College of Oncology

NATIONAL EXPERT – BASED PRACTICE GUIDELINES

OVARIAN CANCER

Guidelines V1.2022

Expert panel

COLLEGE OF ONCOLOGY

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INTRODUCTION

This document provides an overview of the good clinical practice guidelines for **ovarian cancer** and covers a broad range of topics such as screening, diagnosis, treatment and follow-up.

These guidelines are developed by a panel of experts comprising clinicians of different specialties and designated by their respective scientific societies.

The guidelines are based on the best evidence available at the time they are derived (2022).

The aim of these guidelines is to assist all national care providers involved in the care of patients with ovarian cancer and serve as a base and supporting tool for the local institutional guidelines and MOC (multidisciplinary oncological consult) discussions in Belgium.

SEARCH FOR EVIDENCE

This national guideline is derived from existing international guidelines and have been updated and adapted to the Belgian context by the expert panel. The following guidelines have mostly been used: ESMO-ESGO Consensus Conference on Ovarian Cancer (2019), ESMO eUpdate epithelial ovarian carcinoma (2021), ESGO guideline early stage (2016), ESMO Clinical Practice guideline on non-epithelial ovarian cancer (2018) and the Belgian national guideline (2010) for ovarian cancer (N. Colombo et al. 2019; N. Colombo and Ledermann 2021; ESGO 2016; Ray-Coquard et al. 2018). The expert panel consisted of experts in various settings and representatives of the relevant professional Belgian societies, implicated in the management of ovarian cancer.

This national guideline will be regularly updated as new evidence with practice implications emerges.

An adapted version of the 'Infectious Diseases Society of America-United States Public Health Service Grading System' was used (Table 1) to define the level of evidence and strength of each recommendation proposed by the group. Finally, a vote was conducted to determine the level of agreement among the expert panel for each of the recommendations.

Table 1 Levels of evidence and grades of recommendation

Levels of evidence	
I	Evidence from at least one large randomized controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of other trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case report, expert opinions

Levels of recommendations	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

LIST OF ABBREVIATIONS

AFP: alpha-fetoprotein

AGCT: adult granulosa cell tumor

AMH: antiMüllerian hormone

BEP: bleomycin, etoposide and cisplatin

β-HCG: beta human chorionic gonadotrophin

BOT: borderline tumor

BRCA: breast cancer gene

BSO: bilateral salpingo-oophorectomy

CA 125: Cancer Antigen 125

CAP: cyclophosphamide-doxorubicin-cisplatin

CEA: carcinoembryonic antigen

CT: computed tomography

cfDNA: circulating free deoxyribonucleic acid

EE: ESMO-ESGO guideline

EP: etoposide-cisplatin

FIGO: International Federation of Gynecology and Obstetrics

FDG: fluorodeoxyglucose

FSS: fertility sparing surgery

GCT: germ cell tumor

HDCT: High-dose chemotherapy

HGSC: high-grade serous ovarian cancer

HIPEC: Hyperthermic intraperitoneal chemotherapy

HR: homologous repair

HRD: Homologous recombination deficiency

ICCR: International Collaboration on Cancer Reporting

LDH: lactate dehydrogenase

LGSC: low-grade serous carcinoma

LN: lymph node

mBOT: mucinous borderline tumors

MRI: Magnetic Resonance Imaging

MOC: multidisciplinary oncological consult

PARP: poly (ADP-ribose) polymerase

PET: positron emission tomography

PFS: progression-free survival

PLD: pegylated liposomal doxorubicin

QoL: quality of life

sBOT: serous borderline tumors

SCST: Sex cord stromal tumor

SEE-FIM: Sectioning and extensively examining the fimbriated end

SLCT: Sertoli leydig cell tumor

STIC: serous tubal intraepithelial carcinoma

WT1: Wilms' tumor suppressor gene 1

WG: working group

WHO: World Health Organization

1. EPITHELIAL OVARIAN CANCER

1.1 Invasive epithelial ovarian cancer

1.1.1 Screening and prophylactic interventions

- There is no evidence for cancer antigen 125 (CA 125) or sonographic screening in the general population (Menon et al. 2021). (Belgian guideline 2010; I, A)
- Removal of the fallopian tubes is considered in the general population at the time of hysterectomy. This should be discussed with the patients. When the patient asks for a surgical sterilization, complete salpingectomy should be discussed. (Consensus working group (WG); IV, C)
- Six monthly screening with at least vaginal ultrasound and gynaecological examination is recommended for high risk women (breast cancer gene (BRCA) 1, BRCA 2, BRIP1, RAD51C or D or microsatellite instability (Lynch Syndrome) or familial breast and/or ovarian cancer) until preventive bilateral salpingo-oophorectomy (BSO) has been performed starting from the age of 35-40. (Belgian guideline 2010 + consensus WG; III, C)
- In the above mentioned high risk population, preventive removal of the fallopian tubes and ovaries is recommended (starting at 40 years for BRCA1 and Lynch Syndrome and at an age between 45 and 50 for the other mutations) taking the family history into account. (Consensus WG; III, A)
- In the framework of a study, salpingectomy can be performed in younger patients after fulfilment of the child wish and oophorectomy can be postponed to a later stage (depending on the type of mutation). (Harmsen et al. 2015) (Consensus WG; V, C)
- Patients with high risk of ovarian cancer should be advised to use oral contraceptive due to the protective effect until prophylactic surgery is done. (Consensus WG; IV, B) (Beral et al. 2008)
- The use for pre-implantation diagnostics should be offered to the patient to prevent the spread of BRCA1/2 to the next generation. (Consensus WG; III, A)

1.1.2 Pathology and molecular biology

1.1.2.1 Site of origin of high-grade serous ovarian cancer (HGSC)

- A large majority of the HGSCs arise in the fallopian tube from serous tubal intraepithelial carcinoma (STIC). Sectioning and extensively examining the fimbriated end (SEE-FIM) sectioning of both fallopian tubes should be carried out in all cases of HGSC where the tubes are grossly normal, and also in risk-reducing prophylactic surgery specimens. (ESMO-ESGO 2019; III, A)
- HGSC can only be assigned as ovarian in origin if both fallopian tubes are grossly normal, and histologically contain no mucosal disease following examination using a SEE-FIM protocol. (ESMO-ESGO 2019; III, A)
- Cases in which HGSC is present in the endometrium and the tube/ovary are very likely to represent a primary at one site with metastasis to the other; these are very unlikely to represent synchronous independent

neoplasms. (ESMO-ESGO 2019; V, A)

- The distinction between primary endometrial and primary tubal/ovarian HGSC requires assessment of a constellation of pathological features; negative Wilms' tumor suppressor gene 1 (WT1) staining favours an endometrial primary, but this is not always definitive. (ESMO-ESGO 2019; V, A)
- The use of uniform criteria is important in site assignment for cancer registry and epidemiological reasons. The use of International Collaboration on Cancer Reporting (ICCR) and College of American Pathologists guidelines is recommended. (ESMO-ESGO 2019; V, A)
- Correct and uniform use of site assignment criteria is particularly important for accurate staging of early HGSC. (ESMO-ESGO 2019; III, A)
- STIC should count as a disease site for staging purposes; for example, a case with a STIC and HGSC confined to the ovary should be staged as stage IIA fallopian tube HGSC. (ESMO-ESGO 2019; IV, A)
- True primary peritoneal HGSC is extremely rare. (ESMO-ESGO 2019; IV, A)
- Multifocal origin of extrauterine HGS is exceptionally rare and thus HGSC currently staged as IB should be considered as stage IIA. (ESMO-ESGO 2019; IV, A)
- Criteria for assignment of the primary site in extrauterine HGSC can be found in the Appendix I (Table 2). (ESMO-ESGO 2019)
- If there is only a small biopsy and it is not possible to examine the tubes, then you have to assign it as tubo-ovarian until there is more tissue to examine. (Consensus WG; criteria of the WHO 5th edition)
- Extensive pathological examination is recommended in patients with a family history of ovarian cancer. When the ovaries or the fallopian tubes are removed to prevent ovarian or fallopian tube cancer, it is preferred to use the SEE-FIM protocol. (Consensus WG; III, A)

1.1.2.2 Preoperative examination and staging of suspected invasive ovarian cancer

- A detailed history including family history should be taken. (Belgian guideline 2010; V, B)
- A complete clinical examination, including gynecological recto-vaginal examination, should be done. (Belgian guideline 2010; V, B)
- Systemic treatment cannot be started without pathological confirmation of ovarian cancer. (Consensus WG; V, A)
- If ovarian cancer is suspected, the following pre-operative examinations should be performed:
    - Biochemical studies
    - Routine blood count (Belgian guideline 2010; V, C)
    - Serum tumor marker: CA 125 (Belgian guideline 2010; IV, A)
    - If < 35y: α-fetoprotein, beta human chorionic gonadotrophin (β-HCG), lactate dehydrogenase (LDH). (Belgian guideline 2010; V, B)
    - If postmenopausal with solid unilateral suspicious tumor: inhibin B and/or antiMüllerian hormone (AMH). (Belgian guideline 2010; IV, B)

  - In case of masculinization: testosterone. (Belgian guideline 2010; IV, B)
  - RX mammography if performed more than two years ago (Consensus WG)
- Diagnostic work-up with abdominal and chest computed tomography (CT), positron emission tomography (PET)-CT or diffusion-weighted whole body magnetic resonance imaging (MRI) should be used to assess the extent of disease. (ESMO-ESGO 2019; III, A)
- A diagnostic laparoscopy cannot replace CT, PET-CT or MRI. (ESMO-ESGO 2019; III, A)
- For differentiation between benign and malignant at diagnosis, transvaginal and abdominal ultrasound + Doppler ultrasound must be performed by a physician with experience and/or specialist training in this area. If doubt about the diagnosis, MRI of the pelvis can be considered (D Timmerman et al. 2008; Dirk Timmerman et al. 2021). (IOTA-ESGO statement; I, A)
- Testing for germline and somatic BRCA1/2 mutations is recommended for all patients with high-grade non-mucinous ovarian cancer. (ESMO-ESGO 2019 + consensus WG; I, A)
- Testing for mutations in other homologous repair (HR) genes, in particular RAD51C/D, BRIP1 and PALB2, should be included. (ESMO-ESGO 2019 + consensus WG; III, A)
- Patients are not candidates for primary surgery if the following spread of disease, among other factors, is present:
  - Diffuse deep infiltration of the root of small bowel mesentery
  - Diffuse carcinomatosis of the small bowel involving such large parts that resection would lead to a short bowel syndrome (remaining bowel <1.5 m)
  - Diffuse involvement/deep infiltration of:
    - stomach/duodenum
    - head or middle part of pancreas
  - Involvement of coeliac trunk, hepatic arteries, left gastric artery
  - Central or multisegmental parenchymal liver metastases
  - Multiple parenchymal lung metastases (preferably histologically proven)
  - Non-resectable LN
  - Brain metastases
- Clinical staging
  - Gastroduodenoscopy and colonoscopy in case of mucinous tumors or other imaging e.g. PET-CT or diffusion weighted MRI should be considered (in case of doubt on the origin of the tumor). (Belgian guideline 2010; V, B)
  - If clinically indicated: rectoscopy, cystoscopy and other examinations should be done. (Belgian guideline 2010; V, B)
  - In case of pleural fluid: pleural punction for cytologic examination should be performed. (Belgian guideline 2010; V, A)

1.1.2.3 Identification of tumors that will respond to targeted therapies

- There are no validated predictive molecular biomarkers of bevacizumab benefit. (ESMO-ESGO 2019; IV, A)
- Poly (ADP-ribose) polymerase (PARP) inhibitors have greatest activity in patients with BRCA1/2 mutations. (ESMO-ESGO 2019; I, A)
- Current assays of HR function cannot be used to exclude patients from PARP inhibitor therapy. (ESMO-ESGO 2019; I, A)
- Moderate-strong ER staining may be a predictor of response to hormone therapy. (ESMO-ESGO 2019; III, B)
- There are currently no prospectively validated predictive biomarkers of response to immune checkpoint inhibitors that are specific to ovarian cancer. (ESMO-ESGO 2019; V, A)
- Testing for BRCA1/2 somatic mutations is recommended for all patients with non-mucinous high-grade ovarian cancer. (ESMO-ESGO 2019 + consensus WG; I, A)
- Testing for mutations in other HR genes, in particular RAD51C/D, BRIP1 and PALB2, should be considered. (ESMO-ESGO 2019; III, A)
- Homologous recombination deficiency (HRD) test should be considered in all patients. (Consensus WG; I, A)

1.1.2.4 Identification of patients with acquired/intrinsic resistance to chemotherapy

- There are no validated predictive markers of primary platinum refractory or resistant disease. (ESMO-ESGO 2019; IV, A)

1.1.2.5 Development of accurate and sensitive circulating and tissue biomarkers (response/relapse)

- The CA125 criteria for response and progression as agreed by GCIG have utility in routine practice but should be used in combination with radiological and clinical assessment during treatment. (ESMO-ESGO 2019 + consensus WG; III, A)
- The role of CA125 as a marker of response and progression in non-HGSC is less clear. (ESMO-ESGO 2019; V, A)
- The use of CA125 in assessing response and progression to targeted therapies is not yet proven; thus, radiological and clinical assessment should be used. (ESMO-ESGO 2019; V, A)
- HE4 should not be used routinely to assess response and progression due to conflicting results. (ESMO-ESGO 2019; IV, A)
- Quantification of circulating free deoxyribonucleic acid (cfDNA) has not been established as a tool to assess response and relapse. (ESMO-ESGO 2019; IV, A)
- Pathological chemotherapy response score after neoadjuvant chemotherapy may provide an objective and reproducible prognostic measure of outcome in HGSC, but this has currently no therapeutic consequences. (ESMO-ESGO 2019 + consensus WG; IV, A)

1.1.3 Surgical staging

- Staging should be done according to the revised International Federation of Gynecology and Obstetrics (FIGO) 2018 classification (Appendix I).
- Adequate staging is essential to differentiate between early ovarian and advanced metastatic disease and has important implications for further management. (Belgian guideline 2010; III, A) (Trimbos et al. 2003).

EARLY STAGE DISEASE

- Accurate documentation of the peroperative findings is strongly recommended (Dirk Timmerman et al. 2021; Verleye et al. 2009). (Belgian guideline 2010 + ESGO-IOTA guideline; V, A)
- To determine macroscopic or occult microscopic metastasis, a complete peroperative inspection and exploration of the intra-and retroperitoneal cavity should be performed (Trimbos et al. 2003). (Consensus WG; III, A). This includes:
    - Inspection of the colon, ileum, jejunum, appendix, liver, spleen, diaphragm, all peritoneal surfaces
    - Multiple blind biopsies from the pouch of Douglas, bladder peritoneum, paracolic gutters, and diaphragm or/and of any suspect lesion.
    - Infracolic omentectomy
    - Pelvic and para-aortic lymphadenectomy up to the level of the left renal vein with the exception of stage I expansile type mucinous adenocarcinomas, low-grade serous tumors and low-grade endometrioid tumors (ESMO-ESGO 2019; IV, A)
    - Washings of the peritoneal cavity for cytology taken prior to manipulation of the tumor are is recommended. (ESGO 2016; IIII, A)
- Biopsies of the primary ovarian tumor are contra-indicated if stage I or stage II disease is suspected (Nicoletta Colombo et al. 2006; I Vergote et al. 2001). (Belgian guideline 2010; III, A)

ADVANCED STAGE DISEASE

- To determine the tumor load and to 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, omentum, pelvic and para-aortic lymph nodes (LN) (Consensus WG; III, A)
- The amount of residual tumor (i.e. no residual tumor after primary or interval debulking) is the most important independent prognostic variable (Andreas du Bois et al. 2009; Ignace Vergote et al. 2010). (Belgian guideline 2010; III, A)

1.1.4 Restaging

- Peritoneal restaging surgery is mandatory even if it does not alter the indication for adjuvant chemotherapy. (ESMO-ESGO 2019; V, B)
- Peritoneal restaging should be considered in cases of incidentally detected, apparently isolated STIC lesions. (ESMO-ESGO 2019; IV, B)

- Restaging for the only purpose of performing appendectomy is not mandatory even in case of mucinous histology. (ESGO 2016; IV, B)
- When early carcinoma is incidentally found at surgery for a suspected 'benign' condition, a second surgical procedure will be required. When the patient has not been comprehensively staged, a second surgical procedure must be considered routinely. (ESGO 2016; III, A)
- Minimally invasive surgery can be carried out for restaging. (ESMO-ESGO 2019; IV, B)

1.1.5 Treatment

1.1.5.1 Surgery

STAGE I

- Midline laparotomy is required to manage early ovarian cancers, with the exception of apparent stage I which can be managed laparoscopically by a gynaecological oncologist with specific expertise in laparoscopy, without rupture and without contamination of the abdominal cavity and wall. (ESMO-ESGO 2019; IV, A)
- A total hysterectomy and BSO and staging is the standard treatment in invasive epithelial ovarian cancer. (ESGO 2016; III, A)
- Hysterectomy can be avoided for stage I expansile mucinous tumors. (Consensus WG; IV, B)
- Rupture of the cyst should be avoided in early ovarian cancer because of the negative effect on the prognosis (I Vergote et al. 2001). (Belgian guideline 2010; III, A)
- Visual assessment of the entire peritoneal cavity is recommended. (ESGO 2016; III, A)
- Complete surgical staging as outlined above (see 1.1.3)

Fertility sparing surgery (FSS)

- In case of young patients with a child wish AND apparent stage IA AND a well differentiated tumor or a mucinous carcinoma of the expansile type (Muyldermans et al. 2013):
    - Conservative surgery which consists of a unilateral salpingo-oophorectomy (without hysterectomy and contralateral salpingo-oophorectomy) can be an option in combination with staging procedures as outlined above. (Nicoletta Colombo et al. 2006) (Belgian guideline 2010 + consensus WG; IV, B)
    - After the child wish is fulfilled, a contralateral salpingo-oophorectomy with a total hysterectomy can be considered especially in HGSC. (Belgian guideline 2010; V, B)
    - A biopsy of the contralateral ovary can be considered in case of conservative surgery but only when clinically suspect. (Consensus WG; V, B). Routine performance of wedge biopsy of normally looking contralateral ovary can be associated with postoperative adhesions that may negatively influence fertility and does not improve surgical staging. (Belgian guideline 2010; V, B)
    - Endometrial curettage is recommended in case of endometrioid or SCSTs to exclude an associated primary endometrial cancer. (Consensus WG; IV, A)

STAGE II, III AND IV (based on malignant pleural effusion)

- The selection of patients for primary debulking surgery or neoadjuvant treatment to be carried out by gynecological oncologist and in multidisciplinary setting. Management of ovarian cancer in high volume hospitals seems to be associated with improved survival and improved quality of life (QoL). (ESMO-ESGO 2019; IV, A)
- Criteria for primary chemotherapy and for interval debulking surgery can be found in Table 3 in the Appendix I) in FIGO stage IIIC and IV ovarian carcinoma (Ignace Vergote et al. 2013).
- Optimal cytoreductive surgery is defined as no residual tumor and should be aimed for. Leaving any residual tumor is sometimes unavoidable but has a strong negative impact on survival (Andreas du Bois et al. 2009; Ignace Vergote et al. 2010). (Belgian guideline 2010; IV, B)
- Primary cytoreductive surgery is the standard of care in advanced ovarian cancer when complete resection is feasible based on imaging and/or open laparoscopy and the general condition of the patient (ESMO-ESGO 2019; IV, B)
- If a complete cytoreductive surgery is not feasible at primary debulking based on imaging, neoadjuvant therapy should be chosen for those tumors that are sensitive. (Ignace et al. 2010). (Consensus WG; I, A)
- If primary cytoreductive surgery is not possible, an open laparoscopy to obtain histological diagnosis, to exclude early disease or other primaries, can be considered. If not done, an image guided biopsy of one of the metastases is recommended (I Vergote et al. 2001, 2005). (Belgian guideline 2010; IV, A)
- Patients with a good response after neoadjuvant chemotherapy are candidates for interval debulking surgery (preferentially after 3 courses of chemotherapy) (Ignace Vergote et al. 2010). (Belgian guideline 2010; I, A)
- To obtain optimal surgical cytoreduction, the following surgical procedures can be necessary (Ignace Vergote et al. 2013). (Belgian guideline 2010; IV, A)
    - Resection of the rectosigmoid
    - Partial resection of the diaphragm
    - Hemicolectomy or total colectomy
    - Splenectomy
    - Partial liver resection
    - Cholecystectomy
    - Small bowel resection
    - Resection of all intra- and/or retroperitoneal tumors.
    - Resection of inguinal, axillary, paracardiac or retrocrural LN
- In case of stage IV due to malignant pleural cytology, a radical cytoreductive surgery is recommended as in stage III. (Belgian guideline 2010; IV, A)
- Accurate documentation of the peroperative findings should be done. (Consensus WG; V, A). The report should include at least:
    - 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 mesentery, pelvic peritoneum, parietal peritoneum and the internal genitals.
- There is no evidence to support a second look surgery (= surgery when chemotherapy is finalised) (A du Bois et al. 2005). (Belgian guideline 2010; IV, A)
- In case of stage III: pleural puncture for cytological examination of pleural fluid

1.1.5.2 Adjuvant treatment

STAGE I

- Tumor grade, staging quality, tumor substage (A,B,C), histological type according to World Health Organization (WHO) classification and rupture are the most significant independent prognostic factors in stage I ovarian cancer and have direct impact on adjuvant treatment decision. (Belgian guideline 2010; IV, A)
- In patients with high grade tumors, clear cell tumors, or mucinous carcinoma of the infiltrative type, platinum-based chemotherapy is recommended (Trimbos et al. 2003). (Belgian guideline 2010; I, A)
- For patients receiving i.v. carboplatin and paclitaxel, a minimum of 3 cycles is recommended except for the high-grade serous subgroup or stage IC (any histological type), for whom 6 cycles are recommended (ESMO-ESGO 2019; II, B)
- Adjuvant chemotherapy should be offered to patients with early stage (stage I–IIA) with the exception of fully staged patients with the following (ESMO-ESGO 2019; II, A):
  - Low grade serous FIGO stage I
  - Low grade endometrioid FIGO stage I
  - Expansile type mucinous FIGO stage IA
- For patients with early-stage disease requiring adjuvant chemotherapy, acceptable treatment regimens are (ESMO-ESGO 2019; A):
  - Carboplatin alone
  - Carboplatin/paclitaxel
- Standard chemotherapy: 4-6 courses of i.v. paclitaxel 175 mg/m² over 3 hours in combination with i.v. carboplatin AUC 5 – 6.q 3 weeks (A du Bois et al. 2005). (Belgian guideline 2010; I, A)
- For patients receiving single-agent adjuvant carboplatin, 6 cycles are recommended. (ESMO-ESGO 2019; I, A)
- Hyperthermic intraperitoneal chemotherapy (HIPEC) is not standard of care. (Consensus WG; II, B)

STAGE II

- Standard chemotherapy: 6 courses of i.v. paclitaxel 175 mg/m² over 3 hours in combination with i.v. carboplatin AUC 5 – 6.q 3 weeks (A du Bois et al. 2005). (Belgian guideline 2010 evidence; V, A)
- The schedule of weekly chemotherapy with carboplatin (AUC2-2.7) and paclitaxel (60 mg/m^2) shows better QoL and reduced toxicity (e.g.,

alopecia, neuropathy) compared with the standard 3-weekly schedule and can be considered. (ESMO-ESGO 2019; I, B)

- Weekly chemotherapy cannot be regarded as a substitute for bevacizumab. (ESMO-ESGO 2019; V, B)
- HIPEC is not standard of care. (Consensus WG; V, A)

STAGE III-IV

- Standard chemotherapy: 6 courses of i.v. paclitaxel 175 mg/m² over 3 hours in combination with i.v. carboplatin AUC 5 – 6.q 3 weeks. (Consensus WG; I, A)
- The schedule of weekly chemotherapy with carboplatin (AUC2-2.7) and paclitaxel (60 mg/m^2) shows better QoL and reduced toxicity (e.g., alopecia, neuropathy) compared with the standard 3-weekly schedule and can be considered. (ESMO-ESGO 2019; I, B)
- Testing for genomic instability (HRD) is recommended (although it is not yet reimbursed in Belgium). It identifies a subgroup of women who are BRCA wild type but derive greater benefit from a PARP inhibitor. (ESMO-ESGO 2019; I, A)
- Different scenario's in patients who had partial or complete response on first line platinum-based chemotherapy (N. Colombo and Ledermann 2021):
    - HRD+/BRCA+: Patients should receive maintenance treatment with a PARP inhibitor (two years for olaparib or three years for niraparib). The combination of olaparib and bevacizumab should be used when bevacizumab is added to front-line chemotherapy although it is not clear that this provides superior results to the use of olaparib alone. The combination bevacizumab and olaparib is not yet reimbursed in Belgium. (ESMO 2021; I, A)
    - HRD+/BRCA-: Patients should receive maintenance treatment with a PARP inhibitor, either olaparib/bevacizumab (if bevacizumab is started with chemo) or niraparib monotherapy. However, the olaparib and bevacizumab combination therapy is not yet reimbursed in Belgium. (ESMO 2021; I, A)
    - HRD-/BRCA-: Patients receiving bevacizumab with front-line chemotherapy and who are HRD-negative do not have a progression-free survival (PFS) benefit from the addition of olaparib to maintenance bevacizumab. If no bevacizumab is given, niraparib should be considered. (ESMO 2021; I, B)
- Weekly chemotherapy cannot be regarded as a substitute for bevacizumab. (ESMO-ESGO 2019; V, B)
- Bevacizumab (15 mg/kg every 3 weeks for maximum of 15 months) improves PFS in patients with stage III–IV ovarian cancer and should be considered in addition to carboplatin and paclitaxel. Subgroups that benefit the most are (ESMO-ESGO 2019+ consensus WG; I, A):
    - Patients with stage III ovarian cancer with residual tumor of more or equal to 1 cm (no reimbursement in Belgium).
    - Patients with stage IV ovarian cancer (reimbursement in Belgium)
- If niraparib is given, it is important to adapt the dose to the weight and number of platelets of the patients (Berek et al. 2018). (Consensus WG; III, A)

- Niraparib monotherapy is licensed for all patients with stage III-IV ovarian cancer (except for stage III who underwent complete primary debulking) who have responded to chemotherapy. Long-term outcome data are not available. (ESMO-ESGO 2019; I, A)
- HIPEC can be considered at interval debulking surgery in multidisciplinary setting when a complete surgical debulking is an option. HIPEC after primary debulking can be considered in multidisciplinary setting but only within a study protocol. (Consensus WG; II, B)

1.1.5.3 Treatment of recurrent disease

- For diagnosis of recurrent disease, abdominal/thoracic CT or MRI or fluorodeoxyglucose (FDG)-PET/CT can be considered. (Belgian guideline 2010 + consensus WG; IV, A)
- Health-related quality of life and patient-reported outcomes should be integrated into the decision-making and the evaluation of treatment efficacy in all patients with recurrent ovarian cancer. (ESMO-ESGO 2019; V, A)
- Secondary debulking surgery can be considered in operable patients with a disease free interval of more than 6 months, a good performance status, no ascites or estimated to be less than 500 ml, and complete resection at primary (or interval) surgery. The aim of secondary cytoreductive surgery should be no residual tumor (Andreas Du Bois et al. 2020; Harter et al. 2009). (Belgian guideline 2010; I, A)
- Complete cytoreductive surgery followed by systemic treatment improves PFS/OS and extends benefit to the next line of treatment in selected patients with first recurrence of ovarian cancer. Patients eligible for cytoreductive surgery should be informed about this option. (ESMO-ESGO 2019; I, A)
- In recurrent ovarian cancer, HIPEC added to cytoreductive surgery has not been proven to be beneficial in appropriately designed prospective studies. It can be considered in multidisciplinary setting but only within a study protocol (Spiliotis et al. 2019; Wang et al. 2019). (ESMO-ESGO 2019 + consensus WG; IV, A)
- The treatment of choice depends on the length of the treatment free interval and previous treatment (A du Bois et al. 2005).
    - If platinum sensitive (> 12 months platinum-free interval): a combination of carboplatin with gemcitabine and bevacizumab, or paclitaxel-carboplatin or pegylated liposomal doxorubicin (PLD)-carboplatin should be considered. In patients with poor general condition, single agent carboplatin or weekly carboplatin-paclitaxel can be considered (Parmar et al. 2003; Pfisterer et al. 2006; Pujade-Lauraine et al. 2010). (Consensus WG; I, A)
    - If intermediate platinum-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 (N. Colombo et al. 2020). (Belgian guideline 2010; I, A)
    - If platinum resistant or platinum refractory: paclitaxel weekly, PLD, or topotecan with bevacizumab should be considered for

patients that have received maximum two lines of chemotherapy. Bevacizumab should be avoided in patients with a history of bowel obstruction or infiltration. In some patients, weekly carboplatin and paclitaxel regimens are indicated. Clinical trial inclusion is recommended (Cadron, Leunen, Amant, et al. 2007; Gordon et al. 2001; Pujade-Lauraine et al. 2010). (Belgian guideline 2010 + consensus WG; I, A)

- For non-platinum chemotherapies, treatment may be continued as long as there is clinical benefit and treatment is well tolerated. (ESMO-ESGO 2019; V, B)
- For platinum-based chemotherapy, 6 cycles are recommended. More or fewer cycles have not been shown to be beneficial, and consideration should be given to the toxicity. (ESMO-ESGO 2019; V, B)
- PARP inhibitors when given as maintenance therapy following a response to platinum-based second or later line of treatment, have proven benefit with respect to PFS and could be recommended. The benefit is greatest in, but is not limited to, patients with a BRCA mutation (only olaparib for BRCA mutations is reimbursed in Belgium). (ESMO-ESGO 2019; I, A)
- For patients with recurrent platinum-sensitive ovarian cancer and a BRCA mutation unable to receive platinum-based therapy, PARP inhibitor monotherapy is an option (not reimbursed in Belgium). (ESMO-ESGO 2019; III, A)
- Malignant bowel obstruction should be managed on an individual basis. There is a lack of evidence for optimal management and a need for clinical trials to evaluate medical, endoscopic and surgical approaches. (ESMO-ESGO 2019; V, A)
- When stopping?
    - Bevacizumab: Recommended length of treatment remains unclear. Treatment is usually continued until disease progression. The continuation of bevacizumab beyond progression has not been evaluated in the recurrent setting. (ESMO-ESGO 2019; V, B)
    - PARP inhibitors: Recommended length of treatment remains unclear. Treatment is usually continued until disease progression. Despite an increase in time to first subsequent therapy or death demonstrated for olaparib and niraparib, the benefit of continuing treatment beyond progression has not been demonstrated conclusively to date. (ESMO-ESGO 2019 + consensus WG; III, A)

1.1.6 Follow-up

- Follow-up should be offered, and the value should be discussed individually with patients, as there is no evidence about the benefit of early diagnosis and treatment of recurrent disease (Andreas Du Bois et al. 2020). (ESMO-ESGO 2019 + consensus WG; II, C)
- Follow-up consultations can be organized according to local practice. (Belgian guideline 2010; V,)
- Routine imaging examinations to screen for recurrent disease are not recommended. (Belgian guideline 2010; IV, C)

1.2 Low grade clear cell serous tumor

In low-grade serous ovarian tumors, chemotherapy is not effective. For low-grade tumors, it is preferred to do primary debulking surgery, even when an optimal debulking cannot be obtained. Hormonal therapy and secondary debulking showed promising response rates (Gershenson et al. 2012). (Belgian guideline 2010 + consensus; IV, B)

1.3 Borderline tumor

A table that explains the difference between invasive epithelial tumors and borderline tumors can be found in the Appendix I (Table 4).

1.3.1 Pathology

- Serous borderline tumors (sBOT) are defined as low-grade epithelial neoplasms, generally in younger women with a favorable prognosis when diagnosed at an early stage (WHO 5th edition)
- According to the most recent WHO classification, extraovarian invasive implants in association with a sBOT are synonymous with extraovarian low-grade serous carcinoma (LGSC). (ESMO-ESGO 2019; V, A)
- In case of extraovarian invasive implants, you should put the diagnosis of BOT in doubt and you should consider it as LGSC. (Consensus WG; IV, A)
- In the 2014 WHO classification, the micropapillary variant of sBOT is also termed non-invasive LGSC but the WG does not support this terminology because it may be misleading for clinical management. (ESMO-ESGO 2019; V, A)
- A borderline endometrioid tumor is an epithelial tumor composed of crowded endometrioid glands lacking confluent of destructive invasion (WHO 5th edition). More than 5 mm of confluent or destructive invasion is considered an endometrioid carcinoma. Microinvasion has been described, but the criteria are difficult to apply. (Consensus WG; IV, B)
- Borderline endometrioid tumors can be differentiated from grade I endometrioid carcinoma using similar criteria as used to differentiate atypical hyperplasia from grade I endometrioid carcinoma in the uterine corpus. (ESMO-ESGO 2019; V, A)
- Mucinous borderline tumors (mBOT) are defined as noninvasive mucinous neoplasm with complex architecture and gastrointestinal type differentiation.
- Destructive stromal invasion is no longer necessary for carcinoma diagnosis (carcinomas may exhibit expansile invasion). (ESMO-ESGO 2019; V, A)
- The term implant should not be used in the context of mBOTs; extraovarian disease in association with an mBOT should be considered as metastasis (from ovary or another organ). (ESMO-ESGO 2019; V, A)

Microinvasion (<5 mm) can be seen in BOTs but these cases should still be regarded as borderline for classification and management purposes. (ESMO-ESGO 2019; V, A)

1.3.2 Staging

- In BOTs, there is no indication for pelvic or para-aortic lymphadenectomy unless they are clinically enlarged. (Belgian guideline 2010; IV, B)
- Peritoneal staging surgery is recommended for BOTs. (ESMO-ESGO 2019; III, B)
- The benefit of restaging is not clear but should be considered in patients with (ESMO-ESGO 2019; IV (micropapillary) III (peritoneal)):
    - sBOTs with micropapillary pattern
    - sBOTs with incomplete visual exploration of the peritoneal cavity

1.3.3 Treatment

- Fertility preserving surgery can be safely offered to all stage IA and IC1 low-grade ovarian carcinomas. (ESMO-ESGO 2019; IV, B)
- In case of apparent stage IA disease in women with a (future) child wish, conservative surgery which consists of a unilateral salpingo-oophorectomy with omentectomy can be performed (Cadron, Leunen, Van Gorp, et al. 2007). Cystectomy can also be considered given the fact it increases the recurrence rate without affecting survival. (Belgian guideline 2010 + consensus WG; IV, B) In case of a cystectomy, the patient should be informed that the chances of having a recurrence is higher and that this is not standard treatment. This decision should be taken during a MOC. (Consensus WG; IV, B)
- In case of apparent stage IB disease and with a child wish, a unilateral salpingo-oophorectomy and cystectomy of the contralateral ovary can be performed or bilateral cystectomy if it is possible. (Belgian guideline 2010 + consensus WG; IV, B)
- 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. (Belgian guideline 2010 + consensus WG; IV, B)
- Close follow-up of the remaining ovary is recommended in this case of fertility sparing surgery. (Belgian guideline 2010 + consensus WG; IV, B)
- There is no role for appendectomy in mBOT when the appendix is macroscopically normal. It should always be inspected during surgery. (ESMO-ESGO 2019 + consensus WG; V, A)
- In advanced stages (II or higher) a total hysterectomy and BSO should be performed, unless the implants are non-invasive and there is a child wish. Fertility preserving surgery could be considered in selected patients with stage II or III sBOTs. (Belgian guideline 2010 + consensus WG; IV, B) (ESMO-ESGO 2019; V, B)
- There is no proven benefit of systematic LN dissection in stage II/III sBOTs. (ESMO-ESGO 2019; IV, B)
- In case of BOTs with invasive implants, lymphadenectomy can be considered if there are suspicious LN. (Belgian guideline 2010 + consensus WG; IV, B)
- A laparoscopic unilateral salpingo-oophorectomy can be considered under the following conditions:
    - A complete inspection and staging of the abdomen is possible and not hampered by adhesions. (Consensus WG; V, B)

- 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. (Consensus WG; V, B)

- Management of sBOT with extraovarian implants
  - All peritoneal implants must be removed. (ESMO-ESGO 2019; IV, A)
  - Adjuvant systemic treatment is not recommended for primary treatment of sBOTs with extraovarian invasive/non-invasive implants. (ESMO-ESGO 2019; III, B)

1.3.4 Follow-up

- CA125 is not reliable in the follow-up of BOTs because it only rises in case the patient has an invasive tumor. Vaginal sonography should be used during follow-up. (Consensus WG; IV, A)

  Patients should be informed about the chance of late recurrence after more than 10 years. (Consensus WG; IV, A)

2. MALIGNANT GERM CELL TUMORS (GCT)

2.1 General recommendations

2.1.1 Diagnosis

- In young adult patients, HCG, a-FP, LDH and inhibin B levels, full blood count and liver and renal function tests should be carried out. (ESMO 2018)
- Diagnostic work-up should include pelvic ultrasound, abdomino-pelvic CT scan and chest X-ray and FDG PET/CT scan in selected cases (GCTs). (ESMO 2018; III, B)
- Histological second opinion by an expert pathologist should always be considered. Diagnosis can be made on conventional histological material. (ESMO 2018; V, B)
- A surgical approach can be carried out through open route or, in selected cases, by laparoscopy and robotics approaches, thereby avoiding tumor rupture during surgery. (ESMO 2018)
- An examination of the abdominal cavity is required. (ESMO 2018)
- The staging procedure includes infracolic omentectomy, biopsy of the diaphragmatic peritoneum, paracolic gutters, pelvic peritoneum and peritoneal washings (macroscopic stage I disease). (ESMO 2018)
- Unilateral salpingo-oophorectomy with preservation of the contralateral ovary and the uterus is considered an adequate surgical treatment for patients with GCTs. This should be considered even in advanced disease because of the sensitivity of the tumor to chemotherapy. (ESMO 2018; V, B)
- No systematic ovarian biopsy is necessary when the contralateral ovary is macroscopically normal. (ESMO 2018; III, A)
- Given the very high chemosensitivity of GCTs, potential nodal metastasis should be cured by adjuvant chemotherapy in these patients. (ESMO 2018; III, A)
- Nodal dissection should be carried out only if evidence of nodal abnormality. (ESMO 2018; III, A)
- The patients should be referred to a center specialized in treating rare ovarian tumors. (Consensus WG; V, A)

2.1.2 Follow-up

- Serum tumor markers (HCG, a-FP and LDH) can correlate with tumor response during chemotherapy. (ESMO 2018 + consensus WG; V, A)
- Early stage GCT: The close surveillance schedule involves regular clinical review with clinical examination, radiological imaging including abdomen-pelvic intravaginal sonography at regular intervals and the monitoring of tumor markers to detect relapse over a period of 10 years, with a gradual increase of the interval between clinical appointments. (ESMO 2018; III, C)
- For GCT, follow-up visits must include history, physical examination with pelvic examination and tumor markers every 3 months for the first 2 years, then every 6 months during the third year and then yearly until progression. (ESMO 2018; V, A)
- A CT scan of the abdomen, pelvis and chest (in case of suspected lung

metastases) and pelvic ultrasound are the most common and useful imaging techniques to evaluate the response to chemotherapy. (ESMO 2018; V, A)

- A pelvic ultrasound should be carried out every 6 months in those patients who have undergone fertility sparing surgery, whereas a CT scan of the abdomen and pelvis is carried out according to clinical indication. (ESMO 2018)
- FDG PET-CT scan for tumor response evaluation or follow-up is not yet recommended. (ESMO 2018; V, D)

2.2 Dysgerminoma

2.2.1 Diagnosis and staging

- Preoperative determination of LDH, alpha-fetoprotein (AFP) and HCG in addition to the diagnosis and staging as described for epithelial tumors is recommended. (Belgian guideline 2010; III, A)
- In premenarchal girls, genetic testing is recommended. (Belgian guideline 2010; V, A)
- Dysgerminomas in stage I can be bilateral in 10-20% of patients. (Belgian guideline 2010; IV, A)

2.2.2 Treatment

A flowchart can be found in the Appendix I (Figure 1). (ESMO 2018)

2.2.2.1 Surgery

- A unilateral salpingo-oophorectomy with surgical staging (see epithelial tumors) is recommended in the following cases. (Belgian guideline 2010; IV, A)
    - Stage IA
    - Unilateral IC stage
- In patients with a child wish and in case of stage IB–disease with macroscopic invasion of both ovaries, a cystectomy/tumorectomy or partial ovariectomy can be considered. (Belgian guideline 2010; IV, A)
- Fertility sparing surgery should be considered also in advanced stages (FIGO stage II-IV). The aim of surgery is to remove as much gross tumor as possible; however, the procedure should be moderated to avoid delays in postoperative chemotherapy and long-term morbidity. (ESMO 2018; IV, B)
- In postmenopausal women with advanced-stage disease or with bilateral ovarian involvement, abdominal hysterectomy and BSO could be carried out with surgical staging. (ESMO 2018; III, A)
- Nodal dissection should be carried out only if evidence of nodal abnormality. (ESMO 2018; III, A)
- In case of incomplete surgical staging for stage I, restaging may be discussed whether it has consequences for the adjuvant treatment. (ESMO 2018 + consensus WG; IV, A)

2.2.2.2 Primary chemotherapy

- Prior to initiation of chemotherapy, fertility preservation should be discussed with a fertility specialist. (Belgian guideline 2010s; V, A)
- 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-cisplatin (EP) with or without bleomycin (BEP). (Belgian guideline 2010; III, A) In case of toxicity or medically ill patients, paclitaxel and carboplatin can be considered. (Consensus WG; III, A)
- Platinum-based regimens are the treatment of choice with the BEP regimen being the most widely used (bleomycin should be omitted to reduce the risk of lung toxicity after the third cycle) for patients with macroscopic residual disease [III, A]. It is recommended to monitor the long diffusion capacity if bleomycin is used. (Belgian guideline 2010; IV, A)
- Bleomycin cannot be given to patients older than 40 years old. (ESMO 2018 + consensus WG; IV, A)

2.2.2.3 Adjuvant treatment

- Stage IA pure dysgerminoma should be treated with surgery only. (ESMO 2018; III, A)
- Adjuvant chemotherapy in IB-IC dysgerminomas is recommended but active surveillance is an option. (ESMO 2018; III, B)
- (B)EP chemotherapy is recommended in stage II, III and IV patients who underwent radical surgery. In case of toxicity or medically ill patient paclitaxel and carboplatin can be considered. (Belgian guideline 2010 + consensus WG; IV, A)

2.2.2.4 Treatment of recurrent or progressive disease

- In patients previously treated with platinum, with platinum-sensitive relapse (progression > 4–6 months after completion of chemotherapy), combinations with platinum should be considered. (ESMO 2018 + consensus WG; IV, C)
- High-dose chemotherapy (HDCT) for recurrent ovarian GCTs may result in durable and prolonged remissions. This should only be offered in specialized centers, capable of performing stem cell transplantation. (ESMO 2018 + consensus WG; IV, C)

2.3 Endodermal sinus tumor and mixed GCT

2.3.1 Treatment

2.3.1.1 Surgery

- Fertility sparing surgery should be considered also in advanced stages. The aim of surgery is to remove as much gross tumor as possible; however, the procedure should be moderated to avoid delays in postoperative chemotherapy and long-term morbidity. (ESMO 2018; IV, B)
- In postmenopausal women with advanced-stage disease or with bilateral ovarian involvement, abdominal hysterectomy and BSO could be carried out with surgical staging. (ESMO 2018; III, A)

2.3.1.2 Adjuvant treatment

- All patients with stage I yolk sac tumors are treated with adjuvant chemotherapy after surgery. (ESMO 2018; III, C)
- Platinum-based regimens are the treatment of choice with the BEP regimen being the most widely used, generally, three cycles of 5-day BEP regimen in completely resected disease and four cycles (bleomycin should be omitted to reduce the risk of lung toxicity after the third cycle) for patients with macroscopic residual disease. (ESMO 2018; III, A)
- 5-day BEP is the most used regimen (early stage GCT). (ESMO 2018; III, A)

2.3.1.3 Treatment of recurrent or progressive disease

- In patients previously treated with platinum, with platinum-sensitive relapse (progression > 4–6 months after completion of Chemotherapy), combinations with platinum should be considered. (ESMO 2018 + consensus WG; IV, C)
- HDCT for recurrent ovarian GCTs may result in durable and prolonged remissions. This should only be offered in specialized centers, capable of performing stem cell transplantation. (ESMO 2018 + consensus WG; IV, C)

2.3.2 Follow-up

- Regular determination of the AFP level in patients with an endodermal sinus tumor is recommended. (Belgian guideline 2010; IV, A)

2.4 Pure immature teratoma

2.4.1 Diagnosis

- Immature tumors are graded based on the amount of immature neuroepithelial tissue according to the classification of Norris et al (Norris, Zirkin, and Benson 1976). (Belgian guideline 2010; IV, A)

2.4.2 Treatment

A flowchart can be found in the Appendix I (Figure 2). (ESMO 2018)

2.4.2.1 Surgery

- Unilateral salpingo-oophorectomy with preservation of the contralateral ovary and the uterus is now considered as the standard surgical treatment for young patients. (ESMO 2018; IV, B)
- Systematic ovarian biopsy is not necessary when the contralateral ovary is macroscopically normal. (ESMO 2018; III, B)
- In case of macroscopic bilateral ovarian diseases, preservation of at least a healthy part of one ovary (unilateral salpingo-oophorectomy and contralateral cystectomy) and the uterus should be encouraged. (ESMO 2018; IV, B)
- In postmenopausal women and in patients with advanced-stage disease or with bilateral ovarian involvement, abdominal hysterectomy and BSO could be carried out with surgical staging. (ESMO 2018; III, A)
- Any resectable residual disease should be removed, particularly for patients with normal serum marker and for patients with immature

teratoma in order to avoid the growing teratoma syndrome. A second look debulking might be indicated. (ESMO 2018; III, A)

2.4.2.2 Adjuvant treatment

- Patients with stage IA grade 1 immature teratoma do not require further adjuvant chemotherapy after adequate surgical staging. (ESMO 2018; III, A)
- Adjuvant chemotherapy in stage IA-IC G2-G3 immature teratoma is recommended but active surveillance is an option. (ESMO 2018; III, B)
- Adjuvant chemotherapy in stage II-IV immature teratoma is recommended. (Consensus WG; III, A)
- Platinum-based regimens are the treatment of choice with the BEP regimen being the most widely used, generally, three cycles of 5-day BEP regimen in completely resected disease and four cycles (bleomycin should be omitted to reduce the risk of lung toxicity after the third cycle) for patients with macroscopic residual disease. (ESMO 2018; III, A)

2.4.3 Follow-up

- A yearly abdominal MRI should be considered life-long in cases with incomplete resection or mature residuals after chemotherapy. (Belgian guideline 2010 + consensus WG; V, B)

3. SEX CORD STROMAL TUMOR (SCST)

3.1 General recommendations

3.1.1 Diagnosis and staging – general

- In young adult patients, hCG, a-FP, LDH and inhibin B levels, full blood count and liver and renal function tests should be carried out (ESMO 2018)
- Histological second opinion by an expert pathologist should always be considered. Diagnosis can be made on conventional histological material. Additional mutational analysis can be useful in differentiation between different tumor types. (ESMO 2018 + consensus WG; V, B)
- For SCSTs, retroperitoneal evaluation is not mandatory. (ESMO 2018; III, A)
- Conservative surgery is also an acceptable approach in young patients with stage I SCSTs. Endometrial curettage is recommended when considering FSS. (ESMO 2018; IV, B)
- In postmenopausal women and in patients with advanced-stage disease or with bilateral ovarian involvement, abdominal hysterectomy and BSO should be carried out with surgical staging for SCST. (ESMO 2018; III, A)
- The patients should be referred to a center specialized in treating rare ovarian tumors. (Consensus WG; V, A)

3.2 Granulosa cell tumor

3.2.1 Diagnosis

- Neoplasms of pure ovarian stroma: in morphologically ambiguous cases, an immunopanel of inhibin alpha, calretinin and FOXL2, plus mutational analysis for FOXL2 (402C-G), is useful to confirm adult granulosa cell tumor (AGCT). (ESMO 2018; V, B)
- An endometrial curettage must be carried out to rule out concomitant uterine cancers in patients with AGCT. (ESMO 2018; IV, B)
- Determination in serum of inhibin B and/or AMH should be performed in all cases with suspicion of an AGCT. (ESMO 2018; IV, A)

3.2.2 Treatment

A flowchart can be found in the Appendix I (Figure 3) (ESMO 2018)

3.2.2.1 Surgery

- Conservative surgery is also an acceptable approach in young patients with stage I. (ESMO 2018; IV, B)
- Preservation of the uterus and contralateral ovary seems to be safe in macroscopic stage IA disease but should not be carried out in stages > I (ESMO 2018; IV, B).
- In postmenopausal women and in patients with advanced-stage disease or with bilateral ovarian involvement, abdominal hysterectomy and BSO should be carried out with surgical staging. (ESMO 2018; III, A)
- Retroperitoneal evaluation is not mandatory because of the very low

incidence of retroperitoneal metastases in early stage disease. (ESMO 2018; III, A)

- Debulking surgery remains the most effective treatment of advanced ACGT. (ESMO 2018; III, A)

3.2.2.2 Adjuvant treatment

Stage I AGCT

- Stage IA AGCT disease has an excellent prognosis after surgery alone and does not require adjuvant therapy. (ESMO 2018; III, A)
- Adjuvant therapy should be considered for AGCT stage IC2-IC3. In these cases, platinum-based chemotherapy is the treatment of choice. (ESMO 2018; III, A)
- BEP is the most commonly used regimen. (ESMO 2018; III, A)
- Alternative chemotherapy options include paclitaxel and carboplatin [III, B], EP, cyclophosphamide-doxorubicin-cisplatin (CAP) or platinum agent alone. (ESMO 2018; III, A)

Stage II, III and IV AGCT

- Platinum-based chemotherapy is currently used for patients with advanced-stage AGCTs. (ESMO 2018 + consensus WG; III, A)
- In case of residual disease, 4 cycles of BEP are recommended. In case of no residual disease, 3 cycles of BEP are recommended (ESMO 2018 + consensus WG; III, A)

3.2.2.3 Treatment of recurrent or progressive disease

- Debulking surgery remains the most effective treatment of recurrent AGCT. (ESMO 2018 + consensus WG; III, A)
- Platinum-based chemotherapy is currently used for patients with recurrent disease: (B)EP (if not used before) or carboplatin/paclitaxel. (ESMO 2018 + consensus WG; III, A)
- Response to GnRH agonists, tamoxifen, progestin and AIs has been reported and could be an interesting option specifically for adult GCT. (ESMO 2018; IV, B)
- BEP regimen for three cycles or six cycles of carboplatin/paclitaxel is recommended for postoperative chemotherapy and patients with recurrent AGCTs. (ESMO 2018; III, A)

3.2.3 Follow-up

- For AGCTs, follow-up visits including physical exam and tumor markers must be carried out every 6 months starting from the third year and this frequency should be maintained indefinitely. (ESMO 2018; V, B)
- Serum tumor markers (inhibin B or AMH) can correlate with tumor response during chemotherapy. (ESMO 2018 + consensus; WG V, A)
- A pelvic ultrasound should be carried out every 6 months in those patients who have undergone FSS, whereas a CT scan of the abdomen and pelvis is carried out according to clinical indication. (ESMO 2018)
- FDG-PET/CT scan for tumor response evaluation or follow-up is not yet recommended. (ESMO 2018; V, D)

3.3 Sertoli leydig cell tumor (SLCT)

3.3.1 Diagnosis and staging

- If available, DICER1 determination can support the pathological diagnosis (Goulvent et al. 2016). (No evidence level in Belgian guideline 2010s; IV, A)
- Determination of serum testosterone should be performed in all cases with suspicion of a SLCT in addition to the diagnosis and staging as described for epithelial tumors. (Belgian guideline 2010; V, A)

3.3.2 Treatment

A flowchart can be found in the Appendix I (Figure 4) (source EE)

3.3.2.1 Surgery

- Conservative surgery is also an acceptable approach in young patients with stage I. (ESMO 2018; IV, B)
- In postmenopausal women and in patients with advanced-stage disease or with bilateral ovarian involvement, abdominal hysterectomy and BSO should be carried out with surgical staging. (ESMO 2018; III, A)
- Retroperitoneal evaluation is not mandatory because of the very low incidence of retroperitoneal metastases in early stage disease. (ESMO 2018; III, A)
- Debulking surgery remains the most effective treatment of advanced AGCT. (ESMO 2018; III, A)

3.3.2.2 Adjuvant treatment

- BEP is the most commonly used regimen [III, A]. Alternative chemotherapy options include paclitaxel and carboplatin [III, B], EP, CAP or platinum agent alone. (ESMO 2018; III, A)
- For SLCTs, postoperative adjuvant chemotherapy should be considered for patients with stage I poorly differentiated or heterologous elements (mesenchymal type). (ESMO 2018; IV, B)
- Platinum-based chemotherapy is currently used for patients with advanced-stage SCSTs or recurrent disease. (ESMO 2018; III, A)
- BEP regimen for three cycles or six cycles of carboplatin/paclitaxel is recommended for postoperative chemotherapy and patients with recurrent SCSTs. (ESMO 2018; III, A)
- For patients with persistent SLCTs, adjuvant chemotherapy should be considered. (ESMO 2018; III, B)

3.3.2.3 Treatment of recurrent or progressive disease

- Debulking surgery remains the most effective treatment or recurrent AGCT. (ESMO 2018; III, A)
- Platinum-based chemotherapy is currently used for patients with recurrent disease. (ESMO 2018; III, A)
- BEP regimen for three cycles or six cycles of carboplatin/paclitaxel is recommended for postoperative chemotherapy and patients with recurrent SCSTs. (ESMO 2018; III, A)

3.3.3 Follow-up

- A CT scan of the abdomen, pelvis and chest (in case of suspected lung metastases) and pelvic ultrasound are the most common and useful imaging techniques to evaluate the response to chemotherapy. (ESMO 2018; V, A)
- For SCSTs, follow-up visits including physical exam and tumor markers must be carried out every 6 months starting from the third year and this frequency should be maintained indefinitely. (ESMO 2018; V, B)
- A pelvic ultrasound should be carried out every 6 months in those patients who have undergone FSS, whereas a CT scan of the abdomen and pelvis is carried out according to clinical indication. (ESMO 2018)
- FDG PET-CT scan for tumor response evaluation or follow-up is not yet recommended. (ESMO 2018; V, D)
- Regular determination of the serum testosterone level can be performed in case these levels were increased at diagnosis. (Belgian guideline 2010; V, B)

3.4 Small cell carcinoma of the ovary hypercalcemic type

- All suspected cases should benefit from a review by an expert pathologist and be discussed in a specialized tumor board. (ESMO 2018; V, A)
- Optimal treatment: a multimodal approach including chemotherapy (ESMO 2018; III, B), radical surgery (ESMO 2018; IV, A), HDCT (ESMO 2018; II, C) and RT (ESMO 2018; IV, C)
- Debulking surgery (initial or interval) remains the most effective treatment. (ESMO 2018; IV, A)
- Combination of a cisplatinum- and etoposide-based therapy is the most appropriate for all stages. (ESMO 2018; III, B)
- The use of pelvic radiotherapy, either concurrently or sequentially to HDCT and autologous stem cell transplantation, may be considered for patients after surgery. (ESMO 2018; IV, C)
- Efforts should be made to treat patients in a more homogeneous way through international networks. (ESMO 2018; V, A)
- The patients should be referred to a center specialized in treating rare ovarian tumors. (Consensus WG; V, A)
- A flowchart can be found in the Appendix I (Figure 5) (ESMO 2018)

Appendix I:

Table 2 Criteria for assignment of primary site in extrauterine HGSC

Criteria	Primary site	Comment
STIC present	Fallopian tube	Regardless of presence and size of ovarian and peritoneal disease
Invasive mucosal carcinoma in tube, with or without STIC	Fallopian tube	Regardless of presence and size of ovarian and peritoneal disease
Fallopian tube partially or entirely incorporated into tubo-ovarian mass	Fallopian tube	Regardless of presence and size of ovarian and peritoneal disease
No STIC or invasive mucosal carcinoma in either tube in presence of ovarian mass or microscopic ovarian involvement	Ovary	Both tubes should be clearly visible and fully examined by a standardised SEE-FIM protocol Regardless of presence and size of peritoneal disease
Both tubes and both ovaries grossly and microscopically normal (when examined entirely) or involved by benign process in the presence of peritoneal HGSC	Primary peritoneal HGSC	As recommended in the 2014 WHO classification [7], this diagnosis should only be made in specimens removed at primary surgery before any chemotherapy; see below for samples following chemotherapy
HGSC diagnosed on small sample, peritoneal/omental biopsy or cytology, OR HGSC examined post-chemotherapy	Tubo-ovarian	Note: this should be supported by clinicopathological findings to exclude mimics, principally uterine serous carcinoma

HGSC, high-grade serous carcinoma; SEE-FIM, Sectioning and Extensively Examining the FIMbriated End; STIC, serous tubal intraepithelial carcinoma; WHO, World Health Organization.

FIGO Staging 2018

STAGE I: Tumor confined to ovaries

- IA Tumor limited to 1 ovary, capsule intact, no tumor on surface, negative washings.
- IB Tumor involves both ovaries, otherwise like IA.
- IC Tumor limited to 1 or both ovaries
    - IC1Surgical spill
    - IC2 Capsule rupture before surgery or tumor on ovarian surface.
    - IC3 Malignant cells in the ascites or peritoneal washings

STAGE II: Tumor involves 1 or both ovaries with pelvic extension (below the pelvic brim) or primary peritoneal cancer

- IIA Extension and/or implant on uterus and/or Fallopian tubes
- IIB Extension to other pelvic intraperitoneal tissues

STAGE III: Tumor involves 1 or both ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal LNs

- IIIA (Positive retroperitoneal LN and /or microscopic metastasis beyond the pelvis)
    - IIIA1 Positive retroperitoneal LN nodes only
        - IIIA1(i) Metastasis ≤ 10 mm
        - IIIA1(ii) Metastasis > 10 mm
- IIIA2 Microscopic, extrapelvic (above the brim)peritoneal involvement ± positive retroperitoneal LN
- IIIB Macroscopic, extrapelvic, peritoneal metastasis ≤ 2 cm ± positive retroperitoneal LN. Includes extension to capsule of liver/spleen.
- IIIC Macroscopic, extrapelvic, peritoneal metastasis > 2 cm ± positive retroperitoneal LN. Includes extension to capsule of liver/spleen.

STAGE IV: Distant metastasis excluding peritoneal metastasis

- IVA Pleural effusion with positive cytology
- IVB Hepatic and/or splenic parenchymal metastasis, metastasis to extra-abdominal organs (including inguinal LN and LN outside of the abdominal cavity)

Table 3 Criteria for primary chemotherapy and for interval debulking surgery in FIGO stage IIIC and IV

Criteria	Belgian criteria
diagnosis:	Biopsy with histologically proven epithelial ovarian (or tubal or peritoneal) cancer FIGO stage IIIC-IV **or** if a biopsy is impossible: fine needle aspiration proving the presence of carcinoma cells in patients with a suspicious pelvic mass if CA125 (KU/L)/carcinoembryonic antigen (CEA) (ng/mL) ratio is > 25. If the serum CA125/CEA ratio is ≤ 25, imaging or endoscopy is obligatory to exclude a primary gastric, colon or breast carcinoma
abdominal metastases:	involvement of the superior mesenteric artery
	diffuse deep infiltration of the radix mesenterii of the small bowel
	diffuse and confluent carcinomatosis of the stomach and/or small bowel involving such large parts that resection would lead to a short bowel syndrome or a total gastrectomy
	intrahepatic metastases
	infiltration of the duodenum and/or pancreas and/or the large vessels of the ligamentum hepatoduodenale, truncus coeliacus or behind the porta hepatis
extra-abdominal metastases:	all excluding: - resectable inguinal LN - solitary resectable retrocrual or paracardial nodes - pleural fluid containing cytologically malignant cells without proof of the presence of pleural tumors
patients characteristics / others	impaired performance status and co-morbidity not allowing a "maximal surgical effort" to achieve a complete resection
	patients' non-acceptance of potential supportive measures as blood transfusions or temporary stoma
Criteria for interval debulking:	- No progressive disease in high-grade serous tumors, **and** - In case of extraabdominal disease at diagnosis the extraabdominal disease should be in complete response or resectable, **and** - Performance status and co-morbidity allowing a maximal surgical effort to no residual diseases.

Table 4 Difference between invasive epithelial tumors and borderline tumors

Invasive epith. tumors	Borderline tumors
• 55 y	• 45 & >1/3 are younger than 40 y
• Serous: >80%	• Mucinous 50% en serous 50%
• 2/3 stage III-IV	• 2/3 Stage I = Fertilityconserving surgery even in stage III
• Surgery / lymphadenectomy	• Surgery without lymphadenectomy
• 6 cycles Carbo/Taxol	• No adjuvant chemotherapy
• Bad survival & rapid relapse	• Excellent survival & few relapse on longterm follow up (10- 15 ys-
• Horm receptor: negative	• Horm receptor: positive
• IVF doesn't increase risk	• IVF increases risk of BOT
• CA 125 follow-up: reliable	• CA 125 follow-up: not reliable
• Increased heridty risk	• No increase in risk of heridty

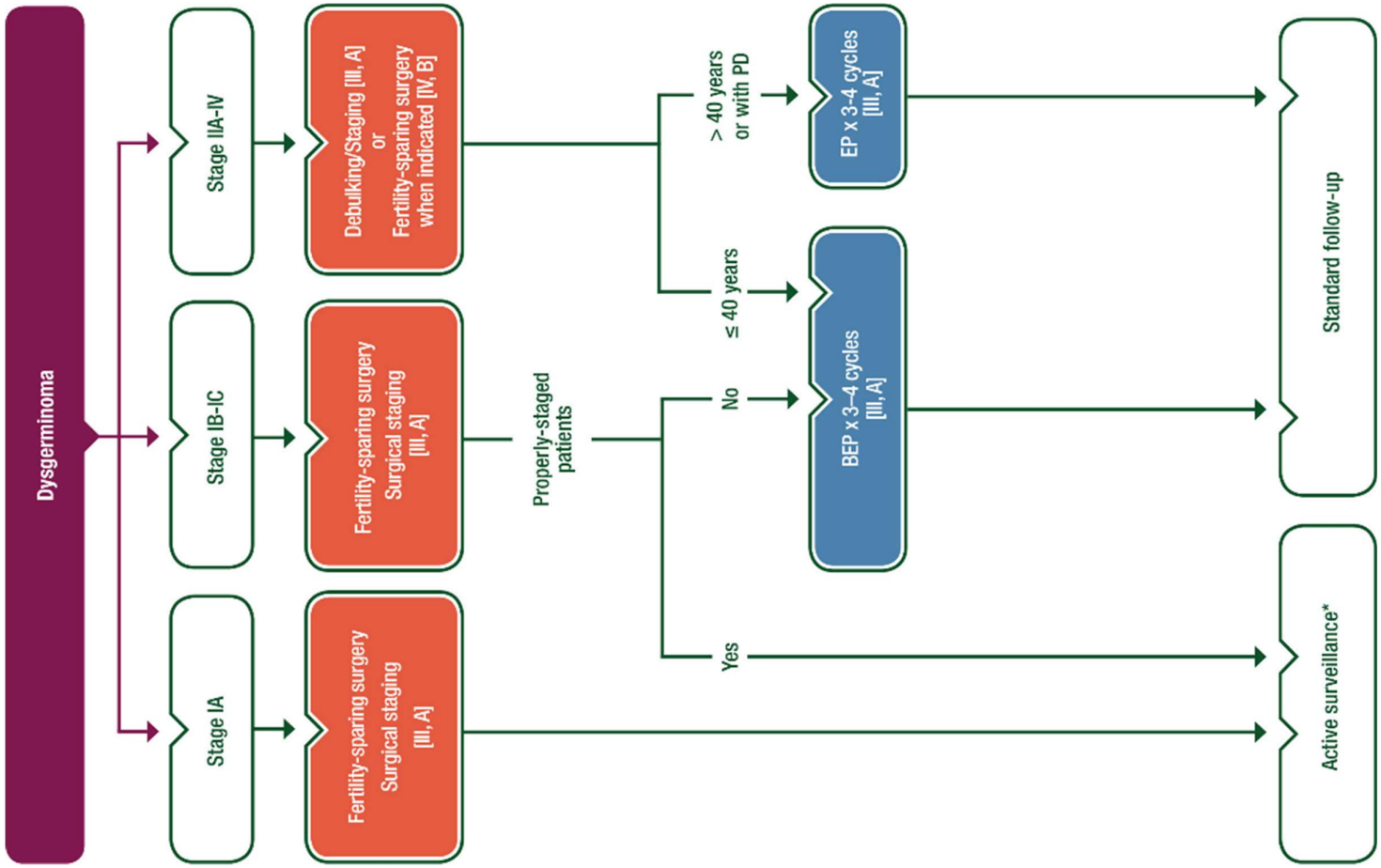

Figure 1 Management of GCTs of the ovary - dysgerminoma

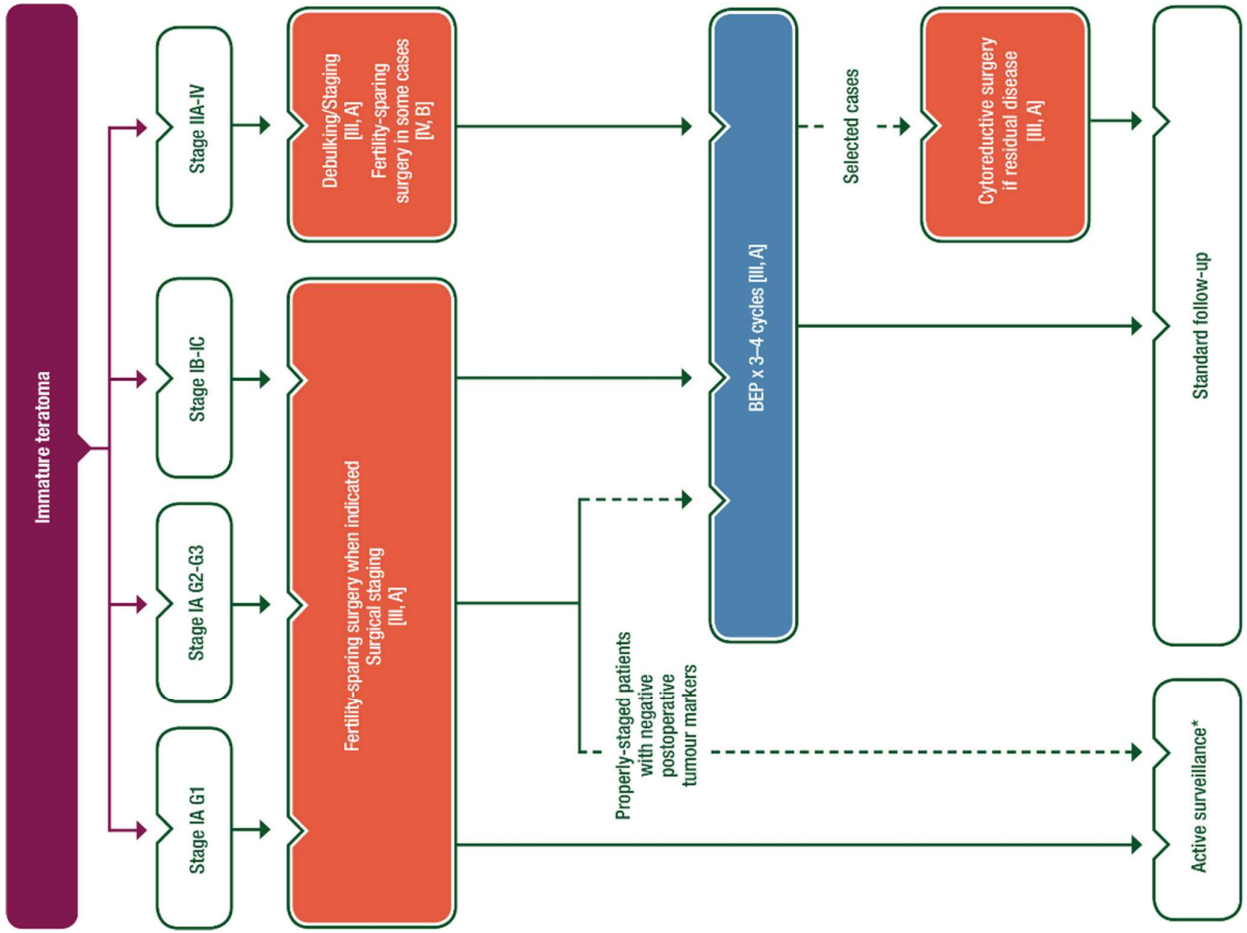

Figure 2 Management of GCTs of the ovary - immature teratoma

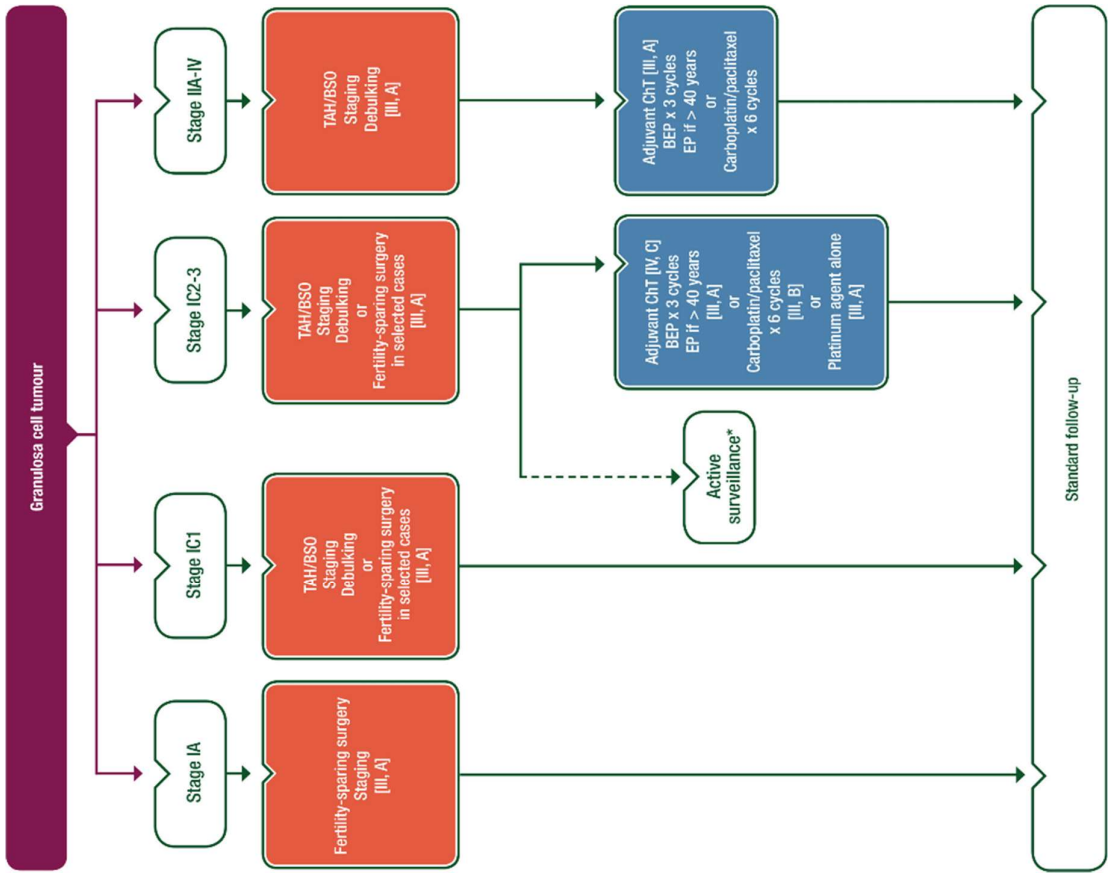

Figure 3 Management of SCSTs of the ovary - granulosa cell tumor

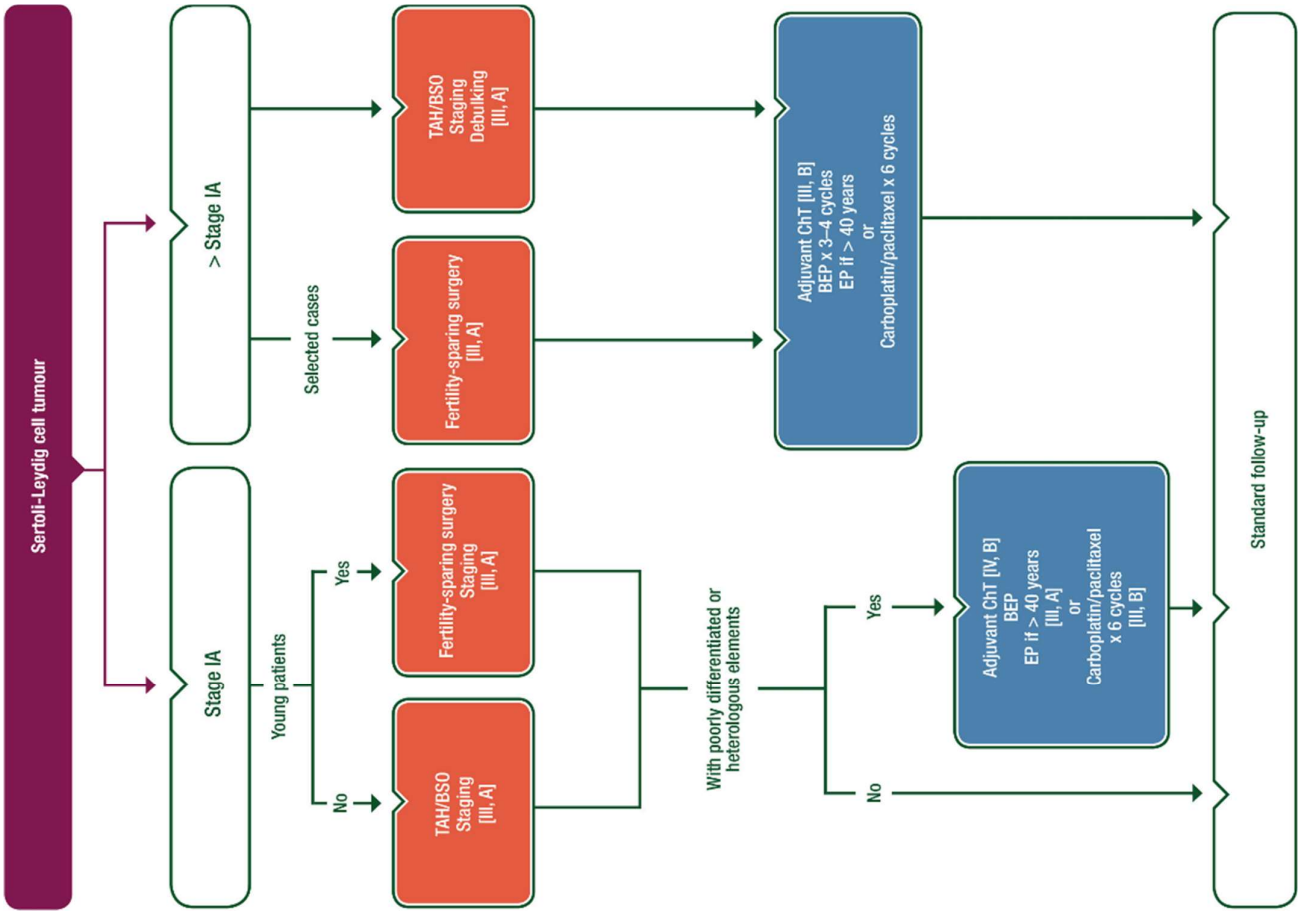

Figure 4 Management of SCSTs of the ovary - Sertoli-Leydig tumor

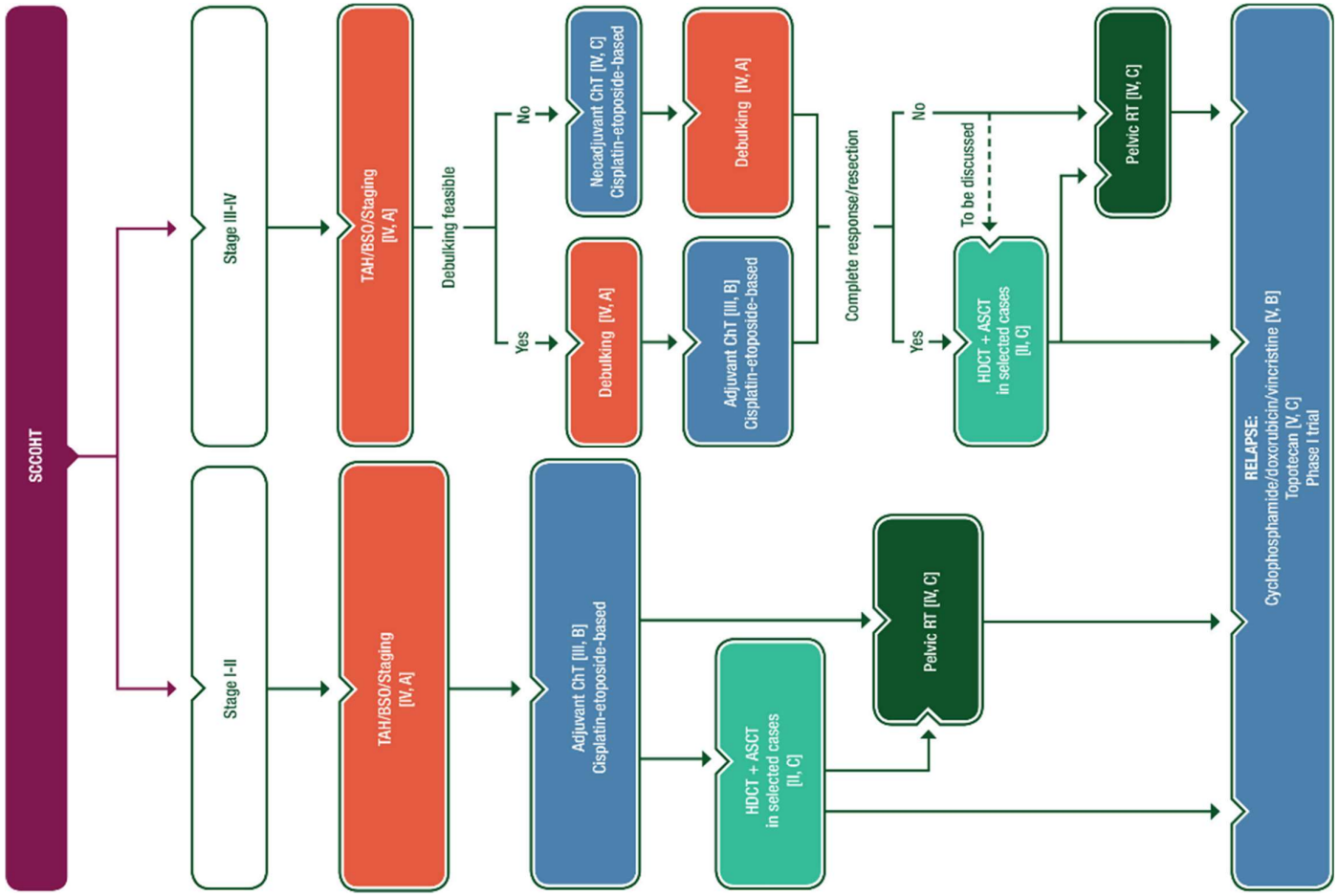

Figure 5 Management of SCCOHT

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