Ovarian Cancer

**UpToDate:**
1. For women with a known BRCA mutation, PARP inhibitor (olaparib and rucaparib) are approved for relapsed ovarian cancer patients who have progressed on multiple previous lines of chemotherapy.
2. Niraparib is approved as maintenance therapy in relapse setting after remission is achieved by chemotherapy.

**Introduction:**
- Median age = 59
- Epithelial ovarian cancer (90%), fallopian tube and primary peritoneal cancer (10%) are considered a single clinical entity because of shared biology and treatment.

**Risk Factors:**
1) Age (strongest)
2) Reproductive factors: ↑ risk, a/w nulliparity, first birth after 35, involuntary infertility, late menopause, or early menarche
   - ↓ risk: oral contraceptive (long-term use >5yrs)
3) Genetic factors:
   - BRCA1 (35-60% risk), BRCA2 (15-25% risk), HNPCC (6-20% risk).
   - Peutz-Jeghers (STK11) → Sex cord tumors.

**Biology:**
- Sporadic occurrence.
- Genetic predisposition (See risk factors)

**Symptoms:**
- Early (35%), advanced disease (65%) at diagnosis
- Pelvic or abdominal pain/distention, bloating, G.I. Symptoms
- Bowel obstruction, ascites, pleural effusion.
- Pelvic mass

**Diagnosis:**
1) Screening: √ CA125/transvaginal US for high-risk population.
2) Pelvic Mass Diff Dx: from ovary vs colon
   - Cytokeratin (CK 7): (+) for ovarian cancer, (-) for colon cancer.
   - Cytokeratin (CK20): (-) for ovarian cancer, (+) for colon cancer.
3) Diagnostic work-up
   - Biopsy, pericentesis
   - Abdominal/pelvic, chest imaging to rule out metastatic disease.
   - Surgical evaluation → possibility for debulking
   - Surgical staging

**Pathology:**
A. Classification:
1) Epithelial ovarian/fallopian/primary peritoneal cancer:
   - serous 50%
   - endometroid 25%
   - mucinous 20%: normal CA125, not respond to chemo well, good prognosis
   - clear cell (considered as grade 3) 5%
   - Boardline tumor (15%): low malignant potential, no invasive component, → better prognosis. Tx: surgical resection, then observe only even for advanced stage
2) Sex-cord stromal tumors
   - Granulosa cell tumor: estrogen (+)
   - Sertoli-Leydig tumor: androgen (+)

3) Germ-cell tumors:
   - Dysgerminoma (50%): favorable (∼ seminoma), confined to one ovary
   - Non-dysgerminoma: ∼ nonseminoma
     * Teratoma: Immature or Mature (adult, solid or cystic)
     * Yolk sac tumor
     * Embryonal tumor
     * Non-gestational choriocarcinoma
     * mixed tumor

B. Staging:

Important: Complete surgical staging prior to treatment!!
Stage I: Tumor limited to the ovary
   IA: One ovary. IB: Two ovaries
   IC: One or both ovaries + surface tumor, ruptured capsule, ascites or malignant cells in peritoneal washings.

Stage II: Tumor involves both ovaries with pelvic extension
   IIA: Involvement of uterus and/or tubes
   IIB: Involvement of other pelvic tissues
   IIC: Stage IIA or IIB with factors as in stage IC

Stage III: Peritoneal implants outside pelvis ± (+) retroperitoneal or inguinal nodes
   IIIA: limited to true pelvis, microscopic abdominal seeding, (-) nodes.
   IIIB: Implants of abdominal peritoneum ≤2 cm, nodes negative
   IIIC: Abdominal implants >2 cm and/or positive retroperitoneal or inguinal nodes
   (this is most common stage at presentation)

Stage IV: Distant metastases

Prognosis:
   - Stage: most important
   - Optimal debulking: extent of residual disease left
   - Tumor grade: particularly for stage I disease
   - Histology: clear cell and mucinous histology (shorter survival).

Tx Principle:
A. Stage I:
   1) IA, IB (neg peritoneal washing): → complete TAH-BSO staging → observe for grade 1.
   2) IC (pos peritoneal washing or high grade (>2), or clear cell histology: → Adj IV chemo (paclitaxel/carboplatin x 3 cycles)

B. Stage II, III, IV: → complete staging and debulking surgery!
1) Optimally debulked (<1cm) stage II and III: IP Cis + IV/IP Paclitaxel (category 1 for stage III)
   * ↑ PFS and OS by 15 months c/t IV chemo.
2) Suboptimally debulked (>1cm) stage II and III: → adj IV chemo x 6-8 cycles.
   * No role for second surgery after suboptimal debulking.
3) After complete clinical remission, the risk of relapse is approximately 70%. At this point, no therapy has proven to be of survival benefit.
   * Observe, or maintenance paclitaxel x 12 mos (category 2B) → ↑ PFS by 7 months but no OS benefit.

** Carbo = Cis in this setting. Carbo can be given with taxel (3 hrs infusion), but Cis must be given with taxel of 24hrs infusion to minimize neurotoxicity.

C. Recurrent Disease:
1) Primary refractory: → clinical trial or BSC
2) Platinum-sensitive disease (>6 months from last tx):
   - Radiographic and/or clinical relapse → consider secondary cytoreduction surgery → then COMBINATION platinum-based chemo (curative intent, category 1):
3) Platinum-resistant disease (< 6 months from last tx): → nonplatinum SINGLE agent:
     Doxil (most active), weekly paclitaxel, docetaxel, etoposide, topotecan, tamoxifen, gemcitabine.

D. Low-malignant potential tumor of ovary (LMP): make sure no invasive disease!
   - Stage I-IV Fertility desired: → fertility-sparing surgery and comprehensive staging → NO adj chemo for any stage of LMP if no invasive implants. If there is an invasive implant, tx as ovarian cancer.
   - Stage I-IV Fertility not desired: → complete surgery and comprehensive staging.

E. Non-epithelial ovarian cancers
1) Sex-cord stromal cell tumors of ovary
   - Granulosa cell tumor (estrogen-producing): typically stage I, screen for endometrial cancer.
     * Tx: surgical resection (fertility-sparing) → observe if stage I. √ inhibin for monitoring.
     * StageII-IV, completely resected: → Observation vs Hormone (Pregestin) vs Chemo (BEP).
     * Incompletely resected/recurrent: → Hormone vs Chemo vs XRT
   - Sertoli-Lydig tumors (androgen-producing): platinum-based chemo for advanced or poorly differentiated disease.

2) Germ cell tumors of ovary: most are stage I at dx. Good prognosis even with stage IV.
   - Dysgerminoma (stage I) or grade 1 and stage I immature teratoma (Non-dysderminoma):
     * Tx: fertility-sparing surgery alone, DO NOT require adj chemo
Follow-Up:
A. Follow-up after CR: CA 125 q2-4 mos for 2yr, then q3-6 mos for 3rys, then annually.
CBC and chemistry as indicated. CT A/P/C, MRI, PET-CT, CXR as clinically indicated. √
Family history.

B. Rising CA125: No benefit for early treatment of rising CA125 without clinical relapse.

Pharmacology:
A. ICON-7, GOG-218, Ocean Trials: Bev maintenance → ↑ PFS
   - Carbo/Taxel + Bevacizumab → Bev maintenance (ICON-7)
   - Carb/Gem + Bevacizumab → Bev maintenance (Ocean)

B. Paclitaxel IV + Cisplatin IP + Paclitaxel IP
   - Paclitaxel (Taxol) 135 mg/m², IV over 24hrs, d1
   - Cisplatin 100mg/m², IP d2
   - Paclitaxel (Taxel) 60mg/m², IP, d8
   Q3w x 6 cycles