**AN ADAPTED EVIDENCE-BASED CLINICAL PRACTICE GUIDELINE**

**ON**

**MANAGEMENT OF EPITHELIAL OVARIAN TUMORS**

**Overview**

This is an adapted evidence-based clinical practice guideline for the prevention and management of epithelial ovarian tumors.

**Guideline adapter**

**This guideline has been adapted by the Egyptian Universities Obstetrics & Gynecology Guideline Working Group (EUOBGYN-GWG).**

**Release date**

November 2023

**GUIDELINE ADAPTATION METHODOLOGY**

This guideline was produced in accordance with the ADAPTE methodology and procedure for the adaptation of evidence-based clinical practice guidelines published by the ADAPTE Group (Fervers B, et al., Adaptation of clinical guidelines: literature review and proposition for a framework and procedure. Int J Qual Health Care 2006; 18(3): 167-176).

**sources of the guideline**

**This guideline was adapted from:**

1. Fotopoulou C, Planchamp F, Aytulu T, et al. European Society of Gynaecological Oncology guidelines for the peri-operative management of advanced ovarian cancer patients undergoing debulking surgery. Int J Gynecol Cancer. 2021 Sep;31(9):1199-1206.
2. Timmerman D, Planchamp F, Bourne T, et al. ESGO/ISUOG/IOTA/ESGE Consensus Statement on preoperative diagnosis of ovarian tumors. Ultrasound Obstet Gynecol. 2021 Jul;58(1):148-168
3. Fotopoulou C, Hall M, Cruickshank D, et al. British Gynaecological Cancer Society (BGCS) epithelial ovarian/fallopian tube/primary peritoneal cancer guidelines: recommendations for practice. Eur J Obstet Gynecol Reprod Biol. 2017 Jun;213:123-139
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# **INTRODUCTION**

Among Egyptian women, ovarian cancer is the fourth most common cancer, and is the most common gynecologic malignancy in 2020.

* It accounts for 4.1% of all new cases of cancer in Egyptian women.
* A total of 2787 new cases were reported in Egypt in 2020.
* The crude incidence rate is 6 ovarian cancer cases for every 100,000 women.
* A total of 1839 mortality cases of ovarian cancer were reported in Egypt in 2020.

Epithelial ovarian cancer (EOC) is the most common type ovarian cancer. the incidence of EOC is most common in post-menopausal women, peaking in the 60-64 years’ age group.

Unfortunately, about 70% of ovarian cancer cases are detected at advanced stage (FIGO stage-III or IV).

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Number of new cancer cases in Egyptian females in 2020 (Globocan; 2020).

# **DIAGNOSIS**

**Clinical diagnosis of EOC:**

* Women with ovarian cancer will usually report non-specific symptoms, that may be overlooked, misdiagnosed, causing late presentation with advanced disease (Stage III & IV), contributing to the poor prognosis of ovarian cancer.
* Any woman, especially if post-menopausal, with recurrent and persistent symptoms of bloating, dyspepsia, nausea, changes in bowel habits (constipation or diarrhea), early satiety, distension, abdominal or pelvic pain or discomfort, or symptoms suggestive of intestinal obstruction, should be evaluated thoroughly to exclude ovarian cancer.
* Women with recurrent or persistent pelvic symptoms as urinary frequency, urgency, dyspareunia, or changes in menstrual patterns, should be evaluated thoroughly to exclude ovarian cancer.
* Women with a palpable pelvic or abdominal mass, ascites, pleural effusion, persistent or recurrent cough or breathlessness, should be evaluated thoroughly to exclude ovarian cancer.

**Biochemical markers for diagnosis of EOC:**

* Biochemical markers should not be used for diagnosis of ovarian cancer. They may be helpful in establishing a diagnosis as a part of a full evaluation, or for providing baseline values that may be useful in follow up.
* CA-125 serum levels are less useful for providing diagnostic or prognostic information in premenopausal women with suspected ovarian cancer, as it is a nonspecific biochemical marker, that may be elevated in cases of pelvic inflammatory disease, bowel diseases and endometriosis.
* Measuring the serum CA-125 alone is not validated for diagnostic use; however, if the serum level is more than 300 IU/mL, it may be suggestive of serous ovarian cancer.
* When histologic-based diagnosis cannot be obtained, a CA-125 to carcinoembryonic antigen (CEA) ratio of **more than 25:1**, may support the primary diagnosis of ovarian cancer.
* In women with an elevated CA-125, but with a ratio to CEA of **less than 25:1**, and in the presence of elevated CA-19.9, the probability of peritoneal carcinomatosis from GIT tumor is suspected.
* Serum alpha-fetoprotein (AFP)and beta-hCG should be measured in women less than 35 years of age with an ovarian mass, as germ cell tumors are suspected.
* Serum inhibin levels may be done when sex cord stromal tumor of the ovary is suspected or diagnosed.
* Human epididymis protein-4 (HE4), may be a more sensitive diagnostic and prognostic indicator for younger women, as it is not raised in cases of pelvic inflammatory disease and endometriosis, in contrast to CA-125 that is elevated in these conditions.

**The role of histopathology, cytology and frozen section for diagnosis of EOC:**

* **Histopathologic** confirmation through CT guided biopsies, laparoscopic biopsies, or minimally invasive biopsy procedures including paracentesis and thoracocentesis for cytology or needle tissue biopsy, should precede any systemic therapy. **Epithelial ovarian cancer is diagnosed with histologic confirmation in all settings.**
* All patients with histology or cytology showing suspected or actual carcinoma of gynecological origin, should be reviewed at a gynecology multidisciplinary team (MDT) meeting, where a decision for upfront (neoadjuvant) chemotherapy may be offered.
* The provision of a minimum set of clinical and surgical information on the histopathology request form, is crucial to ensure accurate diagnosis and appropriate management. The information should include clinical information about the case, the primary site of the tumor as seen during surgery, the extent of the disease, and the description of the lesions.
* **Cytology**: may be nonspecific, and may not differentiate the histologic type of the ovarian tumor, and may not exclude non ovarian primary malignancies.
* The absence of malignant cells in ascitic fluid does not exclude ovarian malignancy, especially in the presence of cytological evidence of inflammation.
* In about two thirds of patients with known ovarian carcinoma, malignant cells are seen in the ascitic fluid. However, there are strong reservations about using peritoneal or ascitic cytology without histological confirmation in the primary diagnosis of ovarian cancer.
* Where biopsy is not feasible, in patients with poor performance status and advanced disease (Stages III- IV), cytology, together with a CA125/CEA ratio of **>25:1**, may be sufficient for diagnosis.
* In women with pleural effusions, aspiration and examination for malignant cells and cytology should be considered to confirm staging.
* **Frozen section** during surgery may be performed where feasible, especially in cases of exploration of a suspicious adnexal mass, as the results will alter the intra-operative management. The reported accuracy of the technique is more than 95%, however, there remains logistic and expertise limitations to general application of the technique.
* The availability of frozen section may allow the necessary surgical assessment to be completed at the time of initial surgery.
* Frozen section may not be conclusive, and that definitive pathology is the criterion standard of diagnosis.
* In the absence of facilities for frozen section, or in cases of inconclusive frozen section results, a 2-step procedure, where cytoreductive surgery is postponed till after a definitive histopathologic diagnosis is reached, should be preferred.

**Immuno-histochemical studies for epithelial ovarian cancer:**

* Routine histologic processing of formalin-fixed tissue is sufficient for pathologic diagnosis.
* The capabilities for Immuno-histochemical studies will be present in certain centers, the information provided by these studies may be helpful in providing additional confirmatory evidence critical for diagnosis.

**Hormone receptor evaluation in cases with epithelial ovarian cancer:**

* Moderate to strong estrogen receptor staining may be a predictor of response to hormone therapy.

**Requirements for the pathology report:**

* Accurate pathology reports are critical for optimal management of patients with ovarian cancer.
* The Royal College of Pathologists reporting system (RC-Path), the College of American Pathologists (CAP) system and the International Collaboration on Cancer Reporting (ICCR) dataset, are commonly used reporting systems, that should be adopted by histopathologists reporting on epithelial ovarian cancer.

**The role of ultrasound in differentiation between benign and malignant ovarian neoplasms:**

* Ultrasound examination, both abdominal and vaginal, is a fundamental measure for the evaluation of women with a clinical presentation suggestive of ovarian cancer.
* Subjective assessment by an expert (Level III) ultrasound examiner, has shown to have the best chance for distinguishing between benign and malignant ovarian tumors.

**The role of CT, MRI, PET-CT in diagnosis of ovarian neoplasms:**

* CT abdomen, pelvis with oral and IV contrast is recommended to document the actual burden of the disease.
* CT chest is not mandatory in every case, chest x-ray is more cost-effective in limited resource circumstances.
* MRI may be used as a second step diagnostic modality, to further differentiate between benign and malignant masses.
* In cases of suspected recurrence, CT thorax, abdomen and pelvis is recommended as the primary imaging modality.
* PET-CT may be required in cases of suspected recurrence, due to the limitations in availability and cost, it should only be requested by a multidisciplinary team (MDT)consultation, and only when CT has not demonstrated recurrence.
* PET-CT cannot differentiate reliably between borderline and benign tumors.

**The indications of preoperative image-guided biopsy/FNAC:**

* Percutaneous-image guided biopsy, or fine needle aspiration cytology (FNAC), are only indicated in advanced (stage III/IV) tumors prior to neoadjuvant chemotherapy
* If percutaneous image guided biopsy is not possible or inadequate, diagnostic laparoscopy and biopsy may be required.
* Histopathological examination of tissue samples is preferred to cytology.

**The role of laparoscopy in diagnosis and staging of EOC:**

* Laparoscopy has been investigated as a tool to assess operability and remains the best approach at present before proceeding to laparotomy. Laparoscopy can be used to obtain tissue for histologic diagnosis and assessment of the extent of disease for determination of whether to use neoadjuvant chemotherapy (NACT) in limited or enhanced settings.
* The preferred approach to surgical staging of suspected ovarian cancer is via a midline vertical incision; data have not yet been provided to validate the safety and equivalence of minimally invasive surgery (MIS) for newly diagnosed EOC care in any resourced setting.
* The use of laparoscopy for surgical staging in patients with apparent early-stage ovarian cancer is not recommended for basic or limited-resource settings because of the lack of access to expert laparoscopic oncology surgeon(s) and access to necessary equipment for advanced laparoscopy.
* The safe selection of patients for MIS requires surgical oncology experience beyond laparoscopy surgical techniques.
* In enhanced settings with capacity for frozen section pathology, MIS may be offered for apparent early-stage ovarian cancer. In such select cases, patients and surgeons must be prepared to convert to a laparotomy procedure if comprehensive surgical staging cannot be completed via MIS

# **SURGICAL TREATMENT OF EARLY OVARIAN CANCER CASES: STAGE I & II**

**Where and who should perform the surgery?**

* Cases of early ovarian cancer, stage I and II, should be performed at a specialised centre with capabilities for cytoreductive surgery.
* It is recommended that the surgery is carried out by a Gynaecologic Oncologist trained and experienced in the management of ovarian cancer.

**What is the aim of surgery?**

* The aim of surgery for early ovarian cancer (stage I and II) is complete macroscopic tumour resection and adequate surgical staging.

**What are the steps of surgery?**

* A midline vertical incision laparotomy with adequate exposure for thorough examination of the entire abdomen and pelvis.
* Aspiration of ascites when present or peritoneal washings (lavage) for cytological examination. The specimen should reach the laboratory as early as possible.
* All peritoneal surfaces should be visualized and any abnormal peritoneal surface or adhesions excised and biopsied. In case of normal peritoneal surfaces, random peritoneal biopsies should be taken from pelvis, utero-vesical peritoneal fold, recto-uterine pouch, bilateral paracolic gutters, under-surface of the diaphragm etc.
* Total abdominal hysterectomy with bilateral salpingo-oophorectomy, excising the mass intact as far as possible using an extraperitoneal approach to prevent intra-operative spillage.
* In case of the rupture of the capsule, it is important to differentiate between pre-operative spontaneous tumour rupture and intra-operative rupture caused by the surgeon and document the same.
* Total omentectomy (usually infracolic)
* Pelvic and para-aortic lymph node assessment.
* Appendicectomy (in mucinous tumours)

**Prognostic values of full surgical staging in early ovarian cancer**

* Full surgical staging in early stage EOC will
  + Upstage about 30% of cases.
  + Allow for assessing the benefit of adjuvant chemotherapy in early-stage disease.

**The role of lymphadenectomy in early ovarian cancer**

* Complete pelvic and retroperitoneal lymphadenectomy should be performed in all cases.
* The upper limit of lymphadenectomy should be at the level of the renal vessels in high-risk patients, and should at least be to the level of inferior mesenteric artery in lower risk patients.
* Present evidence does not allow recommendation of a formal systematic lymphadenectomy in patients where the disease is low grade and is confined to the ovaries.
* The rate of positive lymph nodes in stage I mucinous cancer is extremely low (near 0%), and there is no value in performing lymphadenectomy given the potential morbidity of the procedure**.**

**The role for fertility-sparing surgery in young women with early ovarian cancer**

* Fertility-sparing surgery can be considered following thorough discussion with the patient about the potential risk of recurrent epithelial ovarian cancer.
* Patients with grade 1 or 2 mucinous, serous, endometrioid, or mixed histology and FIGO **stage IA or stage IC with unilateral ovarian involvement**, may be eligible for uterus/contra-lateral ovary preserving surgery, in combination with surgical staging of the remaining peritoneal surfaces and/or retroperitoneal lymph node chains (dependent upon histological subtype).
* These patients should be encouraged to have completion surgery after their childbearing has been completed.

**What should the surgical report include?**

* The surgeon should carefully document
  + Extent of initial disease.
  + Amount, extent and location of the residual disease.
  + Whether complete or incomplete resection has been performed.
  + If there was rupture of the tumour mass.

**What is the role of frozen section in surgery?**

* Whenever exploration is being done for a suspicious adnexal mass, frozen section facility is required as it can have a significant impact on extent of surgery and the outcomes.
* The reported accuracy of frozen section is about 95-97%.
* In the absence of frozen section or in the case of an inconclusive frozen section, a two-step procedure should be preferred.

**Is there a role for robotic or laparoscopic intervention?**

* Presently, there is no evidence to suggest that laparoscopic or robotic staging of early epithelial ovarian cancer is equivalent or superior to staging by laparotomy.
* In select patients, minimally invasive procedures may be used for surgical staging and to achieve surgical goals surgery is performed by an experienced Gynaecologic Oncologist trained in advanced minimal access surgery.

# **SURGICAL TREATMENT OF ADVANCED CASES OF OVARIAN CANCER**

**Who should operate on advanced ovarian cancer?**

* Evidence suggests that patients treated by a Gynecologic Oncologist are more likely to undergo proper staging, optimal cytoreduction, receive chemotherapy and have better survivals than those treated by General Gynecologists or surgeons.

**What is the difference between Primary debulking surgery (PDS) and Interval debulking surgery (IDS)?**

* Neo-adjuvant chemotherapy (NACT), with up to three cycles of platinum-based chemotherapy, followed by interval debulking surgery (IDS), is non-inferior to primary upfront debulking surgery, followed by adjuvant platinum-based chemotherapy.
* NACT-IDS has reduced morbidity compared to PDS, in patients presenting with significant disease burden, or in situations where there is uncertainty about the possibility of optimal removal of tumor.

**What is the goal of Cytoreductive surgery (CRS)?**

* The goal of CRS is to achieve **complete** cytoreduction where there is no visible or palpable disease, leaving no more than microscopic residual disease.
* If complete CRS is not possible, the goal would be to achieve **optimal** cytoreduction, where residual disease is less than 1cm in maximum diameter or thickness.
* **Structures removed in CRS:**
* CRS should include excision of all ovarian masses, Fallopian tubes, total hysterectomy, total omentectomy, pelvic and para-aortic lymphadenectomy, peritoneal cytology of aspirated ascitic or peritoneal lavage fluid, and removal of any other visible or palpable metastatic deposits within the abdomen and pelvis.
* **Para-aortic lymphadenectomy (PAL):**
* Bulky lymph nodes in advanced disease should be removed, if this will complete macroscopic clearance, as this has been shown to significantly prolong survival and is part of the debulking.
* **The role of Minimally Invasive Surgery in CRS:**
* It should be emphasized that the surgical approach for cytoreductive surgery for ovarian cancer should be open laparotomy and not by minimal access route.
* Minimally invasive procedures like laparoscopy or mini-laparotomy may be used to assess whether optimal cytoreductive surgery is feasible and safe in an individual patient.
* **The role of ultraradical surgery:**
* To achieve the goal of complete or optimal cytoreduction, extensive resection of abdominal metastatic disease has been recommended for patients who can tolerate this surgery.
* The procedures include peritonectomy, bowel resections, diaphragmatic stripping or excision, splenectomy, distal pancreatectomy, partial hepatectomy, cholecystectomy, appendicectomy, porta hepatic nodal excision, urinary tract excisions including partial cystectomy or ureteric resection with suitable reconstruction.

# **CHEMOTHERAPY IN OVARIAN CANCER**

**Assignment of patients for Neo-Adjuvant chemotherapy (NACT):**

* Prior to initiation of therapy, women with suspected stage III/IV invasive epithelial ovarian cancer should be evaluated by a multidisciplinary team, including a gynaecologic-oncologists, medical oncologists, pathologists, intensivists, clinical pharmacologists, in a multidisciplinary dedicated setting, to determine the optimum primary treatment for that patient.
* NACT is associated with less peri-operative morbidity and mortality at interval cytoreductive surgery.
* NACT should be offered to patients with high peri-operative risk features:
  + Advanced age
  + Multiple co-morbidities
  + Presence of thromboembolism
  + Poor nutritional status with low serum albumin
  + Likelihood of not achieving optimum or complete cytoreduction
* Patients planned to receive NACT should have a histological confirmation of invasive malignancy by core biopsy.
* When it is not possible to safely obtain a biopsy, cytological confirmation of ascitic or pleural fluid could be relied upon for diagnosis, in addition to a Ca-125: CEA ratio of 25 or more, to exclude GIT malignancy.
* 3-4 cycles of NACT are given and the response to treatment is evaluated:
  + Patients with favourable response will probably require surgery alone.
  + Patients with partial response, may be offered extension of NACT up to 6 cycles.
  + Patients with no response will need post-operative Adjuvant chemotherapy (ACT) with different protocol for persistent or recurrent disease.

**Adjuvant Chemotherapy (ACT)for early-stage ovarian cancer (stages I–IIA)**

* Adjuvant chemotherapy does not improve survival for early-stage ovarian cancer patients who have had a **Complete** cytoreductive surgery.
* Patients with stage IA or IB low grade (grade 1) endometrioid, serous, or mucinous ovarian carcinoma who had complete cytoreduction will not require ACT.
* Patients with potential early-stage disease who have an inadequate cytoreductive surgery, should undergo complete surgical cytoreduction prior to ACT decision-making. If this is not possible for any reason, such patients should be offered ACT.
* ACT should be offered to patients with early-stage ovarian cancer with the following:
  + Clear cell Epithelial ovarian cancer **stage I (A, B and C)**
  + Endometrioid Epithelial ovarian cancer **stage IB**
  + Low-grade Serous Epithelial ovarian cancer **stage IB and IC**
  + Mucinous Epithelial ovarian Cancer:
    - **Stage I (A, B)** with infiltrative invasion.
    - **Stage 1C**.

**ACT protocols used for early-stage EOC**

* Acceptable treatment regimens are Carboplatin alone or Carboplatin/paclitaxel
* For patients receiving single-agent adjuvant carboplatin, 6 cycles are recommended.
* For patients receiving carboplatin and paclitaxel, a minimum of 3 cycles is recommended except for the high-grade serous subgroup or **stage more than IC** (any histological type), for whom 6 cycles are recommended.
* Dose dense schedules, intraperitoneal administration, maintenance strategies and targeted therapies are not recommended in early-stage patients.
* Patients receiving primary chemotherapy will be monitored as follows:
  + Every 1–3 cycles: Physical examination, and consider pelvic examination.
  + Interim CBC and chemistry profiles as clinically indicated.
  + CA-125 or other tumor markers levels, as clinically indicated.
  + Chest, abdominal, pelvic CT or MRI with contrast, PET/CT (skull base to mid-thigh), or PET as indicated.
* Carboplatin/paclitaxel every **Three weeks**, remains the standard-of-care chemotherapy of first-line ovarian cancer treatment.
  + **Weekly** chemotherapy with carboplatin (AUC2) and paclitaxel (60 mg/m2) shows better quality of life results and reduced toxicity (e.g., alopecia, neuropathy) compared with the standard three weekly schedule and can be considered.
* **Bevacizumab** (AVASTIN) is a vascular endothelial growth factor inhibitor (VEGFI), given as 10-15 mg/kg, every 3 weeks for up to 22 weeks, improves PFS in patients with stage III–IV ovarian cancer, should be considered in addition to carboplatin and paclitaxel and may be used as upfront (NACT) or adjuvant (ACT) therapy.
* **Single agent platinum** (carboplatin or cisplatin) is an alternative regimen in some patients who are considered unsuitable to receive the combination regimen of paclitaxel and carboplatin.

**What are other regimen options if paclitaxel is not suitable?**

* Patients who are considered unsuitable for paclitaxel-platinum (for example due to risk of peripheral neuropathy), alternative combination regimens include docetaxel (60-75 mg/m2)-carboplatin, gemcitabine-carboplatin or pegylated liposomal doxorubicin (PLD 30 mg/sqm)-carboplatin AUC 5 to be given once in 4 weeks.

**Is there a role for Dose dense chemotherapy?**

* Paclitaxel 80 mg/m2 every 3 weeks, plus carboplatin AUC 5-6 on day 1, improves progression-free (PFS) and overall survival (OS) every 21-day or 28-day schedule in patients who can tolerate this regimen.

# Standard of management of non-high-grade serous EOC

**Role of Adjuvant Chemotherapy (ACT) effective in advanced (Stage III and IV) non-high-grade serous ovarian cancer:**

* PDS with no macroscopic residual disease is of pivotal importance due the low chemosensitivity in low-grade serous, mucinous and clear cell ovarian carcinoma. Even debulking with residual disease <1 cm in low-grade serous ovarian cancer may improve survival when complete cytoreduction is not feasible.
* Carboplatin in combination with paclitaxel is the standard chemotherapy. Addition of bevacizumab should be considered.
* Maintenance antioestrogen therapy after chemotherapy can be considered in low-grade serous ovarian cancer.

**Role of ACT in recurrent non-high-grade serous ovarian cancer:**

* In recurrent low-grade serous, low-grade endometrioid, mucinous and clear cell ovarian carcinoma, chemotherapy is an option, but the magnitude of benefit is uncertain.
* Antioestrogen therapy can be considered in low-grade serous ovarian cancer and low-grade endometrioid ovarian carcinoma.

**The role of Targeted therapy:**

* All patients with high-grade ovarian cancer should be tested for BRCA1 and BRCA2 mutation (germline/ somatic) at diagnosis.
  + Patients with a BRCA mutation and a partial or complete response to front-line platinum-based chemotherapy should receive maintenance treatment with a PARP inhibitor; 2 years for Olaparib.
  + The combination of Olaparib and Bevacizumab should be used when Bevacizumab is added to front-line chemotherapy, though it is not clear that this provides superior results to the use of Olaparib alone.
* Testing for genomic instability (HRD) is recommended. It identifies a subgroup of women who are BRCA wild type but derive greater benefit from a PARP inhibitor**.**
  + Patients with a positive HRD test and a partial or complete response to front-line platinum-based chemotherapy, with or without Bevacizumab, should receive maintenance treatment with a PARP inhibitor, Olaparib.
* Patients receiving Bevacizumab with front-line chemotherapy and who are HRD negative, do not have a benefit from the addition of Olaparib to maintenance bevacizumab.

**The role of intraperitoneal chemotherapy and hyperthermic intraperitoneal chemotherapy:**

* There is evidence for the benefit of intraperitoneal (plus intravenous) chemotherapy compared to intravenous chemotherapy in terms of PFS and OS and may be offered to patients with completely (nil residual) or optimally debulked (low volume residual disease <1cm) stage II-III disease-
* Paclitaxel 135 mg/m2 as 24-hour IV infusion on day 1, cisplatin 75-100 mg/m2 IP on day 2 and paclitaxel 60 mg/m2 IP on day 8 – repeated every 3 weeks for 6 cycles, are an acceptable alternative to standard intravenous adjuvant regimens.
* Patients with low performance status, stage IV disease, pre-existing co-morbidities or elderly patients may not tolerate intraperitoneal chemotherapy and should be offered IV chemotherapy.
* Giving IV fluids hydration is essential before and after IP chemotherapy to reduce renal toxicity and to prevent dehydration. Complications following IP chemotherapy can be severe and may be catheter related, drug related (e.g., leukopenia, infection, fatigue, renal toxicity, abdominal discomfort, neurotoxicity) or procedure related and may lead to discontinuation of IP chemotherapy.
* HIPEC is not a standard of care as first-line treatment.

**What about Platinum sensitivity?**

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| Risk Stratification Groups | | | |
|  | **Platinum-Sensitive** | **Platinum-Resistant** | **Platinum-Refractory** |
| **Platinum-free interval** | Failure in ≥ 6 months following completion of platinum based  chemotherapy (partially sensitive, according to some guidelines 6-12 months) Patients with no prior platinum-based therapy are also in this group | Failure in < 6 months following completion of platinum-based  chemotherapy | Disease progression while receiving first-line platinum-based chemotherapy |
| NOTE. Platinum-sensitive if the platinum-free interval is 6 months or more; some guidelines have a partially sensitive group if the platinum-free interval is between 6 and 12 months. There are no approvals internationally that apply this definition | | | |

**Recommendations for Platinum sensitive disease:**

* Patients with a durable response to first line platinum-based chemotherapy have a high probability of responding to a re-challenge with platinum-based chemotherapy regimen. The choice of platinum agent – cisplatin or carboplatin depends on previous agent used, its toxicity and tolerability.
* The combinations, which may be used in these patients, are Paclitaxel plus platinum, Carboplatin plus weekly paclitaxel, Docetaxel plus platinum, Liposomal doxorubicin plus platinum, Gemcitabine plus platinum, Single agent carboplatin or cisplatin in patients who cannot tolerate combination therapy, Nanoparticle albumin-bound paclitaxel, Chemotherapy plus bevacizumab
* PARP inhibitor **Olaparib** is active in patients with BRCA- 1 and BRCA-2 mutations. and is now recommended in women who have received 3 or more cycles of chemotherapy and have a germ-line BRCA mutation.
* **Olaparib** monotherapy has been shown to have response rate of 34% in women with recurrent advanced ovarian cancer in a recent trial.

**Recommendations for Platinum resistant disease:**

* Typically, the response rates to any chemotherapy are limited, the prognosis poor and the intent of treatment palliation. Altering the schedule of paclitaxel may produce short-term responses.
* Re-challenge with paclitaxel and platinum combination yields response rates of less than 10%, so Single non-platinum agent is the preferred chemotherapy in this situation. These drugs can be used as single agent chemotherapy in a sequential fashion, e.g., docetaxel, topotecan, gemcitabine, oral etoposide, liposomal doxorubicin, vinorelbine, ifosfamide, pemetrexed, capecitabine, cyclophosphamide, altretamine, irinotecan, oxaliplatin, doxorubicin, nanoparticle albumin-bound paclitaxel etc have been used in the literature with consistently low response rates of about 20-27%,
* Single agent bevacizumab may be used and is associated with a response rate of about 21%, or in combination with chemotherapy significantly improved PFS and OS in patients with recurrent ovarian cancer, with an increased incidence of common adverse events. The bevacizumab combination regimens **are contraindicated** in patients at an increased risk for gastrointestinal perforation and unlikely to be beneficial in those patients who have received bevacizumab earlier.
* Metronomic chemotherapy with oral etoposide or cyclophosphamide which work mainly as antiangiogenic agents when given in small doses at more frequent intervals.
* Patients who cannot tolerate or have failed cytotoxic chemotherapy may be considered for hormonal therapy with tamoxifen, megestrol acetate, LH-RH analogues, aromatase inhibitors etc.
* Platinum resistant or refractory patients have a lower response rate to Olaparib.
* Patients with platinum refractory / resistant disease should be enrolled in clinical trials.

**How to evaluate?**

* In both platinum sensitive and platinum resistant patients, evaluation of response is recommended after 2-3 cycles of chemotherapy irrespective of the regimen or agent used.
* Responding patients may be treated with further chemotherapy and assessed for cytoreductive surgery when appropriate while patients who do not respond to 2 consecutive regimens of chemotherapy are unlikely to respond to further chemotherapy and may be considered for supportive care or clinical trials.

# Follow up of a patient with ovarian cancer

**How to follow up clinically a patient treated for ovarian cancer?**

* Patients should have the contact details of their key worker so that they access an early review for unexpected symptoms.
* A careful history, assessment of new and potentially tumor-related symptoms and clinical examination is essential at follow up visits.

**How often is the follow up planned?**

* Every 3 months for first 2 years,
* Every 4 months during the third year and
* Every 6 months subsequently until documented progression.
* The follow up then continues annually.

**What type of imaging can be helpful?**

* Ultrasonography of the abdomen & pelvis may be adequate if clinical examination and serum Ca-125 are normal. Patients should also be counseled and educated about the symptoms and signs indicative of a recurrence.
* If the clinical examination and / or Ca-125 levels suggest a possibility of relapse, CT scan or a PET scan (which is more sensitive for detecting multiple sites of relapse and for subsequent planning of therapy) is recommended.

**Is routine measurement of CA125 helpful for follow up?**

* Rising CA125 alone, without clinical or radiographic evidence of recurrence, should not routinely be used as an indication to commence systemic chemotherapy.

**Does early treatment based on elevated level of CA125 improve overall survival?**

* A prospective randomized European multi-institutional study of early detection of relapse with Ca-125 and early treatment versus delayed treatment at the onset of clinical manifestation of the disease showed no difference in the overall survival between the immediate and delayed treatment arms.

**What is the role of 2nd look operation?**

* Although sound in principle, it has not been shown to improve survival. Second look surgery may be used a part of clinical trials after obtaining informed consent of the patient.

# Management of recurrent ovarian cancer

**What is the role of surgery in recurrent ovarian cancer?**

* Secondary cytoreductive surgery can be discussed for highly selected platinum-sensitive patients; survival benefit is limited to patients for whom clinicians can achieve complete cytoreductive surgery.
* Patients should however be aware that the disease will remain chronic, and that no prospective trials have yet proven a survival benefit.
* Patients should be selected if they have a high probability of having a complete resection and the following predictors for resection should be considered which are:
* Platinum treatment-free interval (TFI) of more than 6 months,
* Positive AGO (Arbeits gemeinschaft Gynäkologische Onkologie) score
  1. Good performance status (PS), ECOG 0).
  2. Complete resection at primary surgery and the absence of large volume (>500 ml) ascites]
  3. Score suggested by DESKTOP III study.
* Absence of probably irresectable lesions on imaging
* Absence of contraindications to surgery (e.g., comorbidities, prior severe complications of surgery).

**What is the role of systemic therapy?**

* Platinum-sensitive (including partially sensitive): combination chemotherapy with carboplatin with or without bevacizumab
* Platinum-resistant or Platinum refractory: Single-agent nonplatinum

**Palliative What is the palliative therapy in ovarian cancer**

* Generally, not recommended as the patient has progressive incurable disease with limited life expectancy.
* Intestinal obstruction is the commonest clinical situation for which palliative surgery is contemplated.

**What is the role of multi-modal approach for pain management?**

* A multi-modal approach to post-operative analgesia, including systemic and regional techniques, should be used for ovarian cancer surgery.

**What is the role of epidural analgesia?**

* There is evidence that epidurals provide benefits in addition to analgesia and these should be considered

**What about the use of opioids?**

* Prolonged use of opioids is not recommended.

**What about ERAS implementation?**

* The implementation of enhanced recovery after surgery protocols in gynecological oncology is recommended, whereby monitoring of adherence is of fundamental importance.
* Rehabilitation and enhanced recovery programs should be applied as a new and relevant global concept in ovarian cancer surgery.
* Early mobilization after surgery is recommended.

**What about general & Psychological care**

* Women with a high level of distress should be offered psycho-oncological interventions in addition.

**What about hormone replacement therapy (HRT) after treatment?**

* Hormone replacement therapy is not recommended

# Management of border line ovarian tumor (BOT)

**What about the diagnosis of border line ovarian tumor (BOT)?**

* Borderline (LMP) tumors are epithelial tumors with cytological characteristics suggestive of malignancy but without frank invasion
* Microinvasion (<5 mm) can be seen in borderline tumors but these cases should still be regarded as borderline for classification and management purposes
* They can be serous, mucinous, sero-mucinous or endometroid
* They may have peritoneal implants, which may be non-invasive or invasive.
* The micropapillary pattern and presence of microinvasion within these tumors signify increased risk of invasive implants in extraovarian tissue.
* The term implant should not be used in the context of mBOTs; extraovarian disease in association with an mBOT should be considered as metastasis
* 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.

**What is the role of surgery in BOT?**

* Complete surgical resection and adequate peritoneal surgical staging
* borderline mucinous tumors are more commonly metastatic and thereby warrant an appendectomy
* Pelvic and para-aortic lymph node sampling to stage cases of BOT is not recommended in the absence of bulky lymph nodes.

**What about fertility preservation in BOT?**

* It is safe for young patients with BOT to receive fertility sparing surgery but given the higher risk of relapse within any remaining ovarian tissue.
* sonographic follow up is recommended since they have a significantly higher risk of relapse in the remaining ovaries
* There is no value in the routine CA125 based follow up for BOT patients

**What about the role of adjuvant therapy in BOT?**

* There is no evidence-based indication for cytotoxic chemotherapy in BOT

**What about recurrence in BOT?**

* Relapse of borderline disease should be mainly treated surgically, if disease seems operable, since response to chemotherapy is poor