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FIGO CANCER REPORT 2012

Cancer of the ovary, fallopian tube, and peritoneum

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1. Introduction

1.1. Primary sites: Ovarian, fallopian tube, and peritoneal cancers

The staging system used in this chapter is that accepted by FIGO in 2006. The Gynecology Oncology Committee of FIGO is currently revising the staging to incorporate ovarian, fallopian tube, and primary peritoneal cancer in the same system. Changing the staging system requires extensive international consultation. The proposed staging will be presented at the FIGO Congress in Rome 2012. The primary site (i.e. ovary, fallopian tube, or peritoneum) would be designated where possible. In some cases, it may not be possible to clearly delineate the primary site, and these should be listed as "undesignated" [1,2].

In the past, it has been presumed that fallopian tube malignancies were rare [2]. However, recent histologic, molecular, and genetic evidence shows that many tumors that were classified as high-grade serous carcinomas of the ovary or peritoneum may have originated in the fimbrial end of the fallopian tube [3–8]. Therefore, the incidence of fallopian tube cancers may have been substantially underestimated. These new data support the view that high-grade serous ovarian, peritoneal, and fallopian tube cancers should be considered collectively, and that the convention of designating malignancies as having an ovarian origin if it is unclear should no longer be used. It has been suggested that a more accurate term is "pelvic serous carcinomas" (defined as tumors of serous histology arising in the ovary, fallopian tube, or peritoneum) [9].

Although there has been no formal staging for peritoneal cancers, the FIGO staging system is used with the understanding that it is not possible to have a Stage I peritoneal cancer.

1.1.1. Primary site

Ovarian epithelial tumors may arise within either endometriosis or cortical inclusions. These include low-grade endometrioid carcinomas, clear cell carcinomas, borderline and low-grade serous carcinomas, and mucinous carcinomas. These tumors are thought to evolve slowly from lower-grade precursor conditions (endometriotic cysts, cystadenomas, etc.) and are classified as type I tumors [5]. Fallopian tube carcinomas arise in the distal fallopian tube and the majority of these are high-grade serous carcinomas. These are thought to evolve rapidly from more obscure precursors and are designated as type II tumors [5,6]. This group also encompasses high-grade endometrioid carcinomas and carcinosarcomas. All of these high-grade carcinomas are highly associated with mutations in the *TP53* gene [5].

1.1.2. Lymphatic and lymph node drainage

The lymphatic drainage of the ovaries and fallopian tubes is via the utero-ovarian, infundibulopelvic, and round ligament pathways and an external iliac accessory route into the following regional lymph nodes: external iliac, common iliac, hypogastric, lateral sacral, para-aortic lymph nodes and, occasionally, to the inguinal nodes [1,10–12]. The peritoneal surfaces can drain through the diaphragmatic lymphatics and then to the major venous vessels above the diaphragm.

1.1.3. Other metastatic sites

The peritoneum, including the omentum and pelvic and abdominal viscera, is the most common site for dissemination of ovarian and fallopian tube cancers. This includes the diaphragmatic and liver surfaces. Pleural involvement is also seen. Other extraperitoneal or extrapleural sites are relatively uncommon, but can still occur [1, 10–12]. Once systematic pathologic analysis has excluded a tubal or ovarian site of origin, malignancies that appear to arise primarily on the peritoneum have an identical spread pattern, and frequently may involve the ovaries and fallopian tubes secondarily.

1.2. Classification rules

Although CT scans can delineate the intra-abdominal spread of disease to a certain extent, ovarian, fallopian tube, and peritoneal cancers should be staged surgically. Operative findings determine the precise histologic diagnosis, stage, and therefore the prognosis of the patient [1,9,10,12–14].

In selected patients with advanced-stage disease, it may be appropriate to initiate chemotherapy prior to surgical intervention, and in these cases, there should be histological confirmation of the diagnosis prior to starting neoadjuvant chemotherapy (see 5.2.2. below).

Chest radiograms may serve as a screen for pleural effusions. As distant metastases are infrequent, there is no requirement for other radiological evaluation unless symptomatic. Serum CA 125 levels may be useful in determining response to chemotherapy, but they do not contribute to staging.

1.2.1. Fallopian tube involvement

Fallopian tube involvement can be divided into 3 categories. In the first, a fallopian tube mass is present, including tubal intraepithelial carcinoma (carcinoma in situ). These cases should be staged surgically with a histological confirmation of disease. Tumor extension into the submucosa or muscularis and to and beyond the serosa can therefore be defined. These features, together with the laterality and the presence or absence of ascites, should all be taken into consideration [1,3,6,7].

In the second scenario, a widespread serous carcinoma is associated with a tubal intraepithelial carcinoma, which should be

noted in the pathology report and may represent a presumptive tubal primary.

In the third scenario – the risk-reducing salpingo-oophorectomy – tubal intraepithelial carcinoma may be the only finding. It should be reported as originating in the tube and managed accordingly.

1.2.2. FIGO staging

The most common staging system is the FIGO system, as modified in 1988, and is based on findings made mainly through surgical exploration (as outlined above). Tables 1 and 2 provide the current (2006) FIGO staging classification for cancer of the fallopian tube and ovary, respectively. However, it is also useful to be aware of the equivalents within the Union for International Cancer Control (UICC) TNM classification (Table 3, Table 4).

The staging includes a revision of the Stage III patients whose disease spread and allotment to Stage III is based on spread to the retroperitoneal lymph nodes without intraperitoneal dissemination, because an analysis of these patients indicates that their survival is significantly better than those who have intraperitoneal dissemination [15].

Table 1
Cancer of the fallopian tube (FIGO 2006).

FIGO Stage	Description
0	Carcinoma in situ (limited to tubal mucosa)
I	Growth limited to the fallopian tubes
IA	Growth is limited to one tube, with extension into the submucosa and/or muscularis, but not penetrating the serosal surface; no ascites
IB	Growth is limited to both tubes, with extension into the submucosa and/or muscularis, but not penetrating the serosal surface; no ascites
IC	Tumor either Stage Ia or Ib, but with tumor extension through or onto the tubal serosa, or with ascites present containing malignant cells, or with positive peritoneal washings
II	Growth involving one or both fallopian tubes with pelvic extension
IIA	Extension and/or metastasis to the uterus and/or ovaries
IIB	Extension to other pelvic tissues
IIC	Tumor either Stage IIa or IIb and with ascites present containing malignant cells or with positive peritoneal washings
III	Tumor involves one or both fallopian tubes, with peritoneal implants outside the pelvis and/or positive regional lymph nodes. Superficial liver metastasis equals Stage III. Tumor appears limited to the true pelvis, but with histologically-proven malignant extension to the small bowel or omentum
IIIA	Tumor is grossly limited to the true pelvis, with negative nodes, but with histologically-confirmed microscopic seeding of abdominal peritoneal surfaces
IIIB	Tumor involving one or both tubes, with histologically-confirmed implants of abdominal peritoneal surfaces, none exceeding 2 cm in diameter. Lymph nodes are negative
IIIC	Abdominal implants >2 cm in diameter and/or positive retroperitoneal or inguinal nodes
IV	Growth involving one or both fallopian tubes with distant metastases. If pleural effusion is present, there must be positive cytology to be Stage IV. Parenchymal liver metastases equals Stage IV

1.2.2.1. Regional lymph nodes (N)

- NX: Regional lymph nodes cannot be assessed.
- N0: No regional lymph node metastasis.
- N1: Regional lymph node metastasis.

1.2.2.2. Distant metastasis (M)

- MX: Distant metastasis cannot be assessed.
- M0: No distant metastasis.
- M1: Distant metastasis (excluding peritoneal metastasis).

Table 2
Cancer of the ovary (FIGO 2006).

FIGO Stage	Description
I	Growth limited to the ovaries
IA	Growth limited to one ovary; no ascites present containing malignant cells. No tumor on the external surface; capsule intact
IB	Growth limited to both ovaries; no ascites present containing malignant cells. No tumor on the external surfaces; capsules intact
IC[a]	Tumor either Stage IA or IB, but with tumor on surface of one or both ovaries, or with capsule ruptured, or with ascites present containing malignant cells, or with positive peritoneal washings
II	Growth involving one or both ovaries with pelvic extension
IIA	Extension and/or metastases to the uterus and/or tubes
IIB	Extension to other pelvic tissues
IIC[a]	Tumor either Stage IIA or IIB, but with tumor on surface of one or both ovaries, or with capsule(s) ruptured, or with ascites present containing malignant cells, or with positive peritoneal washings
III	Tumor involving one or both ovaries with histologically confirmed peritoneal implants outside the pelvis and/or positive regional lymph nodes. Superficial liver metastases equals Stage III. Tumor is limited to the true pelvis, but with histologically proven malignant extension to small bowel or omentum
IIIA	Tumor grossly limited to the true pelvis, with negative nodes, but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces, or histologic proven extension to small bowel or mesentery
IIIB	Tumor of one or both ovaries with histologically confirmed implants, peritoneal metastasis of abdominal peritoneal surfaces, none exceeding 2 cm in diameter; nodes are negative
IIIC	Peritoneal metastasis beyond the pelvis >2 cm in diameter and/or positive regional lymph nodes
IV	Growth involving one or both ovaries with distant metastases. If pleural effusion is present, there must be positive cytology to allot a case to Stage IV. Parenchymal liver metastasis equals Stage IV

[a] In order to evaluate the impact on prognosis of the different criteria for allotting cases to Stage IC or IIC, it would be of value to know if rupture of the capsule was spontaneous, or caused by the surgeon; and if the source of malignant cells detected was peritoneal washings, or ascites.

Table 3
Cancer of the fallopian tube: FIGO staging (2006) compared with TNM classification.

FIGO Stage	Union for International Cancer Control (UICC)		
	T (tumor)	N (lymph nodes)	M (metastasis)
IA	T1a	N0	M0
IB	T1b	N0	M0
IC	T1c	N0	M0
IIA	T2a	N0	M0
IIB	T2b	N0	M0
IIC	T2c	N0	M0
IIIA	T3a	N0	M0
IIIB	T3b	N0	M0
IIIC	T3c	N0	M0
	Any T	N1	M0
IV	Any T	Any N	M1

Table 4
Cancer of the ovary: FIGO staging (2006) compared with TNM classification.

FIGO Stage	Union for International Cancer Control (UICC)		
	T (tumor)	N (lymph nodes)	M (metastasis)
IA	T1a	N0	M0
IB	T1b	N0	M0
IC	T1c	N0	M0
IIA	T2a	N0	M0
IIB	T2b	N0	M0
IIC	T2c	N0	M0
IIIA	T3a	N0	M0
IIIB	T3b	N0	M0
IIIC	T3c	N0	M0
	Any T	N1	M0
IV	Any T	Any N	M1

1.3. Histopathologic classification

The majority of cases of ovarian cancer are of epithelial origin. FIGO endorses the WHO histological typing of epithelial ovarian tumors. It is recommended that all ovarian epithelial tumors be subdivided according to the classification given below [16].

The histologic classification of ovarian, fallopian tube, and peritoneal neoplasia is as follows:

- Serous tumors.
- Mucinous tumors.
- Endometrioid tumors.
- Clear cell tumors.
- Brenner tumors.
- Undifferentiated carcinomas (this group of malignant tumors is of epithelial structure, but they are too poorly differentiated to be placed in any other group).
- Mixed epithelial tumors (these tumors are composed of 2 or more of the 5 major cell types of common epithelial tumors. The types are usually specified).
- Cases with intraperitoneal carcinoma in which the ovaries and fallopian tubes appear to be incidentally involved and not the primary origin should be labeled as peritoneal carcinoma.

Epithelial tumors of the ovary and fallopian tube are also further subclassified by grading. This is important because histological grading is proportional to prognosis. This grading system does not apply to non-epithelial tumors [17].

- GX: Grade cannot be assessed.
- G1: Well differentiated.
- G2: Moderately differentiated.
- G3: Poorly differentiated.

Currently, histologic grading of ovarian carcinomas is under revision, particularly with regard to the endometrioid and serous tumors. In practice, endometrioid and serous tumors are classified in a 2-grade system. Well-differentiated (grade 1) tumors are designated as low grade, and moderate to poorly differentiated (grade 1–3) tumors are designated as high grade. High-grade serous and endometrioid carcinomas are similar histologically and carry a high frequency of mutations in *TP53*. Most moderately differentiated tumors in this group carry mutations in *TP53* and are thus combined with the poorly differentiated carcinomas under the high-grade designation [17–20].

Nonepithelial cancers, although uncommon, are also extremely important. These include granulosa cell tumors, germ cell tumors, sarcomas, and lymphomas. They shall be discussed as separate entities.

More than 90% of fallopian tube carcinomas are serous or high-grade endometrioid adenocarcinoma. Other cell types have been reported, but are rare [1,2,21].

2. Epidemiology

Malignant tumors of the ovaries occur at all ages with variation in histological subtype by age. For example, in women younger than 20 years of age, germ cell tumors predominate, while borderline tumors typically occur in women in their 30s and 40s – 10 or more years younger than in women with invasive epithelial ovarian cancers, which mostly occur after the age of 50 years.

The lifetime risk of a woman in the USA developing ovarian cancer is approximately 1 in 70. Approximately 23% of gynecologic cancers are ovarian in origin, but 47% of all deaths from cancer of the female genital tract occur in women with ovarian cancer. Overall, epithelial ovarian cancer accounts for 4% of all new cancer diagnoses in women and 5% of all cancer related deaths [1,2,22].

The overall incidence of epithelial tumors varies from 9–17 per 100 000 and is highest in industrialized countries, with the exception of Japan [23]. However, this incidence rate increases proportionately with age. The largest number of patients with epithelial ovarian cancer is found in the 60–64 years age group.

Established risk factors for epithelial ovarian tumors include reproductive risk factors. Women who have never had children are twice as likely to develop this disease. First pregnancy at an early age, early menopause, and the use of oral contraceptives have been associated with lower risks of ovarian cancer [24]. The relationship of these variables to fallopian tube cancer is unclear.

As noted above, it has been previously presumed that fallopian tube malignancies were rare; however, this has been challenged by evidence to show that many tumors that were classified as serous carcinomas of the ovary or primary peritoneal cancers appear to have their origin in the fallopian tube [3–7]. These data support the contention that ovarian, fallopian tube, and primary peritoneal cancers should be considered collectively. Furthermore, when the origin is uncertain, the convention of designating all serous cancers as originating in the ovary should no longer be used.

2.1. Genetics

Hereditary factors are implicated in approximately 5%–10% of all ovarian, as well as many fallopian tube and peritoneal cancers. Mutations that have been identified include [25–29]:

1. Inherited pathological mutations in the BRCA1 and the BRCA2 genes. Women who carry germline mutations in BRCA1 and BRCA2 have a substantially increased risk of ovarian, tubal, and peritoneal cancer – about 20%–50% with BRCA1 and 10%–20% with BRCA2 [26–29]. Typically these cancers occur at an earlier age than sporadic cancers, particularly in BRCA1 mutation carriers, with a median age of diagnosis in the mid-40s.
2. Inherited mutations in the mismatch repair genes associated with Type II Lynch Syndrome. Women carrying these mutations have an increased risk of a number of cancers including colon, endometrial, and ovarian cancer. Typically, the ovarian cancers that occur are endometrioid or clear cell histologically and are usually Stage I.
3. Inherited mutation in ARID1 is associated with clear cell and endometrioid carcinomas [30].

Patients with a strong family history of epithelial ovarian, fallopian tube, or peritoneal cancers, particularly if there is a documented germline mutation, are advised to have a risk-reducing bilateral salpingo-oophorectomy after appropriate counseling and at the completion of childbearing. All women who are suspected of possibly carrying a BRCA germline mutation, based on family history or young age of diagnosis and a high-grade serous or high-grade endometrioid cancer, should be evaluated by a genetic

counselor for genetic testing. BRCA mutations may also occur in women without a family history of breast/ovarian cancer, and genetic testing should be considered in patients from ethnic groups where there is a high incidence of founder mutations (e.g. Ashkenazi Jewish ancestry), as well as in women with high-grade serous cancers under the age of 50 years [26–30]. Women whose family history suggests the Lynch II syndrome should undergo appropriate genetic counseling and testing.

3. Screening

To date, there are no documented effective screening methods that have been found to reduce the mortality of ovarian, fallopian tube, or peritoneal cancers. Studies using CA125, ultrasonography of the pelvis, and pelvic examination have not produced an acceptable level of sensitivity and specificity, but trials are in progress in women in the general population as well as those in the high-risk population. Women at increased genetic risk should be encouraged to consider risk-reducing bilateral salpingo-oophorectomy, as this is the most effective way to reduce mortality in this population of women [31,32].

4. Diagnosis

Patients with epithelial ovarian cancers confined to the ovary or fallopian tube at initial diagnosis have a very good prognosis [33–36]. The symptoms are often very insidious and the duration of symptoms not very different between patients with early stage or advanced stage disease [13,14]. This may reflect the different biological behavior of the various histological subtypes; for example, grade 1 serous, clear cell, mucinous, and endometrioid cancers are commonly early stage at presentation, whereas high-grade serous cancers are most often Stage III because of early dissemination by a more aggressive cancer. Tumor markers such as human gonadotropin (hCG) and alpha-fetoprotein (AFP) are mandatory to exclude germ cell tumors in younger patients with a pelvic mass or suspicious enlargement of an ovary.

Approximately two-thirds of all epithelial "ovarian" cancers are Stage III or Stage IV at diagnosis. Presenting symptoms include vague abdominal pain or discomfort, menstrual irregularities, and dyspepsia and other mild digestive disturbances, which may only have been present for a few weeks [13,14,37]. As the disease progresses, abdominal distention and discomfort from ascites generally worsen, and may be associated with respiratory symptoms from increased intra-abdominal pressure or from the transudation of fluid into the pleural cavities. Abnormal vaginal bleeding is an uncommon symptom.

Fallopian tube and peritoneal cancers likely present the same as ovarian cancer. Past analyses have been biased because many fallopian tube cancers have been presumed to arise in the ovaries.

A detailed medical history must be taken to ascertain possible risk factors, history of other cancers, and history of cancer in the family. Then a complete physical examination, including general, breast, pelvic, and rectal examination, must be performed [1].

Prior to surgery a chest radiograph should be taken to screen for a pleural effusion while a CT scan of the abdomen and pelvis should be performed to delineate the extent of intra-abdominal disease. However, in the absence of extra-abdominopelvic disease, radiological scanning does not replace surgical staging with laparotomy. Tumor markers including CA125, and carcinoembryonic antigen (CEA) should be considered [1]. With a high CA125 titer, the most common diagnosis would be epithelial ovarian, fallopian tube, or peritoneal cancer.

A gastric or colonic primary with metastases to the ovaries may mimic ovarian cancer, and if the CEA is elevated, this should be considered. A current mammogram should also be considered as patients are frequently in the age group where breast cancer is prevalent. A colonoscopy is indicated should symptoms suggest possible bowel cancer [1].

The following factors point to the presence of a malignancy, and are useful in the clinical assessment of masses:

- Age of the patient (young for germ cell, older for epithelial malignancies).
- Bilaterality.
- Tumor fixation clinically.
- Ascites.
- Ultrasonographically complex, especially if solid areas.
- CT finding of metastatic nodules.
- Elevated tumor markers.

5. Primary surgery

In general, the prognosis of epithelial ovarian, fallopian, and peritoneal malignancies is independently affected by the following [1,38,39]:

- Stage of the cancer at diagnosis.
- Histological type and grade.
- Maximum diameter of residual disease after cytoreductive surgery.

5.1. Staging laparotomy

A thorough staging laparotomy is an important part of early management. If the preoperative suspicion is malignancy, the laparotomy should be performed. If there is no visible or palpable evidence of metastasis, the following should be performed for adequate staging [1,10,11,13,14]:

- Careful evaluation of all peritoneal surfaces.
- Retrieval of any peritoneal fluid or ascites. If there is none, washings of the peritoneal cavity should be performed.
- Infracolic omentectomy.
- Selected lymphadenectomy of the pelvic and para-aortic lymph nodes, at least ipsilateral if the malignancy is unilateral.
- Biopsy or resection of any suspicious lesions, masses, or adhesions.
- Random peritoneal biopsies of normal surfaces, including from the undersurface of the right hemidiaphragm, bladder reflection, cul-de-sac, right and left paracolic recesses, and both pelvic sidewalls.
- Total abdominal hysterectomy and bilateral salpingo-oophorectomy in most cases.
- Appendectomy for mucinous tumors.

Upon entering the abdominopelvic cavity, the peritoneal fluid should be sent for cytology. In the absence of ascites, irrigation should be performed and washings sent for cytology.

The laparotomy should then proceed with a detailed examination of the contents, including all the peritoneal surfaces. In addition to all the suspicious sites, biopsies from the peritoneal reflection of the bladder, the posterior cul-de-sac, both paracolic gutters, subdiaphragmatic surfaces, and both pelvic sidewalls should be taken. The primary tumor, if limited to the ovary, should be examined to look for capsular rupture. All obvious sites of tumor must be removed wherever possible in addition to total hysterectomy and bilateral salpingo-oophorectomy. Further, the omentum, pelvic, and para-aortic lymph nodes should also be removed for histological examination.

In younger women, fertility may be an issue. In these patients, conservative surgery, with preservation of the uterus and contralateral ovary, should be considered after informed consent [34].

Clinical judgment is important in the approach to a pelvic mass in the young, reproductive-aged woman. If the suspicion is strong for malignancy, open laparotomy is generally indicated. Laparoscopy

Table 5
Chemotherapy for epithelial malignancies of the ovary, fallopian tube, and peritoneum.

Chemotherapy type	Dose and route	Cycle
Intravenous chemotherapy		
Paclitaxel	175 mg/m^2 IV over 3 h 80 mg/m^2 IV over 3 h	Every 3 weeks × 6 Day 1, 8, 15
Carboplatin	AUC = 5–6 IV[a]	
Paclitaxel	135 mg/m^2 IV infusion over 24 h	Every 3 weeks × 6
Cisplatin	75 mg/m^2 IV	
Intraperitoneal chemotherapy		
Paclitaxel	135 mg/m^2 as a 24-h infusion IV	Day 1 every 3 weeks × 6 cycles
Cisplatin	75–100 mg/m^2 IP	Day 2
Paclitaxel	60 mg/m^2 IP	Day 8
Alternative drugs[b]		
Docetaxel	75 mg/m^2 IV	Every 3 weeks

[a] Bevacizumab 7.5–15 mg/kg every 3 weeks can be added to any of these regimens. For carboplatin, dosing is based on AUC (area under the curve) of creatinine clearance, and calculated by using Calvert et al. [51] or Cockroft–Gault, Jelliffe, Modified-Jelliffe, Wright, or Chatelut formulas [52].
[b] Can be substituted for paclitaxel if hypersensitivity to that drug occurs.

may be more appropriate if the suspicion is more for benign disease, where tumor markers (including hCG and AFP) are normal.

Ovaries and fallopian tubes should be evaluated as thoroughly as possible to establish the site of origin. If visible, the entire tube, particularly the distal portion, should be submitted for pathology and examined using the SEE-FIM protocol [29]. Ovaries should be scrutinized for coexisting endometriotic cysts, adenofibromas, or other benign conditions that could serve as a nidus of tumor development.

5.2. Cytoreductive (debulking) surgery for advanced stage disease

5.2.1. Primary debulking

At least two-thirds of patients with ovarian cancer present with Stage III or IV disease. This may affect the performance status and fitness for surgery. However, the most important prognostic indicator in patients with advanced stage ovarian cancer is the volume of residual disease after surgical debulking. Therefore, patients whose medical condition permits should generally undergo a primary laparotomy with total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and maximal attempt at optimal cytoreduction [1,38–40]. This may necessitate bowel resection, and occasionally partial or complete resection of other organs. Systematic pelvic and para-aortic lymphadenectomy does not improve overall survival, when compared with removal of bulky nodes only, although there is a modest improvement in progression-free survival [41]. **Level of Evidence A**

5.2.2. Interval debulking

In selected patients with cytologically proven Stage IIIC and IV disease who may not be good surgical candidates, neoadjuvant chemotherapy may be given initially for 2–3 cycles, followed by interval surgical cytoreduction and additional chemotherapy [42]. This is particularly useful in patients with a large pleural effusion and/or gross ascites. In selected patients whose primary cytoreduction is considered suboptimal, particularly if a gynecologic oncologist did not operate initially, interval debulking may also be considered after 2–3 cycles of systemic chemotherapy [1,42,43].

6. Chemotherapy

6.1. Chemotherapy for early stage cancer

The prognosis of adequately staged patients with Stage IA and Stage IB grade 1–2 epithelial cancers of the ovary is very good, and adjuvant chemotherapy does not provide further benefits. For higher-grade tumors and for patients with Stage IC disease, adjuvant platinum-based chemotherapy is given to most patients, although there has been debate about the absolute benefit in women with Stage IA and IB cancers who have had thorough surgical staging [33]. All patients with Stage II disease should receive adjuvant chemotherapy. The optimal number of cycles in patients with Stage I disease has not been definitively established, but typically between 3 and 6 cycles are administered. The Gynecologic Oncology Group (GOG) 157 study suggested that 3 cycles of carboplatin and paclitaxel was equivalent to 6 cycles, but in subgroup analysis, 6 cycles appeared superior in patients with high-grade serous cancers [40].

There is no evidence to support adjuvant therapy for carcinoma in situ of the fallopian tube and it is not recommended [1,2,35]. **Level of Evidence A**

6.2. Chemotherapy for advanced stage ovarian cancer

Patients who have had primary cytoreduction should receive chemotherapy following surgery [1,44] (Table 5). The accepted standard is systemic platinum-based combination chemotherapy, with a platinum (carboplatin or cisplatin) and a taxane (paclitaxel or docetaxel) [45–49]. Docetaxel may be considered in some patients as it has less neurotoxicity, but it is more myelosuppressive than paclitaxel [45]. At the end of 6 cycles of chemotherapy, 1 study reported that maintenance chemotherapy with monthly paclitaxel improved disease-free interval but not overall survival [50]. The role of maintenance chemotherapy is uncertain, is not standard practice, and is being investigated in clinical trials.

The role of intraperitoneal chemotherapy remains controversial and is not widely used internationally because of increased toxicity and catheter-related problems [53–57]. The GOG 172 trial compared intravenous paclitaxel plus cisplatin with intravenous paclitaxel plus intraperitoneal cisplatin and paclitaxel in patients with Stage III ovarian or primary peritoneal carcinoma, with no residual disease

greater than 1 cm in diameter [55]. Only 42% of patients in the intraperitoneal group completed 6 cycles of the assigned therapy, but the intraperitoneal group had an improvement in progression-free survival of 5.5 months (23.8 vs 18.3 months; $P = 0.05$) and an improvement in overall survival of 15.9 months (65.6 vs 49.7 months; $P = 0.03$). Further studies of intraperitoneal therapy are ongoing. **Level of Evidence A**

Combination chemotherapy with either intravenous carboplatin and paclitaxel or intraperitoneal cisplatin and paclitaxel (using the GOG 172 protocol) is the treatment of choice for patients with advanced disease. The advantages and disadvantages of the intravenous versus intraperitoneal routes of administration of these drugs should be discussed with the patient. Intraperitoneal chemotherapy is only applicable to patients with advanced disease who have had optimal debulking and have less than 1 cm residual disease. It should only be used in centers that have experience with intraperitoneal chemotherapy.

The recommended doses and schedule for intravenous chemotherapy are: carboplatin (starting dose AUC 5–6), and paclitaxel (175 mg/m^2), every 3 weeks for 6 cycles [47], or the dose-dense regimen of carboplatin AUC 6 every 3 weeks for 6 cycles and weekly paclitaxel 80 mg/m^2 [57]. The latter regimen has been reported by the Japanese GOG to improve progression-free survival and overall survival [58]. This regimen is being compared with standard every 3 weeks intravenous and intraperitoneal regimens in several clinical trials.

The recommended doses and schedule for intraperitoneal chemotherapy are paclitaxel 135 mg/m^2 intravenously on day 1, followed by cisplatin 75–100 mg/m^2 intraperitoneally on day 2, followed by paclitaxel 60 mg/m^2 intraperitoneally on day 8, every 3 weeks for 6 cycles, as tolerated [53–55]. Many centers modify the dose of cisplatin to 75 mg/m^2 rather than 100 mg/m^2 to reduce toxicity. Others substitute carboplatin (AUC 6) for cisplatin in the regimen. The impact on outcome of these pragmatic modifications is unknown.

Bevacizumab 7.5–15 mg/kg every 3 weeks can be added to these regimens [59,60]. Two studies have reported a modest but statistically significant increase in progression-free survival in patients receiving maintenance bevacizumab following carboplatin, paclitaxel, and bevacizumab [59,60]. There is no evidence as yet to demonstrate an overall survival benefit and the role of bevacizumab is still controversial.

In patients who cannot tolerate combination chemotherapy, single-agent, intravenously administered carboplatin (AUC 5–6) can be given.

In patients who have a hypersensitivity to paclitaxel or carboplatin, an alternative active drug can be substituted (e.g. docetaxel or nanoparticle paclitaxel). In the case of carboplatin hypersensitivity, desensitization could be attempted or alternatively cisplatin (50–75 mg/m^2) can be used.

The treatment of all patients with advanced stage disease is approached in a similar manner, with dose modifications based on the toxicity of therapy. Care should be taken when considering combination chemotherapy in patients with a very poor performance status or with compromised renal function.

7. Secondary surgery

7.1. Second-look laparotomy

A second-look laparotomy (or laparoscopy) has been performed in the past in patients who have no clinical evidence of disease after completion of first-line chemotherapy to determine response to treatment. However, although of prognostic value, it has not been shown to influence survival, and is no longer recommended as part of the standard of care [61]. **Level of Evidence C**

7.2. Secondary cytoreduction

Secondary cytoreduction may be defined as an attempt at cytoreductive surgery at some stage following completion of first-line chemotherapy. Retrospective studies suggest that patients benefit if all macroscopic disease can be removed, which usually means patients with a solitary recurrence. Patients with a disease-free interval longer than 12–24 months and those with 1–2 sites of disease only appear to derive most benefit [62,63]. **Level of Evidence C**

8. Follow-up for malignant epithelial tumors

There is no evidence to show that intensive clinical monitoring during follow-up after completion of primary surgery and chemotherapy with early initiation of chemotherapy in asymptomatic women with recurrent disease improves overall survival or quality of life. In asymptomatic patients with CA125 progression and small volume disease or no radiological evidence of recurrence, it is appropriate to delay starting chemotherapy. However, there may be a subset of patients who are suitable for secondary debulking surgery at the time of recurrence.

The objectives of follow-up include:

- Assessment of response to the treatment.
- Early recognition and prompt management of treatment-related complications, including provision of psychological support.
- Early detection of symptoms or signs of recurrent disease.
- Collection of data regarding the efficacy of any treatment and the complications associated with those treatments in patients treated in clinical trials.
- Promotion of healthy behavior, including screening for breast cancer in patients with early stage disease, and screening for cervical cancer in patients having conservative surgery.

There are no evidence-based guidelines regarding the appropriate follow-up schedule. In general, during the first year following treatment, patients are seen every 3 months with a gradual increase in intervals to every 4–6 months after 2 years and then annually after the fifth year. At each follow-up, the patient should have her history retaken, including any change in family history of cancers as well as attention to any symptoms that could suggest recurrence; complete physical examination (including breast, pelvic, and rectal examination) should be performed. The CA125 has traditionally been checked at regular intervals, but there has been debate regarding the clinical benefit of using CA125 progression alone as a trigger for initiating second-line chemotherapy. A large EORTC study showed that treating asymptomatic patients with recurrent ovarian cancer with chemotherapy on the basis of CA125 progression alone did not improve survival or quality of life [64]. The timing of treatment should be based on symptoms as well as clinical and radiological findings. Imaging tests such as ultrasonography of the pelvis, CT, MRI, and/or positron emission tomography (PET) scans should only be performed when the clinical findings or the tumor markers suggest possible recurrence

All patients with an intact cervix should undergo a regular Pap test and all patients above the age of 40 years should undergo routine mammography, as should younger patients with a family history of breast cancer.

9. Chemotherapy for recurrent epithelial malignancies

The majority of patients who present with advanced epithelial cancers of the ovary/fallopian tube/peritoneum will relapse with a median time to recurrence of 16 months. Patients with recurrent ovarian cancer constitute a heterogeneous group with a very variable prognosis, as well as a variable response to further treatment. The most widely used clinical surrogate for predicting response to subsequent chemotherapy and prognosis has been

the progression-free interval or the "platinum-free interval," which is defined as the time from cessation of primary platinum-based chemotherapy to disease recurrence or progression [65,66]. This has been useful to define specific patient populations, but it has a number of limitations and depends on how patients are followed. In particular, it depends on how recurrence is detected and defined. Patients with a treatment-free interval of less than 6 months are classified as platinum resistant and generally treated with nonplatinum-based chemotherapy, while those with a treatment-free interval of more than 6 months are considered to be platinum sensitive and commonly treated with platinum-based chemotherapy. Patients who progress while on treatment or within 4 weeks of stopping chemotherapy are classified as platinum refractory [65,66].

There have been modifications to these definitions, and time to progression or recurrence rather than treatment-free interval or platinum-free interval have been used to define specific patient populations. There has been significant change in practice over the last 20 years and patients have been routinely followed with regular CA125 testing after completion of chemotherapy. For example, the "platinum-resistant" subgroup may include asymptomatic patients with CA125 progression alone at 3 months post chemotherapy or radiological evidence of recurrence as well as those who are symptomatic with clinical recurrence. The 4th Ovarian Cancer Consensus Conference reached agreement that distinct patient populations should be based on the interval from last platinum therapy and the time to progression. The progression-free interval is defined from the last date of platinum dose until progressive disease is documented [65,66].

For patients whose disease is considered platinum sensitive, the ICON 4 study showed advantage in terms of overall survival and progression-free survival for a combination of carboplatin and paclitaxel versus single-agent carboplatin [67]. **Level of Evidence A**

For patients with neurotoxicity, gemcitabine [68] or liposomal doxorubicin [69] may be substituted for the paclitaxel. **Level of Evidence A**

There is evidence that the addition of bevacizumab to the regimen of carboplatin and gemcitabine improves progression-free survival over the use of the carboplatin and gemcitabine in platinum-sensitive disease [70].

For patients with platinum-resistant disease, enrollment on available clinical trials or treatment with nonplatinum chemotherapy should be considered. There are a number of chemotherapy options including liposomal doxorubicin [71], topotecan [71], etoposide [72,73], and gemcitabine [74,75]. The reported response rates are low and in the order of 10%, with a median time to progression of 3–4 months and a median survival of 9–12 months. The impact of chemotherapy on quality of life and symptom control in patients with platinum-resistant or refractory disease is unclear and currently being investigated.

The optimal management of a patient with platinum-resistant or refractory disease is complex and requires a careful assessment of the patient's performance status, symptoms, and extent of disease. Attention to symptom control and good palliative care is an essential component of management.

There appears to be no benefit to initiating chemotherapy in an asymptomatic patient with recurrent disease based on rising CA125 titers alone in the absence of clinical symptoms or radiological evidence of recurrence. The optimal timing of chemotherapy in these patients is controversial. In asymptomatic patients with small volume disease and no radiological evidence of recurrence, close observation is an option, as well as entry into a relevant clinical trial.

A Cochrane database systematic review of tamoxifen in unselected women with recurrent ovarian cancer reported a 10% objective response and a 32% disease stabilization rate [76]. The patients treated were very heterogeneous and included asymptomatic patients with rising CA125 titers, as well as symptomatic patients with chemotherapy-resistant disease who had been heavily pretreated and had a poor performance status. More recently, GOG 198 compared tamoxifen and thalidomide in women with recurrent FIGO Stage III or IV epithelial ovarian, tubal, or primary peritoneal cancer who had completed first-line chemotherapy, and who subsequently had GCIG-documented CA125 progression. The study reported that women who received thalidomide had a 31% increased risk of disease progression (hazard ratio, 1.31), compared with those who were given tamoxifen [77]. The median progression-free survival was 3.2 months in the thalidomide group versus 4.5 months in the tamoxifen group. This suggests that tamoxifen may have a role in selected patients with a rising CA125 titer, and the relationship between estrogen receptor positivity and benefit of tamoxifen in this patient population is being evaluated in current studies.

With very few exceptions, recurrent disease is not curable and the aim of treatment is to maintain quality of life and palliate symptoms [78]. There are many potential treatment options, including chemotherapy, radiation therapy, or surgery in selected patients [63]. There is a subset of patients who may benefit from secondary surgical debulking, but they constitute a minority. The role of secondary surgical debulking is currently being addressed in prospective randomized clinical trials. **Level of Evidence C**

10. Management of epithelial tumors of low malignant potential (borderline tumors)

Compared with invasive epithelial cancers, borderline tumors tend to affect a younger population and constitute 15% of all epithelial tumors of the ovary [79]. Nearly 75% of these are Stage I at the time of diagnosis. The following can be said for these tumors [80]:

- The diagnosis must be based on the pathology of the primary tumor.
- Extensive sectioning of the tumor is necessary to rule out invasive cancer.
- The prognosis of these tumors is extremely good, with a 10-year survival of about 95%.
- Invasive cancers that arise in borderline tumors are often indolent and do not respond well to platinum-based chemotherapy.
- Spontaneous regression of peritoneal implants has been observed.
- Early stage, serous histology, and younger age at diagnosis are associated with a more favorable prognosis.
- Although gross residual disease after primary laparotomy is associated with poorer prognosis, mortality from the disease remains low.
- Those patients who have invasive implants in the omentum or other distant sites are more likely to recur earlier, and should be treated as low-grade serous carcinomas with cytotoxic chemotherapy.

The causes of death include complications of disease (e.g. small bowel obstruction) or complications of therapy, and only rarely malignant transformation. The mainstay of treatment is primary surgical staging and cytoreduction. For patients with Stage I disease who still desire to have children, conservative surgery with unilateral salpingo-oophorectomy can be considered after intraoperative inspection of the contralateral ovary to exclude involvement [81]. For patients with only 1 ovary, or bilateral cystic ovaries, a partial oophorectomy or cystectomy can be considered for fertility preservation. For all other patients, total hysterectomy and bilateral salpingo-oophorectomy are recommended, with maximal cytoreduction if the disease is metastatic.

Optimally cytoreduced patients in all stages of disease should receive only expectant treatment without adjuvant chemotherapy, provided the metastases are also borderline tumors histologically. A small percentage of patients may potentially benefit from chemotherapy and these include patients with invasive implants on the peritoneal surfaces or omentum, but the response to chemotherapy is unpredictable and generally much lower than that observed in high-grade serous cancers. Uncommonly, some patients recur early and probably had undetected invasive cancers at presentation. This group may also potentially benefit from chemotherapy [82].

In patients with late recurrence of the disease, secondary cytoreduction should be considered, and chemotherapy only given if invasive disease is present histologically.

Follow-up of patients with no evidence of disease is the same as for those with malignant epithelial carcinomas, but at less frequent intervals. If the contralateral ovary has been retained, it should be followed by transvaginal ultrasonography, at least on an annual basis [1,80,83]. **Level of Evidence C**

11. Management of granulosa cell tumors

Granulosa cell tumors account for about 70% of sex-cord stromal tumors, and 3%–5% of all ovarian neoplasms. There are 2 types of granulosa cell tumors: the juvenile and the adult types. Because of the high estrogen production, the juvenile type typically presents with sexual precocity, while the adult type may present with postmenopausal bleeding. The majority of patients are diagnosed with Stage I tumors. The peak incidence is in the first postmenopausal decade.

Granulosa cell tumors are generally indolent (i.e. with a tendency to late recurrence). Stage at diagnosis is the most important prognostic indicator. Other prognostic factors include age at diagnosis, tumor size, and histological features. If metastatic, adequate cytoreduction is the mainstay of treatment. If the patient is young and the disease is confined to 1 ovary, conservative surgery should be performed [84].

The infrequency of the disease, and its protracted course, has resulted in a lack of prospective studies. There is no evidence that adjuvant chemotherapy or radiotherapy improves the results of surgery alone for Stage I disease. The value of postoperative adjuvant chemotherapy for higher-risk Stage I disease (tumor size >10 cm, capsule rupture, high mitotic count) is uncertain, and has not been tested in randomized studies. Platinum-based chemotherapy is used currently for patients with advanced or recurrent disease, with an overall response rate of 63%–80% [85–87].

Follow-up is clinical. Serum inhibin is a useful tumor marker. **Level of Evidence C**

12. Management of germ cell malignancies

This group of ovarian tumors consists of a variety of histologically different subtypes that are all derived from the primitive germ cells of the embryonic gonad. Malignant germ cell tumors represent a relatively small proportion of all ovarian tumors. Prior to advances in chemotherapy, the prognosis for these aggressive tumors was poor. The use of platinum-based chemotherapeutic regimes has made germ cell malignancies among the most highly curable cancers.

12.1. Presentation

The highest incidence of malignant germ cell tumors occurs in the second and third decades of life. They are frequently diagnosed by finding a palpable abdominal mass in a young woman who complains of abdominal pain. The following are the symptoms of germ cell tumors in order of frequency [1]:

- Acute abdominal pain.
- Chronic abdominal pain.
- Asymptomatic abdominal mass.
- Abnormal vaginal bleeding.
- Abdominal distention.

12.2. Histological classification

The classification of germ cell tumors of the ovary is important to determine prognosis and for treatment with chemotherapy. Germ cell tumors are classified as follows [2]:

- Dysgerminoma.
- Embryonal carcinoma.
- Polyembryoma.
- Teratoma (immature; mature; mature with carcinoma [squamous cell, carcinoid, neuroectodermal, malignant struma, etc]).
- Extraembryonal differentiation (choriocarcinoma; endodermal sinus tumor [yolk sac tumor]).

12.3. Diagnosis, staging, and surgical management

Ovarian germ cell tumors are staged similarly to epithelial carcinomas, although the staging system used for male germ cell tumors is probably more useful. The approach to treatment is also based on the principles of management of metastatic germ cell tumors of the testis (i.e. low, intermediate, and poor risk). Dysgerminoma is the equivalent of seminoma in testicular cancer [88]. It is exquisitely sensitive to platinum-based chemotherapy and is also radiosensitive. The cure rate is high irrespective of the stage. The other histological subtypes are equivalent to nonseminomatous testicular cancer. The aggressiveness of the disease is dependent on the type, the most aggressive being endodermal sinus and choriocarcinoma, but with combination chemotherapy, they are also highly curable [89–93].

As chemotherapy can cure the majority of patients even with advanced disease, conservative surgery is standard in all stages of all germ cell tumors. Conservative surgery means laparotomy with careful examination and biopsy of all suspicious areas, with limited cytoreduction, thereby avoiding major morbidity. The uterus and the contralateral ovary should be left intact. Wedge biopsy of a normal ovary is not recommended as it defeats the purpose of conservative therapy by potentially causing infertility. Patients who receive conservative surgery with the preservation of 1 ovary retain acceptable fertility rates despite adjuvant treatment with chemotherapy. There has been no report of higher adverse obstetric outcome or long-term unfavorable sequelae in the offspring [94–97].

Secondary surgery is of no proven benefit, except in those patients whose tumor was not completely resected at the initial operation and who had teratomatous elements in their primary tumor. Surgical resection of residual masses may be beneficial in such patients, as there may be mature teratomatous nodules that can continue to increase in size [98].

12.4. Postoperative management and follow-up of dysgerminoma

Patients with Stage IA disease may be observed after surgery. A small proportion of patients may recur, but they can be treated successfully at the time of recurrence with a high rate of cure. Patients with disease beyond the ovary should receive adjuvant chemotherapy. Although radiation therapy is effective, ovarian failure makes it undesirable for patients with an intact ovary. The long-term adverse effects are greater than with chemotherapy and it is now rarely used.

Table 6
Follow-up regime for Stage I germ cell malignancies.[a]

Regimen	Description
Surveillance	Baseline CT chest, abdomen, and pelvis, if not performed preoperatively
	Repeat CT or MRI, abdomen and pelvis at 3 months after surgery
	Repeat CT or MRI abdomen plus pelvis at 12 months
	Pelvic ultrasound alternate visits (not when having CT scan) for 2 years if non-dysgerminoma and for 3 years if dysgerminoma
	Chest X-ray at alternate visits
Clinical examination	
1 year	Monthly
2nd year	2 monthly
3rd year	3 monthly
4th year	4 monthly
Years 5–10	6 monthly
Tumor marker follow-up	Samples: serum AFP and hCG, LDH and CA125 (regardless of initial value)
0–6 months	2 weekly
7–12 months	4 weekly
12–24 months	8 weekly
24–36 months	12 weekly
36–48 months	16 weekly
48+ months	6 monthly until year 10

AFP, alpha-fetoprotein; hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase.
[a] Adapted from Patterson et al. [99].

A follow-up regime for patients with Stage 1A dysgerminoma is outlined in Table 6. This is based on the follow-up of seminomas in males, and the follow-up by Patterson et al. [99] and Dark et al. [100].

12.4.1. Chemotherapy for dysgerminoma

Dysgerminoma is extremely sensitive to chemotherapy, and treatment with chemotherapy cures the majority of patients even with advanced disease [101]. The recommended chemotherapy regime is as follows:

- Etoposide (E) 100 mg/m^2 IV per day for 5 days every 3 weeks for 3 cycles.
- Cisplatin (P) 20 mg/m^2 IV per day for 5 days every 3 weeks for 3 cycles.
- Bleomycin (B) 30 000 IU IV/IM on days 1/8/15 for 12 weeks (Optional) (Note: bleomycin is now dosed in International Units).

For EP or BEP, various schedules of bleomycin are used.

When there is bulky residual disease, it is common to give 3–4 courses of combination BEP chemotherapy [101]. **Level of Evidence B**

The optimal follow-up schedule has not been clinically investigated in ovarian germ cancers and the frequency of visits and investigations are controversial. Patients who have Stage I tumors and are offered surveillance need to be seen regularly and one option is to utilize the follow-up regime presented above [100]. Patients who have had chemotherapy have a lower risk of recurrence and the frequency of CT scans may be reduced, which is similar to the approach for testicular germ cell tumors [99]. Each follow-up visit should involve a medical history taken, physical examination, and tumor marker determination. Although tumor markers are important, radiological imaging is also pertinent, especially for patients whose tumor markers were not raised at diagnosis. CT or MRI scans should be performed as clinically indicated [100].

Patients who have not received chemotherapy should be followed more closely. Ninety percent of relapses in these patients occur within the first 2 years. At relapse, these patients can be successfully treated [100]. **Level of Evidence D**

12.5. Postoperative management and follow-up of non-dysgerminoma germ cell malignancies

These tumors are also highly curable with chemotherapy, even with advanced disease. Patients with Stage IA grade 1–2 immature teratoma have a very good prognosis and should only be observed after primary conservative surgery. It is controversial whether adjuvant chemotherapy adds any survival benefit in this subgroup of patients. All other patients with non-dysgerminomas, and higher-stage and higher-grade immature teratomas should receive postoperative adjuvant chemotherapy [102].

The recommended chemotherapy regime is etoposide 100 mg/m^2 per day for 5 days with cisplatin 20 mg/m^2 per day for 5 days, and bleomycin at 30 000 IU IM/IV on days 1, 8, and 15 for a total of 12 weeks of treatment. For patients with good prognosis disease, 3 cycles of BEP are recommended, while patients with intermediate/poor risk disease should receive 4 cycles of BEP.

Patients who relapse after BEP may still attain a durable remission with salvage chemotherapy regimens such as paclitaxel–ifosfamide–cisplatin (TIP) [91]. High-dose chemotherapy and autologous marrow rescue may be considered in selected patients.

After chemotherapy, patients with metastatic immature teratomas can sometimes have residual masses, which are composed entirely of mature elements. These masses can grow, and should be resected after the completion of chemotherapy. **Level of Evidence B**

All patients should have lactate dehydrogenase (LDH), alpha-fetoprotein (AFP), and human gonadotropin (beta hCG) blood tests performed to monitor response to treatment. All patients treated with chemotherapy should be followed-up with medical history, physical examination, and appropriate tumor markers in the same

way as dysgerminomas. CT or MRI scans should be performed as clinically indicated.

Relapses in patients usually occur within the first 2 years after diagnosis [91,102]. **Level of Evidence D**

13. Sarcoma of the ovary

Ovarian sarcomas are rare and occur primarily in postmenopausal patients [102,103]. Nevertheless, accurate diagnosis and differentiation from other types of primary ovarian cancer are important, as the prognosis is generally poor.

There are two types of sarcoma. Malignant mixed mullerian tumors (MMMTs), the more common of the two, are biphasic tumors composed of both carcinomatous and sarcomatous elements [103,104]. Most authors now agree that most MMMTs are monoclonal in origin and should be thought of and managed as a high-grade epithelial cancer. The sarcomatous component is derived from the carcinoma or from a stem cell that undergoes divergent differentiation. Thus, ovarian carcinosarcomas are best regarded as metaplastic carcinomas.

Pure sarcomas are very rare and should be treated according to the specific histological subtype. These rare sarcomas include fibrosarcomas, leiomyosarcomas, neurofibrosarcomas, rhabdomyosarcomas, chondrosarcomas, angiosarcomas, and liposarcomas. Their management is not discussed here.

Patients with early stage MMMTs have a better outcome than those with advanced stage disease, but the overall prognosis is poor. They should be managed similarly to high-grade pelvic serous cancers. Their rarity prohibits any prospective randomized trials.

The principles of surgical management of ovarian MMMTS are the same as for pelvic serous cancers [102]. Following surgery, patients should receive platinum-based chemotherapy [100–102]. The follow-up schedule is as recommended for epithelial malignancies. **Level of Evidence C**

Conflict of interest

The authors have no conflicts of interest to declare.

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