

# NON-EPITHELIAL OVARIAN CANCERS IN ADOLESCENTS AND YOUNG ADULTS

POCKET GUIDELINES

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## **POCKET GUIDELINES**

**Based on**

**ESGO-SIOPe guidelines  
for the management of non-epithelial  
ovarian cancers  
in adolescents and young adults**

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The European Society of Gynaecological Oncology (ESGO) and the European Society for Paediatric Oncology (SIOPe) jointly developed clinically relevant and evidence-based guidelines for adolescents and young adults (AYAs) with non-epithelial ovarian cancers, including malignant ovarian germ cell tumour (MOGCT), sex cord-stromal tumour (SCST), or small cell carcinoma of the ovary of hypercalcemic type (SCCOHT).

These guidelines cover diagnosis, pathology, staging, work-up, management and follow-up for each tumour type. Management covers early and advanced stages and refractory/recurrent disease. General principles of management and pathological evaluation are also defined. Even if arbitrary, the definition of AYAs in these guidelines includes women from age 15 to 25.

#### A five-step development process was followed:



The objectives of these ESGO/SIOPe guidelines are to improve and to homogenise the management of AYAs within a multidisciplinary setting. They are intended for use by paediatric oncologists, paediatric surgeons, reproductive endocrinologists, psycho-oncologists, psychologists, gynaecologic oncologists, general gynaecologists, surgeons, radiation oncologists, pathologists, medical and clinical oncologists, radiologists, general practitioners, palliative care teams, and allied health professionals.

These guidelines do not include any economic analysis of the strategies. Any clinician seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment.

To ensure that the statements were evidence-based, the current literature was reviewed and critically appraised. A comprehensive literature review of the studies published between January 1998 and May 2018 was carried out.

The guidelines were adopted if they were supported by sufficient high-level scientific evidence and/or when a large consensus among experts was obtained. The reliability and quality of the evidence given throughout this document has been graded following the Scottish intercollegiate guidelines network grading system:

- A** At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or  
A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
- B** A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or  
Extrapolated evidence from studies rated as 1++ or 1+
- C** A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or  
Extrapolated evidence from studies rated as 2++
- D** Evidence level 3 or 4; or  
Extrapolated evidence from studies rated as 2+
- ✓** Recommended best practice based on the clinical experience of the guideline development group

**1++** high quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias;

**1+** well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias;

**2++** high quality systematic reviews of case control or cohort studies or high quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal;

**2+** well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal;

**3** non-analytic studies, e.g., case reports, case series;

**4** expert opinion

ESGO would like to thank the international development group for their constant availability, work, and for making possible the development of these guidelines for adolescents and young adults with non-epithelial ovarian cancers (see below).

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## GENERAL PRINCIPLES OF MANAGEMENT

- ✓ Due to the rarity of the various non-epithelial ovarian tumours covered in these guidelines, the patients should be referred to a specialized centre, with a multi-disciplinary setting, including adult and paediatric expertises.
- ✓ Therapy should be adequately monitored by trained oncologists.
- ✓ Patients should be staged according to the FIGO 2014 staging system.
- D In patients with suspected ovarian tumours, the preoperative diagnostic work-up should include, in addition to abdominal and pelvic ultrasound (US), an abdomino-pelvic magnetic resonance imaging (MRI) with thoracic computed tomography (CT) scan, and the serum tumour markers alpha-fetoprotein (AFP), -human chorionic gonadotropin (-HCG), inhibin B, anti-Mullerian hormone (AMH) and lactate dehydrogenase (LDH).
- ✓ A serum calcium level should also be measured.
- ✓ In cases where immediate surgery has been performed before these investigations, the investigations should be performed as soon as possible after surgery. Abdominal and pelvic MRI is preferred to CT scan whenever possible to reduce radiation exposure.
- D Preoperative pelvic MRI is helpful to assess potential bilateral ovarian involvement (for example in dysgerminoma and teratoma) and to better characterize the mass to guide the surgical strategy (choice of approach).
- ✓ There is no indication for positron emission tomography-computed tomography (PET-CT) because of low negative predictive value.
- ✓ In the case of a cystic component within the suspicious tumour mass, diagnostic puncture is to be avoided.
- ✓ The surgical approach should be carefully selected on the basis of initial imaging to avoid intraoperative rupture of the tumour. Oophorectomy should be preferred to cystectomy/tumorectomy. Biopsies of the tumour are contraindicated, except in patients with extraovarian spread.
- ✓ Median laparotomy is the preferred option in suspected malignant tumours. A minimally invasive approach is an acceptable option only if:
  - The surgeon is trained in laparoscopic oncologic surgery
  - The removal of the tumour can be performed without rupture
  - No morcellation of the specimen occurs during the removal
  - Full exploration of the peritoneal cavity can be done

- ✓ Before manipulating the tumour, peritoneal fluid should be sent for cytological examination. If there is no fluid in the abdominal cavity, peritoneal washing should be performed.
- ✓ Staging of tumours also includes examination of the peritoneal surfaces, biopsy of diaphragmatic peritoneum, paracolic gutters, pelvic peritoneum, examination and palpation of pelvic and paraaortic lymph nodes, excision of enlarged lymph nodes, inspection, palpation and large biopsy of the omentum if normal, removal of adherent or abnormal omentum and inspection of the contralateral ovary with biopsy of abnormal appearing areas.
- D Fertility sparing surgery (FSS) (saving the uterus and at least a part of one adnexa) is the first surgical option for consideration when awaiting the definitive pathological results.
- ✓ In the case of macroscopic extraovarian disease, a precise description of the spread (location and size) should be clearly documented and at least, biopsies of the extraovarian disease should be performed.
- ✓ Supportive care should take into consideration acute and delayed side effects of chemotherapy drugs. The use of steroids should be avoided, if possible.
- ✓ Oncofertility counseling has to be offered to all AYA patients before therapy.
- D Psycho-oncological support tailored to the specific needs should be offered to all AYA patients and their relatives at each step of the initial treatment and follow-up.
- ✓ If tumour markers are elevated at diagnosis, they should be measured after surgery and before the start of surveillance or any adjuvant treatment. In the case of chemotherapy, tumour markers should be measured before each cycle of treatment. The decrease of tumour markers should be in line with their half-life.
- ✓ AYAs with MOGCT, SCST or SCCOHT should be treated, whenever feasible, within clinical trials. The aims of clinical trials in "high-risk" patients should be to improve efficacy while maintaining the degree of safety already accepted. The aims of clinical trials in "low- to medium-risk" patients should be to maintain the efficacy while decreasing the toxicity. In cases where no standard treatment options are available, participation in clinical trials evaluating new therapeutic approaches should be considered. When no clinical trials are open, clinical data should at least be reported to clinical registries.

## GENERAL PRINCIPLES OF PATHOLOGICAL EVALUATION

- ✓ Tumours should be classified according to the 2014 World Health Organization classification.
- D Confirmation of diagnosis by an experienced specialist gynaecological or paediatric pathologist is strongly advised given the rarity of these neoplasms and the significant risk of misdiagnosis. Exchange of specimens between the experts is strongly encouraged.
- D Immunohistochemistry and molecular tests are often necessary for diagnosis and these are not available in many pathology laboratories.
- D With certain tumour types, a familial tumour syndrome should be considered and genetic counseling including psychological consultation service and germline mutation analysis are advised. In particular, these should be undertaken in case of bilateral GCT, unilateral GCT with streak gonad or pubertal retardation, Sertoli-Leydig cell tumour (SLCT), and SCCOHT.



## MALIGNANT OVARIAN GERM CELL TUMOURS

### Diagnosis and pathology/Staging and work-up

- ✓ The clinical staging follows the recommendations provided in the general principles of management within this guideline. MOGCT comprise dysgerminoma, yolk sac tumour (YST), immature teratoma, embryonal carcinoma (extremely rare within the ovary) and non-gestational choriocarcinoma.
- ✓ The presence or absence of lymphovascular space involvement should be reported.
- D These neoplasms may be difficult to diagnose and immunohistochemical markers can be of value:
  - SALL4 is typically positive in all MOGCT, including the immature neuroepithelium in immature teratomas
  - OCT3/4, PLAP, D2-40, NANOG and CD117 are commonly positive in dysgerminoma
  - PLAP can be positive in YST
  - AFP and glypican-3 are commonly positive in YST
  - OCT3/4, CD30, NANOG and SOX10 are usually positive in embryonal carcinoma
  - Non-gestational choriocarcinomas are typically immunoreactive with -HCG and inhibin.
- ✓ In general, because of overlap between the various immunohistochemical markers and unexpected aberrant staining patterns, it is best to use panels of markers rather than rely on individual markers.
- D There are a number of incompletely characterised chromosomal and genetic abnormalities in MOGCT, the clinical significance of which has not yet determined. The most frequent chromosomal aberration in MOGCTs is isochromosome 12, a gain of the p arm of chromosome 12, abbreviated i(12p). As MOGCTs may arise in the context of gonadal dysgenesis (e.g., Swyer syndrome), genetic evaluation for sex chromosomal aberrations should be recommended.

## Management of early stage

- D** In case of the presence of a solid or partially solid ovarian mass on US, an additional MRI should be performed.
- C** If a solid component is present on MRI, surgery is required which is the initial treatment of early stage MOGCT.
- ✓ The choice of the approach should be carefully evaluated to avoid any rupture during intervention.
- C** In the case of bilateral tumours, bilateral salpingo-oophorectomy (BSO) is strongly discouraged and the preservation of at least a part of one ovary should be promoted.
- C** In the case of a solid unilateral tumour, total en-bloc oophorectomy is the treatment of choice. In cystic tumours, cystectomy should be avoided.
- C** FSS is now considered as the standard surgical treatment for young patients with MOGCT.
- C** With a contralateral macroscopically normal ovary and negative imaging, ovarian biopsy is not necessary.
- C** In the case of macroscopic bilateral ovarian disease (mainly dysgerminoma), preservation of at least a healthy part of one ovary (unilateral salpingo-oophorectomy and contralateral partial oophorectomy) and the uterus should be encouraged unless genetic analysis reveals dysgenetic gonads. In the latter case, removal of the remaining ovary is encouraged.
- ✓ In the case of bilateral tumours, genetic analysis for sex chromosomal aberrations should be performed in combination with genetic counseling and psychological support. Due to the risk of gonadoblastoma and dysgerminoma, in case of dysgenetic gonad, BSO could be performed.
- ✓ If an initial cystectomy/tumorectomy has been performed with no indication for adjuvant treatment on the basis of the final pathology report and serum tumour markers have normalised, additional surgery to remove the residual ovary is required to reduce the risk of recurrence. When adjuvant medical treatment is required, such additional surgery could be avoided.
- ✓ For dysgerminoma and teratoma, there is a risk of bilateral involvement and postoperative US monitoring of the left ovary is recommended.

- C** If a tumour is considered likely to be malignant (secreting, imaging of tissular or mixed, important extraovarian spread), a laparotomic approach is appropriate for removal of the tumour for staging and to minimize the risk of intra-peritoneal spillage of tumour content.
- ✓ For masses where the risk of malignancy is low or uncertain, a minimally invasive approach (laparoscopy or robotic) could be discussed.
- ✓ If the diagnosis is made postoperatively, reoperation for comprehensive surgical staging with lymphadenectomy is to be avoided.
- C** Nodal removal should be carried out only where there is evidence of nodal abnormalities during surgical exploration and/or MRI or CT scan (lymphadenopathy).
- C** In completely resected stage IA neoplasms with normalizing or negative post-operative tumour markers, active surveillance is the preferred approach.
- ✓ In stage IA YST and non-compliant patients, adjuvant chemotherapy (maximum 2 cycles) is an option.
- ✓ The management of stage IB neoplasms (rare cases) is complex and should be discussed according to the histotype of the tumours in both ovaries.
- ✓ In stage IC1 MOGCT, the situation is equivocal. Both options (chemotherapy (maximum 2 cycles) or active surveillance) could be considered.
- C** Patient with stage IC2 and IC3 MOGCT of all types should receive adjuvant chemotherapy (maximum 3 cycles).



## Management of advanced stage

- C** FSS should be considered even in the case of advanced disease because of the high chemosensitivity of MOGCT.
- ✓ Because of the high chemosensitivity of MOGCT, extensive cytoreductive surgery should be avoided during initial management.
- ✓ Surgical resection is only required in rare cases of residual disease after chemotherapy (in peritoneum, remaining ovary, and/or lymph nodes).
- ✓ A careful close surveillance could be discussed for patients with dysgerminoma with minimal residual disease on imaging following treatment because this residual disease is usually non-viable.
- C** Standard chemotherapy for stage III-IV disease is as used in adult protocols, bleomycin, etoposide and platinum (BEP) for 3 to 4 cycles with bleomycin omitted after cycle 3 (maximum total cumulative dose 270 IU) to avoid lung toxicity.
- C** In adolescent patients, other options are cisplatin, etoposide and ifosfamide (PEI), cisplatin, etoposide and dose-reduced bleomycin (PEb) or carboplatin, etoposide and bleomycin (JEB) as used in paediatric protocols, for 3-4 cycles.
- ✓ Patients with raised tumour markers at presentation who do not achieve negative markers after cycle 4 are considered failure.
- ✓ Patients with raised tumour markers at presentation in whom tumour markers are not falling according to their half-life after the second cycle of treatment should be considered high-risk, and intensification of therapy should be discussed.
- ✓ In cases of immature teratoma with extra ovarian disease which comprises gliomatosis peritonei (morphologically benign glial tissue with no immature elements), complete surgical resection of the peritoneal disease is not required (if the surgery is too invasive), but large and multiple biopsies should be then performed to ensure that all the tissues are mature and glial.

## Management of refractory/recurrent disease

- ✓ The need for and the type of treatment including chemotherapy and irradiation has to be discussed in a multidisciplinary team decision-making setting.
- ✓ In cases of immature teratoma or mixed tumours with a component of immature teratoma and subsequent recurrence and normal serum markers following chemotherapy, a growing teratoma syndrome should be suspected (presence of exclusively mature elements in extraovarian sites (peritoneal and/or nodal) following chemotherapy). In this situation, the treatment is exclusively surgical resection provided that on histological examination all the tissues (all of which should be examined in total) are mature. The surgical resection should be conservative preserving the uterus and a part of one ovary if technically feasible.
- ✓ In the other situations, a biopsy is essential to have histological confirmation of recurrence before starting an additional treatment.
- ✓ All specimens should be carefully histologically examined to confirm or exclude only pure mature tissues.
- D** There is no defined treatment strategy for patients who relapsed after completion of chemotherapy. Treatment options to be considered can include platinum-based combinations and should take into account the previous lines of therapy and the delay between initial tumour and relapse. In pure dysgerminoma, radiotherapy could also be discussed.
- D** Intensified chemotherapy with stem cell support can be considered.
- D** The role of salvage surgery in recurrent disease is not well defined.



## Follow-up



The surveillance program in the management of MOGCT is based on clinical examination, tumour markers and imaging as follows:

	Clinical examination*	Abdominal/pelvic US	Tumour markers	Chest X-ray / low dose CT	MRI/CT abdomen/pelvic**	PROs#
First 6 mos						
• surgery only	Monthly##	Monthly##	Monthly##	Every 6 mos	Every 6 mos	✓ ###
• other treatments	Every 2 mos	Every 2 mos	Every 2 mos	Every 6 mos	Every 6 mos	✓ ###
6th–12th mos	Every 2 mos	Every 2 mos	Every 2 mos	Every 6 mos	Every 6 mos	-
2nd year	Every 3 mos	Every 3 mos	Every 3 mos	Every 6 mos	Every 6 mos	✓
3rd year	3–6 mos	3–6 mos	3–6 mos	-	-	-
4th–5th year	Every 6 mos	Every 6 mos	-	-	-	✓
6th–10th year	Yearly	Yearly	-	-	-	-

\* monitoring of potential long-term toxicities (organ, endocrine, hearing function) should be performed;

\*\* to avoid radiation exposure, MRI should be preferred whenever possible;

# age-appropriate self-report questionnaires should be used to screen for psychological late effects;

## until tumour markers are normalised, then every 2 months;

### at the beginning of treatment;

PROs Patient-reported outcomes.

## SEX CORD-STROMAL TUMOURS

### Diagnosis and pathology/Staging and work-up



serum AFP, -HCG, CA-125, inhibin, AMH, calcium, and LDH are required. Estrogen, dehydroepiandrosterone, testosterone, luteinizing hormone and follicle stimulating hormone are also required with signs of hormonal production.



The clinical staging follows the recommendations provided in the general principles of management within this guideline.



A variety of immunohistochemical markers are of value in the diagnosis of ovarian SCST: these include inhibin (the most specific), calretinin, CD56, melan A, CD99, steroidogenic factor-1 (SF-1), FOXL2, and WT1. As all these markers suffer with problems regarding sensitivity and specificity, they should be used in combination rather than relying on a single marker. These markers, while of value in diagnosing a SCST, are of limited value in distinguishing between the various neoplasms in this group.



Pathologic evaluation of SLCT should include a description of the grade (well, moderate, poorly differentiated) and the presence of specific histologic features such as retiform pattern or presence of heterologous elements (most commonly mucinous glandular, skeletal muscle or cartilage). In all SLCT or gynandroblastomas, patients should be screened for other disorders which may be associated with DICER1 syndrome, in particular thyroid disease and a variety of uncommon neoplasms. A family history should be taken and genetic analysis of DICER1 should be initiated along with genetic counseling.



Given the risk of endometrial associated proliferative lesions (hyperplasia and/or endometrioid carcinoma) due to the hormonal production, endometrial sampling is conventionally recommended in adult patients with granulosa cell tumour.



There is no data to support the need for endometrial sampling in AYAs.



However, endometrial imaging should be performed to assess the thickness of the endometrium.



In the absence of data, the role of PET-CT cannot be defined.

## Management of early stage

- C** Comprehensive staging includes submission of peritoneal fluid or peritoneal washings, examination of the contralateral ovary, random blind peritoneal sampling and resection of any suspicious lesions, large omental biopsy or infracolicomentectomy. Systematic lymph node dissection is not recommended. Resection of lymph nodes should be performed only in cases of suspicious nodes on imaging or intraoperative examination.
- C** After comprehensive staging, if confirmed as stage IA, most tumours should be managed with surgical resection alone. Exceptions are poorly differentiated SLCT or SLCT with heterologous elements or retiform patterns, where adjuvant treatment could be considered.
- C** Tumours that are staged higher than IA may require chemotherapy.
- ✓ Surgery alone is an option in stage IC1 granulosa cell tumours.
- C** All stages IC2 and IC3 juvenile granulosa cell tumours and all stages IC SLCT should receive adjuvant chemotherapy. Most patients receive 3–4 cycles of cisplatin-based chemotherapy.

## Management of advanced stage

- ✓ The decision on the surgical management is to be taken in a multidisciplinary team decision-making setting.
- D** Chemotherapy is recommended. Most commonly used regimens are BEP and PEI for at least 4 cycles depending on response.
- D** In SCST, if cisplatin is contraindicated, carboplatin/paclitaxel is an option.
- ✓ In case of incomplete initial macroscopic resection for stage III disease and residual disease after chemotherapy, a delayed surgical attempt should be considered after neoadjuvant chemotherapy.

## Management of refractory/recurrent disease

- ✓ The need for and the type of treatment including chemotherapy and irradiation has to be discussed in a multidisciplinary team decision-making setting.
- ✓ Management of recurrent disease is dependent on the site of recurrence, dissemination, tumour-free interval, previous therapy and histological subtype.

- D** Re-surgery aiming for maximum cytoreduction is the best option in the management of recurrent disease.
- D** Additional treatment options to be considered preferentially within clinical trials are hormone therapy and treatment with antiangiogenetic or targeted drugs alone or in combination.

## Follow-up

✓	The follow-up is based on clinical examination, tumour markers, and imaging as follows:			
		Stage IA	Stage IC	Stage II-III
	Clinical Examination*	Every 4 mos (2 yrs) Then yearly**	Every 4 mos (2 yrs) Then every 6 mos (5 yrs) Then yearly**	Every 2–4 mos (2 yrs) Then every 6 mos (5 yrs) Then yearly**
	Blood markers#	Every 4 mos (2 yrs) Then yearly**	Every 4 months (2 yrs) Then every 6 mos (5 yrs) Then yearly**	Every 4 mos (2 yrs) Then every 6 mos (5 yrs) Then yearly**
	Abdominal/pelvic US	Every 4 mos (2 yrs) Then yearly**	Every 4 mos (2 yrs) Then every 6 mos (5 yrs) Then yearly**	If FSS, every 4 mos (2 yrs) Then every 6 mos (5 yrs) Then yearly**
	Abdominal/pelvic MRI	No	Every 6 mos (2yrs)	Every 6 mos (5 yrs)
	PROs##	Yes (at the beginning of treatment, 2 yrs and 5 yrs)	Yes (at the beginning of treatment, 2 yrs and 5 yrs)	Yes (at the beginning of treatment, 2 yrs and 5 yrs)
	* monitoring of potential long-term toxicities (organ, endocrine, hearing function) should be performed; ** minimum 10 years; # if elevated at diagnosis; ## age-appropriate self-report questionnaires should be used to screen for psychological (late) effects; FSS fertility-sparing surgery; PROs Patient-reported outcomes.			

- ✓ Patients with SLCT and a germline *DICER1* mutation should be screened for other associated diseases, including thyroid disease (multinodular goitre, thyroid carcinoma).

## Small Cell Carcinoma of the Ovary of Hypercalcemic Type

### Diagnosis and pathology/Staging and work-up

- ✓ When the diagnosis is suspected before the surgery, preoperative staging includes abdominal/chest CT scan, serum CA-125, calcemia, chromogranin A, and neuron specific enolase (NSE).
- ✓ In the absence of data, the role of preoperative PET-CT cannot be defined.
- ✓ Surgery should be performed by a team trained in nodal and peritoneal debulking surgery. The surgical approach is more extensive compared to other histotypes, similar to epithelial ovarian cancer.
- C Establishing a diagnosis of SCCOHT may be difficult given the wide differential diagnosis, including a variety of small round cells tumours. Immunohistochemical staining for SMARCA4 (BRG1) may be extremely useful since over 95% of these neoplasms exhibit loss of nuclear immunoreactivity with this marker while there is retention of nuclear immunoreactivity in almost all the histological mimics. Dual loss of SMARCA4 (BRG1) and SMARCA2 (BRM) expression may also be useful in diagnosis.
- C Since in a significant proportion of cases a germline SMARCA4 mutation is present, all females with SCCOHT should undergo genetic counseling and SMARCA4 sequencing in germline.
- ✓ The efficacy of regular follow-up visits with abdominal US and MRI for *SMARCA4* mutation carriers is undetermined.
- ✓ Prophylactic oophorectomy should be discussed with healthy *SMARCA4* mutation carriers. However, the optimal age for this oophorectomy is undetermined, because of the lack of penetrance data.

### Management of early stage

- D When the pathologic diagnosis is ensured, surgical treatment includes total abdominal hysterectomy and BSO with peritoneal staging and full pelvic and paraaortic lymphadenectomy for macroscopically stage I patients, because of the poor prognosis, the high risk of extraovarian spread and the loss of function of the remaining ovary after intensive adjuvant treatment.
- ✓ A conservative approach is not recommended.
- D Adjuvant chemotherapy with combinations including platinum (usually, cisplatin and etoposide) is indicated.

- D The inclusion of paclitaxel in platinum combination can be considered.

- D Radiotherapy can be used in a multimodality approach following chemotherapy. However, its role is still not well defined.

- D In patients without evidence of disease after initial chemotherapy, dose-intensive chemotherapy with stem cell support can be used in a multimodality approach for consolidation.

### Management of advanced stage

- D Removal of peritoneal disease (so called debulking surgery) including omentectomy and pelvic and para-aortic lymphadenectomy, if complete removal of the peritoneal disease can be achieved, is recommended (as initial surgery or after 3-6 cycles of chemotherapy).
- D Six cycles of chemotherapy with platinum/etoposide combinations are recommended.
- D In patients in complete remission after initial surgery and chemotherapy, dose-intensive regimen followed by high-dose chemotherapy with stem cell support and pelvic radiotherapy can be considered.

### Management of refractory/recurrent disease

- D There is no standard treatment.
- ✓ Clinical trials with new drugs tailored to the biology of the tumour are strongly recommended.

### Follow-up

- ✓ Oncofertility counseling should be proposed. There is no defined follow-up strategy. Due to the aggressive course of the disease, close follow-up is recommended in a multidisciplinary setting according to patient condition, status of disease and therapeutic resources available.



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