**PRINCESS MARGARET CANCER CENTRE**
**CLINICAL PRACTICE GUIDELINES**

# GYNECOLOGIC CANCER

## OVARIAN

**Site Group: Gynecology – Ovarian Cancer**

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## 1. Introduction

There are three major types of ovarian cancer: epithelial, germ cell and stromal cell. The most common, epithelial, account for 85% of all ovarian cancers and 95% of the deaths. Epithelial ovarian cancer generally presents at an advanced stage and is the most common cause of gynaecological cancer death. Most of these cancers are detected in late stages because they tend not to be symptomatic until they have spread to the abdomen. Treatment includes a combination of surgery and chemotherapy and in some situations radiation. Advanced ovarian cancer is difficult to cure but in the last 10 years overall survival rates are improving.

Epithelial ovarian cancers are in some situations hereditary. Fifteen to 20% of high grade serous epithelial ovarian cancers are related to *BRCA 1* and *BRCA2* germline mutations. All women diagnosed with this type of cancer are referred for genetic testing. Relatives of individuals who test positive for a *BRCA* gene mutation are also eligible for testing and are encouraged to participate in screening and prevention programs at Princess Margaret Cancer Centre. Individuals with *BRCA1/2* germline mutations are also at high risk of developing breast cancer. Additional genes beyond *BRCA1/2* are now also tested with a panel of 19 genes for women diagnosed with high grade serous ovarian cancer.

Germ cell tumours affect children and young women. In general, they are eligible for fertility sparing surgery and almost all of these cancers can be cured with a combination of surgery and chemotherapy. These patients are also followed by the germ cell team at Princess Margaret Cancer Centre.

Stromal cell cancers are uncommon, representing <5% of all ovarian tumours. They are usually slow growing and are generally treated with surgery and in some situations adjuvant radiation.

On occasion, the ovary can be the site for metastatic disease, most commonly from the stomach, colon, and breast.

## 2. Prevention

There are no effective strategies to prevent ovarian cancer in the general population. Epidemiologic studies have shown that the use of birth control pills and pregnancy reduce the risk of developing ovarian cancer.

In women with a *BRCA 1* or *2* germline mutation, surgery to remove the ovaries and tubes has been shown to prevent ovarian cancer. It has also been shown to reduce the risk of breast cancer as much as 50% when done in premenopausal women.

## 3. Screening

In 2011, CPAC reviewed the literature on ovarian cancer screening and published a report which is available on its website.

Ovarian Cancer Screening: Expert Panel: Summary of Existing and New Evidence: https://www.partnershipagainstcancer.ca/wp-content/uploads/2019/01/Ovarian-Cancer-Screening-EN.pdf

Ovarian Cancer Screening Supplement: https://www.partnershipagainstcancer.ca/wp-content/uploads/2019/01/Ovarian-Cancer-Screening-Supplement-EN.pdf

Below is their summary statement on ovarian cancer screening.

*There is considerable interest in screening for ovarian cancer because the disease is highly lethal and currently most often detected in its advanced stages. If screening could detect more early-stage ovariancancers, the hope is that survival rates would improve.*

*Ovarian cancer is a complex disease and not all of its histologies act in the same way. While some are detected more often in early stage, serous histology, the most common ovarian cancer usually presents as Stage 3 or 4.*

*The evidence to date has not demonstrated that ovarian cancer screening reduces mortality from ovarian cancer.*

## 4. Diagnosis

**TABLE 1. 2014 International Federation of Obstetrics and Gynecology Ovarian, Fallopian Tube, and Peritoneal Cancer Staging System and Corresponding TNM**

| |
|---|
| **Stage I. Tumor confined to ovaries or fallopian tube(s)** |
| T1-N0-M0 |
| IA: Tumor limited to one ovary (capsule intact) or fallopian tube; no tumor on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings |
| T1a-N0-M0 |
| IB: Tumor limited to both ovaries (capsules intact) or fallopian tubes; no tumor on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings |
| T1b-N0-M0 |
| IC: Tumor limited to one or both ovaries or fallopian tubes, with any of the following: |
| IC1: Surgical spill |
| T1c1-N0-M0 |
| IC2: Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface |
| T1c2-N0-M0 |
| IC3: Malignant cells in the ascites or peritoneal washings |
| T1c3-N0-M0 |
| **Stage II. Tumor involves one or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or primary peritoneal cancer** |
| T2-N0-M0 |
| IIA: Extension and/or implants on uterus and/or fallopian tubes and/or ovaries |
| T2a-N0-M0 |
| IIB: Extension to other pelvic intraperitoneal tissues |
| T2b-N0-M0 |
| **Stage III. Tumor involves one or both ovaries or fallopian tubes, or primary peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes** |
| T1/T2-N1-M0 |
| IIIA1: Positive retroperitoneal lymph nodes only (cytologically or histologically proven): |
| IIIA1(i): Metastasis up to 10 mm in greatest dimension |
| IIIA1(ii): Metastasis more than 10 mm in greatest dimension |
| IIIA2: Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes |
| T3a2-N0/N1-M0 |
| IIIB: Macroscopic peritoneal metastasis beyond the pelvis up to 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes |
| T3b-N0/N1-M0 |
| IIIC: Macroscopic peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes (includes extension of tumor to capsule of liver and spleen without parenchymal involvement of either organ) |
| T3c-N0/N1-M0 |
| **Stage IV. Distant metastasis excluding peritoneal metastases** |
| Stage IVA: Pleural effusion with positive cytology |
| Stage IVB: Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity) |
| Any T, any N, M1 |

Adapted from Prat J; FIGO Committee on Gynecologic Oncology. FIGO's staging classification for cancer of the ovary, fallopian tube, and peritoneum: abridged republication. J Gynecol Oncol. 2015;26:87-89. doi:10.3802/jgo.2015.26.2.87[58]

| **RMI 2 – Risk of Malignancy Index**<br>***To estimate the risk of malignancy in a pelvic mass**<br>• RMI = US score x Menopausal status x CA125 u/ml | |
|---|---|
| **Feature**<br>Ultrasound features:<br>• Multilocular cyst<br>• Solid areas<br>• Bilateral lesions<br>• Ascites<br>• Intra-abdominal metastases<br><br>• Pre-menopausal<br>• Post-menopausal<br>• CA 125 | **RMI Score**<br>0 = none<br>1 = one abnormality<br>4 = two or more abnormalities<br><br><br><br><br><br>1<br>4<br>u/ml |
| • RMI score >200 – refer to gynecologic oncologist | |

The RMI index (3 versions exist) is a tool used to evaluate the likelihood that a pelvic mass is malignant. It includes menopausal status, ultrasound findings and CA-125. A score greater than 200 is suggestive of malignancy and should prompt a referral to a gynecologic oncologist.

Evaluation:
History and physical exam
Laboratory: include CA-125, CEA, CA19-9 as indicated
Imaging: Ultrasound pelvic/transvaginal, CT of thorax, abdomen and pelvis, MRI
Cytology of ascites and/or pleural effusion, or biopsy of omentum, peritoneal disease for diagnosis.

## 5. Pathology

The majority of ovarian malignancies are of epithelial origin – most common being high grade serous histology.

Epithelial tumours can be divided in 5 different histology subtypes: most common is high grade serous, low grade serous, endometrioid, clear cell and mucinous.

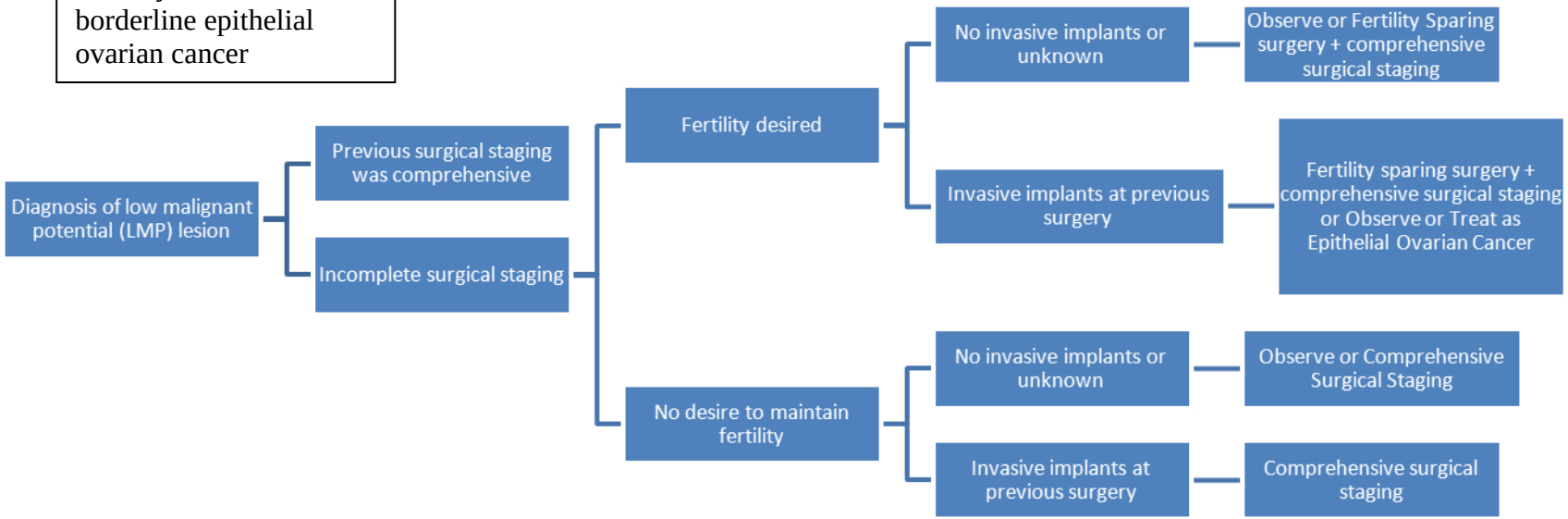
All high grade serous ovarian cancer should get a reflex *BRCA1/2* tumour testing.

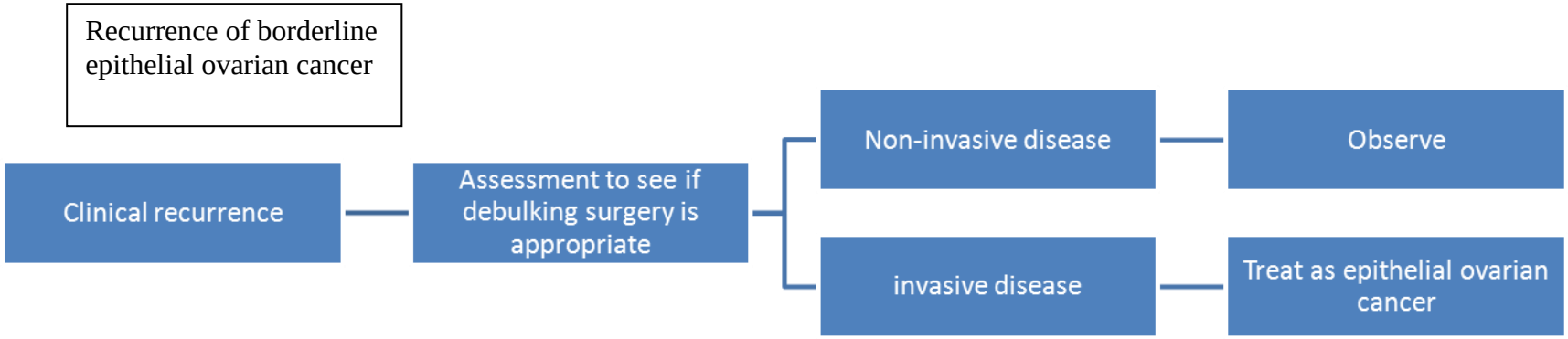
## 6. Management

### 6.1 Management Algorithms

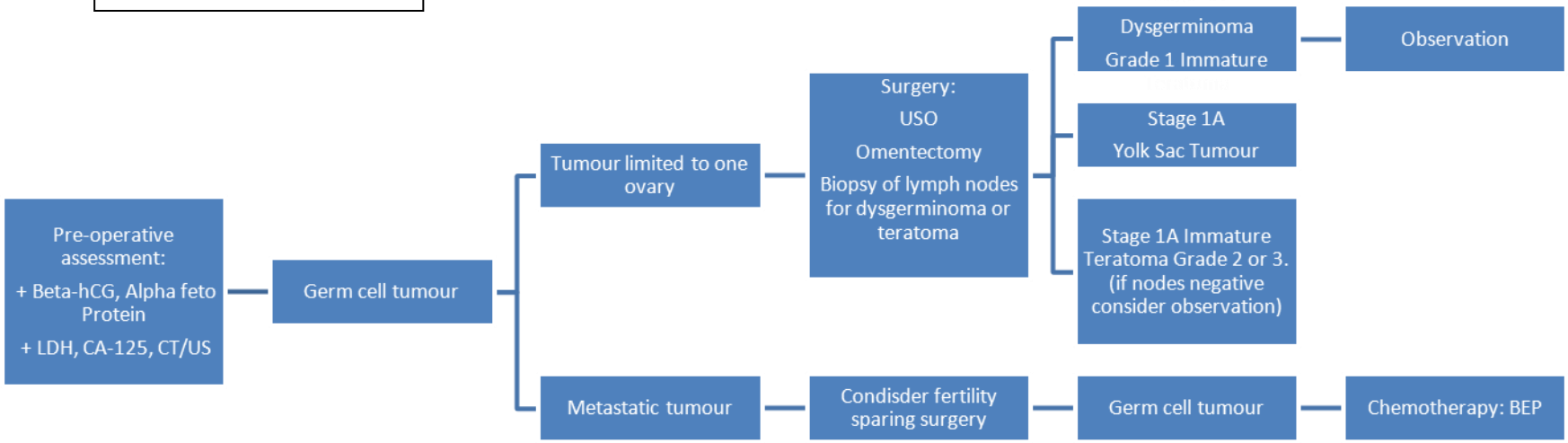
The treatment of ovarian cancer has matured over the last 50 years to an evidence-based approach that integrates optimal surgery and systemic therapy with ovarian cancer subtype specificity; it has also matured to offer a well-developed algorithm of integrated, multidisciplinary care, albeit with some important unanswered questions. Treatment decisions are based on disease stage and biology, prior therapy, and comorbidities.

Primary treatment for borderline epithelial ovarian cancer

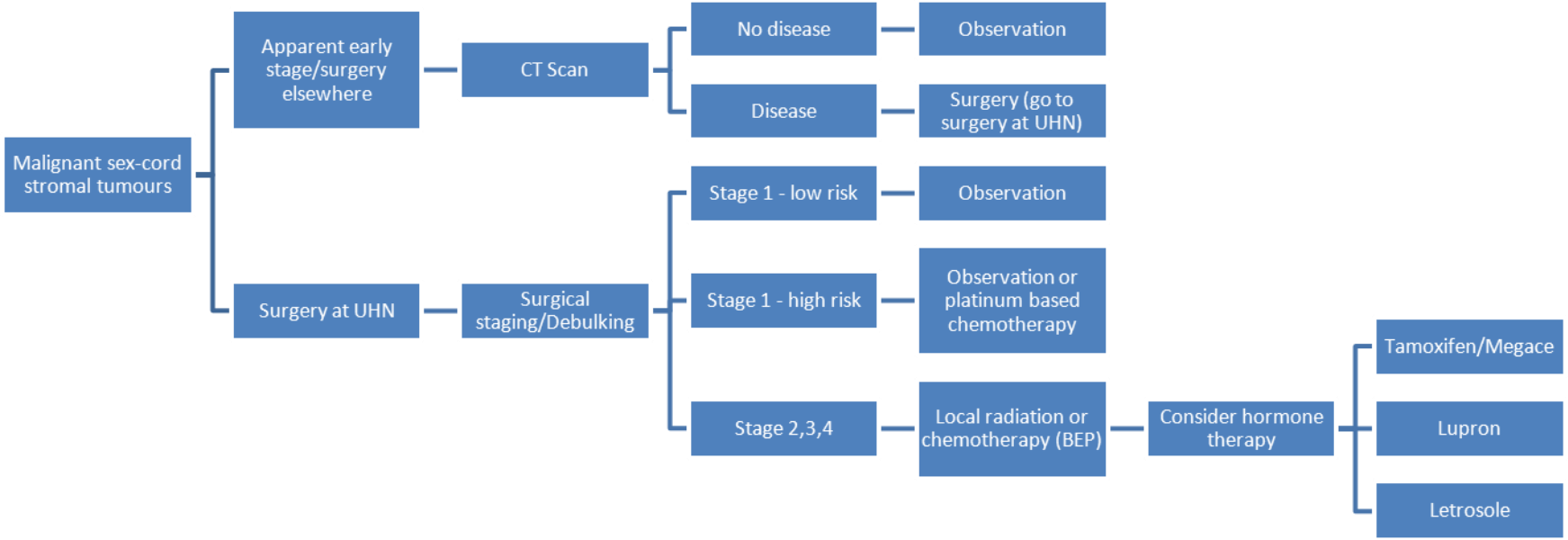



Recurrence of borderline epithelial ovarian cancer
Clinical recurrence
Assessment to see if debulking surgery is appropriate
Non-invasive disease
Observe
invasive disease
Treat as epithelial ovarian cancer

Primary treatment of germ cell tumour



Primary treatment of malignant sex-cord stromal tumours



### 6.2 Surgery

Surgical staging operation includes:

- Aspiration of ascites or washings for cytology
- Inspection and palpation of all peritoneal surgaces
- Hysterectomy and bilateral salpingo-oophorectomy
- Infracolic omentectomy
- Staging biopsies of:
    - All suspicious macroscopic lesions and adhesions
    - All locations to which the ovarian tumour is adherent
- Biopsies of the peritoneum from the pouch of Douglas, bladder peritoneum, pelvic sidewalls, paracolic gutters, diaphragm.
- Pelvic and para aortic lymph node dissection

**Debulking Surgery; for patients with clinically advanced (stage 2, 3, 4) disease who are suitable for surgery.**
The aim of debulking surgery is to remove all visible tumour (complete cytoreduction) Surgery consists of hysterectomy, bilateral salpingo-oophorectomy, infracolic omentectomy and removal of all visible tumour.
To achieve complete cytoreduction, surgery many need to include: 1. Pelvic Peritonectomy (bladder and cul de sac) 2. Peritonectomy in other sites including para-colic gutters, diaphragm, surface of liver 3. Bowel resection may include small bowel, large bowel, or a low anterior.
In some situations, debulking surgery may require consultation with other surgical specialists including hepatobiliary, thoracic, urologic and general surgery.

The recent LION study (Lymphadenectomy In Ovarian Neoplasms) showed that systematic pelvic and paraaortic lymphadenectomy of clinical negative lymph nodes in patients with advanced epithelial ovarian cancer and complete resection may be omitted to reduce postoperative morbidity and mortality. All areas of disease should be resected, ideally with no macroscopic residual disease.
IP chemotherapy may be offered in a specific subgroup of patients.

### 6.3 Chemotherapy

Standard practice now takes into account histology, stage, genomic profile, and residual disease.

**Chemo Carboplatin/Paclitaxel**
Postoperative adjuvant chemotherapy consists of 6 cycles of Paclitaxel 175 mg/m2 in 3 hrs and carboplatin AUC 6 every three weeks for 6 cycles. Bevacizumab has been approved in combination with chemotherapy and maintenance therapy for 12 infusions for stage 4 and residual disease post surgery.

**Neo-adjuvant chemotherapy**

Some patients with ovarian cancer will not be eligible for debulking surgery as initial treatment if:

1. tumour is likely unresectable because of extent of disease and location
2. patient's co-morbidities do not allow for surgery at this time ; this may change after 3-4 cycles of chemotherapy
3. poor performance status

Prior to starting neoadjuvant chemotherapy it is recommended that the patient has

1. CA 125 and relevant blood work
2. Cytology or histology confirming presence of malignancy
3. Baseline imaging – CT scan of thorax, abdomen and pelvis

After 3-4 courses of carbo/paclitaxel the patient should be assessed with a combination of physical exam, CT scans of thorax, pelvis and abdomen and serial CA125, to determine if surgical intervention – delayed primary surgery – is feasible. If the patient is deemed surgical, surgery should take place 4 weeks after completion of chemotherapy. The intent of the surgery is to debulk to microscopic disease.

If the patient's medical condition is not suitable for surgery and/or she has not responded to treatment it is recommended to continue chemotherapy to a total of 6 cycles. In some situations chemotherapy can be extended to 8 cycles if the patient is continuing to respond.

If the patient is not responding to neoadjuvant chemotherapy, or progressing on chemotherapy:

1. re-evaluate diagnosis
2. consider second line chemotherapy
3. consider clinical trial

**PARP inhibitor Maintenance therapy**

The PARP inhibitor therapy. Olaparib, has been approved as maintenance post response to platinum based chemotherapy as first line therapy in patients diagnosed with high grade ovarian cancer, *BRCA1/2* mutation.

## Summary

| | Epithelial ovarian cancer subtype | Approved treatment with Level I evidence | NCCN guidelines | Treatments in academic development |
|---|---|---|---|---|
| Incomplete surgery | HGSOC | Carboplatin/Paclitaxel<br>Bevacizumab | Platinum-based chemo<br>Bevacizumab concurrent and maintenance | PARP inhibitor<br>Immunotherapy<br>Folate receptor targeting |
| | HGSOC with BRCA1/2m | Carboplatin/Paclitaxel<br>Bevacizumab<br>Olaparib | Platinum-based chemo<br>Bevacizumab concurrent and maintenance<br>or Olaparib maintenance | Bevacizumab + PARP inhibitor<br>Immunotherapy + PARP inhibitor |
| | LGSOC | | Chemotherapy<br>Hormonal therapy<br>Bevacizumab | Letrozole *vs.* letrozole/chemo |
| | Clear cell | | Platinum-based chemo<br>Bevacizumab | Immunotherapy<br>Radiation<br>PARP inhibitor |
| | Endometrioid OC | Carboplatin/Paclitaxel<br><br>Bevacizumab<br>High grade endometrioid BRCAm: olaparib | Grade 1: Chemotherapy or Hormonal therapy<br><br>Grade 2/3: Platinum-based chemo<br>Bevacizumab<br>or Olaparib maitenance for BRCA1/2m | Immunotherapy<br><br>PARP inhibitor |
| | Mucinous | | Platinum based Chemo + Bevacizumab or<br>5-FU+leucovorin+oxaliplatin+/-bevacizumab or<br><br>capecitabine+oxaliplatin +/- bevacizumab | |
| Complete surgery No residual disease | HGSOC | Carboplatin/Paclitaxel<br>Bevacizumab | Platinum-based chemo<br>Bevacizumab concurrent and maintenance | Bevacizumab + PARP inhibitor<br>Bevacizumab + PARP inhibitor +<br>Immunotherapy<br>Folate receptor targeting |
| | HGSOC with BRCA1/2m | Carboplatin/Paclitaxel<br>Bevacizumab<br>Olaparib | Platinum-based chemo<br>Bevacizumab concurrent and maintenance<br>or Olaparib maintenance | Bevacizumab + PARP inhibitor +<br>Immunotherapy |
| | LGSOC | | Chemotherapy<br>Hormonal therapy | Letrozole *vs.* letrozole/chemo |
| | Clear cell | | Platinum-based chemo<br>Bevacizumab | |
| | Endometrioid OC | Carboplatin/Paclitaxel<br><br>High grade endometrioid BRCAm: olaparib | Grade 1: Chemotherapy or Hormonal therapy<br><br>Grade 2/3: Platinum-based chemo<br>Bevacizumab<br>or Olaparib maitenance for BRCA1/2 m | Immunotherapy |
| | Mucinous | | Platinum based Chemo +/- Bevacizumab or<br>5-FU+leucovorin+oxaliplatin+/-bevacizumab or<br><br>capecitabine+oxaliplatin +/- bevacizumab | |
| Early stage | HGSOC | Carboplatin/Paclitaxel | Platinum-based chemo | |
| | LGSOC | | Stage IA/IB: Observe<br>Stage IC: Observe or Platinum-based chemo or Hormone therapy | |
| | Clear cell | | Stage IA: platinum-based chemo or Observe<br><br>Stage IB/IC: Platinum-based chemo | |
| | Endometrioid OC | Carboplatin/Paclitaxel | Grade 1, Stage IA/IB: Observe<br>Grade 1, Stage IC: Observe or Platinum-based chemo or Hormone therapy | |
| | Mucinous | | Stage IA/IB: Observe<br>Stage IC: Observe or Platinum-based chemo or 5-FU+leucovorin+oxalplatin or<br>Capecitabine+oxalplatin | |

### 6.4 Radiation Therapy

- Can be offered in the palliative setting, or part of clinical trial or in specific type of ovarian cancer

### 6.5 Other Therapy

- Hormone therapy may be used in low grade serous ovarian cancer or adult type granulosa cell tumour.
- Clinical trials can be an option at any time of treatment

### 6.6 Oncology Nursing

*Refer to general oncology nursing practices*

## 7. Supportive Care

### 7.1 Patient Education

*Refer to general patient education practices*

### 7.2 Psychosocial Care

*Refer to general psychosocial oncology care guidelines*

### 7.3 Symptom Management

*Refer to general symptom management care guidelines*

### 7.4 Clinical Nutrition

*Refer to general clinical nutrition care guidelines*

### 7.5 Palliative Care

*Refer to general oncology palliative care guidelines*

## 8. Follow-up Care

### Epithelial ovarian cancer:

*For stages 1-4 with complete response:*
Every 3-4 months for 2 years after completion of treatment then every 3-6 months for 1 year, then annually after 5 years
+ CA-125 every visit
+ CT scan Abdomen / Pelvis ± Chest at completion of Chemo
± MRI
± PET scan
± Chest XRay
Serous should all be referred for genetic counselling

*Progression, stable or persistent disease after Chemotherapy:*
Clinical Trials or Supportive/Palliative Care or Chemotherapy or 2nd Debulking/Palliative Surgery

Decisions to offer clinical trials, palliative care only, or additional therapy should be made on an individual basis.

<u>Recurrence</u>
Recurrent epithelial ovarian cancer is divided into platinum sensitive and platinum resistant disease.

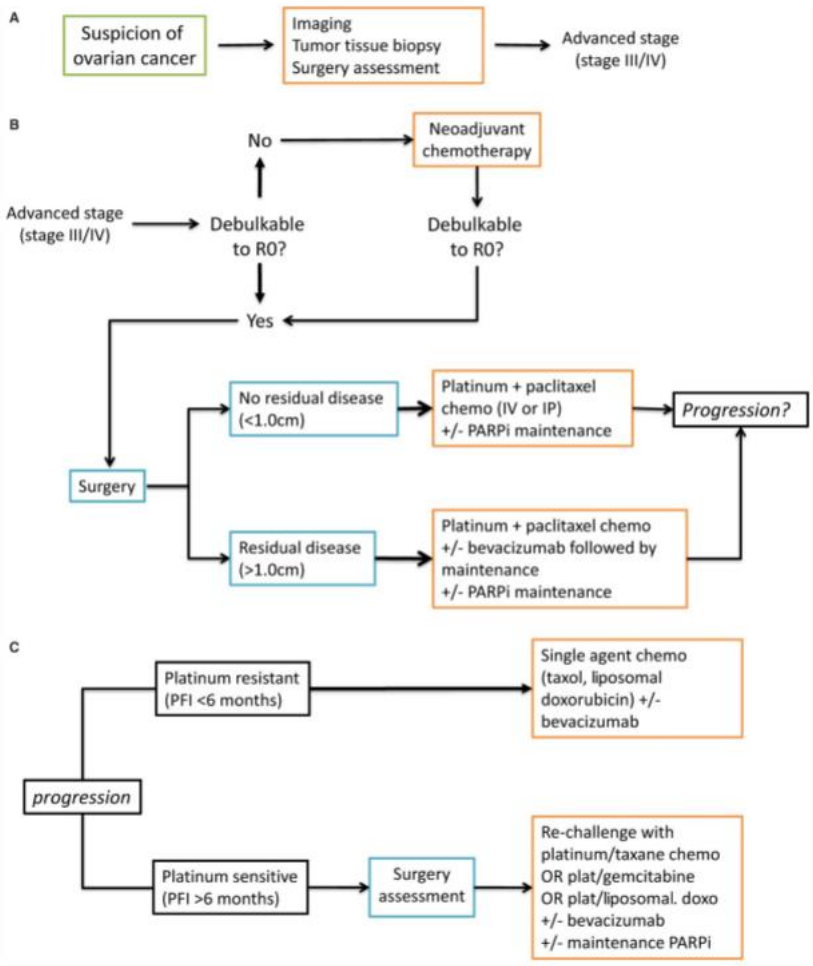
- Platinum resistance: Recurrence within 6 months of completion of chemotherapy

In this situation, standard of care is mon-chemotherapy, such as weekly paclitaxel or Caelyx, in combination with bevacizumab

- Platinum sensitive: Recurrence after 6 months of completion of chemotherapy.

Treatment includes re challenging with platinum based chemotherapy. For patients, PARP inhibitor naïve, with high grade serous or endometrioid BRCA1/2 mutated, olaparib should be considered as maintenance post response to platinum chemotherapy.

Secondary debulking surgery should be considered for selected patients with platinum-sensitive recurrence where R0 is achievable.




Borderline epithelial ovarian cancer:
Every 3-6 months for up to 5 years, then annually afterwards
+ Physical Exam - Abdominal/Pelvic exam
± CA-125 every visit if initially elevated
± Consider completion surgery after childbearing in patients who underwent USO
± Ultrasound

References:

Lheureux S, Braunstein M, Oza AM. Epithelial ovarian cancer: Evolution of management in the era of precision medicine. CA Cancer J Clin. 2019 Jul;69(4):280-304.

Lheureux S, Gourley C, Vergote I, Oza AM. Epithelial ovarian cancer. Lancet. 2019 Mar 23;393(10177):1240-1253.

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https://www.cancercareontario.ca/en/pathway-maps/ovarian-cancer