients were pre-menopausal and four had conservative surgery. Tumour sizes were < 10 cm in two patients, 10–20 cm in two, > 20 cm in one, and unknown in one. Stage distribution was II = 1, III = 1, IV = 1, and unknown in three patients. Five of the patients had residual disease post-surgery, and all six were treated with chemotherapy; PEB was given to four patients, and PVB to two. Four patients received 4 cycles, while the other two were given 5 and 7 cycles, respectively. Four patients achieved CR and remain disease-free, while two had PD, could not be salvaged, and have since died. Out of two eligible patients, one had a successful pregnancy.

Treatment failures

Of the total 67 patients, 5 patients as described above could be considered treatment failures, 1 with immature teratoma, 2 with endodermal sinus tumour, and 2 with mixed histology. These patients are described in detail, to ascertain whether failure could be attributed to correctable factors such as treatment, or whether it reflected aggressive biologic behaviour by the disease. The patient with immature teratoma was diagnosed in 1981, had Stage III disease, and had initial surgery at a referral hospital, without information on primary tumour size. She received only 2 cycles of PVB chemotherapy post-surgery, showed no response, and was not given any second-line chemotherapy. She died 14 months after initial diagnosis.

Of the two patients with endodermal sinus tumour, the first was diagnosed in 1980, had Stage I with tumour size not stated at outside surgery, and received 4 cycles of non-PEB/PVB combination chemotherapy. She progressed on treatment, and was not given second-line chemotherapy. The second patient with endodermal sinus tumour

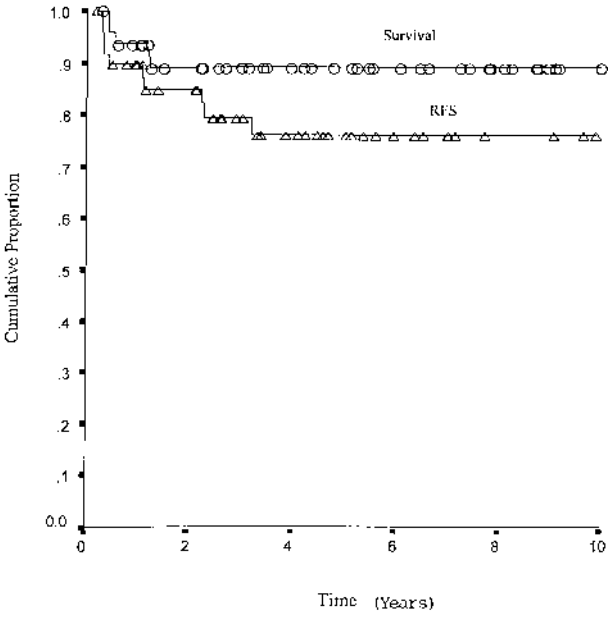

Fig. 1. Overall and disease-free survival for all patients.

was diagnosed as Stage II in 1989, had an incomplete resection, received 3 cycles PVB chemotherapy, and achieved CR including pathologic CR on second laparotomy. However, she relapsed the following year, and between 1990 and 1996, had four more laparotomies and two regimens of chemotherapy for recurrent disease with no sustained remission. Up until the last occasion, all her relapses were in the pelvis with rising AFP, but she eventually developed multiple lung metastases and was placed on palliative care.

Of the two patients with mixed histology, the first had immature teratoma with yolk-sac elements. The patient presented with a primary tumour >10 cm in size and Stage IV with metastases to omentum, para aortic lymph nodes, and the liver. She had a high initial αFP of 48000, good PR and a fall in αFP to 33 with 4 cycles of PEB chemotherapy, but then progressed. Her αFP rose to 2300 and she was tried on second-line chemotherapy with vinblastine, ifosfamide, and cisplatin, but was lost to follow-up after 2 cycles. She returned 4 months later with an αFP of 16000, refused further treatment, and eventually died 14 months after diagnosis. The other patient had immature teratoma with large component of endodermal sinus tumour. She presented with bulky disease >20 cm, Stage III, and had residual disease after surgery as well as αFP of 4200. Within 3 weeks of surgery, she also developed multiple liver metastases and a right-sided pleural effusion. After 5 cycles of PEB chemotherapy when her αFP plateaued at 1700, liver lesions remained unchanged, and pelvic mass increased. She underwent a laparotomy, and debulking. However, extensive metastases were seen in mesentery, bowel wall and bladder, and her αFP rose to 20500. The patient's general condition did not permit further chemotherapy, and she died 7 months after diagnosis.

Survival and prognostic factors

Of the 67 patients, 62 (93%) were rendered disease-free with initial treatment. Of these patients, 60 remain alive, while 2 died in CR of other causes. In a logistic regression analysis, three factors emerged with borderline significance for achieving CR, namely histology with dysgerminomas ($p = 0.04$), absence of residual disease ($p = 0.05$), and use of conservative surgery when chemotherapy was also given ($p = 0.05$). For the whole group of 67 patients, OS is 94% and 89% respectively at 1, 2 and 5 years (95% CI 81–97) with a median follow-up of 5.2 years, and median survival is 12.5 plus years. RFS for the whole group is 89% at 1 year, 85% at 2 years, and 76% at 5 years, and median RFS is 12.5 plus years. Fig. 1 shows OS and RFS for the whole group.

Though all the aspects of germ cell tumours which might influence survival are not known, many studies quote bulk of disease (tumour volume), presence of residual disease after surgery, stage at presentation, and histologic subgroup as being important. In this review, a number of factors with potential prognostic impact on OS and RFS were investigated including age, duration of symptoms, type of surgery, histology, tumour size, pathology stage, residual disease, and β HCG level. In the Cox regression model, only stage at presentation is unequivocally significant with p-values of 0.0001 for OS and 0.0003 for RFS at 5 years. The more advanced the stage, the worse the outcome: OS and RFS figures were—Stage I 100% and 91%, Stage II 100% and 62% and Stage III 74% and 64%. One out of two patients with Stage IV achieved RFS. Survival by stage is presented in Fig. 2. The other

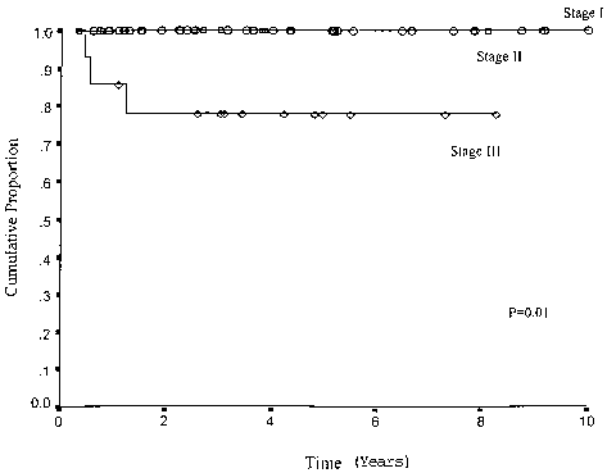

Fig. 2. Overall survival by stage.

important prognostic factor was residual disease post-surgery with a p-value of 0.002 RFS and 0.05 for OS.

Fertility

Of 44 patients with pregnancy potential after treatment, 16 subsequently had successful pregnancies, 12 of these in the dysgerminoma group.

DISCUSSION

The patients in this review accounted for 10% of ovarian, and 3.5% of all gynaecologic malignancies referred to KFSH & RC during the study period (1980–1996). It is recognized that there may be an element of referral bias since these are single hospital data. Nevertheless, given the rarity of this disease, this study is one of the biggest single institution experiences reported. Like all uncommon cancers, consensus on management is difficult. We sought to identify factors that would help in prognostication and management decisions. The fact that this is a disease of young women is clearly shown by the median age of 20, and 46 patients (69%) were under 25 years of age at diagnosis. The importance of proper staging has been established for many years, yet a review of the current literature reveals that incomplete staging is common. In our series, stage could not be ascertained in six patients due to inadequate data. Our results highlight the need for proper staging in determining prognosis, and therefore in deciding on appropriate management.

Surgery with adequate staging remains the cornerstone of management in these cancers. Unlike epithelial ovarian cancers, the role of maximum cytoreductive debulking has been extensively debated in OGCT. This is because of fertility issues associated with the young age of these patients coupled with the excellent responses to chemotherapy. In recent years, there is an increasing trend towards conservative surgical procedures when feasible.

In this review, 53 (79%) patients underwent conservative surgery, 51 of them remaining alive with no evidence of disease while 1 patient in CR died of other causes. Our experience suggests that conservative surgery will not adversely affect the outcome. There is little place for second-look laparotomy. This is mainly restricted to malignant teratoma with persistent radiologic abnormalities following chemotherapy, where it may help to avoid systemic chemotherapy in patients who no longer have viable tumour. It also serves to remove mature teratoma, which is non-responsive to chemotherapy, but may dedifferentiate to a malignant form and even metastasize at a later time. Peccatori et al., in a recent review, have shown the limited value of initial extensive debulking and second-look laparotomy (7).

The advent of chemotherapy, in particular platinum compounds, has served to transform the natural history of this disease. Even prior to availability of platinum compounds, the chemosensitivity of this disease was clearly demonstrated by use of regimens such as VAC (vincristine, dactinomycin, cyclophosphamide) (8). In recent years, cisplatin combination chemotherapy, particularly the PEB regime, has come to be considered as the standard treatment (9). Since randomized comparative trials of different chemotherapy regimes are not feasible, much of the current practice is extrapolated from knowledge gained in the relatively more common male germ cell malignancies. Most series report durable remission rates in excess of 90% (10–12). Schwartz et al. in their series of 81 patients (which included 28 patients on whom their role was confined to consultation only) reported 88% alive with no evidence of disease (ANED) with minimum follow-up of two years (10). They emphasized the importance of stage in treatment planning, and the role of conservative surgery. Cheung et al. (11) in their series of 37 patients with a median follow-up of 48 months report 94% ANED, and comment on the vital role of chemotherapy in management. A comparison of our experience with that reported in literature can be found in Table 1. With the exception of dysgerminoma, all other OGCT are resistant to radiation therapy. However, it has become virtually redundant even in dysgerminoma, given the morbidity of infertility and the availability of equally effective chemotherapy.

Even though OGCT as a whole can be considered as curable malignancies, failure of treatment in five patients underscores the need to standardize management and identify high-risk cases initially in order to attempt curative therapy for all patients. In three of the patients who failed to respond, it could be argued that chemotherapy was inadequate, although the number of cycles required is not clearly established. But the remaining two patients had biologically aggressive disease, and raise issues such as high-dose chemotherapy in management. This appears to be particularly so in non-dysgerminomas, given the 100% success rate in dysgerminomas with standard treatment.

Since this is a disease of women of childbearing age, fertility is an important consideration in management. This has been shown to be feasible at all stages of the disease (13, 14). Successful pregnancy has been reported even after treatment of bilateral ovarian dysgerminoma (15). The safety of conservative surgery and chemotherapy is demonstrated in this review. Of 44 women eligible to conceive, 16 had successful pregnancies. None of the children born subsequent to chemotherapy are reported to have any congenital abnormalities. The other major issue in cured patients is second malignancy induced by chemotherapy. In their series Williams et al. report two patients with leukaemia and lymphoma, respectively, following combination chemotherapy including etoposide, which has been identified as the causative agent in other tumour treatments (16). None of the patients in this series have had second malignancies as yet.

CONCLUSION

This review is one of the biggest in number of patients, with a long follow-up, and therefore of value in understanding the natural history of the disease following treatment. Our experience serves to highlight not only the uncommon incidence of ovarian germ cell tumours, but also certain aspects of management and outcome. Conservative surgery is almost always feasible without jeopardizing outcome. Stage of disease remains the most significant prognostic factor and dysgerminoma as a single group has the best prognosis. Fertility can be preserved with current chemotherapeutic strategies. Further improvement can be achieved by developing treatments that lack long-term morbidity such as second cancers, and by identifying high-risk cases up front.

REFERENCES

1. Gershenson DM. Update on malignant ovarian germ cell tumours. Cancer 1993; 71: 1581–90.
2. Kaplan EL, Meier P. Non parametric estimation from incomplete observations. J Am Stat Assoc 1958; 53: 457–81.
3. Simon R, Lee YK. Non parametric confidence limits for survival probabilities and median survival time. Cancer Treat Rep 1982; 66: 37–41.
4. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 1966; 50: 163–70.
5. Cox DR. Regression models and life tables. J R Stat Soc (B) 1972; 34: 187–220.
6. Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data. New York, NY: Wiley, 1980.
7. Peccatori F, Bonazzi C, Chiari S, et al. Surgical management of malignant ovarian germ-cell tumours: 10 years' experience of 129 patients. Obstet Gynecol 1995; 86: 367–72.
8. Slayton RE, Hreshchyshyn MM, Silverberg SG, et al. Treatment of malignant ovarian germ cell tumours—response to vincristine, dactinomycin and cyclophosphamide. Cancer 1978; 42: 390–8.
9. Gershenson DM, Morris M, Cangir A, et al. Treatment of malignant germ cell tumours of the ovary with bleomycin, etoposide, and cisplatin. J Clin Oncol 1990; 8: 715–20.
10. Schwartz PE, Chambers SK, Chambers JT, et al. Ovarian germ cell malignancies—the Yale University experience. Gynecol Oncol 1992; 45: 26–31.
11. Cheung MMC, Lau WH, Chan M, et al. Experience with the management of ovarian germ cell tumours in Chinese patients. Gynecol Oncol 1994; 52: 306–12.
12. Culine S, Lhomme C, Kattan J, et al. Cisplatin-based chemotherapy in dysgerminoma of the ovary: thirteen-year experience at the Institute Gustave Roussy. Gynecol Oncol 1995; 58: 344–8.
13. Gershenson DM. Menstrual and reproductive function after treatment with combination chemotherapy for malignant ovarian germ cell tumours. J Clin Oncol 1988; 6: 270–5.
14. Piura B, Dgani R, Zalel Y, et al. Malignant germ cell tumours of the ovary: a study of 20 cases. J Surg Oncol 1995; 15: 155–61.
15. Hudson CN, Slevin ML, Tebbutt H. Successful pregnancy after treatment of Stage III bilateral ovarian dysgerminoma. Br J Obstet Gynaecol 1995; 102: 1015–6.
16. Williams S, Blessing JA, Liao SY, et al. Adjuvant therapy of ovarian germ cell tumours with cisplatin, etoposide, and bleomycin—a trial of the Gynaecology Oncology Group. J Clin Oncol 1994; 4: 701–6.