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Malignant ovarian germ-cell tumours

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Malignant ovarian germ-cell tumours account for about 5% of all ovarian malignancies and typically present in the teenage years. They are almost always unilateral and are exquisitely chemosensitive. As such, the surgical approach in young women with such tumours confined to a single ovary should aim to preserve fertility. In early disease, a unilateral salpingo-oophorectomy with careful surgical staging is of great importance in selecting appropriate adjuvant therapy. In advanced disease, the role of aggressive cytoreducation is not well defined, and removal of both ovaries does not confer improvement in outcome. Bleomycin, etoposide and cisplatin combination chemotherapy is regarded as the gold standard for adjuvant therapy. Studies evaluating ovarian and reproductive capacity after conservative surgery and chemotherapy for malignant ovarian germ-cell tumours have consistently demonstrated excellent prognosis, with the return of normal menstrual function and fertility rates in these women with no increase in the risk of teratogenicity.

Introduction

Malignant ovarian germ-cell tumours (MOGCTs) account for 5% of all ovarian malignancies in Western countries. Because they principally occur during adolescence and early adulthood, decisions on

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treatment used to present a challenge to the gynaecologic oncologist. Before the mid-1960s, virtually all women with advanced non-dysgerminomatous disease died. Even for the exquisitely radiosensitive dysgerminomas, women who had been radiated were left with their fertility destroyed. Subsequent introduction of effective combination chemotherapy brought about dramatic improvements in the prognosis for MOGCTs. These have largely been extrapolated from the experience of treating the more common testicular germ-cell tumours. Many randomised-controlled trials for testicular germ-cell tumours have provided a strong evidence base for treatment decision making in MOGCT.[1,2] In the evolution of care, combination chemotherapy using vincristine, dactinomycin, and cyclophosphamide (VAC regimen) was able to achieve cure rates of 86% in women with International Federation of Gynecology and Obstetrics (FIGO) Stage I non-dysgerminomatous disease,[3] but women with metastatic disease then had a 50–70% mortality.[3,4] The introduction of cisplatin-containing drug regimens, notably the BEP (bleomycin, etoposide and cisplatin) regimen from the 1980s onward, resulted in a 5-year survival rate of up to 100% for dysgerminomas and 85% for non-dysgerminomatous MOGCT.[5–7] Prompt initiation of appropriate chemotherapy is the critical factor for young women with an advanced MOGCT.[8] Contemporary principles of surgery for MOGCTs dictate that fertility preservation is appropriate even in the face of extensive metastatic disease if fertility is desired, because there is no evidence that removing an uninvolved ovary enhances survival. Hence, the focus of subsequent studies on MOGCT has shifted to long-term sequelae for these young women, with particular emphasis on ovarian and reproductive function, including teratogenicity, especially after combination chemotherapy.

Classification of malignant ovarian germ-cell tumours

The current 2003 World Health Organization classification of system for MOGCT is as shown in Table 1.[9]

Table 1
Histological classification of malignant ovarian germ-cell tumours.[9]

Primitive germ-cell tumours
Dysgerminoma
Yolk-sac tumour
Polyvesicular vitelline tumour
Glandular variant
Hepatoid variant
Embryonal carcinoma
Polyembryoma
Non-gestational choriocarcinoma
Mixed germ-cell tumour, specify components
Biphasic or triphasic teratoma
Immature teratoma
Mature teratoma
Solid
Cystic, dermoid cyst
Fetiform teratoma, homunculus
Monodermal teratoma and somatic-type tumours associated with biphasic or triphasic teratoma
Thyroid tumour group
Carcinoid group
Neuroectodermal tumour group
Carcinoma group
Melanocytic group
Sarcoma group
Sebaceous tumour group
Pituitary-type tumour group
Retinal anlage tumour group
Others

The most clinically practical approach would be to subdivide MOGCT into the dysgerminomatous tumour, which is the most common type and the counterpart of the male seminoma, and non-dysgerminomatous tumours. The most common types of non-dysgerminomatous tumours are yolk-sac tumour, immature teratoma, and mixed germ-cell tumours. The embryonal carcinomas, non-gestational choriocarcinomas, and polyembryomas are much less common varieties.

Epidemiology and clinical presentation

Although 20–25% of all benign and malignant ovarian neoplasms are of germ-cell origin, only about 3% of these tumours are malignant.[10] Although MOGCTs account for fewer than 5% of all ovarian cancers in Western countries, they represent as much as 15% of ovarian cancers in Asian and black societies, where epithelial ovarian cancers are much less common. In the first 2 decades of life, almost 70% of ovarian tumours are of germ-cell origin, and one-third of these are malignant.[10,11] Malignant ovarian germ-cell tumours also are seen in the third decade, but thereafter they become quite rare.

These tumours typically present in the teenage years, with symptoms of abdominal pain and a palpable pelvi-abdominal mass. In about 10% of women, the mass may grow rapidly, resulting in acute abdominal pain related to capsular distention, necrosis, haemorrhage, rupture or torsion of the ovarian tumour. The initial workup should include serum tumour markers, pelvic sonography and a computed tomography of the abdomen and pelvis if extra-ovarian metastases are suspected. A radiograph of the chest is important because MOGCTs can metastasise to the lungs or mediastinum. The tumour markers should include serum alpha-fetoprotein (AFP), lactate dehydrogenase (LDH), beta human chorionic gonadotropin (β-hCG) and cancer antigen 125 titers. Yolk-sac tumour and ovarian choriocarcinoma produce AFP and β-hCG, respectively. Both embryonal carcinoma and polyembryoma may produce β-hCG and AFP, the former more commonly. A small percentage of dysgerminomas may display elevated levels of LDH or may produce low levels of β-hCG related to the presence of multinucleated syncytiotrophoblastic giant cells. About one-third of immature teratomas produce AFP. Mixed germ-cell tumours may produce any of the tumour markers, or none, depending on the type and quantity of elements present.[12–14] Elevated serum tumour markers can serve as an adjunct in initial diagnosis, monitoring during therapy, and post-treatment surveillance. A karyotype should ideally be obtained preoperatively on all premenarchal girls because of the propensity of these tumours to arise in dysgenetic gonads.[13,14]

Surgical treatment

The modern surgical approach to MOGCTs has been derived from data that emerged from several large studies from the Armed Forces Institute of Pathology in the 1970s[15–17] and from other relatively large studies.[18–21] These articles underscored the finding that most MOGCTs are unilateral, with the exception of pure dysgerminomas, which are bilateral in 10–15% of cases, although bilaterality in up to 23.1% has been reported from a study of 26 cases at Yale University.[22] Bilateral involvement may also occur in cases of advanced disease in which there is metastasis from one ovary to the other.[23] These large studies also showed that benign cystic teratomas are found on the contralateral ovary in 5–10% of women with MOGCTs. Therefore, if a benign dermoid cyst is discovered, only ovarian cystectomy with preservation of normal ovarian tissue is recommended.[22,24,25]

A unilateral salpingo-oophorectomy, with preservation of the contralateral ovary and the uterus, is considered the appropriate surgical treatment for women with MOGCT.[12,23–30] In women with advanced disease (e.g. para-aortic lymph-node metastases), preservation of reproductive function is also possible, particularly if the contralateral ovary is normal.[22,25–27] Evidence from several large studies[3,4,15–17,20,21,31] suggests at least equivalent survival after conservative surgery (i.e. unilateral salpingo-oophorectomy) compared with bilateral salpingo-oophorectomy with or without hysterectomy. Review of the data from the Gynecologic Oncology Group[4] showed that 44 out of 70 primary lesions treated with VAC were Stage I and none was Stage IB. Removing both ovaries did not seem to improve survival.

Subsequent experience over the past 25 years or so has further strengthened the principle of carrying out conservative surgery to preserve ovarian function and fertility for most young women with MOGCTs[32] (Table 2).

During surgery, routine biopsy of the contralateral ovary should be avoided. Although occult bilaterality has been reported, biopsy of the contralateral ovary could lead to future infertility related to peritoneal adhesions or ovarian failure.[23,38] Meticulous technique and the avoidance of unnecessary surgery are therefore of paramount importance. Buttram and Vaquero[39] reported on 59 women with previous ovarian wedge resection, and 40 of whom were subsequently found to have pelvic adhesions. Conversely, Weinstein and Polishuk[38] reviewed 198 women with tubal factor infertility, and found 28 with a history of ovarian-wedge resection. Bilateral involvement in the absence of metastatic disease (i.e. Stage IB disease) is a rare occurrence in MOGCT. In a study from Queensland,[26] contralateral ovarian biopsy was carried out in seven women, and none showed occult involvement. A recurrence in the contralateral ovary still could be treated by local resection or cystectomy followed by chemotherapy if fertility was desired, thereby preserving some normal ovarian tissue. Therefore, to carry out routine contralateral ovarian-wedge resections for all women with early stage MOGCT would be unproductive. A long-term study of ovarian function after conservative surgery for benign pelvic conditions[40] concluded that there were no significant effects on ovulatory and menstrual function over a prolonged follow-up period. In the event of bilateral macroscopic involvement, unilateral or bilateral ovarian cystectomy is an attractive option,[41] especially when combined with postoperative chemotherapy, as long as the woman does not have dysgenetic gonads. This surgical option has not been well studied.

Chemotherapy

Many of the recent advances in combination chemotherapy for MOGCTs have arisen from studies of testicular carcinoma, the male counterpart, which is 10 times more common. The first effective combination chemotherapy regimen for advanced MOGCT was the VAC regimen. Despite a high response rate, over 50% of women with advanced MOGCTs died of the disease.[3,33] The introduction of cisplatin-based chemotherapy led to a significant improvement in survival for women with testicular tumours[42,43] The PVB regimen (cisplatin, vinblastine, and bleomycin) proved to be active and more effective than the VAC regimen in women with MOGCTs.[44–48] Subsequently, the substitution of etoposide for vinblastine proved to be equally active but less toxic in the treatment of women with testicular carcinoma.[43] This was incorporated into the treatment of MOGCTs, with bleomycin, etoposide, and cisplatin (BEP regimen) becoming the most widely used chemotherapeutic regimen.[44,49] The overall survival of women treated with platinum-based chemotherapy currently ranges from 87%[5,50] to 98%.[44,49]

The treatment policy at our centre has been surgery alone for surgically staged and histologically confirmed Stage IA pure dysgerminomas and low-grade immature teratomas.[51] All other women receive adjuvant BEP chemotherapy. On the basis of promising data, however, from Bonazzi et al.,[52]

Table 2
Type of surgery and survival.

Study	Survival (number of women)			
	Ovarian conservation	%	Bilateral oophorectomy	%
Slayton et al.[33]	22/28	79	7/11	64
Krepart et al.[34]	5/5	100	—	
Schwartz[35]	17/17	100	2/2	100
Gershenson et al.[20]	12/15	80	3/6	50
Creasman et al.[36]	19/19	100	11/13	85
Low et al.[25]	55/56	98	7/8	88
Khi et al.[27]	43/43	100	6/6	100
Chan et al.[32]		97.9		95.6
Zanetta et al.[37]	135/138	98	27/31	87

Dark et al.,[53] the Pediatric Oncology Group and Children's Cancer Group Intergroup,[54,55] Gobel et al.,[56] and Baranzelli et al.,[57] a strategy of surgery plus close clinical, radiological and serological surveillance only, for surgical stage I MOGCT, is emerging as a safe option. Surgical staging includes assessment of peritoneal fluid cytology, biopsy of any suspicious areas on the peritoneal surfaces, retroperitoneal lymph-node sampling, including the pelvic and high para-aortic lymph nodes, and an infracolic omentectomy. Women referred with an incompletely staged dysgerminoma or low-grade immature teratoma apparently confined to the ovary have their histology reviewed, are evaluated with tumour markers (lactate dehydrogenase, AFP and β-hCG) to detect non-dysgerminomatous elements, and undergo a computed tomography scan to detect any unsuspected residual tumour. If these studies are normal, the woman is not surgically restaged and is followed with tumour markers and computed tomography scans or ultrasonography. Using this approach, a case study from Australia reported a 98.2% recurrence-free survival rate for women with Stage I disease and 88.9% for women with advanced-stage disease in the chemotherapy group.[25] Thomas et al.[58] reported a 10-year survival rate of 88.6% after conservative surgery for women with dysgerminoma confined to the ovary; less than 10 cm in size; with an intact, smooth capsule unattached to other organs; and without ascites.[58] Women with recurrent dysgerminoma can also be successfully salvaged with systemic chemotherapy (BEP regimen).[44]

Ovarian function

The long-term effect of antineoplastic chemotherapy on ovarian function has been studied extensively, especially in women treated for various malignancies, such as Hodgkin's disease, leukaemia, trophoblastic disease and breast carcinoma.[59–64] The observed histologic changes in the ovaries of women receiving chemotherapy include cortical fibrosis, reduction in number of follicles, and impaired follicular maturation.[65–67] These changes lead to increased serum gonadotropins and a decrease in serum oestradiol. Alkylating agents in particular can cause amenorrhoea, although secondary sexual characteristics related to hormonal function generally are less disturbed.[68] Busulfan,[69] chlorambucil,[70] and cyclophosphamide[61,71–73] have been associated with irregular menses and amenorrhea in adult women. Short-term intensive chemotherapy, however, particularly using antimetabolites such as methotrexate,[63,74] vinca alkaloids such as vincristine,[74] and anthracycline antibiotics such as dactinomycin,[63] seems to affect ovarian function less commonly. Factors such as cumulative drug dose, duration of therapy, and age at treatment have been reported to influence the incidence of ovarian dysfunction[63,72,74,75] in adult women. Low et al.[25] reported that 62% of women undergoing chemotherapy were amenorrheic during treatment, but 92% resumed regular menses on completing chemotherapy.[25] In a study from MD Anderson Cancer Center,[76] 68% of women maintained regular menses after completing chemotherapy for MOGCT, and 83% had regular periods at the time of follow up. In the study by Wu et al.[77] from Beijing, 19 out of 20 postpubertal women resumed regular menses after completing chemotherapy for MOGCT. In another report by Pektasides et al.,[78] 16 out of 17 women undergoing cisplatin, vincristine, methotrexate, bleomycin, actinomycin D, cyclophosphamide, etoposide (POMB/ACE) chemotherapy for MOGCT resumed menses at a median time of 4.5 months after chemotherapy, indicating no permanent impairment of gonadal function even with POMB/ACE chemotherapy. Several studies[61,62,75,79–81] have shown that the prepubertal ovary is more resistant to the adverse effects of chemotherapy. It remains unclear whether the use of oral contraceptives during chemotherapy has a protective effect on ovarian function. Chapman and Sutcliffe[82] reported that five out of six patients treated with combination chemotherapy and the oral contraceptive pill for Hodgkin's disease had normal menses and normal serum gonadotrophins at the completion of study, whereas Whitehead et al.[64] found that seven out of nine women who received the oral contraceptive pill and combination chemotherapy for Hodgkin's disease had oligoamenorrhea. In a recent paper by Weinberg et al.,[83] 14 women with MOGCT underwent fertility-sparing surgery followed by adjuvant chemotherapy. All were on oral contraceptive pills during chemotherapy. The investigators found a 100% return to normal menstrual function within 1 year after completing chemotherapy, and one case of menarche occurring 8 months after completing chemotherapy. The results suggest that hormonal suppression with oral contraceptives may have been protective of ovarian function.

Table 3
Reproductive function after fertility-preserving surgery and chemotherapy for malignant ovarian germ-cell tumours.

Study	Number of women attempting pregnancy	Number of live births	Infertility
Khi et al.[27]	6	8	1: male factor
Low et al.[25]	20	14	1: not investigated
Gershenson et al.[87]	34	37	10: unspecified
Weinberg et al.[83]	10	14	2: successful in-vitro fertilisation
Zanetta et al.[37]	20	26	4: unspecified

Fertility

Successful pregnancies after treatment with combination chemotherapy have been documented for Hodgkin's disease,[59,60,64,84] non-Hodgkin's lymphoma,[85] and leukaemia.[85] Many studies now consistently show that reproductive capacity basically is unaffected after chemotherapy[8,22,25–27,35,47,86] for MOGCT and that healthy pregnancies can be anticipated. The true reproductive potential in any of these cohorts is, of course, difficult to ascertain because of the small numbers and relatively short duration of follow up in these young women, many of whom are not desirous of childbearing, even after treatment. The rate of infertility reported among women attempting conception after treatment for MOGCT ranges from 5%[25] to about 10%.[76] This corresponds to the background incidence rate of infertility in the normal population (Table 3).

Teratogenicity

The risk of congenital malformations in the offspring of women treated with chemotherapy also has been a concern. The risk is highest if chemotherapy is administered during the first trimester of pregnancy, especially when antimetabolites (e.g. methotrexate) and alkylating agents are used.

Chemotherapy administration during the second and third trimesters generally is not associated with an increase in fetal anomalies, although to our knowledge the number of women studied to date is relatively small.[68] McKeen et al.[88] reported a high incidence rate of congenital abnormalities in the infants of women treated with combination chemotherapy for Hodgkin's lymphoma, but a subsequent study by the same investigators involving 133 pregnancies in 66 women with malignant neoplasms[89] suggested that the unfavourable pregnancy outcomes were not linked to genetic damage to oocytes. Other studies evaluating pregnancies in women previously treated with modern chemotherapy for MOGCTs do not demonstrate any significant increased risk of teratogenicity.[25,27,60,64,67,85] In reports in which VAC,[76] PVB,[77] and POMB/ACE combination[78] chemotherapy regimens were used in MOGCT, none showed an increase in the risk of congenital abnormalities. Javaheri et al.[90] reported a normal live birth for a woman after 17 cycles of VAC regimen. In a review of 169 women by Zanetta et al.[37] a miscarriage rate of 11% was recorded, which did not differ from the general population. No statistical difference was found in the rates of congenital malformation between women who received chemotherapy and those who did not.

Conclusion

Conservative, fertility-sparing surgery is the procedure of choice in young women with MOGCT confined to a single ovary. Advanced stages are not always accompanied by extensive pelvic disease and should not be a contraindication to preservation of the uterus and contralateral ovary. With the appropriate addition of postoperative adjuvant platinum-based combination chemotherapy, these young women have an excellent prognosis and can expect to maintain normal ovarian function and reproductive capacity.

Conflict of interest

None declared.

Practice points

- Malignant ovarian germ-cell tumours typically occur in the first 2 decades of life.
- Initial clinical work up should include sonography, computed tomography scans, or both, as well as tumour markers, including AFP, LDH, β-hCG, and Ca-125.
- Fertility-sparing surgery with unilateral salpingo-oophorectomy is the standard surgical approach for MOGCT, along with surgical staging in apparently early disease.
- The role of aggressive surgical debulking is not well defined in chemo-sensitive tumours.
- BEP chemotherapy is the regimen of choice in advanced MOGCT, whereas there is now a trend towards close surveillance in surgical Stage 1 MOGCTs.
- After fertility-sparing surgery and BEP chemotherapy, most women will resume their previous baseline menstrual function.
- Fertility rates approximate those of the normal population, with no significant increase in the risk of early pregnancy loss or teratogenicity.

Research agenda

- Safety of close surveillance for surgical stage 1 non-dysgerminomatous MOGCTs.
- Role of combined oral contraceptive pills to preserve ovarian function during chemotherapy.
- Long-term psychological, physical and sexual function after chemotherapy for MOGCT.

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