Royal College of Obstetricians & Gynaecologists

Management of Female Malignant Ovarian Germ Cell Tumours

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1. Background

Female malignant ovarian germ cell tumours (MOGCTs) are rare, but early diagnosis and multiagent chemotherapy are associated with high cure rates of 85.6% (range 81.2–90.0%).[1] While sharing many similarities with male germ cell tumours (GCTs), a group of cancers 20 times more common than MOGCTs, women who relapse with this cancer have poorer outcomes.[2] Although all cases of MOGCTs are managed by multidisciplinary teams, outcomes could be improved by centralisation of care in view of the low incidence of these tumours. Such an approach has been applied to male GCTs; the introduction of cancer peer review and cancer pathways identified the need for a multidisciplinary care approach, and centralisation of the care of rare cancers, such as gestational trophoblastic tumours, has led to improved care and outcomes in the UK.[3,4] This review is confined to the management of non-paediatric cases of MOGCTs.

2. Epidemiology

MOGCTs, which include dysgerminomas, immature teratomas, embryonal tumours and endodermal sinus (yolk sac) tumours, accounted for only 1.5% of ovarian cancers in the EUROCARE study of survival from ovarian cancer in Europe.[1] A review of the Surveillance, Epidemiology, and End Results (SEER) data taken between 1973 and 2002[5] reported an incidence of MOGCTs of 3.4/1 000 000 women in the USA and a survey of GCTs in England between 1979 and 2003[6] reported an incidence of 2.34/1 000 000 women, equating to approximately 75–110 new cases per year. Data from other countries have reported higher incidence (5%) and it is possible that the current UK data under represent the true incidence of MOGCTs.[7–11] Approximately one-third of such cases are dysgerminomas, one-third immature teratomas and a further one-third include embryonal tumours, endodermal sinus tumours, choriocarcinoma and mixed cell types. MOGCTs most commonly occur in the first two decades of life, but can appear at any age, with 82.3% of all MOGCTs occurring between the ages of 14 and 54 years.[1] A review of the Norwegian Cancer registry[12] found that immature teratomas were more common in women over the age of 50 years.

3. Presentation and investigation

The presentation of MOGCTs is varied, but can include pelvic pain (acute and subacute), menstrual disturbance, and a pelvic or abdominal mass. Initial investigation should include pelvic ultrasound. If imaging is suggestive of MOGCT, alphafetoprotein (α-FP) and human chorionic gonadotrophin (hCG) serum levels should be measured to help identify women with GCTs. The current Royal College of Obstetricians and Gynaecologists Green-top Guideline for ovarian masses in premenopausal women[13] recommends determination of serum lactic dehydrogenase (LDH), α-FP and hCG in all women aged under 40 years, whereas the NHS Quality Improvement Scotland 2008 guideline[14] recommends that women aged 30 years or younger require α-FP, hCG, LDH or serum cancer antigen 125 (CA125) levels measured to help differentiate them from women with GCTs. The National Academy of Clinical Biochemistry guideline,[15] which focuses more on tumour markers, states that only α-FP and hCG have been sufficiently studied and validated by independent groups to warrant their measurement. The guideline recommends that α-FP and hCG levels should be determined whenever there is a suspicion of GCT 'particularly in women younger than 40 years or in older women where scan features suggest a germ cell tumour'. Elevation of α-FP and hCG correlates with stage and survival in MOGCT, with higher levels of both markers associated with a more advanced stage of the disease and reduced survival, which is independent of stage.[2,16–18]

The presence of a solid mass on ultrasound examination in younger women may indicate a MOGCT. Additional imaging of the abdomen, pelvis and chest by contrast-enhanced computed tomography (CT)

should be performed if there is a high suspicion of a MOGCT. Magnetic resonance imaging (MRI) may provide additional information over CT imaging of the ovaries.

4. Surgery

The surgical intention when operating on young women who desire future fertility should be conservative, with the goal of obtaining a tissue diagnosis and staging the extent of the disease. MOGCTs are usually unilateral, however, 10–15% of pure dysgerminomas are bilateral. Surgery, when appropriate, should be unilateral oophorectomy, peritoneal washing, omental biopsy and selective removal of enlarged lymph nodes. Biopsy of a normal contralateral ovary is not indicated. Surgery should be by an open procedure to enable removal of the affected ovary with its tumour intact rather than broken or ruptured. Mahdi et al.,[19] reviewing SEER data between 1988 and 2006, found that the presence of lymph node metastases had no adverse effect on long-term outcome. In addition, those women who underwent routine lymphadenectomy did not have a better outcome and consequently, there is no role for systematic lymphadenectomy in MOGCT. If nodes are enlarged, then removal of the affected nodes only is indicated. Liu et al.[20] found that a conservative approach involving unilateral oophorectomy, intraoperative inspection of the abdomen, pelvis, omentum and lymph nodes, and excision of any visible disease was comparable to a more extensive staging laparotomy that included omentectomy and lymphadenectomy. In a further review of SEER data, Chan et al.[21] reported an increased use of fertility-preserving treatments without any negative impact on survival.

For women who present with advanced disease (stage Ic/IIa and greater), consideration should be given to neoadjuvant chemotherapy to help preserve fertility and reduce the complexity of subsequent surgery (see section 6). In women who have completed their family, surgery to remove both tubes and ovaries (bilateral salpingo-oophorectomy) and the uterus (hysterectomy) may be considered, particularly if there are additional gynaecological comorbidities.

5. Surveillance

The majority of MOGCTs (60–70%) are diagnosed with disease confined to the ovaries or to the pelvis.[5,12] In stage I testicular GCTs confined to the testis, surveillance without adjuvant radiotherapy (seminomas) or chemotherapy (seminomas or nonseminomatous GCT) is now the standard of care in the UK and many other countries.[22] This raises the question as to whether such strategies are safe for women with early-stage MOGCT. In the past, women with resected early-stage disease, including stage Ia, received adjuvant radiotherapy for dysgerminomas (the seminoma equivalent) or platinum-based chemotherapy, such as BEP (bleomycin, etoposide, cisplatin), for nondysgerminomatous tumours. The long-term survival rates were around 100%. Data[12,23,24] have shown that women given adjuvant radiotherapy after resection of early-stage dysgerminomas (stage Ia) subsequently suffered infertility due to failure of the remaining ovary and the appearance of secondary cancers later in life. Consequently, radiotherapy is no longer recommended for resected early-stage dysgerminomas. Adjuvant carboplatin or BEP chemotherapy could be considered, but this exposes women to potentially unnecessary toxicity. There is now a growing body of evidence for a 'surveillance only' strategy after resection for women with stage Ia/b dysgerminomas. Relapse rates on surveillance appear to be around 20% for women with resected stage Ia dysgerminomas and virtually all of these are subsequently cured with chemotherapy.[25–27]

It is likely that stage Ia/b nondysgerminomatous MOGCT and all grades of immature MOGCT can also be managed with surveillance after resection of the ovarian mass. The relapse rates may be slightly higher for the nondysgerminomatous group at around 25–35%, but virtually all will be cured with chemotherapy at recurrence.[24,25] At present, there are insufficient data to recommend that women with stage Ic disease be offered surgery followed by surveillance alone. However, women with immature grade I or II teratomas could probably be considered for surveillance. Whether this would also be safe for women with stage Ic grade III disease, which frankly should be viewed as a malignant tumour that has not been completely

excised, is less clear. Interestingly, there is one small series from the Multicenter Italian Trials in Ovarian cancer group[26] suggesting that women with stage Ic immature grade III teratomas can be placed on surveillance. In the 30–40% that relapse, subsequent chemotherapy can save the woman. This suggests that such women should be offered the option of surveillance while recognising that data are still very limited. The alternative would be to give BEP chemotherapy for three cycles, which might be considered by others as the standard of care. We currently suggest that women be given the information and offered the choice until more data are available.

5.1 The UK surveillance programme

Currently in the UK, all women with stage Ia MOGCT are offered surveillance regardless of histological subtype. Operative detail, central pathological review, tumour markers and whole body imaging are important to ensure that the staging is correct.

After surgery, tumour markers, if elevated, should be measured weekly until normal to ensure that they are falling in accordance with the expected half-life (α-FP, 6–7 days; hCG, 1–2 days). Surveillance includes regular clinical review, examination, interval imaging and tumour marker assessments (hCG, α-FP, CA125 and LDH). The value of CA125 and LDH in the monitoring of MOGCTs are, as yet, not well defined and are much less specific than for hCG and α-FP. Nevertheless, most investigators are employing them and until more data are available, it seems reasonable to recommend their continued use.[27] The frequency of surveillance with tumour marker monitoring is highest early on, reflecting present data showing that most relapses occur within 2 years.[24,26] With declining risk, the intensity of surveillance falls over time until annual appointments beyond 7 years. Table 1 shows the Charing Cross surveillance programme. At present, there are insufficient data on the duration of surveillance and it is safe to continue annual surveillance indefinitely. This also enables the collection of longer term outcome data.

6. Role of chemotherapy in MOGCTs

The introduction of cisplatin-based combination chemotherapy for MOGCT has dramatically improved treatment outcomes in women with advanced or incompletely resected disease.[27] The long-term outcomes after chemotherapy and limited surgery, with preservation of the contralateral ovary and fallopian tube, are good; approximately 90% of women with early-stage disease and 75–80% with advanced disease can expect long-term survival, with a high likelihood of resumption of menses and subsequent pregnancies.[5]

The indications for chemotherapy depend on the extent and type of disease at diagnosis. For more advanced disease, stage II or greater, neoadjuvant combination chemotherapy may be a reasonable option. This is because surgery may be more complicated in this group, risking preservation of fertility. Moreover, while the woman is healing, tumour regrowth may reduce the benefits of the surgical cytoreduction. Surgery certainly should not be undertaken in women with advanced stage IIIc and IV disease; instead, neoadjuvant chemotherapy should be started urgently.[28]

6.1 Chemotherapy regimen for MOGCTs

Platinum-containing chemotherapy regimens have been the preferred treatment for GCTs over the past 30 years.[27] The combined BEP regimen is the international standard of care, usually administered for three cycles in completely resected disease and four cycles for macroscopic residual disease.[29–31] Bone marrow growth factors are given, if required, since a reduction in chemotherapy dose intensity may lead to poorer outcomes.[32]

Cisplatin should only be replaced by carboplatin in women with significant renal function abnormalities, peripheral neuropathy or ototoxicity. Excellent treatment outcomes have been reported with adjuvant carboplatin and etoposide for completely resected dysgerminoma.[33]

Table 1. Surveillance policy for stage Ia ovarian GCTs

Clinical follow-up[a]	
Interval	**Frequency**
3–6 weeks after surgery	
3 months after surgery	
0–12 months	Monthly
12–24 months	2 monthly
24–36 months	3 monthly
36–48 months	4 monthly
Years 5 and 6	6 monthly
Year 7 onwards	12 monthly
Clinical examination, ultrasound and chest X-ray	
Interval	**Frequency**
3–6 weeks after surgery	
3 months after surgery	
0–24 months	Clinical examination to include internal examination, unless recent imaging; pelvic ultrasound if no MRI on alternate visits; and chest X-ray on alternate visits.
24–36 months	Clinical examination to include internal examination, unless recent imaging; pelvic ultrasound if no MRI on alternate visits (only dysgerminomas); and chest X-ray on alternate visits.
36–48 months	Clinical examination to include internal examination, unless recent imaging; and chest X-ray on alternate visits.
Years 5 and 6	Clinical examination to include internal examination, unless recent imaging; and chest X-ray on alternate visits.
Year 7 onwards	Clinical examination to include internal examination, unless recent imaging; and chest X-ray on alternate visits.
Specialised imaging	
Interval	**Frequency**
3–6 weeks after surgery	CT chest, MRI or CT abdomen, and MRI pelvis and head all with contrast if not performed preoperatively. Also baseline Doppler ultrasound pelvis.
3 months after surgery	Repeat CT or MRI, abdomen and pelvis, and if normal, consider second-look laparoscopy if inadequate initial staging or glial implants.
6 months	MRI abdomen and pelvis
12 months	MRI abdomen and pelvis
24 months	MRI abdomen and pelvis
36 months	MRI abdomen and pelvis – dysgerminomas only.
Tumour marker follow-up[b]	
Interval	**Frequency**
0–6 months	2 weekly (nondysgerminomas); monthly (dysgerminomas).
7–12 months	Monthly
12–24 months	2 monthly
24–36 months	3 monthly
36–48 months	4 monthly
Years 5 and 6	6 monthly
Year 7 onwards	12 monthly

[a] Women are advised not to get pregnant during the first 2 years of surveillance.

[b] Samples: serum α-FP, hCG, LDH and CA125 (regardless of initial value).

The POMB/ACE regimen (cisplatin, vincristine, methotrexate and bleomycin [POMB] alternating with actinomycin D, cyclophosphamide and etoposide [ACE]) was designed to introduce seven different cytotoxic agents to decrease the risk of drug resistance.[34] POMB/ACE has been shown to be effective and well tolerated for advanced and aggressive testicular GCTs, and a high level of efficacy has been shown for advanced MOGCT.[35,36] This regimen is used in some centres as the regimen of choice for patients with extensive metastatic or recurrent disease, although it has not been compared with BEP in a randomised trial.[35,36]

6.2 Safe delivery of chemotherapy

Women with MOGCT require urgent evaluation and treatment. The disease can progress rapidly, with a short tumour doubling time, and spread to the peritoneum, lungs, liver and brain. Metastatic disease has a higher probability of drug resistance and life-threatening complications, notably intratumoural haemorrhage.

For very ill women with widespread disease and/or poor performance status, a weekly induction regimen of etoposide 100 mg/m^2 and cisplatin 20 mg/m^2 (low-dose induction EP) is recommended to obtain an initial response and improvement in the woman's condition before introducing full-dose chemotherapy.[34,37]

6.3 Follow-up after chemotherapy

Approximately 75% of MOGCT recurrences occur within the first year, so intensive early follow-up every 4–8 weeks appears to be appropriate and should be audited.[27,29] Common sites of recurrence are the peritoneal cavity and, more rarely, the retroperitoneal lymph nodes or lungs. Therefore, the objectives of follow-up should be to determine response to treatment, management of treatment-related complications, and early detection of persistent or recurrent disease. The follow-up strategy should include assessment of tumour markers at each visit and chest X-ray every 2 months for 2 years and then 3–6 monthly for the next 3 years. CT imaging of the pelvis, abdomen and chest (if abnormal at presentation) should be performed 3 months after completion of chemotherapy and then as clinically indicated.

In addition to disease-related follow-up, women should be assessed for adverse physical and cardiovascular complications, as well as psychosocial and psychosexual consequences of treatment.[38–40]

6.4 Disease present at end of primary treatment

Women who have residual masses at completion of chemotherapy should be offered resection even if the tumour markers are normal.[41] This is to exclude residual disease or any residual mature teratoma which can progress as mature teratoma growing syndrome in up to 30% of cases, and more rarely, over time, undergo malignant transformation into an incurable tumour type, such as squamous carcinoma. Early recognition of this syndrome is essential as it offers hope for curative resection and avoids the use of ineffective chemotherapy.[42] In the absence of any residual disease, there is no indication for second-look laparotomy or laparoscopy.[43]

7. Management of MOGCT that relapses following chemotherapy

Women with MOGCT who relapse following initial chemotherapy appear to have low salvage rates (approximately 10%) with subsequent regimens, which normally salvage more than 50% of male patients.[2] The underlying reasons for this are unclear as the numbers of cases involved are low. Women that relapse should be imaged with contrast-enhanced MRI of the brain and pelvis, CT of the chest and abdomen, Doppler ultrasound of the pelvis and fluorodeoxyglucose positron emission tomography/CT. The latter may help to distinguish sites of active disease for surgical resection, although false-positive and -negative results can occur. Repeat biopsy should only be done where it is safe and will not delay the onset of

life-saving treatment. The possibility of mature teratoma growing syndrome, a condition where deposits of mature teratoma start to grow, should be considered as surgery to remove this completely is required.[44,45] Mixed cystic and solid elements on imaging with calcification, and always with normal hCG and α-FP, provide clues that mature teratoma growing syndrome is present. For women with multiple sites of relapse or marker relapse without clear abnormalities on imaging, salvage chemotherapy will be needed. Salvage regimens include TIP (paclitaxel, ifosfamide, cisplatin), TE/TP (paclitaxel, etoposide/paclitaxel, cisplatin) and gemcitabine-TIP.[41] The value of high-dose chemotherapy, employed as a tandem transplant, is still unclear for MOGCT, although most investigators feel that it is helpful in salvaging male GCT relapses.[2,46–48] The role of radiotherapy is limited by the relative radioresistance of nondysgerminomatous tumours and is likely to provide palliation only.[41] However, there may be a role in salvaging selected dysgerminomas which are more radiosensitive.[49] Following salvage chemotherapy, any residual masses left on imaging should be surgically removed if possible, and stereotactic or gamma knife radiosurgery may be of value for residual brain lesions not amenable to resection.

8. A multidisciplinary approach to women with MOGCTs

A multidisciplinary ethos, including access to services for teenage and young adults, defined as those aged 15–24 years, is highly desirable. Females with MOGCTs are often young, likely to be cured and can expect a normal lifespan.[25] Champion et al.[50] suggest that coping with the diagnosis of MOGCT during the transition from adolescence to adulthood is particularly challenging for those who often have little experience of illness, pain or hospitalisation. Nurse specialists are increasingly involved in supporting decision making for women, including discussions about surveillance, treatment fertility options and any accompanying uncertainty.

Body image is of heightened importance in adolescent years and teenage girls are prone to develop negative self-image.[51] The prospect of hair loss can be devastating and helpful interventions may include emotional and practical support encompassing time to talk, help and advice about wigs, scarves, make-up and eyelashes. The potential loss of fertility as an adverse effect of chemotherapy is a major concern and specialist fertility consultation may be required. However, most women (87–100%) will regain menstrual function and fertility within a year of completing chemotherapy, with only a few (3%) experiencing a premature menopause.[25,52,53]

9. Opinion

MOGCTs are a very rare entity with about 100 new cases diagnosed in the UK each year.[6]

Early diagnosis and multi-agent chemotherapy are associated with high cure rates. However, there is evidence of poorer outcomes for women who relapse with this cancer compared with male GCTs. Further research into improving prognosis of women with MOGCT would be desirable.

There is a need for a central registry, annual audits of outcomes and pathways, and the development of a national protocol for patients with relapsed disease.

A multidisciplinary approach, including access to services for teenage and young adults as well as fertility services should be offered to all women with a diagnosis of MOGCT.

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