National Clinical Practice Guidelines

Ovarian Cancer

Version 1.2010
## External reviewers

### Invited professional associations

<table>
<thead>
<tr>
<th>Invited professional associations</th>
<th>Reviewers</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Dr. Gino Pelgrims</td>
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<tr>
<td></td>
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<tr>
<td>The Belgian Association of Clinical Cytology **</td>
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<tr>
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<tr>
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<tr>
<td>Belgische Vereniging voor Radiotherapie-Oncologie - Association Belge de Radiothérapie ***</td>
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<td>Belgian Society of Pathology ****</td>
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<td>Domus Medica ****</td>
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<td>Société Scientifique de Médicine Générale ****</td>
<td>-</td>
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</tbody>
</table>

* Two experts assigned and feedback received.  ** Two experts assigned, but one feedback received.  *** One or two experts assigned, but no feedback received.  ****No experts assigned
Ovarian cancer guidelines expert panel
External reviewers
Table of contents
National guidelines ovarian cancer (Full text)
  - Introduction
  - Search for evidence
  - External review
  - Epithelial ovarian cancer
    - Epidemiology
    - Screening
    - Preoperative diagnosis and staging of suspected invasive ovarian cancer
    - Surgical staging
    - Treatment
      - Borderline and micro-invasive tumors
      - Invasive epithelial tumors
    - Follow-up
    - Treatment of recurrent disease
  - Germ cell tumor
    - Dysgerminoma
      - Diagnosis and staging
      - Treatment
      - Treatment of recurrent or progressive disease
      - Follow-up
  - Endodermal sinus tumor and mixed germ cell tumor
    - Diagnosis and staging
    - Treatment
    - Treatment of recurrent or progressive disease
    - Follow-up
  - Pure immature teratoma
    - Treatment
    - Follow-up
  - Sex cord stromal tumors
    - Granulosa cell tumors
      - Diagnosis and staging
      - Treatment
      - Adjuvant treatment
      - Treatment of recurrent or progressive disease
      - Follow-up
    - Sertoli Leydig cell tumor
      - Diagnosis and staging
      - Treatment
      - Adjuvant treatment
      - Treatment of recurrent or progressive disease
      - Follow-up
  - References
  - Appendix 1: FIGO classification
  - Appendix 2: Surgical report
INTRODUCTION
This document provides an overview of the clinical practice guidelines for ovarian cancer. They are developed by a panel of experts (see 'expert panel') comprising clinicians of different specialties and were reviewed by relevant professional associations (see 'external reviewers'). The guidelines are based on the best evidence available at the time they are derived (date restriction 2009). The aim of these guidelines is to assist all care providers involved in the care of patients with ovarian cancer. The guidelines presented covers screening, diagnosis, treatment and follow up of ovarian cancer.

SEARCH FOR EVIDENCE
Sources
The guidelines are adapted from the guidelines of the Flemish Society for Obstetrics and Gynaecology - Flemish Gynaecological Oncology Group which were revised in September 2008. They are based on existing clinical trials and international guidelines and a broad search on Medline using the search terms 'surgery', 'staging', 'ovarian' and 'epithelial cancer'.

Level of evidence
A level of evidence was assigned to each recommendation:

Level A: randomized studies, prospective cohort study
Level B: retrospective cohort study with consistent protocol, case-control studies, extrapolations from level A studies
Level C: case-series or extrapolations from level B studies
Level D: expert opinion

References are always provided for evidence levels A and B and sometimes for evidence level C.

EXTERNAL REVIEW
The guidelines prepared by the expert panel were circulated to the relevant professional associations (see 'external reviewers'). Each association was asked to assign two key persons to discuss the recommendations during an open meeting. As a preparation of the meeting all invited reviewers were asked to score each recommendation on a 5-point Likert-scale to indicate their agreement with the recommendation, with a score of ‘1’ indicating ‘completely disagree’, ‘2’ indicating ‘somewhat disagree’, ‘3’ indicating ‘unsure’, ‘4’ indicating ‘somewhat agree’, and ‘5’ indicating ‘completely agree’ (it was also possible to answer ‘not applicable’ in case they were not familiar with the underlying evidence). All scores were then summarized into a mean score and % of ‘agree’-scores (score ‘4’ and ‘5’) to allow a targeted discussion. The recommendations were then discussed during a face-to-face meeting on April 21st 2010. Based on this discussion a final draft of the guidelines was prepared, and discussed by the expert panel by email.
EPITHELIAL OVARIAN CANCER

EPIDEMIOLOGY

In Flanders, approximately 900 new cases of epithelial ovarian carcinoma are being recorded yearly. Approximately one quarter of all gynaecological cancers are of ovarian origin [1]. Epithelial ovarian carcinoma is responsible for almost half of all deaths due to a malignant tumor of the female genital tract. In the age group of women aged 40-45 years the incidence is approximately 15.7 cases per 100,000. In women between 75 and 79 years the incidence gradually increases to approximately 54 cases per 100,000. Older women are more likely than younger women faced with an advanced ovarian carcinoma. This is the main reason that 5-year survival in patients older than 65 years is only half compared with patients under 65 years [1].

Heredity is the main risk factor. In addition, an early menarche, late menopause and nulliparity increase the risk to develop ovarian cancer. The use of oral contraception reduces the chance of ever developing epithelial ovarian cancer (5 year use gives 50-70% protection). Hormonal replacement therapy leads to a limited increase in risk (approximately 10%).

Possibly, the likelihood of developing epithelial ovarian cancer is directly correlated to the number of ovulations in a lifetime. Exogenous factors also play a role as ovarian cancer occurs more frequently in the industrialized world. Sterilization has a possible protective effect against this disorder [2].

SCREENING

- There is no place for CA 125 screening in the general population (evidence level C) [3,4].
- Screening can be considered for high risk women (BRCA 1, BRCA 2, or familial breast and/or ovarian cancer) (evidence level B) [5].

PREOPERATIVE DIAGNOSIS AND STAGING OF SUSPECTED INVASIVE OVARIAN CANCER

- A detailed history including family history should be taken (evidence level D).
- A complete clinical examination including gynaecological recto-vaginal examination should be done (evidence level D).
- If ovarian cancer is suspected the following pre-operative examinations should be performed [4,6,7]:
  - Biochemical studies
    - Routine bloodcount (evidence level D).
    - Serum tumormarkers: cancer antigen 125 (CA 125) and carcinoembryonic antigen (CEA) determination (evidence level C).
    - If < 35y: α-fetoproteine, beta human chorionic gonadotrofin (β-HCG), lactate dehydrogenase (LDH) (evidence level D).
    - If postmenopausal with solid unilateral suspicious tumor: inhibin B and/or antiMüllerian hormone (AMH) or inhibin B (evidence level C).
    - In case of masculinisation: testosterone (evidence level C).
OVARIAN CANCER

SURGICAL STAGING

- Adequate staging is essential to differentiate between early ovarian cancer and advanced metastatic disease and has important implications for further management (evidence level A) [9] (see appendix 1).

- If suspected for stage III or IV (clinical presentation of a pelvic mass and ascites and/or omental and/or para-aortic nodes and/or other extra pelvic metastasis):
  - Open laparascopy or image guided biopsy of one of the metastases is recommended. Biopsies of the primary ovarian tumor are contra-indicated (evidence level B) [10].
  - Gastroscopy in case of mucinous tumors (evidence level D).
  - If clinically indicated: rectoscopy, cystoscopy and other examinations (evidence level D).
  - In case of pleural fluid: pleural punction for cytologic examination (evidence level D).
  - In case of para-aortic nodes or pleural fluid or suspected pleural or lung metastasis: thoracic CT (evidence level D).

- Definitive staging should be determined after laparotomy via median vertical incision taking into account preoperative imaging (evidence level A) [9,10].

- To determine macroscopic or occult microscopic metastasis and assess complete resectability, a complete peroperative inspection and exploration of the intra-and retroperitoneal cavity should be performed. This includes inspection of the colon, ileum, jejunum, appendix, liver, spleen, diaphragm, all peritoneal surfaces and multiple, infracolic omentectomy, pelvic and para-aortic lymphadenectomy and multiple biopsies from the pouch of Douglas, bladder peritoneum, paracolic gutters, and diaphragm. Washings of the peritoneal cavity for cytology should be performed [9]. If reliable frozen sections are available and conclude with grade 1 invasive stage 1 ovarian carcinoma, pelvic and para-aortic lymphadenectomy can be omitted (evidence level C).

- Accurate documentation of the peroperative findings should be done (evidence level D) [11] (see appendix 2).

- The amount of residual tumor (i.e. no residual tumor after primary or interval debulking) is the most important independent prognostic variable in advanced ovarian carcinoma (evidence level B) [12,13].

TREATMENT

Borderline and micro-invasive tumors

- Borderline tumors are defined as (evidence level D):
  - Ovarian tumors from the epithelial-stromal type of low malignant potential, exhibiting an epithelial cell proliferation of serous,
mucinous, endometroid, transitional, clear cell or Brenner type greater than seen in the benign counterpart, but without evidence of stromal invasion.
- The designation atypical proliferative tumor is not recommended.
- In case of serous borderline tumors with microinvasion not exceeding 10mm², the behaviour is similar to borderline tumors.

- Micro-invasive tumors are defined as (evidence level D):
  - small foci with stromal invasion of < 2mm of solitary cells or small clusters, sometimes cribriform or round aggregates of papillae
  - minimal stromal reaction

- In all cases biopsies of the diaphragm, pelvis and the paracolic region and omentectomy and cytology of the peritoneal fluid are required and should be obtained routinely (see also staging) (evidence level C).
- In case of apparent stage 1 disease and no child wish, radical surgery which consists of a total hysterectomy and bilateral salpingo-oophorectomy with omentectomy should be performed (evidence level C) [14].
- In case of apparent stage 1A disease and with a child wish, conservative surgery which consists of a unilateral salpingo-oophorectomy with omentectomy can be performed (evidence level C) [14].
- In case of apparent stage 1B disease and with a child wish, a unilateral salpingo-oophorectomy and cystectomy of the contralateral ovary can be performed (evidence level C).
- In case of stage 1C disease and with a child wish, a unilateral salpingo-oophorectomy with or without cystectomy of the contralateral ovary can be performed (evidence level C).
- In advanced stages (2 or higher) a total hysterectomy and bilateral salpingo-oophorectomy should be performed (details see chapter invasive epithelial tumors, stage 2,3 or 4), unless the implants are non-invasive and there is a child wish. Routine systematic pelvic or para-aortic lymphadectomy is not recommended. Removal of enlarged lymph nodes can be considered (evidence level C).
- In case of borderline tumors with invasive implants, lymphadenectomy can be considered (evidence level C).
- In case of mucinous borderline tumors surgery as described above and an additional appendectomy is recommended (evidence level D).
- In case of serous borderline tumors the following can be considered:
  - A biopsy of the contralateral ovary (evidence level D).
  - A total hysterectomy and bilateral salpingo-oophorectomy in case of micropapillary pattern (evidence level C).
  - Resection of the contralateral ovary after the child wish is fulfilled (evidence level C).

- A laparoscopic unilateral salpingo-oophorectomy can be considered under the following conditions (evidence level D):
  - A complete inspection and staging of the abdomen is possible and not hampered by adhesions.
  - Imaging evaluation of the cyst shows that it is not too big to be put in an endoscopic bag during laparoscopy. To prevent spilling by removing the cyst, a minilaparotomy is preferred.
- In case the patient underwent surgery for a suspected benign cyst, a restaging procedure is necessary if an accurate description and staging of the abdominal cavity is not available (evidence level D).
- There is no evidence to support adjuvant treatment (evidence level A) [14,15].
Invasive epithelial tumors

- Tumor grade, staging quality, tumour substage (a,b,c) and rupture are the most significant independent prognostic factors in stage 1 ovarian cancer and have direct impact on adjuvant treatment decision. (evidence level A) [16].

Surgery

Stage 1

- Rupture of the cyst should be avoided in early ovarian cancer because of the negative effect on the prognosis (evidence level A) [17].
- In case of young patients with a child wish AND stage 1A AND a well differentiated tumor (AND if available also DNA diploid tumor)
  - Conservative surgery which consists of a unilateral salpingo-oophorectomy can be performed in combination with staging procedures as outlined above (evidence level C) [10].
  - After the child wish is fulfilled, a contralateral salpingo-oophorectomy with a total hysterectomy is recommended (evidence level D).
  - A biopsy of the contralateral ovary can be considered (evidence level D).
- In all other cases, a total hysterectomy and bilateral salpingo-oophorectomy with staging as outlined above should be performed (evidence level B).

Stage 2,3 and 4 (based on malignant pleural effusion)

- Primary cytoreductive surgery is the standard of care in advanced ovarian cancer (evidence level B) [18].
- An open laparoscopy to evaluate the operability, to obtain histological diagnosis, to exclude early disease or other primaries can be considered. If not done an image guide biopsy of one of the metastases is recommended. Biopsies of the primary ovarian tumor are contra-indicated (evidence level B) [19].
- To obtain optimal surgical cytoreduction the following surgical procedures can be necessary (evidence level C):
  - Resection of the rectosigmoid
  - Partial resection of the diaphragm
  - Hemicolecotomy
  - Splenectomy
  - Partial liver resection
  - Cholecystectomy
  - Small bowel resection
  - Resection of all intra- and/or retroperitoneal tumors.
- In case of stage 4 due to malignant pleural cytology a radical cytoreductive surgery is recommended as in stage III (evidence level C).
- Accurate documentation of the peroperative findings should be done (see appendix 2). The report should include at least (evidence level D):
  - Location, number and size of the primary tumor and metastases.
  - Residual disease status: location, number and size.
  - Status of the diaphragm, liver, spleen, stomach wall, pelvic and para-aortic nodes, omentum, kidneys, colon, small intestine with the mesenterium, pelvic peritoneum, parietal peritoneum and the internal genitals.
- Optimal cytoreductive surgery is defined as no residual tumour and should be aimed for. Leaving any residual tumours is sometimes
unavoidable but has a strong negative impact on survival *(evidence level B)* [12,13].

- There is evidence to suggest that outcome is better in patients treated in high volume centres with dedicated gynaecological oncologists *(evidence level C)* [20].
- There is no evidence to support a second look surgery *(evidence level A)* [21].
- Patients with a good response after neoadjuvant chemotherapy are candidates for interval debulking surgery (preferentially after 3 courses of chemotherapy) *(evidence level A)* [13,22].

**Adjuvant treatment**

**Stage I**

- In patients with moderate and poorly differentiated tumors, or aneuploidy, or clear cell tumors, at least 4 courses of platin-based chemotherapy is recommended *(evidence level A)* [16].

**Stage 2.3 and 4**

- Standard chemotherapy: 6 courses of i.v. paclitaxel 175 mg/m² over 3 hours in combination with i.v. carboplatin AUC 5 – 7.5.q 3 weeks *(evidence level A)* [23].
- In older patients or patients with a poor performance status carboplatinum in monotherapy can be considered *(evidence level A)* [21].
- There is no evidence based intraperitoneal chemotherapy regimen which has a low toxicity profile *(evidence level D)* [21].

- Currently there is not yet evidence to support molecular targeted therapy, except for bevacizumab *(evidence level A)* [24].

**Neoadjuvant chemotherapy and interval debulking surgery**

- Neoadjuvant chemotherapy followed by interval cytoreductive surgery should be considered in the following situations:
  - Stage 3C and 4 where too extensive surgery is needed to achieve a no residual tumor status *(evidence level A)* [14].
    - For instances:
      - Poor general condition
      - Metastases of >2 cm around the truncus coeliacus, arteria mesenterica superior or at posterior side of the porta hepatis.
      - Extensive metastases of the small intestine and colon which requires a bowel resection of >1.5 m
  - Stage 4 with intrahepatic or extra-abdominal metastases (excluding supraclavicular or inguinal lymph nodes *(evidence level C)* [25].

**FOLLOW-UP**

- Follow-up consultations can be organized according to local practice but there is no proven survival benefit *(evidence level D)*.
- After first-line chemotherapy there is no evidence to routinely perform serum CA125 or other serum tumor markers *(evidence level A)* [26].
- Routine imaging examinations to screen for recurrent disease are not recommended *(evidence level C)*.
TREATMENT OF RECURRENT DISEASE

- For diagnosis of recurrent disease abdominal pelvic CT or MRI or FDG-PET/CT can be considered (evidence level C).

- Secondary debulking surgery is recommended in operable patients with a disease free interval of more than 12 months, a good performance status, no ascites or estimated to be less than 500 ml, and complete resection at primary (or interval) surgery (evidence level C). The aim of secondary cytoreductive surgery should be no residual tumor (evidence level C) [27].

- In case of recurrent disease chemotherapy is recommended. The treatment of choice depends on the length of the treatment free interval and previous treatment (evidence level A) [21].
  - if platinum sensitive (>12 months platin-free interval):
    - A combination of carboplatinum with gemcitabine, or paclitaxel or pegylated liposomal doxorubicin (PLD) should be considered. In patients with poor general condition single agent carboplatinum can be considered [28,29,30].
  - if intermediate platin-sensitive (6-12 months treatment-free interval): same as above except that combinations with paclitaxel are less indicated if the patient received carboplatin-paclitaxel in first-line. In this group of patients a non-platinum with PLD and trabectedin is also an option (evidence level A) [31].
  - if platin resistant or platin refractory: pegylated liposomal doxorubicin, topotecan can be considered. In some patients weekly carboplatin and paclitaxel regimens are indicated (evidence level C) [32,33,34].
  - Some patients can have stable disease with tamoxifen (evidence level A) [35].

- Patients with unresectable recurrent disease should be treated preferably in clinical trials (evidence level D).
**GERM CELL TUMOR**

**DYSGERMINOMA**

**Diagnosis and staging**
- Preoperative determination of lactate dehydrogenase (LDH), alfafoetoprotein (AFP) and β-human chorionicgonadotropin (β-HCG) in addition to the diagnosis and staging as described for epithelial tumors is recommended (evidence level C).
- In premenarchal girls, genetic testing is recommended (evidence level D).
- Dysgerminomas in stage 1 can be bilateral in 10-20% of patients (evidence level C).

**Treatment**

**Surgery**
- A unilateral salpingo-oophorectomy with surgical staging (see epithelial tumors) is recommended in the following cases (evidence level C):
  - Stage 1a
  - Unilateral 1c stage
- In patients with a child wish and in case of stage 1b, 2, 3 and 4 disease with macroscopic invasion of both ovaries, a cystectomy/tumorectomy or partial ovarectomy can be considered (evidence level C).
- A para-aortic lymphadenectomy is not indicated given the extreme chemosensitivity of pure dysgerminomas (evidence level D).

**Primary chemotherapy**
- Chemotherapy is the standard treatment for patients in whom not all tumor could be resected. The preferred regimen in those cases is 4 cycles of etoposide and cisplatinum with or without bleomycin (BEP) (evidence level C).

**Primary radiotherapy**
- In selected cases of patients who did not undergo radical surgery, radiotherapy can be an option (evidence level D).

**Adjuvant treatment**
- Adjuvant treatment is not recommended in stage 1 patients in whom all tumor was resected (evidence level C).
- Chemotherapy is recommended in stage 2, 3 and 4 patients who underwent radical surgery. The preferred regimen in those cases is etoposide and cisplatin with or without bleomycin (evidence level C).

**Treatment of recurrent or progressive disease**
- Chemotherapy is the standard treatment for recurrent disease. The preferred regimen is 4 cycles of BEP. (maximum 4 courses with bleomycin) (evidence level C).
- If bleomycin is used lung diffusion capacity should be monitored (evidence level D).
- In case of recurrent disease high dose chemotherapy e.g. with peripheral stem cell support can be considered (evidence level D).
- In selected cases of patients with recurrent disease, radiotherapy can be an option (evidence level C).
• Radiotherapy or second line chemotherapy can be curative (evidence level C).

Follow-up
• In case of recurrent disease or stage 2,3 and 4, an abdominal CT or MRI can be considered yearly during 10 years (evidence level D).
• If HCG or LDH is elevated before surgery they can be useful during follow-up (evidence level D).

ENDODERMAL SINUS TUMOR AND MIXED GERM CELL TUMOR

Diagnosis
• In young patients with an endodermal sinus tumor based on MRI or ultrasonography, alpha-foetoprotein (AFP) level can be performed in addition to the diagnosis and staging as described for epithelial tumors (evidence level C).

Treatment
Surgery
• Because an adequate histology is rarely known during surgery, it is recommended to avoid contralateral surgery at the time of primary surgery (evidence level C).

• Second look surgery in patients with an incomplete resection is not recommended (evidence level D).

Adjuvant treatment
• Adjuvant chemotherapy is indicated in all stages (evidence level C).
  o In stage 1 disease with no residual tumor: 3 cycles of BEP
  o In stage 1 disease where no radical surgery was performed and stage 2,3, and 4: 4 cycles of BEP. (maximum 4 courses with bleomycin).
• In patients with an endodermal sinus tumor, it is suggested to give 2 more cycles for consolidation after normalization of the AFP level (evidence level D).

Treatment of recurrent or progressive disease
• Chemotherapy is the standard treatment for recurrent disease. The preferred regimen is 4 cycles of BEP (evidence level C).
• Radiotherapy or second line chemotherapy is recommended in case of progressive disease during chemotherapy or incomplete tumor response after chemotherapy (evidence level C).

Follow-up
• Regular determination of the AFP level in patients with an endodermal sinus tumor is recommended (evidence level C).
PURE IMMATURE TERATOMA

Treatment

- Immature tumors are graded based on the neuroepithelial component according to the classification of Norris et al. *(evidence level C)* [36].
- Immature teratomas are treated with surgery consisting of an unilateral salpingo-oophorectomy with surgical staging (see epithelial tumors) *(evidence level C)*.
- Stage 1 patients with Norris Grade 2 or 3 areas tumors are treated with chemotherapy after surgery. The preferred regimen is 4 cycles of etoposide and cisplatin *(evidence level C)*.
- Patients with incomplete resection are treated with BEP (maximum 4 course with bleomycin) *(evidence level D)*.
- Second look surgery with multiple biopsies is indicated in all cases with incomplete resection after primary surgery. Additional treatment is not recommended if the biopsies show mature teratoma only (also in case of incomplete resection). Immature teratoma tend to become mature during chemotherapy *(evidence level C)*.

Follow-up

- A yearly abdominal CT or MRI and/or chest RX during the first 5 years can be considered in cases with incomplete resection or mature residuals after chemotherapy *(evidence level D)*.
SEX CORD STROMAL TUMOR

GRANULOSA CELL TUMOR

Diagnosis and staging

- Determination of inhibin B and/or anti-Müllerian hormone (AMH) should be performed in all cases with suspicion of a granulosa cell tumor in addition to the diagnosis and staging as described for epithelial tumors. *(evidence level D)*.
- Granulosa cell tumors are very rarely bilateral *(evidence level C)*.
- Granulosa cell tumors present rarely with lymph node metastases *(evidence level C)*.
- Granulosa cell tumors tend to recur late (i.e. after 10 years) *(evidence level C)*.

Treatment

- In case of young patients with a child wish:
  - Conservative surgery which consists of a unilateral salpingo-oophorectomy with infracolic omentectomy can be performed *(evidence level C)*.
  - A biopsy of the contralateral ovary or routine full pelvic and/or para-aortic lymphadenectomy are not recommended *(evidence level D)*.
- In all other cases, radical surgery which consists of a total hysterectomy and bilateral salpingo-oophorectomy with infracolic omentectomy is recommended *(evidence level C)*.

- Staging should be performed as in epithelial malignant tumors (except lymphadenectomy) *(evidence level D)*.
- An elective lymphadenectomy is only recommended in case of peroperative palpable nodes, or suspicious imaging *(evidence level D)*.

Adjuvant treatment

**Stage 1 granulosa cell tumor adult cell types**

- Adjuvant chemotherapy is only indicated in young patients with a high risk granulosa cell tumor (e.g. mitotic rate of more than 3 mitosis/10 HPF (high-power field)) *(evidence level D)*.
- The preferred regimen is based on etoposide and cisplatin with or without bleomycin *(evidence level D)*.
- If bleomycin is used lung diffusion capacity should be monitored *(evidence level C)*.

**Stage 2 and 3,4 granulosa cell tumor adult cell types**

- In patients with stage 2 and 3, chemotherapy is recommended *(evidence level C)*.
- The preferred regimen is at least 3 cycles of BEP (bleomycin, etoposide, cisplatin) with a maximum of 4 cycles with bleomycin. If the serum inhibine B and/or anti-Müllerian hormone level was increased at diagnosis, at least two cycles should be given after normalization of the level *(evidence level D)*.
- Chemotherapy should be switched to an etoposide-cisplatinum regimen after 4 cycles of BEP *(evidence level D)*.
• Radiotherapy can be considered in selected patients who are not candidate for chemotherapy (evidence level C).

Juvenile type granulosa cell tumor
• Adjuvant treatment of juvenile type granulosacell tumors should always be discussed in a multidisciplinary team meeting (evidence level D).

Treatment of recurrent or progressive disease
• Secundary debulking surgery should be considered in case of recurrent disease, especially in case of late relapse (evidence level D).
• In case of recurrent disease after BEP, high dose chemotherapy e.g. with peripheral stem cell support can be considered (evidence level D).
• Radiotherapy can be considered in case of progressive disease during chemotherapy or incomplete tumor response after primary chemotherapy (evidence level C).
• In case of platinum resistant tumors and tumor localisations not suitable for radiotherapy, LHRH agonists, medroxyprogesterone acetate or megestrol acetate can be considered (evidence level C).

Follow-up
• Regular determination of serum inhibin B variation and/or AMH level can be performed in case these levels were increased at diagnosis (evidence level D).
• In case the level of inhibin B and/or anti-Müllerian tumor were not increased at diagnosis or stage 1,2,3,4 high risk patients or after recurrent disease, an abdominal CT or MRI and/or chest X-ray can be considered yearly (evidence level D).

SERTOLI LEYDIG CELL TUMOR

Diagnosis and staging
• Determination of serum testosterone should be performed in all cases with suspicion of a. Sertoli-Leydig cell tumor in addition to the diagnosis and staging as described for epithelial tumors (evidence level D).
• Sertoli-Leydig cell tumors are very rarely bilateral (evidence level C).
• Sertoli-Leydig cell tumors present rarely with lymph node metastases (evidence level C).

Treatment
Surgery
• A unilateral salpingo-oophorectomy with surgical staging (see epithelial tumors) is recommended in the following cases (evidence level D):
  o Stage 1a
  o Unilateral 1c stage
  o Young patients with a child wish and stage 2,3 and 4 disease without spread to the contralateral ovary
• In case of stage 1b, 2, 3 and 4 disease with macroscopic invasion of both ovaries, a resection of both ovaries is recommended (evidence level D).
• In patients with a child wish and in case of stage 1b, 2, 3 and 4 disease with macroscopic invasion of both ovaries without poor prognostic histological features, a cystectomy/tumorectomy or partial ovarectomy can be considered (evidence level D).

• An elective lymphadenectomy is only recommended in case of peroperative palpable nodes, or suspicious imaging (evidence level D).

Adjuvant treatment

• Adjuvant chemotherapy is advised in stage Ia moderate and poorly differentiated tumors, and stage 1b, 1c, 2, 3, 4 (evidence level C).

• The preferred regimen is at least 3 cycles of BEP (bleomycine, etoposide, cisplatine) with a maximum of 4 cycles with bleomycine. If the serum testosterone level was increased at diagnosis, at least two cycles should be given after normalization of this level (evidence level D).

• Chemotherapy should be switched to a etoposide-cisplatium regimen after for 4 cycles of BEP (evidence level D).

• If bleomycine is used lung diffusion capacity should be monitored (evidence level D).

Treatment of recurrent or progressive disease

• Secundary debulking surgery can be considered in case of recurrent disease (evidence level D).

• Radiotherapy can be considered in case of isolated or inoperable recurrent disease (evidence level D).

• Radiotherapy can be considered in case of progressive disease during chemotherapy or incomplete tumor response after primary chemotherapy (evidence level C).

Follow-up

• Regular determination of the serum testosteron level can be performed in case these levels were increased at diagnosis (evidence level D).

• In case the serum testosteron level was not increased at diagnosis or stage 1,2,3,4 high risk patients or after recurrent disease, an abdominal CT or MRI and/or chest X-ray can be performed yearly (evidence level D).
References


Stage I

Stage I ovarian cancer is limited to the ovaries.

- Stage IA: Tumor limited to one ovary; capsule intact, no tumor on ovarian surface. No malignant cells in ascites or peritoneal washings.*
- Stage IB: Tumor limited to both ovaries; capsules intact, no tumor on ovarian surface. No malignant cells in ascites or peritoneal washings.*
- Stage IC: Tumor limited to one or both ovaries with any of the following: capsule ruptured, tumor on ovarian surface, malignant cells in ascites or peritoneal washings.

* [Note: The term, malignant ascites, is not classified. The presence of ascites does not affect staging unless malignant cells are present.]

Stage II

Stage II ovarian cancer is tumor involving one or both ovaries with pelvic extension and/or implants.

- Stage IIA: Extension and/or implants on the uterus and/or fallopian tubes. No malignant cells in ascites or peritoneal washings.
- Stage IIB: Extension to and/or implants on other pelvic tissues. No malignant cells in ascites or peritoneal washings.
- Stage IIC: Pelvic extension and/or implants (stage IIA or stage IIB) with malignant cells in ascites or peritoneal washings.

Different criteria for allotting cases to stage IC and stage IIC have an impact on diagnosis. To assess this impact, of value would be to know if rupture of the capsule was (1) spontaneous or (2) caused by the surgeon; and, if the source of malignant cells detected was (1) peritoneal washings or (2) ascites.

Stage III

Stage III ovarian cancer is tumor involving one or both ovaries with microscopically confirmed peritoneal implants outside the pelvis. Superficial liver metastasis equals stage III. Tumor is limited to the true pelvis but with histologically verified malignant extension to small bowel or omentum.

- Stage IIIA: Microscopic peritoneal metastasis beyond pelvis (no macroscopic tumor).
- Stage IIIB: Macroscopic peritoneal metastasis beyond pelvis 2 cm or less in greatest dimension.
- Stage IIIC: Peritoneal metastasis beyond pelvis more than 2 cm in greatest dimension and/or regional lymph node metastasis.

Stage IV

Stage IV ovarian cancer is tumor involving one or both ovaries with distant metastasis. If pleural effusion is present, positive cytologic test results must exist to designate a case to stage IV. Parenchymal liver metastasis equals stage IV.
FINDINGS:
Description of the primary ovarian tumors: size, appearance, cystic or solid, rupture?, excrescences in the cyst or capsule, deformities/mobility.

Description of the following organs: Specify for every organ the diameter of the largest metastasis, the number of metastases, and if possible an estimate of the number of grams of metastases. Specify the macroscopic aspect and mobility of the metastases.

Liver (intrahepatic!), kidneys, para-aortic lymphadenectomy, pelvic lymph nodes.

Description of other abnormal findings at the the above mentioned organs or stomach, gallbladder, bladder, colon, rectum, small intestine, uterus, abdominal wall, ...

Description of peritoneal metastasis at the following regions: Specify for every region the diameter of the largest metastasis, the number of metastases, and if possible an estimate of the number of grams of metastases. Specify also the macroscopic aspect and mobility of the metastases.

Omentum, left diaphragm, omentum minus, stomach duodenum, jejunum, ileum, colon ascendens, colon transversum, colon descendens, left para-colic space, right para-colic space, right diaphragm, pelvic peritoneum, parietal peritoneum, liver, serosa, spleen and bursa omentalis.

Presence of ascites? Number of liters, cytology should always be taken. If no presence of ascites, peritoneal wash fluid for cytology should be taken (preferably at different regions). During laparotomy for staging purposes, multiple blind biopsies should be taken (more than 5), preferably of deformities and such.

TECHNIQUE:
Detailed description of the surgical technique.
Number of liters of blood loss, peroperative complications, drainage.
Duration of surgery.

CONCLUSION:
Indicate how many of the tumor is post-operatively still present at each organ and region (number of metastases, size and if possible an estimate of the number of grams).