Ovarian Cancer, Testing and Management

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Disclosure, Potential Conflicts Of Interest, And Bias

No Disclosures

Outline

- Epidemiology
- Types of Ovarian Cancer
- Etiology/Risk
- Signs and Symptoms
- Screening Recommendations
- Workup/Diagnosis
- Staging
- Management

Objectives:

- Promote early intervention through ability to:
  - discern early signs and symptoms of cancer
  - perform adequate physicals.
- Provide appropriate patient education to
  - prevent cancer or progression to cancer.
- Identify appropriate disease specific testing modalities
- Provide treatment options

Epidemiology

- Worldwide, the number of new cases of ovarian cancer each year is approaching 250,000 [3].
- Approximately 6.6 new cases per 100,000 women per year
- The 7th most common cancer in women
- The 2nd most common and the most lethal gynecologic malignancy in the western world.
- For Africa and Nigeria studies have shown that ovarian cancer is the second most common gynecological cancer.
- The incidence of ovarian cancer increases with age.

Ovarian Cancer in the USA

- Incidence in US= 33:100,000 in women older than 50 years
- Average age at diagnosis: 57 yrs
- Life time risk= 1:70
- More common in white women
- Most common cause of gynecologic cancer death in USA

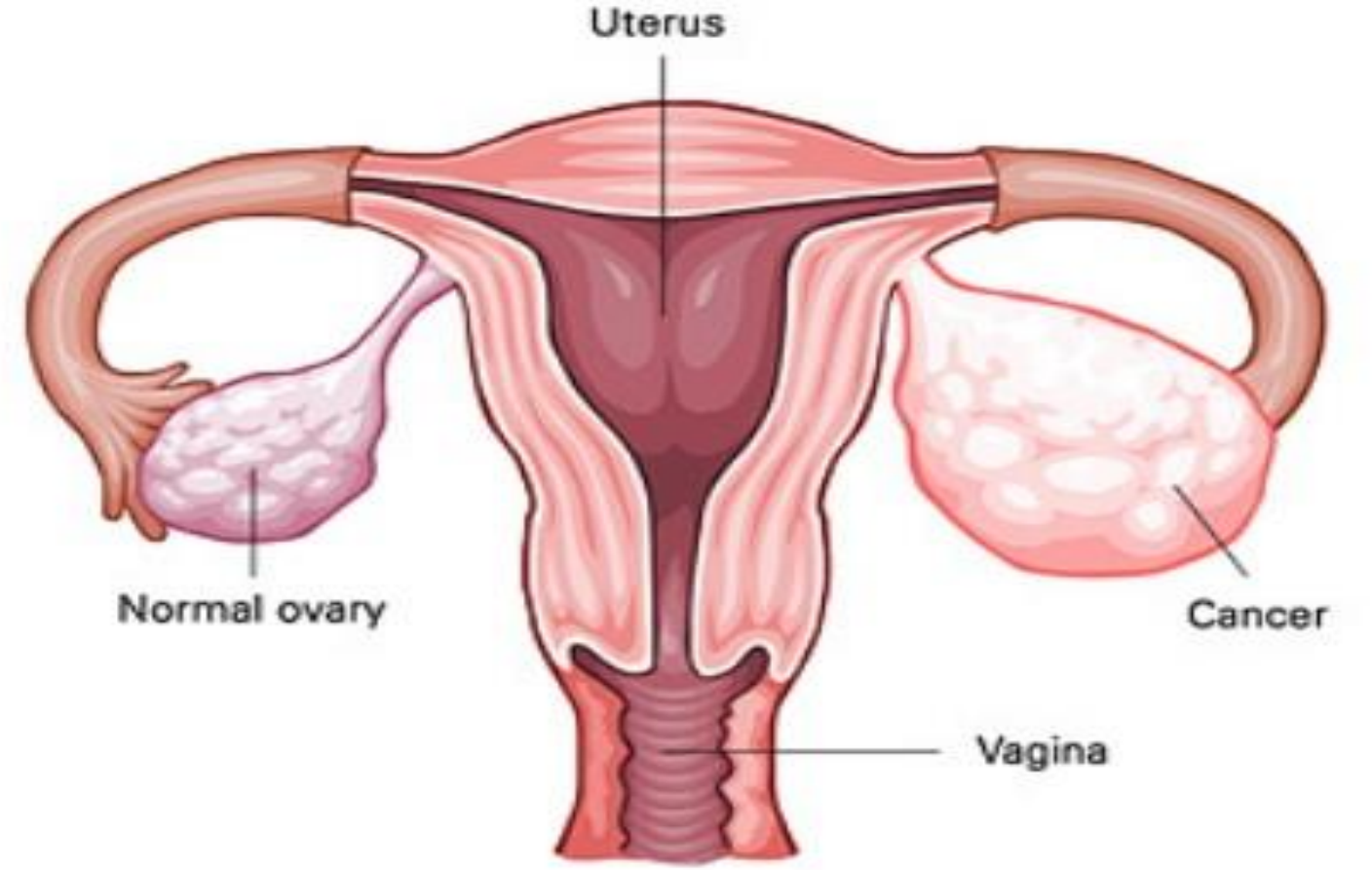
Ovarian cancer in Nigeria

- The second most common gynecological malignancy, first being cervix.
- The mean age at presentation per study in Uni. Lagos was 45.7 ± 4.3 years
- Mean Age at presentation per study by ABU Zaria is for serous cyst adenocarcinoma: 31 years and for epithelial ovarian cancers: 33.5 years.
- For both centers, majority of the patients (58%) were premenopausal, 34% being nulliparous
- Epithelial ovarian cancer is the most common histological variant.

A Lethal Disease

- Survival from ovarian cancer is minimal
- Survival is dependent on stage at Diagnosis
- Stage I disease: five-year survival is over 90%
- Regional spread: about 75 to 80%
- With distant metastases: 25%
- Despite the good prognosis associated with early-stage disease, overall five-year survival is less than 45%.
- Poor survival rate is due to the spread of cancer beyond the ovary at the time of clinical detection in 75% of patients.
- Mortality from ovarian cancer has decreased only slightly in the past 30 years

Ovarian Cancer



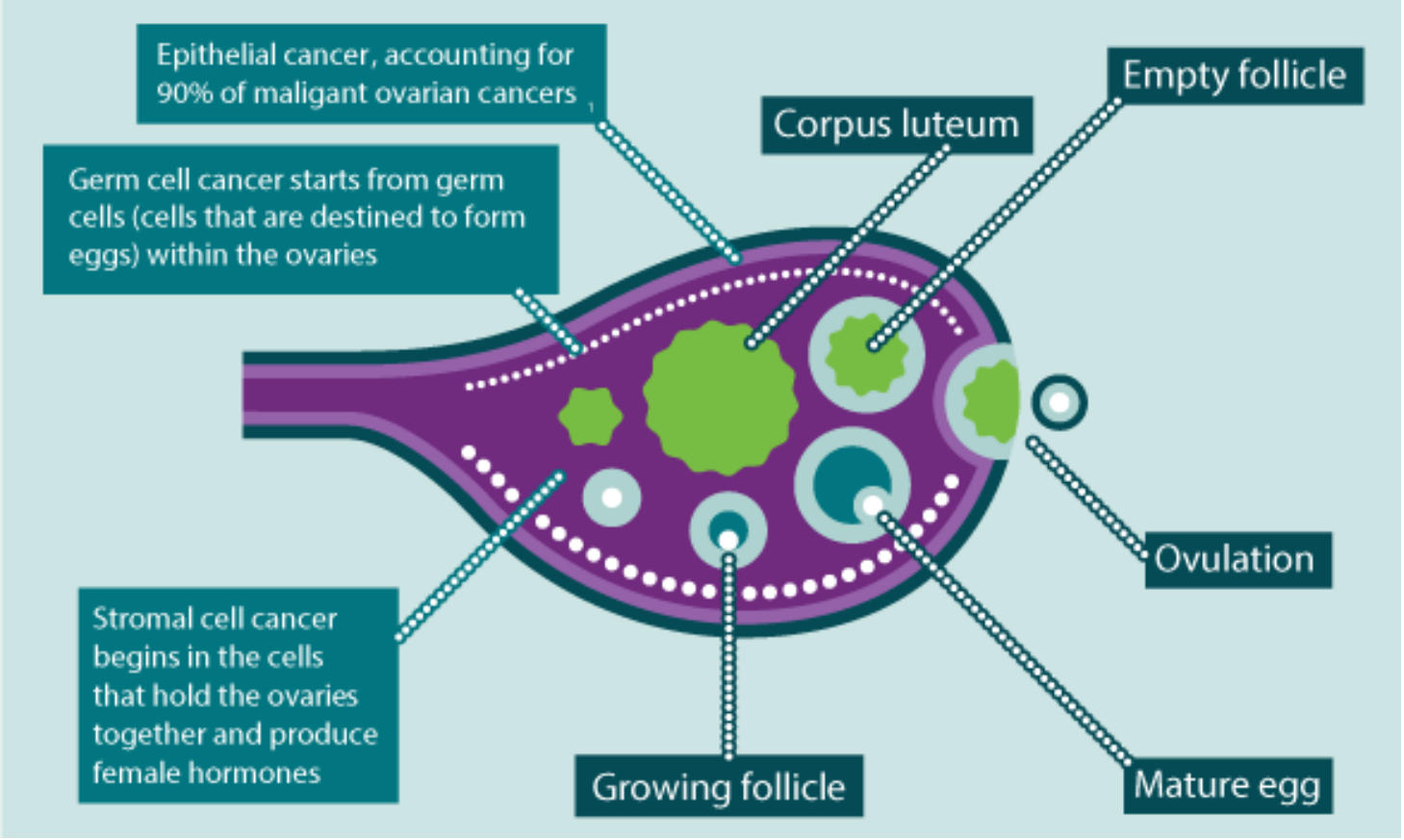
Types of Ovarian Cancer

There are over 30 types of ovarian cancer, and they are defined by the type of cell in which they start.

These occur in three main groups

- Epithelial tumors: Grow in the cells lining the surface of the ovary. They are the most common and the most dangerous, occurring in 85% to 90% of woman with ovarian cancer. In women over 60yrs.
- Germ cell tumors: Occurs in the cells that produce eggs for reproduction. They are often benign, and in the cases where they become cancerous, 90% can be cured. In adolescents and under 40.
- Stromal Cell (sex-cord) tumors. Arise from cells that make female hormones estrogen and progesterone. In women between 40-60 years. They make more estrogen.

Types of Ovarian Cancer



Etiology/Risk Factors

Etiology: Precise cause is unknown

Several Risk and contributing factors have been identified:

- **Age:** >55 years increases risk, for Nigeria: Child bearing age
- **Reproductive Factors:**
  - Parity: Risk increases with nulliparous women
  - Early Menarche and late menopause have higher risk
  - Oral contraceptive use decreases risk
- **Family History:**

Women with close relatives who have had ovarian or breast cancer have a higher risk of developing ovarian cancer, compared with other women.

  - Life time risk in general population 1.6%
  - 1 first degree family member affected, risk is 4-5%
  - 2 relatives affected, risk rises to 7%
- **Genetic:**
  - High grade serous ovarian cancer is characterized by TP53 mutations in all tumors

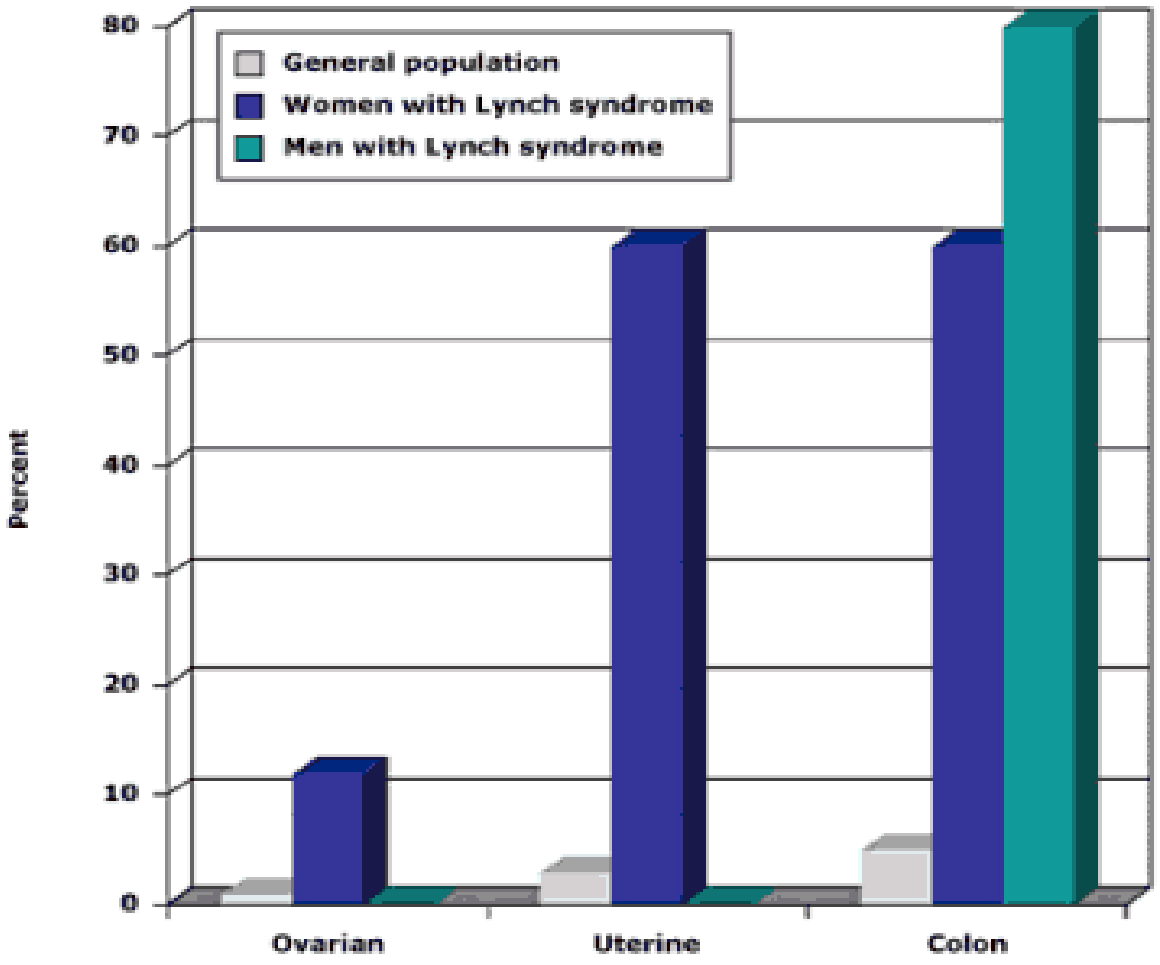
Hereditary Risk factors

Genetic screening can determine whether somebody carries certain genes that are associated with an increased risk.

1. **Most common BRCA1 and BRCA2 mutations**
   - 1:4000 carry BRCA 1 mutation
   - Ashkenazi Jews have much higher rate of mutations
   - BRCA1 & BRCA2 mutations: Carry 50-85% lifetime risk of developing breast cancer
   - BRCA1: 15-45% risk of developing epithelial ovarian cancer
   - BRCA2: 10-20% risk of developing epithelial ovarian cancer

2. Lynch II Syndrome & Cancer Risk

1. Aka: Hereditary Nonpolyposis Colorectal cancer
2. Caused mutation in the mismatched repair gene



Uptodate, 2013

Reproductive History & Use of Birth Control

- Women who have had one or more full-term pregnancies, especially before the age of 26 years, have a lower risk. The more pregnancies they have, the lower the risk.
- Breastfeeding may also decrease the risk.
- Using the contraceptive pill for at least 3 to 6 months appears to reduce the risk. The longer the pill is used, the lower the risk appears to be.
- Using an injectible contraceptive hormone, depot medroxyprogesterone acetate (DMPA or Depo-Provera CI), especially for 3 years or more, reduces the risk further.

Other Risk

Hormone therapy

- HRT slightly increases a women's risk of developing ovarian cancer. The risk appears to increase the longer the HRT continues, and returns to normal as soon as treatment stops.

Androgen therapy: Use of drug may also increase the risk e.g. Danazol

Obesity and overweight

- Ovarian cancer is more common in women with a body mass index (BMI) of over 30.

Gynecologic surgery

- Having surgery on the reproductive organs appear to reduce the risk of ovarian cancer.
- Tubal ligation: May reduce risk by up to two thirds.
- Hysterectomy: May reduce the risk by one third.

Other Risk Factors

- Endometriosis:
  - Women who develop endometriosis have around 30% higher risk of developing ovarian cancer, compared with other women.
- Polycystic Ovarian syndrome
- Infertility
- High fat diet
- Cigarette smoking (Mucinous type)
- Ovulation Inducing drugs (Clomid)

Early Signs and symptoms of Ovarian Cancer

Early ovarian cancer causes minimal, nonspecific, or no symptoms.

Symptoms may include:

- Patient may feel an abdominal mass.
- Pressure or pain in the abdomen, pelvis, back, or legs
- Increased abdominal size or bloated abdomen,
- Nausea/vomiting, constipation, diarrhea
- Feeling very tired all the time

Less common symptoms include:

- Feeling the need to urinate often (Urgency)
- Unusual vaginal bleeding (heavy periods, or bleeding after menopause)

Epithelial Ovarian Cancer

Presents with a wide variety of vague and nonspecific symptoms which includes:

- Bloating; abdominal distention or discomfort
- Pressure effects on the bladder and rectum
- Constipation
- Vaginal bleeding
- Indigestion and acid reflux
- Shortness of breath
- Tiredness
- Weight loss
- Early satiety

Medscape, 2014

Studies Looking at Early Symptoms

Goff et al (2000), surveyed 1725 women with Ovarian Cancer at average age 52 for symptoms prior to cancer diagnosis:

- 70% had stage III or IV dz
- 95% responded

Symptom reported include:

- Abdominal 77%
- Gastrointestinal 70%
- Pain 58%
- Constitutional 50%
- Urinary 34%
- Pelvic 26%
- 11% with stage I/II dz reported no symptoms before diagnosis
- 3% with stage III/IV no symptoms before diagnosis

Observations

- Ignored symptoms significantly impacted stage at diagnosis.
- Time to diagnosis by health care provider reported:
  - 55% as 3 months
  - 26% greater than 6 months
  - 11% great than 1 year.

Factors significantly associated with delay in diagnosis are:

- Omission of pelvic exam at first visit
- Having a multitude of symptoms
- Being diagnosed initially with no problem, Depression, stress, irritable bowel, or gastritis
- Not initially receiving an ultrasound, CT Scan, or CA 125 test
- Younger age.

Conclusion:

- Unusual bloating, fullness, pressure, abdominal or back pain, and lack of energy are prominent symptoms in women with ovarian cancer and distinguish them from controls.
- Information about symptoms may make women and Medical Providers more aware of changes associated with ovarian cancer.

Screening for Ovarian Cancer

- No Known recommended screening and early diagnostic modality.
- As a consequence absence of early warning symptoms and no screening modality, 70% of cases are diagnosed at an advanced stage and have bad prognosis.
- Late-stage ovarian cancer is incurable in the majority of cases
- In recent times, has tended toward chronic disease.
- Due to the progress in surgical technology and contemporary regimes of systemic treatment, as well as development of new drugs.

The Prostate, Lung, Colon & Ovarian (PLCO) Trial A Randomized Controlled Trial to Evaluate Screening

- **Subjects**: Adult women 55 to 74 years of age. Total of 78,216 enrolled.
- **Method**: Women were assigned to undergo either:
  - Annual screening with Transvaginal Ultrasound (TVU) and CA-125 testing or
  - To receive usual care. (Most women in the usual care group underwent bimanual examination with ovary palpation.)
  - Participants were screened at 10 centers across the United States between November 1993 and July 2001 and were followed for up to 13 years

JAMA, 2011

Results:

- There were 118 deaths from ovarian cancer in the screened group
- 100 deaths in the usual-care cohort
- 3,285 women had false-positive results, 1080 underwent surgical follow-up
- Of 1080 women, 163 women (15%) experienced at least one serious complication

Usual care in Ovarian Cancer Detection

- Good history
- Recognition of very early symptoms
- Excellent physical examination.
- Appropriate diagnostic modalities
- Appropriate referral

Screening Recommendations for Ovarian Cancer

The US Preventive Services Task Force recommends against screening the general population with:

- Serum CA125 level or
- Transvaginal Ultrasonography (TVU)

The National Cancer Institute (NCI) recommends that high-risk women:

- Seek advice from their physicians and
- **Annual ultrasonographic** examinations
- **Annual CA125 testing,**
- **Consider oophorectomy** or
- **Participation in a clinical trial**.

Medscape, 2014

Work up/Diagnosis

Consult	Pt. Medical Hx, Family Hx, Pelvic Exam
Test-blood	Elevated levels of markers-CA 125, Elevated HCG, AFP, LDH in germ cell ovarian ca Elevated **inhibin**, **estrogen** & **testosterone** in ovarian stromal tumors
Imaging	Transvaginal ultrasound, MRI, or a CT scan might be used (Gold standard), CXR: To r/o lung involvement (effeusion)
Laparoscopy	Allow the doctor to see the ovaries and, if necessary, to take a tissue sample
Colonoscopy	If constipation or bleeding from the rectum: colonoscopy may be needed, to examine the large intestine, or colon.

Work up Contd

Abdominal Fluid Aspiration	If the patient's abdomen is swollen, there may be ascitic fluid, which needs to be examined.
Biopsy	The usual way to diagnose ovarian cancer is to remove the tumor or part of the tumor to examine for the presence of cancer cells

Staging

Staging should include:

- Definition of histological type of the tumor
- Grading the disease: High-grade/low-grade scale is currently used
- For endometrioid ovarian cancer, a three-grade scale is used (G1, G2 or G3)
- Staging assessment in surgical-pathologic degrees should be done according to current FIGO recommendations

Ovarian tumor staging – FIGO (2014)

Stage	Definition
I	Tumor confined to ovaries.
IA	Tumor limited to one ovary (capsule intact); no tumor on ovarian surface; no malignant cells in the ascites or peritoneal washings.
IB	Tumor limited to both ovaries (capsules intact); no tumor on ovarian surface; no malignant cells in the ascites or peritoneal washings.
IC	Tumor limited to one or both ovaries, with any of the following:
	IC1: Surgical spill intraoperatively.
	IC2: Capsule ruptured before surgery or tumor on ovarian surface.
	IC3: Malignant cells present in the ascites or peritoneal washings.
II	Tumor involves one or both ovaries with pelvic extension (below pelvic brim) or peritoneal cancer (Tp).
IIA	Extension and/or implants on the uterus and/or fallopian tubes and/or ovaries.
IIB	Extension to other pelvic intraperitoneal tissues.

Stage III (FIGO, 1988)

Stage III	**Growth involving one/ both ovaries with peritoneal implants outside the pelvis and/ or retroperitoneal and/or inguinal lymph nodes. Superficial liver metastasis equals stage III. Tumour limited to true pelvis but histologically proven malignant extension to small bowel and omentum.**
IIIA	Tumour grossly limited to true pelvis with negative nodes But histologically confirmed microscopic seeding of abdominal peritoneal surface
IIIB	Tumour of one or bothe ovaries With histologically confirmed implants on abdominal peritoneal surface, none more than 2 cm in diameter, node negative
IIIC	Abdominal implants more than 2 cm diameter And/or retroperitoneal or inguinal lymph nodes or both

Stage IV (FIGO, 2014)

Stage IV	T any N any M1	Distant metastasis excluding peritoneal metastases
IVA		Pleural effusion with positive cytology
IVB		Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

Histologic types

Epithelial Cancers (>90%)

- High-grade serous carcinoma (HGSC-70%)
- Endometrioid carcinoma (EC 10%)
- Clear-cell carcinoma (CCC 10%)
- Mucinous carcinoma (MC 3%)
- Low-grade serous carcinoma (LGSC <5%)
- Undifferentiated (1%)

Malignant germ cell tumors (3%)

- Dysgerminomas
- Yolk sac tumors
- Immature teratomas

Potentially malignant sex cord-stromal tumors (1%–2%)

- Granulosa cell tumors)

Treatment for Ovarian Cancer

Treatment for ovarian cancer can include the following:

- Surgery
- Chemotherapy
- Radiation therapy
- Hormone therapy
- Targeted therapy

Often more than one treatment is used.

Kind of treatment depends on:

- Type of ovarian cancer
- Stage and grade
- General health of the patient.

Surgery

Surgery is usually the first option for cancer removal. Extent of surgery depends on the stage of the cancer.

- Salpingo-oophorectomy: Surgery is done to remove the ovaries and fallopian tubes.
- Hysterectomy: Involves removal of the uterus and any surrounding tissue that is affected.
- Lymph node dissection: Lymph nodes in the pelvis and near the aorta are removed.

Management of Ovarian Cancer

Standard treatment for ovarian cancer:

- Maximal cytoreductive surgical debulking.
  - Confirmation of diagnosis and staging of the disease is performed during surgery.
- Followed by platinum-based chemotherapy.

Cytoreduction Guidelines

According to a large multivariate analysis which showed improved progression-free and overall survival for group of patients with complete resection compared with groups with the so-called optimal (between 0.1 and 1 cm) and suboptimal cytoreduction .

- For **2017 ESGO** ovarian cancer surgery guidelines, the aim of frontline surgery is to achieve complete resection of macroscopic residuals of the disease (complete cytoreduction).

- After surgery, patients are treated with the intravenous platinum/taxane regimes, every 21 days, for six cycles (first-line chemotherapy).
- In patients with stage IA/IB and with G1/G2 tumors, chemotherapy can be omitted

Stage III/IV Disease Management

- Complete cytoreduction is often not possible.
- Most common reason is the seizure of small bowel mesentery and the lesions in the liver hilum.
- Induction chemotherapy (neoadjuvant) for patients with inoperable lesions or have poor performance status
- Followed with chemotherapy x 3 cycles
- If there is response to the treatment, then interval debulking surgery (IDS) can be performed, followed by 3 more cycles of chemotherapy for total 6.

Ovarian Cancer Tratment Regimens

Primary Chemotherapy/Primary Adjuvant Therapy[1abc]
Note: All recommendations are Category 2A unless otherwise indicated.
Stage 1A or 1B (grade 2[d], 3, or clear cell) & Stage 1C (grade 1–3)

REGIMEN	DOSING
Paclitaxel + Carboplatin	Day 1: Paclitaxel 175mg/m2 IV over 3 hours + carboplatin AUC 5-6 mg•min/mL IV over 1 hour. Repeat every 3 weeks for 3 to 6 cycles
Stage 2–4 (IV/IP regimen)	
Paclitaxel + Cisplatin (Category 1)	Day 1: Paclitaxel 135mg/m2 continuous IV infusion over 3 or 24 hours Day 2: Cisplatin 75–100mg/m2 IP Day 8: Paclitaxel 60mg/m2 IP. Repeat every 3 weeks for 6 cycles
Stage 2–4 (IV regimens)	
Paclitaxel + Carboplatin(Category 1)	Day 1: Paclitaxel 175mg/m2 IV over 3 hours + carboplatin AUC 5-6 mg•min/mL IV over 1

Regimen Contd

Stage 2–4 (IV regimens)	
Dose-dense Paclitaxel + Carboplatin (Category 1)5	Day 1: Paclitaxel 80mg/m2 IV over 1 hour + carboplatin AUC 5-6 mg•min/mL IV over 1 hour. Day 8 and 15: Paclitaxel 80mg/m2 IV over 1 hour. Repeat every 3 weeks for 6 cycles.
Paclitaxel + Carboplatin (Category 1)(for elderly patients and those with poor performance status)	Day 1: Paclitaxel 60mg/m2 IV over 1 hour + carboplatin AUC 2 mg•min/mL IV over 30 minutes. Repeat weekly for 18 weeks.
Docetaxel + Carboplatin(Category 1)	Day 1: Docetaxel 60–75mg/m2 IV over 1 hour + carboplatin AUC 5-6 mg•min/mL IV over 1 hour. Repeat every 3 weeks for 6 cycles.

Regimen Contd.

Stage 2-4 (bevacizumab-containing IV regimens)	
Paclitaxel + Carboplatin + Bevacizumab (Category 2B)8–14	Day 1: Paclitaxel 175 mg/m2 IV over 3 hours + carboplatin AUC 5-6 mg•min/mL IV over 1 hour + bevacizumab 7.5 mg/kg IV over 30–90 minutes. Repeat every 3 weeks for 5 to 6 cycles. Continue bevacizumab for up to 12 additional cycles. OR Day 1: Paclitaxel 175 mg/m2 IV over 3 hours + carboplatin AUC 6 mg•min/mL IV over 1 hour. Repeat every 3 weeks for 6 cycles. Starting Day 1 of cycle 2: Bevacizumab 15 mg/kg IV over 30–90 minutes every 3 weeks for up to 22 cycles.

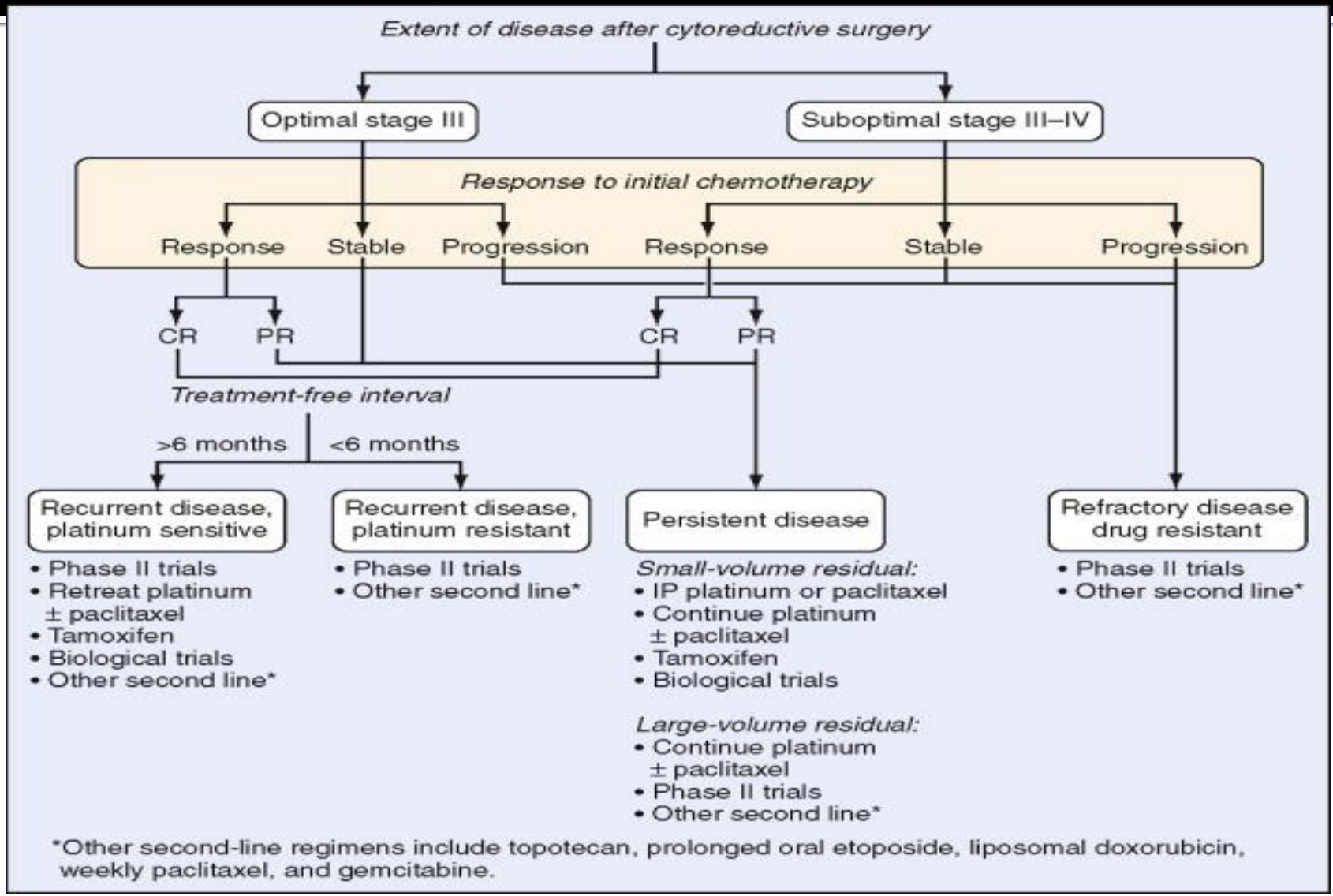
Accessing Treatment Response

- Assessed after the completion of first-line chemotherapy.
- Evaluation of response to the treatment is done based on:
  - Imaging results and
  - According to RECIST 1.1 criteria (Response Evaluation Criteria In Solid Tumors)
- Majority of patients respond well to the first-line chemotherapy, achieving complete response (CR).
- Many will develop recurrence. For patients with:
  - Residual disease < 1 cm: reoccurrence is estimated at 60–70%;
  - For large-volume residual disease: reoccurrence is estimated at 80–85%

Monitoring patients in CR

- Patients with CR should be subjected to periodic controls.
- Increasing level of CA125 can be an early indicator of recurrence, however,
- If not accompanied by clinical symptoms, it is not recommended to implement second-line treatment.
- Deferral of treatment until clinical symptoms occur, does not worsen the survival.
- The consensus is that patients with recurrent disease on the basis of CA125 alone, are eligible for clinical trials

Treament in Reoccurrent Disease



Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

- Combination of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) is increasingly used for the management of peritoneal metastases. This procedure is now accepted as a standard treatment for pseudomyxoma peritonei, peritoneal mesothelioma and the peritoneal metastases from colorectal cancer. **At some medical centers, HIPEC is also used for the treatment of patients with ovarian cancer.**

- In ovarian cancer patients, HIPEC is applied in combination with systemic therapy which starts about three weeks after surgery.
- Cisplatin (optionally with doxorubicin) and taxanes are used most frequently for HIPEC.
- Best results are achieved in the treatment of platinum-sensitive tumors, although it is suggested in patients with late recurrences and after several lines of chemotherapy.

HIPEC Contd.

- Used for the patients with large residual disease after primary surgery and for those who have inoperable lesions.
- In inoperable cases, neoadjuvant chemotherapy is given, and for patients who responds, cytoreductive surgery combined with HIPEC follows.
- Another eligible group include: patients in whom laparoscopy revealed malignancy, instead of apparently benign tumor.
- HIPEC is not recommended when the disease has disseminated to the distant organs outside peritoneum

Palliative treatment for malignant ascites

- Advanced and recurrent ovarian cancer is frequently associated with formation of malignant ascites in the peritoneal cavity.
- Mechanisms leading to development of ascites are associated with intra-peritoneal spread of tumor cells.
- Malignant ascites may be treated with intra-peritoneal administration of radioisotopes or chemotherapy, however, with limited effectiveness.

Palliative Treatment for Malignant Ascites Contd.

- Repetitive paracentesis provides temporary relief of symptoms, but is associated with several side effects, including loss of protein and hypovolemia, circulatory problems and the risk of bowel perforation.
- Various immunotherapeutic modalities are currently being tested for the management of peritoneal metastases and ascites, including T cells, checkpoint inhibitors, antibodies and vaccines (dendritic cell- and virus-based), with promising preclinical results .

Radiation therapy

- Radiation is less often used in ovarian cancer treatment.
- Used if there are small traces of cancer in the reproductive system.
- To treat the symptoms of advanced cancer.

Take home Messages

GI symptoms common with ovarian cancer
Common Constitutional symptoms:

- Fatigue
- Weight loss

Think **prevention/early detection**
Focus on early symptoms and work towards definitive diagnosis.
Order appropriate imaging or refer appropriately early to a specialist.
Remember: new, persistent, and possibly worsening GI or **any change in the body** calls for definitive work-up to rule out cancer.

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Contact Information

Thank You