Clinical review of 55 cases of malignant ovarian germ cell tumors

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Summary

Purpose of investigation: A retrospective analysis of 55 cases of malignant germ cell tumors in a 20-year period was done to evaluate the impact of conservative surgery and adjuvant treatment on survival and fertility.

Methods: Fifty-five cases of malignant ovarian germ cell tumors (MOGCTs) were studied. Mean age was 22 years. Dysgerminoma was the most common histotype (45%).

Results: Thirty-nine patients (71%) presented with FIGO surgical Stage I disease. Fertility-sparing surgery was performed in 39 (71%) women. Postoperative systemic chemotherapy was administered to 40 women (73%), 27 (68%) had received conservative treatment. One woman developed renal failure after the first cycle of chemotherapy and died a few days thereafter and there was one case of bleomycin-induced death due to pulmonary fibrosis. There were eight (14.5%) clinical recurrences. Overall survival rate for relapsing women was 75% (6/8). The recurrence rate for women treated conservatively was 15%, and it was 13% for those treated radically. With a median follow-up of 129 months the overall survival rate for the entire study-population was 90.9%. Eleven pregnancies occurred in 36 women treated with fertility-sparing surgery who were of child-bearing age.

Conclusion: The management of MOGCTs with fertility-sparing surgery is a safe, practicable treatment option. The majority of these patients can retain normal ovarian function and reproductive potential after chemotherapy treatment.

Key words: Malignant germ cell tumors; Dysgerminoma; Surgical treatment; Chemotherapy; Fertility.

Introduction

Malignant ovarian germ cell tumors (MOGCTs) are a specific group of gonadal neoplasms derived from primitive germ cells of the embrionic gonad that migrate into the gonadal ridge at six weeks of embryonic life; they represent approximately 5% of all ovarian neoplasms observed in Europe and North America [1]. In children and adolescence, more than 60% of ovarian tumors are of germ cell origin and one-third are malignant. Germ cell tumors represent most (80%) of the preadolescent malignant ovarian neoplasms; the mean age at diagnosis is 16 to 20 years and they may occasionally be diagnosed during pregnancy or the puerperium [2].

Their importance is greater than their numbers because MOGCTs typically occur in young women and often tend to be rapidly progressing tumors, but they are now curable mainly as a result of great advances in chemotherapy. Finally most women with this disease will survive with little long-term morbidity due to treatment [3].

In 1973 the World Health Organisation (WHO) introduced the current classification system [4]. The pathological classification mainly distinguishes pure dysgerminoma and tumors other than dysgerminomas, so called non-dysgerminomatous malignant ovarian germ cell tumors (nDMOGCT). Dysgerminoma is the most common (45%), followed by mixed germ cell tumors (20%), endodermal sinus tumor (EST) (12%), immature teratoma (IT) (12%), embrional carcinoma (5%) and choriocarcinoma (5%).

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Before the mid-1960s, virtually all patients with advanced nondysgerminomatous disease had a poor prognosis and most of them died of their disease. Even in Stage I disease, only 5-20% of patients survived after treatment with surgery alone [5]. Only for dysgerminoma there was a better prognosis due to its peculiar radiosensitivity; although the cure rate with such treatment was excellent, radiation could produce ovarian failure. Over the past three decades, the introduction of effective combination chemotherapy with an acceptable toxicity profile has not only improved the cure rate of the patients, but has also modified treatment strategies. MOGCTs are now curable solid tumors and as a consequence preservation of fertility has become an important aspect of the management of these malignant tumors and fertility-sparing surgery with the conservation of the uterus and the contralateral adnexum is now considered standard of treatment.

The purpose of the present paper was to retrospectively review the outcome of a series of patients with MOGCTs treated in our Department since 1980 and to assess the menstrual and reproductive function of those who received combination chemotherapy after fertility-sparing treatment.

Materials and Methods

Between 1980 and 2002 a total of 55 patients with primary MOGCTs were treated in the Department of Obstetrics and Gynecology, School of Medicine, University of Brescia, Italy.

Histology reviews were performed by gynecologic pathologists of the Department of Pathology. Histopathology was clas-

sified according to the WHO criteria. Histologic grading of immature teratomas was assigned according to the criteria of Thurlbeck and Scully modified by Norris *et al.* [6, 7]. Tumors were staged according to the International Federation of Gynecology and Obstetrics (FIGO) classification system. All patients underwent surgery as primary treatment. The type of initial surgery was decided depending mainly on the age of the patient, desire for fertility preservation, and clinical stage of tumor. Conservative surgery comprised unilateral salpingo-oophorectomy (USO). A biopsy of the contralateral macroscopically normal ovary was usually not performed; sometimes in the cases of bilaterality the tumor in the least involved ovary was excised with preservation of the uninvolved ovarian tissue. In cases of non-conservative surgery the patients underwent total abdominal hysterectomy (TAH) with bilateral salpingo-oophorectomy (BSO). In all cases peritoneal washing, omentectomy, multiple peritoneal biopsies, retroperitoneal sampling or systematic lymphadenectomy (in early stage dysgerminimas) and debulking in the early 1980s were performed.

No chemotherapy was given to patients with pure dysgerminoma Stage IA and immature teratoma Stage IA, grade 1.

Four different chemotherapy regimens were employed: AC regimen (adriamycin 40 mg/m^2, day 1, cylophosphamide 200 mg/m^2, days 3 to 6) was administered every four weeks from 1980 to 1990 only for dysgerminomas; VAC regimen (vincristin 1.5 mg/m^2, actimomycin-D 350 mg/m^2, cyclophosphamide 150 mg/m^2 days 1 and 15) was administered every four weeks from 1980 to 1982 for nDMOGCT; PVB regimen (cisplatin 20 mg/m^2, days 1 to 5, vinblastine 12 mg/m^2, days 1, bleomycin 30 mg, day 1) was administered every three weeks from 1982 to 1990; PEB regimen (cisplatin 20 mg/m^2, days 1 to 5, etoposide 100 mg/m^2, day 1, bleomycin 30 mg/m^2, day 1) was administered every three weeks from 1990 until now. POMB-ACE (vincristin 1 mg/m^2 day 1, metotrexate 300 mg/m^2 12-hour infusion day 1, bleomycin 15 mg 24-hour infusion days 2-3, cisplatin 120 mg/m^2 12-hour infusion day 4, actimomycin-D 0.5 mg days 15-17, etoposide 120 mg/m^2 days 15-17, cyclophosphamide 500 mg/m^2 day 17) regimen was administered as second-line chemotherapy only to one patient, with Stage I G2 immature teratoma, who recurred and died of disease.

The number of cycles depended on the clinical setting, patient tolerance to chemotherapy and the objective response of any measurable disease. The different regimens were usually administered for 3-4 courses as adjuvant treatment and for six courses in cases of advanced disease and residual tumor after surgery. Toxicity due to chemotherapy was recorded and classified according to the WHO criteria [8] to grade the severity of the adverse effects of antineoplastic drugs.

Adjuvant radiotherapy was administered in the early 1980s with a combination of several fields depending on the sites of disease. These include the whole abdominal field (20 to 40 Gy), whole pelvic field (20 to 30 Gy), pelvic boost (5 to 20 Gy), and paraaortic field (5 to 15 Gy).

Some patients, at the discretion of the attending physician, underwent second-look surgery after completing chemotherapy.

After primary surgery or chemotherapy in the case of adjuvant treatment patients were evaluated at regular intervals of three months for the first year, every four months for the second and third years and every six months thereafter. Follow-up examinations consisted of physical and gynaecological evaluations, imaging of the abdomen and the pelvis, and dosage of serum specific tumor markers. Patients underwent chest X-ray every year.

Information was obtained from medical records of all patients and by telephone interviews with the patients themselves.

Survival was measured from the time of end of treatment to the time of death or until May 2002, with at least one-year follow-up after diagnosis and initial treatment.

Results

Of the 55 patients in the study, 25 women (45.4%) presented with pure dysgerminoma, eleven (20%) with IT (grade 1 = 7 patients, grade 2 = 3, grade 3 = 1), ten (18.1%) with mixed germ cell tumors, eight (14.5%) with EST, and one (1.8%) with non-gestational choriocarcinoma. The youngest patient was 12 years and the oldest was 49 years (mean age 22 years).

Thirty-nine patients (71%) presented with FIGO surgical Stage I disease, three (5%) had Stage II, twelve (22%) had Stage III, and one (2%) had Stage IV. Distribution of cases by stage and histotype is shown in Table 1.

Table 1. — *Distribution of cases by stage and histotype.*

Stage	I	II	III	IV	Total cases
DYS	14	2	9	–	25 (45%)
IT	10	–	1	–	11 (20%)
EST	7	–	–	1	8 (15%)
Mixed	7	1	2	–	10 (18%)
CC	1	–	–	–	1 (2%)
Total cases	39 (71%)	3 (5%)	12 (22%)	1 (2%)	55

DYS: Dysgerminoma; IT: Immature teratoma; EST: Endodermal sinus tumor; Mixed: Mixed germ cell tumor; CC: Choriocarcinoma.

All patients underwent surgery as primary treatment. Fertility-sparing surgery (USO) was performed in 39 (71%) women; non-conservative surgery (2 BSO, 1 USO who had already undergone USO one year earlier for mature teratoma, 11 TAH /BSO and 2 debulking procedures) was performed in 16 women (29%). Distribution of cases by stage and type of surgery (conservative vs non-conservative) is shown in Table 2, and by histotype and type of surgery in Table 3.

Twelve patients (22%) were treated by surgery alone: seven women had pure dysgerminoma Stage IA, and five were diagnosed with IT Stage IA, grade 1.

Table 2. — *Distribution of cases by stage and type of surgery.*

Stage	Type of surgery		Total cases
	Conservative	Non-conservative	
I	28	11	39
II	2	1	3
III	8	4	12
IV	1	–	1
Total cases	39 (71%)	16 (29%)	55

Table 3. — *Distribution of cases by type of surgery and histotype.*

Histotype	Type of surgery		Total cases
	Conservative	Non-conservative	
Dys	16	9	25
IT	8	3	11
EST	7	1	8
Mixed	7	3	10
CK	1	–	1
Total cases	39	16	55

Postoperative systemic chemotherapy was administered to 40 women (73%), 27 (68%) had received conservative treatment. The chemotherapy regimens included AC (8 cases), VAC (5 cases), PVB (14 cases), and PEB (13 cases). Eighteen (45%) cases were dysgerminomas, eight (20%) ESTs, six (15%) ITs, seven (17%) mixed forms and one (3%) non-gestational choriocarcinoma. Transient alopecia, nausea and mild vomiting were universal. There were 14 cases of severe toxicity (grade 3/4) induced by chemotherapy. One woman with IT Stage IIIC, grade 3, treated non-conservatively developed renal failure after the first cycle of first-line systemic treatment (PVB) and died a few days thereafter. There was one case of bleomycin-induced death due to pulmonary fibrosis (death by intervening disease: DID), the patient had IIIA dysgerminomas treated with conservative surgery and PVB chemotherapy for four cycles and who had a complete response at second-look laparoscopy.

Adjuvant radiotherapy was administered in the early 1980s to three women with early stage dysgerminoma who had been treated with non-conservative surgery.

After completion of postoperative adjuvant therapy, all the patients had apparent complete clinical remission with no measurable disease. Twenty-one (38%) patients underwent second-look procedure (laparoscopic or laparotomic) after completing chemotherapy; it was negative in 18 patients (86%), one of whom showed evidence of chemotherapeutic conversion of IT to a mature form. One patient (5%), with mixed germ cell tumor Stage IIB, had partial response after three cycles of PEB regimen (residual immature teratoma grade 1 at second-look laparotomy treated with further surgery), now she is disease-free after the administration of another two cycles of the same chemotherapy regimen. Two patients (9%) with IIIC and IC dysgerminomas presented microscopic residual disease at the second-look procedure (one had positive peritoneal biopsies and the second one presented positive para-aortic lymph nodes). They were treated with RT and remained disease-free thereafter.

There were eight (14.5%) clinical recurrences: four cases of dysgerminoma, three of IT, and one of mixed form (Table 4). Overall survival rate for relapsing women was 75% (6/8). None of dysgerminoma recurring patients died of disease, two were treated either with a combination of surgery/RT/chemotherapy (1 AC and 1 PVB) and two with chemotherapy alone (PEB). Two women survived recurrence of IT. They were treated either with a combination of surgery/RT/chemotherapy (vincrystine) or chemotherapy alone (PEB), and one died of the tumor after further chemotherapy (POMB-ACE). The patient relapsing with mixed germ cell tumor died of disease after second-line treatment (VAC). We observed six relapses in 39 women who were treated conservatively (15%), and two in 16 women who were treated radically (13%) (Table 5). Distribution of recurrences in Stage I cases by adjuvant treatment is shown in Table 6. We observed four relapses (33%) in the group that did not receive adjuvant treatment, however all of them were cured after second-line chemotherapy.

Table 4. — *Distribution of recurrences by histotype.*

Histotype	Recurrence		Total cases
	Yes	No	
Dys	4	21	25
IT	3	8	11
EST	–	8	8
Mixed	1	9	10
CC	–	1	1
Total cases	8	47	55

DYS: Dysgerminoma; IT: Immature teratoma; EST: Endodermal sinus tumor; Mixed: Mixed germ cell tumor; CC: Choriocarcinoma.

Table 5. — *Distribution of recurrences by type of surgery.*

Type of surgery	Recurrence		Total cases
	Yes	No	
Conservative	6	33	39 (15%)
Non-conservative	2	14	16 (13%)
Total cases	8	47	55

Table 6. — *Distribution of recurrences in Stage I cases by adjuvant therapy.*

Adjuvant Therapy	Recurrence		Total cases
	Yes	No	
Yes	2	25	27 (7%)
No	4	8	12 (33%)
Total cases	6	33	39

With a median follow-up of 129 months (range:12-264) the overall survival rate was 90.9%. The survival rate was 96% for dysgerminomas (24/25), 100% for choriocarcinoma (1/1), 87.5% for ESTs (7/8), 81.8% for ITs (9/11), 90% for mixed forms (9/10). The overall survival rate for women in early stages (I/II) was 95% (40/42) and for women in advanced stages (III/IV) 77% (10/13). The overall survival rate was 90% (35/39; 2 DID) for women who had undergone fertility-sparing surgery and 93% (15/16;1 DID) for those who were treated with a non-conservative procedure.

Two deaths were associated with relapse (one IT and one mixed form, both treated conservatively); both cases had received adjuvant chemotherapy. As already mentioned one death was associated with the development of renal failure after the administration of the first cycle of PVB chemotherapy, another one with pulmonary fibrosis due to bleomycin, and one patient, affected by ataxia-teleangectasia, died of pulmonary infection.

Twenty-six (67%) patients maintained their normal ovarian function during and after chemotherapy and they all had regular menses at the time of the interview. Ten women had irregular or absent menses during chemotherapy but regained normal menstrual function within six to nine months of completing chemotherapy. One patient developed early menopause after a few years of completing four cycles of the VAC regimen for early-stage non-gestational choriocarcinoma diagnosed at age 14, while the remaining two women of those treated with conservative surgery recurred and had absent or irregular menses during second-line chemotherapy and then died of disease.

Eleven pregnancies occurred in 36 women treated with

fertility-sparing surgery who were of childbearing age. Ten women delivered 11 healthy babies; there were no miscarriages. None of these patients had difficulty conceiving, and there is no evidence of birth defects or other disabilities in any of the offspring. Two patients had infertility problems and had not had any infertility evaluation at the time of the interview. The remaining 24 patients have not attempted to conceive since completing chemotherapy, most commonly because of young age and lack of a partner or because they had already had children prior to the diagnosis of MOGCTs.

Discussion

Too often in the past, children and young women affected by MOGCTs have been unnecessarily treated with radical surgery due to the supposed risk of microscopic involvement of seemingly normal contralateral ovary and uterus [3, 9]. Data from several large series [1, 9-12] underscored the finding that most MOGCTs are unilateral, with the exception of pure dysgerminomas, which are bilateral in 10-15% of cases. Bilateral involvement with tumor may also occur in cases of advanced-stage in which there is metastasis from one ovary to the other [5]. Approximately 60 to 70% of MOGCTs are FIGO Stage I, 25% to 30% are Stage II, and Stage III and IV are relatively uncommon [13, 14]. Accordingly in the present study 71% of the patients presented with Stage I and 22% with Stage III disease and there was no macroscopic bilateral involvement in any of the patients with early stage disease. The availability of effective chemotherapy that may sterilise microscopic or macroscopic foci of tumor in the residual gonad without the need of removing the contralateral ovary has changed the surgical approach toward this disease.

The type of surgery is presently decided depending mainly on the age of the patient and desire for fertility preservation. Surgical staging should always be performed to evaluate the extent of disease, to determine prognosis and to guide postoperative management. Unilateral salpingo-oophorectomy with preservation of the contralateral ovary and the uterus now is considered the adequate surgical treatment for patients with MOGCTs, even in cases of advanced disease, particularly if the contralateral ovary is normal [9, 13, 15, 16]. There is no evidence that removing an apparently uninvolved ovary enhances survival: several large retrospective studies [10-13, 16-18] show an equivalent cure rate after fertility-sparing surgery compared with non-conservative procedures. If the controlateral ovary appears grossly normal on careful inspection, it should be left undisturbed [5, 19]. Peccatori *et al.* [19] presented a series of 129 women, 108 of whom were treated with conservative surgery; ten subjects recurred and only one relapsed in the contralateral ovary but responded to further treatments and remained disease-free thereafter. During surgery routine biopsies of the contralateral ovary should be avoided since they may result in future infertility due to peritoneal adhesion or ovarian failure [9, 16]. Bettram *et al.* [20] reported that 59 (51.2%) of 111 patients who underwent ovarian wedge resection, were found to have pelvic adhesions at laparoscopy or laparotomy. If the contralateral ovary appears enlarged or suspicious, biopsies must be performed. If frozen section analysis reveals dysgenetic gonad or malignant disease, bilateral salpingo-oophorectomy is indicated [3]. As already mentioned bilaterality in the absence of metastatic disease is rare in MOGCTs but in the case of dysgerminoma. A recurrence in the contralateral ovary still could be treated either by non-conservative surgery or by local resection or cystectomy followed by chemotherapy if fertility is an option [16]. Data from several large studies [5, 13, 16, 21] show that benign cystic teratomas are found in the controlateral ovary in 5-10% of patients with MOGCTs. In these cases only ovarian cystectomy with preservation of the normal ovary is recommended.

Patients with well-documented Stage IA dysgerminoma or Stage IA, grade 1 IT are cured with surgery alone. The rate of recurrences for Stage I dysgerminomas is 15 to 25% [14, 22], but virtually every patient may be salvaged by combination chemotherapy at the time of relapse. In the current series we observed a 30% (3/10) recurrence rate for Stage IA dysgerminoma; this slightly higher rate could be due to inadequate surgical staging, mainly in the early years of the study, or to the presence of occult tumor in the contralateral ovary at the time of the diagnosis. All the patients survived after further treatment. Of the seven patients with Stage IA, grade 1 IT only one recurred and is now disease-free after receiving further chemotherapy (PEB).

The evolution of chemotherapy treatment for MOGCTs has paralleled the advances made in the treatment of testicular germ cell cancer because of the biologic similarity. The first effective progress for nondysgerminomatous MOGCTs was reported with the VAC regimen. This regimen has produced a high cure rate in Stage I disease (86%), but in advanced stages the sustained remission rate was less than 50% [5, 15, 16]. The successful introduction of cisplatin into clinical trials for male germ cell tumors prompted investigators to use a cisplatin-based regimen in patients with MOGCTs. The PVB regimen proved to be active and more effective than the VAC regimen in this group of patients. Subsequently, the substitution of etoposide for vinblastine proved to be equally active but less toxic in the treatment of patients with testicular neoplasms. This was incorporated into the treatment of MOGCTs, with the BEP regimen becoming the most widely used platinum-based chemotherapy [3, 5, 9, 16]. In a multicenter randomised trial, Williams *et al.* [3] concluded that when compared with the PVB combination, the PEB regimen showed equal efficacy and less toxicity in patients with completely resected nondysgerminomatous MOGCTs. The use of etoposide compared to vinblastine has been related to reduce neurologic toxicity, abdominal cramps and constipation, with somewhat better results in terms of survival. The overall survival rate of patients treated with platinum-based chemotherapy currently ranges from 87% to 98% [9, 16]. The optimal duration of therapy is still under debate, but generally many investigators [5, 9, 23] believe that three cycles of BEP with completely resected disease and four cycles for the

others seem appropriate. Some of our patients, mainly with advanced disease, received more than four cycles of chemotherapy. One patient with Stage IIIA dysgerminoma who received four cycles of the PVB regimen, died of pulmonary fibrosis due to bleomycin after second-look laparoscopy had shown a complete pathologic response; another one died due to the development of acute renal failure right after the first cycle of chemotherapy (PVB). The identification of new drugs with milder side-effects as well as a reduction in treatment time when efficacy in terms of cure is maintained could represent appropriate ways for lessening toxicity.

Moreover the availability of effective chemotherapy and improvement in surgical technique allow survival of the majority of patients with recurrence of MOGCTs, irrespective of primary conservative or radical surgery. In our series six (75%) of eight women who developed recurrence survived and remained disease-free after either a combination of surgery/RT/chemotherapy or chemotherapy alone.

Because of the increasing frequency of long-term survivors, attention has focused on a variety of late sequelae of surgery and chemotherapy. One aspect of quality of life for cancer survivors is the preservation of reproductive endocrine function and fertility. The specific effects of cancer therapy on reproductive function are not as well understood, and there is no test for fertility except for a resulting pregnancy proving that fertility is maintained.

There is no available information on the long-term influences of surgery in this disease. However pelvic surgeries in a variety of diseases have been documented to be closely associated with future infertility due to peritoneal, peritubal and periovarian adhesions [3, 9, 15, 20, 23-26]. All precautions must be taken to practise meticulous surgical technique and to avoid unnecessary surgical procedures, such as biopsy of the normal contralateral ovary, to avoid infection and adhesion formation after pelvic surgery [23].

The possible complications of chemotherapy on survivors are still largely unknown, but are based on available evidence. A recognised effect of antiblastic agents is the risk of secondary malignancies [5]. Several studies have documented the development of nonlymphocytic leukemia in patients who received alkylating agent chemotherapy for ovarian cancer [27, 28]. Etoposide has been reported to be associated with the development of acute monomyelocytic leukemia; this effect may be dose and schedule dependent [3, 5]. The incidence of a second neoplasm is nonetheless low, particularly in patients receiving low cumulative etoposide doses that should be adequate for all but a small minority of patients who may need a higher dosage. In an effort to reduce pulmonary toxicity associated with the BEP regimen the role of bleomycin has been investigated [15]. The European Organisation for Research and Treatment of Cancer (EORTC) randomised good-prognosis testicular cancer patients to receive four cycles of etoposide and cisplatin with and without bleomycin [29]; a higher portion of patients in the three-drug arm had a complete response (95% vs 87%). In an Australian randomised study [30], in which patients received cisplatin and vinblastine with and without bleomycin, a reduction of therapeutic efficacy by the deletion of bleomycin and a higher rate of death from cancer (15% vs 5%) were observed. Thus, these results support retention of bleomycin in the standard chemotherapy regimen for good-risk testicular cancer patients and it is therefore reasonable to extrapolate these finding to patients with MOGCTs.

The observed histologic changes in the ovaries of women receiving chemotherapy include cortical and stromal fibrosis, reduction in number of primordial follicles and impaired follicular maturation, resulting in elevated gonadotrophin levels with declined serum estradiol levels [23, 31-33]. Because most patients receive combination regimens, it is difficult to determine the effect of a single drug in inducing ovarian failure. Factors such as older age at initiation therapy, greater cumulative drug dose, and longer duration therapy have an adverse effect on future gonadal function. Several studies [33-36] have shown that the pre-pubertal ovary is more resistant to the adverse effects of chemotherapy. It remains unclear whether the use of oral contraceptives [37] or GnRH analogs [38] during chemotherapy has a protective effect on ovarian function under the hypothesis that suppression of gonadal function during chemotherapy would cause a decrease of gonadal toxicities by chemotherapy. Some authors [39-42] observed that 20 to 30% of patients had disturbed menstrual function while others published a rate around 10% [21]. Gershenson *et al.* [15] reported that 68% of women after completion of chemotherapy for MOGCT maintained regular menses, and 83% of them were having regular menses at the time of the follow-up; 11 women delivered 22 healthy infants, none of whom presented major birth defects. Zanetta *et al.* [9] reported that hypergonadotropic amenorrhea during treatment occurred in 80% of their patients and they observed that the median time to recovery of menstruation was highly correlated to the length of treatment; one patient developed early ovarian failure and one had primary amenorrhea. During follow-up at 67 months, 12 chemotherapy untreated and 20 treated patients had 55 conceptions, including 40 term pregnancies, six terminations and nine miscarriages. In the present study 26 (67%) patients maintained their normal ovarian function during and after chemotherapy while the others regained normal menstrual function within six to nine months of completing chemotherapy, and one patient developed early menopause. Ten women delivered 11 healthy babies, there were no miscarriages, two patients had infertility problems but had not had any infertility evaluation at the time of the interview.

The risk of congenital malformations in the offspring of patients treated with chemotherapy is also a consideration. Zanetta *et al.* [9], differing from other reports [15, 43], recorded four fetuses with documented malformations. Such an incidence is slightly higher than in the general population. Longer follow-up is needed to clarify the impact of chemotherapy on the malformation rate.

Conclusion

The results of our study, in agreement with the data from the literature, confirm that management of

MOGCTs with fertility-sparing surgery is a safe, practicable treatment option, and that wedge biopsy of the contralateral ovary is not needed. The majority of these patients can retain normal ovarian function and reproductive potential after chemotherapy treatment. Goals for the future include the search for effective but less toxic new chemotherapy regimens and for improved surgical techniques in order to minimize the risk of ovarian dysfunction and/or sterility after treatment.

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