# TREATMENT OPTIONS IN OVARIAN CANCER

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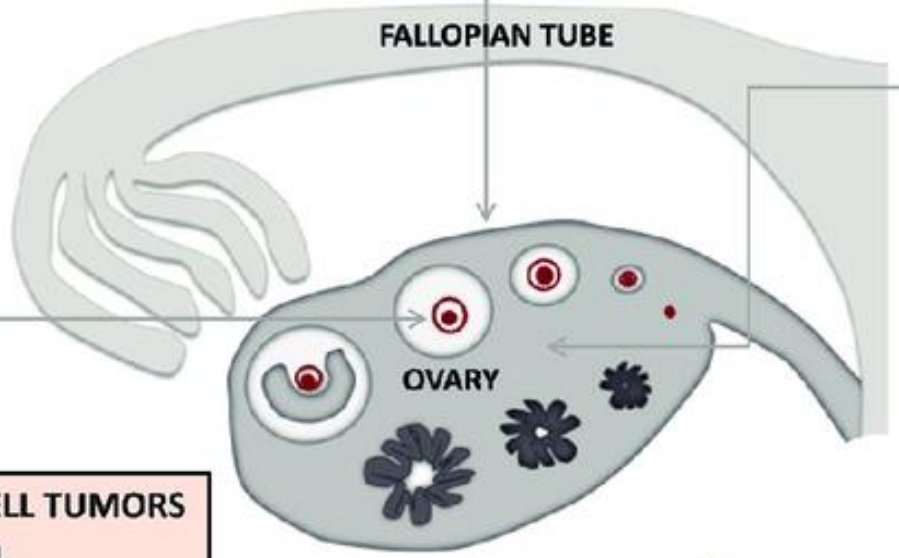
- **Ovarian cancer accounts for 4% of cancers occurring in women,**
- **Women without a significant family history or known gene mutations have a 1–2% lifetime risk of developing the disease**
- Approximately 85% of cases occur after age 50,
- 80–85% of cancers are epithelial in origin.
- High-grade serous tumors are the most common, present at an advanced stage, and have the poorest outcome

# Types of Ovarian Cancer & Their Origin

90% of all ovarian cancer

**OVARIAN EPITHELIAL CANCER**
- High-Grade Serous Carcinomas
- Low-Grade Serous Carcinomas
- Clear cell carcinoma
- Endometrioid
- Mucinous




**OVARIAN SEX CHORD-STROMAL TUMORS**

Stromal tumors
1. Fibroma
2. Thecoma
3. Fibrosarcoma
4. Leydig cell tumor
5. Steroid cell tumor
6. Sclerosing stromal tumor

Sex chord tumors
1. Adult granulosa cell tumor
2. Juvenile granulosa tumor
3. Sertoli cell tumor
4. Sex chord tumor with annular tubules

Mixed sex chord-stromal tumors
1. Sertoli-Leydig cell tumor

90% of all hormone producing cancer

70% of all ovarian cancer in 1st 2 decades of life

**OVARIAN GERM CELL TUMORS**
1. Dysgerminoma
2. Immature teratoma
3. Yolk sac tumors
4. Mixed germ cell tumors

**SMALL CELL CARCINOMA OF THE OVARY**
1. SCCO - hypercalcemic type
2. SCCO - pulmonary type

Ravindran, Febina & Choudhary, Bibha. (2021). Ovarian Cancer: Molecular Classification and Targeted Therapy. 10.5772/intechopen.95967.

# Staging

| | | |
|---|---|---|
| **I** | **Tumour confined to ovaries or fallopian tube(s)** | **T1** |
| IA | Tumour limited to one ovary (capsule intact) or fallopian tube.<br>No tumour on ovarian or fallopian tube surface.<br>No malignant cells in the ascites or peritoneal washings. | T1a |
| IB | Tumour limited to both ovaries (capsules intact) or fallopian tubes.<br>No tumour on ovarian or fallopian tube surface.<br>No malignant cells in the ascites or peritoneal washings | T1b |
| IC<br>IC1<br>IC2<br>IC3 | Tumour limited to one or both ovaries or fallopian tubes, with any of the following:<br>Surgical spill intraoperatively<br>Capsule ruptured before surgery or tumour on ovarian or fallopian tube surface<br>Malignant cells present in the ascites or peritoneal washings | T1c |
| **II** | **Tumour involves one or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or peritoneal cancer (Tp)** | **T2** |
| IIA<br>IIB | Extension and/or implants on the uterus and/or fallopian tubes/and/or ovaries<br>Extension to other pelvic intraperitoneal tissues | T2a<br>T2b |
| **III** | **Tumour 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** | **T3** |
| IIIA<br><br>IIIA1<br><br>IIIA1(i)<br>IIIA1(ii) | Metastasis to the retroperitoneal lymph nodes with or without microscopic peritoneal involvement beyond the pelvis<br>Positive retroperitoneal lymph nodes only (cytologically or histologically proven)<br>Metastasis ≤ 10 mm in greatest dimension (note this is tumour dimension and not lymph node dimension)<br>Metastasis *N* 10 mm in greatest dimension<br>Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes | T1, T2, T3aN1<br><br>T3a/T3aN1 |
| IIIA 2<br>IIIB<br><br>III C | Macroscopic peritoneal metastases beyond the pelvic brim ≤ 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes<br><br>Macroscopic peritoneal metastases beyond the pelvic brim *N* 2 cm in greatest dimension, with or without metastases to the retroperitoneal nodes (Note 1) | T3a/T3aN1<br>T3b/T3bN1<br><br>T3c/T3cN1 |
| **IV** | **Distant metastasis excluding peritoneal metastases** | **Any T, Any *N*, M1** |
| Stage IV A<br>Stage IV B | Pleural effusion with positive cytology<br>Metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of abdominal cavity) (Note 2) | Any T, Any *N*, M1 |

Based on 'DG Mutch and J Prat. 2014 FIGO staging for ovarian, fallopian tube and peritoneal cancer. Gynecologic Oncology 2014;133:401-04'

**Notes:**

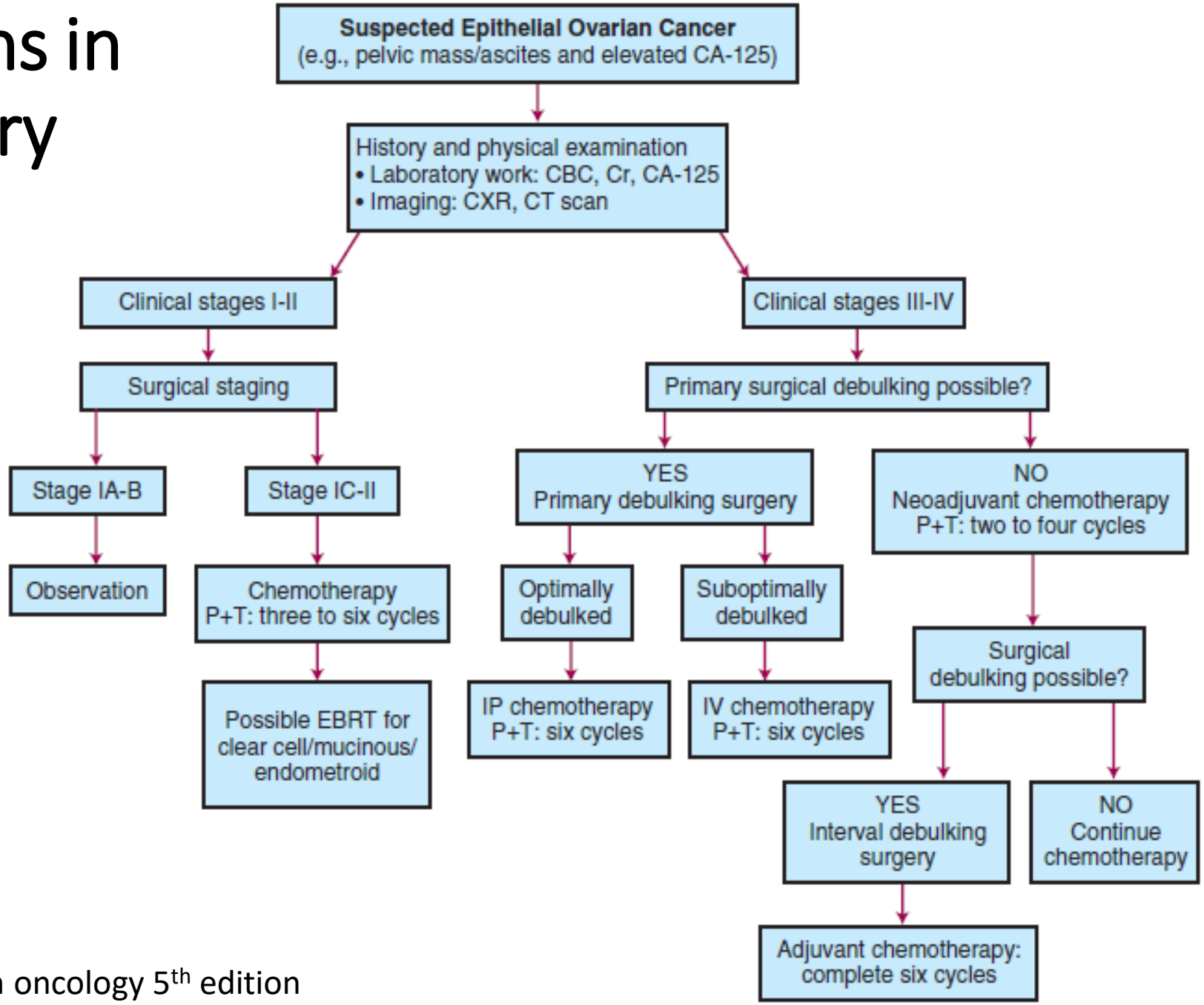
1. Includes extension of tumour to the capsule of liver and spleen without parenchymal involvement of either organ.
2. Parenchymal metastases are Stage IV B.

# Epithelial Ovarian Cancer Outcomes

| FIGO Stage | Patients (*n* = 4,825) (%) | 5-Year Overall Survival (%) |
|---|---|---|
| IA | 13 | 90 |
| IB | 1 | 86 |
| IC | 14 | 83 |
| IIA | 2 | 71 |
| IIB | 2 | 66 |
| IIC | 5 | 71 |
| IIIA | 3 | 47 |
| IIIB | 6 | 42 |
| IIIC | 42 | 33 |
| IV | 13 | 19 |

Adapted from Heintz APM, Odicino F, Maisonneuve P, et al. Carcinoma of the ovary. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. *Int J Gynaecol Obstet*2006;95(Suppl 1):S161–S192.

# Treatment options in Epithelial Ca Ovary




Guderson & Teppers' clinical radiation oncology 5th edition

# Treatment Overview

| | |
|---|---|
| Low risk, early stage | |
| Stage IA/B, grade 1 | Observation |
| Stage IA/B, grade 2 | Observation or IV taxane/carboplatin for 3–6 cycles |
| High risk, early stage | |
| Stage IC, all grades | IV taxane/carboplatin for 3–6 cycles |
| Stage IA/B, grade 3 | IV taxane/carboplatin for 3–6 cycles |
| Stage II | IV taxane/carboplatin for 6 cycles<br>IP chemotherapy in optimally cytoreduced patients |
| Advanced stage | |
| Optimal cytoreduced stage III | IP chemotherapy<br>IV taxane/carboplatin for 6 cycles<br>Clinical trial |
| Suboptimal cytoreduced stage III/IV | IV taxane/carboplatin for 6 cycles<br>Clinical trial<br>Interval cytoreduction if indicated by tumor response and resectability |

# Surgery

- Types
  - Primary cytoreductive surgery
  - Interval cytoreduction
  - Secondary cytoreductive surgery

*Comprehensive surgical staging*

- *Early Stage -TAH + BSO, B/L NODAL DISSECTION (Pelvic + PA) & INFRACOLIC OMENTECTOMY*
- *Advanced stage – (IIB-IV) – (LION study* N Engl J Med 2019; 380:822-832*)*
  - *LN dissection for only Gross disease if documented (clinical /Radiological)*
  - *No systematic Nodal dissection or exploration if clinically negative*

# Primary Cytoreductive Surgery

- ***Primary cytoreduction*** - *D*ebulking surgery prior to administration of first-line chemotherapy .

- ***Optimal cytoreduction*** - *Residual disease of 1 cm* or smaller in maximum individual diameter. (GOG)

- **Goal is no not leave behind any visible disease**

| | Current Grading system for reporting |
|---|---|
| **CC 0** | **No Peritoneal Nodule seen** |
| **CC 1** | **Tumour nodule <2.5 mm** |
| **CC 2** | **Tumour nodule 2.5 mm – 2.5 cm** |
| **CC 3** | **Tumour nodule >2.5 cm** |

# Interval cytoreductive surgery

- Chemotherapy followed by surgery.
- Used in patients who are not good operative candidates or where it is known that an optimal cytoreductive surgery can not be performed.
- Helps determine patients who have chemoresistant disease and won’t be helped by surgery

# Secondary Cytoreductive Surgery

- The use of cytoreductive surgery in the setting of recurrent disease is not well defined

- Selection should be based on

  Disease-free interval from completion of primary therapy.

  The number of sites of recurrence.

  Probability that cytoreduction to minimal residual disease can be achieved

- Benefit appears confined to patients likely to respond to additional chemo:
  - >12 month PFI
  - Isolated site of recurrence
  - Disease completely resectable

# Technique for Surgical Staging

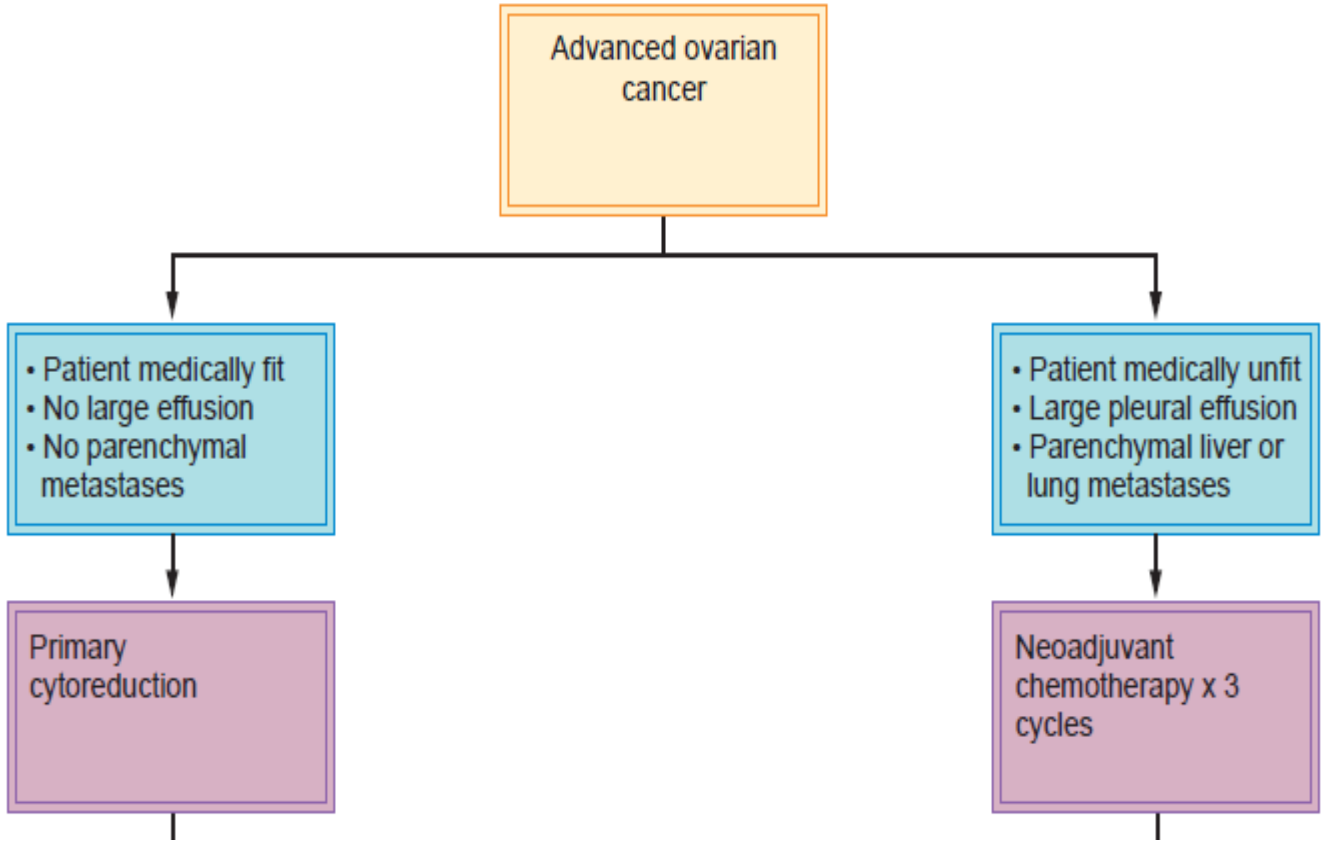
- The ovarian tumor should be removed intact.
- If possible, and a frozen histologic section obtained.
- Peritoneal fluid - Any free fluid is present or peritoneal washings (pelvic cul de sac, B/L hemidiapragm, Paracolic gutter) to be submitted for cytology
- A systematic exploration of all the intra-abdominal surfaces and viscera –Biopsy from suspicious Area
- Diaphragm -Sampled either by biopsy or by scraping for smear
- Omentum- Resected from the transverse colon (*infracolic omentectomy)*
- Retroperitoneal space - Dissected and explored for pelvic & PA nodes

# Fertility Preservation in Early-Stage Ovarian Cancer

- In Pre menopausal with wish for fertility preservation
- Thorough staging laparotomy and confirm of no spread beyond ovary
- Stages IA–IC (Grade 1& 2) –satisfactory low recurrences
- Higher stage or Grade 3 - Significantly higher recurrence rate and lower survival.
- Close follow up - with routine TVS & CA 125.
- Generally, the other ovary and the uterus should be removed at the completion of childbearing

# Advanced Stage Ovarian Cancer

- If medically fit, no large effusion and No parenchymal mets – upfront Surgery
- If upfront surgery not feasible NACT  followed by interval cytoreduction



# Assessment of operability

- USG – not reliable
- CA125 – cutoff of 500 is suggested but not relieble
- CT & MRI – Accuracy in prediciting complete resectibility low
- Laparoscopy – optimal but risk of port site metastasis

# Nelson score

- CT scan prediction index

- Indicators of unresectability
  - Attachment of omentum to spleen
  - Disease > 2 cm on diaphragm,liver surface or parenchyma, pleura, mesentry, GB fossa.
  - Suprarenal para-aortic nodes

- CT scan prediction of surgical outcome
  - 92.3% sensitive, 79.3% specific

# Cytoreductive Surgery

- Includes the performance of a total abdominal hysterectomy and bilateral salpingo-oophorectomy, along with a complete omentectomy and resection of any metastatic lesions from the peritoneal surfaces or from the intestines.
- Rationale for cytoreductive Sx
  - **the physiologic benefits of tumor excision**
  - **the improved tumor perfusion and increased growth fraction**
- According to the Gynecologic Oncology Group (GOG), optimal cytoreduction is defined as the largest residual tumor nodule measuring 1 cm or less. However, the goal is not to leave any visible disease.

# Interval Cytoreduction

- In Advanced CA Ovary (Stage III & IV) – NACT → Cytoreduction Surgery → Adjuvant CT

| Study | Design | Study Years | N | CR Rate (%) | | mOS (months) | HR |
|---|---|---|---|---|---|---|---|
| EORTC 55971 | Noninferiority | 1998-2006 | 670 | PCS | 19 | 29 | 0.98 (90% CI, 0.84 to 1.13) |
| | | | | ICS | 51 | 30 | |
| CHORUS | Noninferiority | 2004-2010 | 550 | PCS | 17 | 23 | 0.87 (95% CI, 0.72 to 1.05) |
| | | | | ICS | 39 | 24 | |
| JCOG 0602 | Noninferiority | 2006-2011 | 301 | PCS | 12 | 49 | 1.05 (90.8% CI, 0.83 to 1.33) |
| | | | | ICS | 64 | 44 | |
| SCORPION | Superiority | 2011-2016 | 171 | PCS | 48 | 41 | 1.05 (95% CI, 0.77 to 1.44) |
| | | | | ICS | 77 | 43 | |

- should be reserved for patients with a poor performance and nutritional status, as these patients will usually have decreased postoperative morbidity if given chemotherapy prior to their planned debulking operation. These are usually patients with large volume ascites or pleural effusions.

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# Indications of adjuvant chemotherapy

- Adjuvant chemotherapy is indicated in :
  I. Grade 3 tumors.
  II. Clear cell histology,
  III. Disease extension beyond the ovarian capsule into the abdominal wall or peritoneum(Stage IC – III)

Standard <u>front-line</u> chemotherapy is

- Carboplatin, AUC 6 to 7.5.
- Paclitaxel 175 mg/$m^2$ every 21 days for 6 cycles

# Adjuvant Chemotherapy

- **Early-Stage Low-risk Ovarian Cancer – Stage IA,IB – Grade I-II**
  - **No further adjuvant treatment**

- **Early-Stage High-risk Ovarian Cancer – Grade III, capsular breach, +ve ascetic fluid cytology, any grade with clear cell histology**
  - **Adj Treatemnt- Chemo/WAI**

- **Borderline Tumours – fertility sparing surgery should suffice**

# Early Stage Ovarian Cancer Chemotherapy

| | N | INCLUSION | ARMS | Results | Comments |
|---|---|---|---|---|---|
| ICON 1 | 447 | Most stage I and II, **optimal staging not required** | 1. Platinum based CT<br>2. OBSERVATION | 5 Yr OS - 73% Vs 62% (S) | Surgery suboptimal |
| ACTION | 448 | Stage I high risk, IIA, **one-third staged** | 1. Platinum based CT<br>2. OBSERVATION | OS – No benefit (P =.10)<br>RFS – chemo better (p= 0.02) | benefit from Adj CT- limited to the patients with suboptimal staging |
| GOG 157 | 457 | Stage I high risk/II **30% incomplete staged** | 1. 3# P+C<br>2. 6# P+C | 5 yr OS – 81% Vs 83% (NS)<br>5 yr DFS - 75% Vs 80% (NS) | 3# CT is equivalent to 6# CT |
| GOG 175 | 542 | Stage I high risk/II | 1. 3# P+C<br>2. 3#P+C + WKLY PACLI FOR 24WKS | 5Yr OS- 85.7% Vs 84.5% (NS)<br>5 Yr DFS – (NS) | Maintenance not beneficial |

# Advanced Stage Disease

| Trials | N | Inclusion | Arms | Results | Remarks |
|---|---|---|---|---|---|
| **GOG 111** | 386 | FIGO III, IV suboptimal resection | *Pacli (135) + cis* Vs *Cis* + Cyclo each 6 #s | PFS (18m Vs 13m (S)<br>OS (38 m Vs 24 m (S) | Pacli + cis better |
| **OV 10 EORTC, NOCOVA, NCIC** | 680 | FIGO IIb—c, III, IV Opt & suboptimal Sx | *Pacli (175) + cis* Vs *Cis* + Cyclo upto 9 #s | PFS – 15.5 m Vs 11.5 m (s)<br>OS – 35.6 m Vs 25.8 m (s) | Pacli + cis better |
| **SCOT-ROC** | 1077 | stages IC to IV ovarian carcinoma | *Doce+ cis* Vs<br>*Pacli + cis Each 6 #s* | PFS – 15 m VS 14.8 m(NS)<br>2 yr OS - 64.2% Vs 68.9% (NS) | Doce ≈ Pacli<br>Toxicity – Different |
| **GOG 158** | 792 | Advanced Optimally staged | Pacli (135)+ cis (75) Vs Pacli (175)+ carbo AUC 7.5 | PFS – 19.4m Vs 20.7m (NS)<br>OS – 48.7 m Vs 57.4 m (NS) | Pacli + carbo less toxic<br>Similar outcome |
| **GOG 182, ICON 5** | | FIGO IIb—c, III, IV Opt & suboptimal Sx | Pacli + carbo Vs Pacli +carbo + 3$^{rd}$ agent | | No benefit of addition of 3$^{rd}$ agent |

# Intraperitoneal chemotherapy

| Trials | N | Inclusion | Arms | Results | Remarks |
|---|---|---|---|---|---|
| GOG 104 | 546 | Stage III<br><2 cm residual | Cis + cyclo IV 6#s Vs<br>Cis IP + Cyclo IV 6#s | Med OS – 41m Vs 49 m (S) | Only 58% completed 6# CT |
| GOG 114 | 462 | Stage III<br><1 cm residual | Pacli + cis IV 6#s Vs Carbo (9)<br>IP + Pacli IV+ cis IP X6 #s | PFS – 22m Vs 28 m (s)<br>OS - 52m VS 63 m (S) | <18% on IP arm received <2 IP CT |
| GOG 172 | 416 | Stage III<br><1 cm residual | Pacli + cis IV 6#s Vs<br>Pacli IV + cis IP + Pacli IP x6#s | PFS – 19m Vs 24m (S)<br>OS – 50m Vs 67 m (S) | Only ≈ 50 % completed IP chemtherapy |
| GOG 252 | 1380 | (Sub group)<br>Stage III<br><1 cm residual | IV pacli + carbo 6#s<br>IV pacli + IP carbo<br>IV pacli + IP cis + IP pacli<br>All received Bev # 2-22 | PFS – 26.9m Vs 28.7 m Vs 27.8 m | Too complicated to interpret<br>QOL best in IV arm |
| Meta-anlysis 2007 | 6 RCT 1716 | pooled HR for PFS - IP *Cis Vs IV Cis* -0.792 (95% CI: 0.688 to 0.912, $p$ = 0.001)<br>pooled HR for OS - IP *Cis Vs IV Cis* -0.799 (95% CI: 0.702 to 0.910, $p$ = 0.0007)<br>**Supported IP *cisplatin* regimen in the 1st line treatment of stage III optimally debulked CA Ovary** | | | |
| Cochrane DB | 9 RCT 2119 | Pooled HR OS – IP VS IV - 0.81; (95% CI: 0.72 to 0.90)<br>Pooled HR DFS - IP VS IV - 0.78; (95% CI: 0.70 to 0.86)<br>**IP chemotherapy increases OS & PFS from advanced ovarian cancer** | | | |

# NCI clinical alert

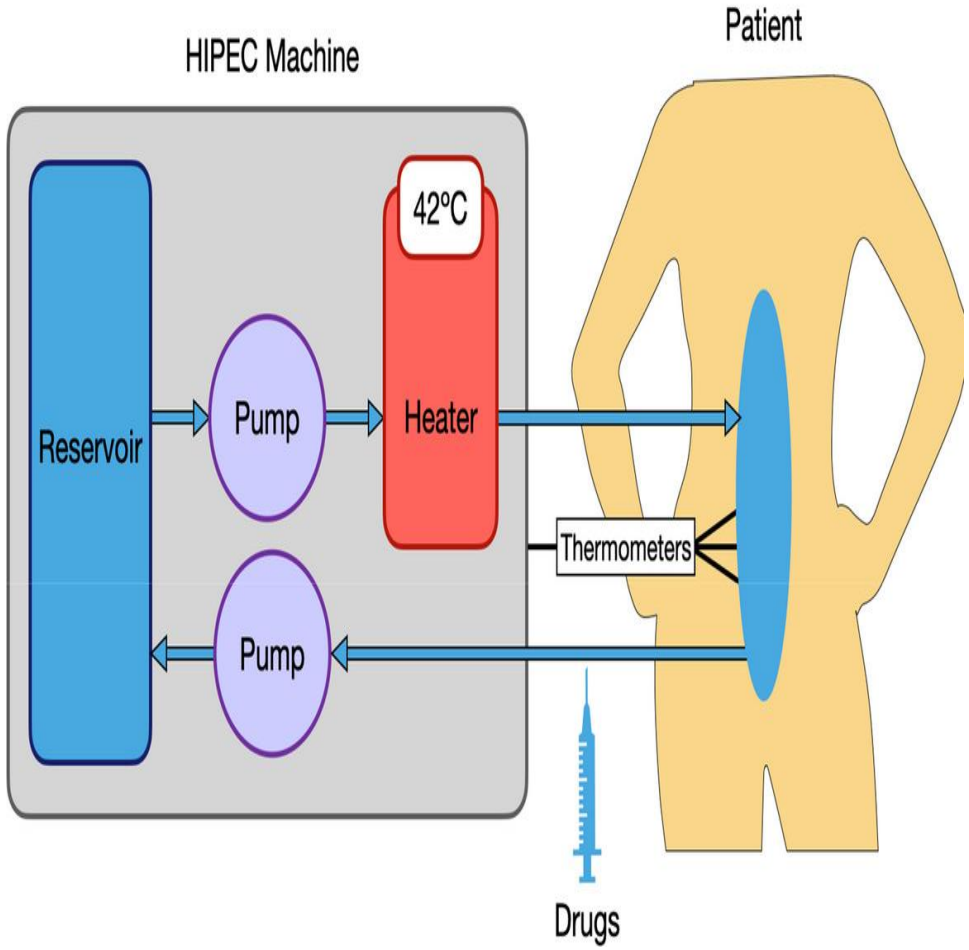
- **Women with optimally debulked stage III ovarian cancer should be considered for IP cisplatin chemotherapy.**

**Caveats**

- The role of IP chemotherapy remains contentious, with some researchers arguing that the trials to date have been flawed.
- Concerns have been raised about the technical difficulties and increased toxicity of IP therapy
- The heterogeneity and toxicity of the IP regimens used have left some confusion as to what the most important elements of the ideal IP therapy regimen are.

# HIPEC (Hyperthermic Intraperitoneal Chemotherapy)

- Combines the pharmacokinetic advantage inherent to the intracavitary delivery of certain cytotoxic drugs with the direct cytotoxic effect of hyperthermia
- The chemotherapeutic agents used in HIPEC need to have a cell cycle nonspecific mechanism of action and should ideally show a heat-synergistic cytotoxic effect




| Authors | N | Inclusion | Results |
|---|---|---|---|
| Van Driel et al<br>Phase III | 245 | Stage III<br>interval CRS | RFS – 15m Vs 11 m (s)<br>OS – 48m VS 34 m (s)<br>Grade 3/4 side effects similar |
| Lim et al.<br>Phase III | | Stage III<br>Optimal Sx<br>Primary or<br>Interval CRS | No significant diff between OS<br>But in interval CRS + HIPEC<br>5 Yr OS 47.9% Vs 27.7% |

# Targeted Therapy

| | | | | | |
|---|---|---|---|---|---|
| GOG 218 | **1,873** | **stage III to IV WITH** macroscopic residual disease. | 1. 6 # PACLI + CARBO<br>2. 6 # Pacli + carbo + bev (15 mg/kg)<br>3. 6 # Pacli + carbo + bev (15 mg/kg) + bev maintance bev tototal of 22 cycles | **PFS**<br>**OS** | **Arm 1Vs arm 2 - (NS) [HR], 0.908; *p* = 0.16)**<br>**Arm 1 Vs arm 3 – [s] (HR, 0.717; *p* < 0.001).**<br>**OS no diff.** |
| ICON 7 | **1,528** | **patients with high-risk (clear cell or grade 3 tumors)**<br>Stage 1- IV | 1- 6# pacli + carbo<br>2. 6 # Pacli + carbo + bev (7.5mg/kg) + maintance bev 12#s | PFS(PRIMARY)<br>OS | 17.3M VS 19 M (P=0.004)<br>OS - improvement in survival in the **high risk subgroups (stage III with >1 cm residual and stage IV** [HR, 0.64; *p* = 0.002]) |

# Recurrent Ca Ovary

# Diagnosis

- CA 125 - Gynecologic Cancer Intergroup (GCIG)

| Scenario | Pre Treatment | Post Treatment | Failure definition |
|---|---|---|---|
| 1 | increased | Normal | >2 times upper limit of normal on 2 occasions at least 1 week apart |
| 2 | increased | Increased from normal | >2 times of Nadir on 2 occasions at least 1 week apart |

- CT Scan – Basic investigation but sensitivity – 40-95%, specificity 45-90%, FNR – 45%
- MRI Abdomen – better sensitivity & specificity than CT
- PETCT - sensitivity ≈ 90%, specificity – 85%
- PETCT + CA 125 sensitivity ≈ 98% in recurrence

# EORTC 5595: Early versus Delayed Treatment of Recurrence

- The primary end point was OS.
- After 370 events of death
- No evidence of a difference in OS between early and delayed treatment (25.7 versus 27.1 months,HR, 0.98; 95% CI, 0.8 to 1.2; *P* = 0.85)

## Criticism-

- Old trial starting in 1997
- Targeted therapy and other chemotherapy were not there
- Treatment to start early t achieve at least good PFS & QOL.
- No secondary CRS

# Definitions

- Platinum Refractory- Progression during primary chemo

- Platinum Resistance – Progression within 6 months of Last CT
  - Options - single agents such as pegylated liposomal doxorubicin (PLD) or topotecan and other agents.

- Partial Platinum sensitive – Progression with in 6-12 months of last CT
  - can benefit from platinum-based re-induction chemotherapy

- Platinum sensitive – if DFI is more than 12 months
  - reinduction of platinum-based chemotherapy. Doublet with Pacli, PLD, Gemcitabine can be considered.

# 2nd Line Chemotherapy

- Platinum sensitive-

| | | | | |
|---|---|---|---|---|
| ICON 4 | | Carbo VS<br>Pacli + carbo | OS 24 m Vs 29 m (s)<br>PFS 9m Vs 12 m (s) | |
| SWOG STUDY | | Carbo vs PLD + C | Better PFS with PLD + C | |
| INTERGRUP STUDY | | Carbo vs<br>Gem + carbo | PFS 5.8 m Vs 8.6 m (s) | |
| CALYPSO | | PLD + Carbo Vs<br>Pacli + carbo | PFS 11.3 m Vs 9.4 m (s) | |
| | | | | |

# Recurrent CA Ovary (Role of Targeted Therapy )

| | | | | |
|---|---|---|---|---|
| GOG 213 | 674 | Platinum sensitive relapsed Ca Ovary. + CRS in eligible patients | Pacli + Carbo Vs<br>Pacli + Carbo + Bev | Median OS, 42.2 m vs. 37.3 m (*P* = 0.056) |
| OCEAN | 242 | Platinum sensitive Recurrent disease | Gem + Carbo x 6 Vs<br>Gem + Carbo x 6 + Bev x11#s | PFS (8.4 m vs. 12 .4 m) (P < 0.0001) |
| ICON 6 | 456 | Platinum sensitive Recurrent disease | Platinum based CT vs<br>Platinum based CT + cediranib vs<br>Platinum based CT + cediranib + maintance cediranib | Median PFS, 11m vs. 8.7m (maintenance vs. CT-only arm);<br>*P* = 0.001<br>No OS benefit |
| AURELIA | 361 | **Platinum-resistant recurrence** | Paclitaxel /Toptecan / Liposomal Doxo VS<br>Above CT + Bev | PFS (3.4m vs. 6.7m) (*P* < 0.0011) |

# HIPEC in relapse

| Author | Study type | Drugs | PFS | OS |
|---|---|---|---|---|
| Zivanovic *et al.* (47) | Prospective phase I, n=12 pts | Cisplatin | 13.6 m | N/A |
| Gonzalez Bayon *et al.* (48) | Prospective n=27 pts | Cisplatin + doxorubicin | N/A | 62.8 m, 1st recurrence |
| Bakrin *et al.* (34) | Retrospective n=470 pts | Cisplatin 76% other drugs 24% | N/A | CC0 51.5 m |
| Fagotti *et al.* (49) | Case control n=30 pts | Oxaliplatin | 26 m | 5 years =42.7% |
| Spiliotis *et al.* (26) | Prospective phase III trial, n=120 pts | Chemosensitive cisplatin + paclitaxel, chemoresistant doxorubicin + paclitaxel or mitomycin | N/A | HIPEC 26.7 m versus control 13.4 m |
| Cascales-Campos *et al.* (50) | Case control n=39 pts | Paclitaxel | 24 m | N/A |

doi: 10.21037/atm-20-1486

# FDA approved PARP Inhibitors in Recurrent Ca Ovary

| Drug | Approval date | Indication |
|---|---|---|
| Olaparib | December 2014 | • Monotherapy in patients with deleterious or suspected deleterious germline BRCA-mutated advanced ovarian cancer<br>• BRCA detected by any FDA-approved testing<br>• Treated with three or more lines of prior chemotherapy |
| Rucaparib | December 2016 | • Monotherapy for patients with advanced ovarian cancer<br>• Germline and/or somatic deleterious BRCA mutation<br>• BRCA detected by FDA-approved companion diagnostic testing<br>• Treated with two or more lines of prior chemotherapy |
| Niraparib | March 2017 | • Maintenance treatment of patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer<br>• No BRCA testing needed<br>• Complete or partial response to platinum-based chemotherapy |

# Other drugs in Recc. CA Ovary (Phase II)

- Sorafenib
- Sunitinib
- Cediranib,
- Pazopanib
- Immune check point inhibitors
  - Pembrlizumab
  - Avelumab
  - Nivolumab
  - Atezolizumab

# Secondary Cytoreduction

- **Secondary cytoreduction is defined as an attempt to resect or optimally debulk selected patients with recurrent disease following first-line chemotherapy**
- **Eligibility –**
  - platinum-sensitive recurrent ovarian cancer (DFI of atleast 12 months)
  - localized late recurrence,
  - Absence of ascites,
  - complete cytoreduction

# Role of Radiotherapy

# Role of Radiotherapy

**TABLE 59-2** Early-Stage Ovarian Cancer: Randomized Trials of Whole-Abdomen Irradiation or $^{32}P$

| Trial/ Author | Year | Stage | Study Design | No. Patients | 5-yr Overall Survival (%) | Comments |
|---|---|---|---|---|---|---|
| NCIC/Klaassen[104] | 1988 | I, II | Pelvic RT + melphalan<br>Pelvic RT + WAI<br>Pelvic RT + $^{32}P$ | 106<br>107<br>44 | 61<br>62<br>66 | $^{32}P$ arm accrual closed early due to toxicity |
| MDACC/Smith[97] | 1975 | I-III | WAI<br>Melphalan | 51<br>57 | 71<br>72 | <2 cm residual disease |
| PMH/Dembo[107] | 1979 | IB, II, III asymptomatic | WAI<br>Pelvic RT ± chlorambucil | 76<br>71 | 64 (10-yr)<br>40 (10-yr) | $p = .007$ |
| DACOVA/Sell[113] | 1990 | IB-IC, II | WAI<br>Pelvic RT + cyclophosphamide | 60<br>58 | 63 (4-yr)<br>65 (4-yr) | |
| GOG 95/Young[49] | 1990 | IA-IBG3, IC, II | $^{32}P$<br>Melphalan | 73<br>68 | 78<br>81 | 6% bowel obstruction in $^{32}P$ |
| NRH/Vergote[105] | 1992 | I-III | $^{32}P$ or WAI<br>Cisplatin | 169<br>171 | 83<br>81 | 28 in $^{32}P$ arm treated with WAI |
| GICOG/Bolis[106] | 1995 | IA-IB, IC | $^{32}P$<br>Cisplatin | 75<br>77 | 79<br>81 | $^{32}P$ not given in 20% of patients |
| GOG 7602/Young[103] | 2003 | IA-IBG3, IC, II | $^{32}P$<br>Cyclophosphamide + cisplatin | 110<br>119 | 78<br>81 | 3% bowel perforation in $^{32}P$ |

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# Consolidative Whole-Abdomen Irradiation or $^{32}P$

| Trial/Author | Stage | Study Design | No. Patients | 5-yr Overall Survival (%) | Bowel Obstruction |
|---|---|---|---|---|---|
| West Midlands/Lawton[156] | IIB residual, III, IV | WAI<br>Chlorambucil | 56<br>53 | 7<br>8 | 9% |
| Italy/Bruzzone[154] | III, IV<br>Minimal residual disease | WAI<br>Chemotherapy | 20<br>21 | 45 (3-yr)<br>85 (3-yr) | 5% |
| NTOG/Lambert[155] | IIB-IV<br><2 cm residual disease | WAI<br>Carboplatin | 58<br>59 | 25<br>30 | 1.7% |
| Sweden- Norway/Sorbe[160] | III | WAI<br>Cisplatin + doxorubicin/epirubicin<br>Observation | 32<br>35<br>31 | 56 (PFS)<br>36 (PFS)<br>36 (PFS) | 10% |
| Germany/Pickel[159] | IC-IV<br>No clinical disease | WAI<br>Observation | 32<br>32 | 59<br>33 | 3.1% |
| NRH/Vergote[162] | IAG2-3, IB, III | $^{32}P$<br>Observation | 25<br>25 | 95 (PFS)<br>82 (PFS) | 4% |
| GOG 93/Varia[163] | III | $^{32}P$<br>Observation | 104<br>98 | 67<br>63 | 2.9% |

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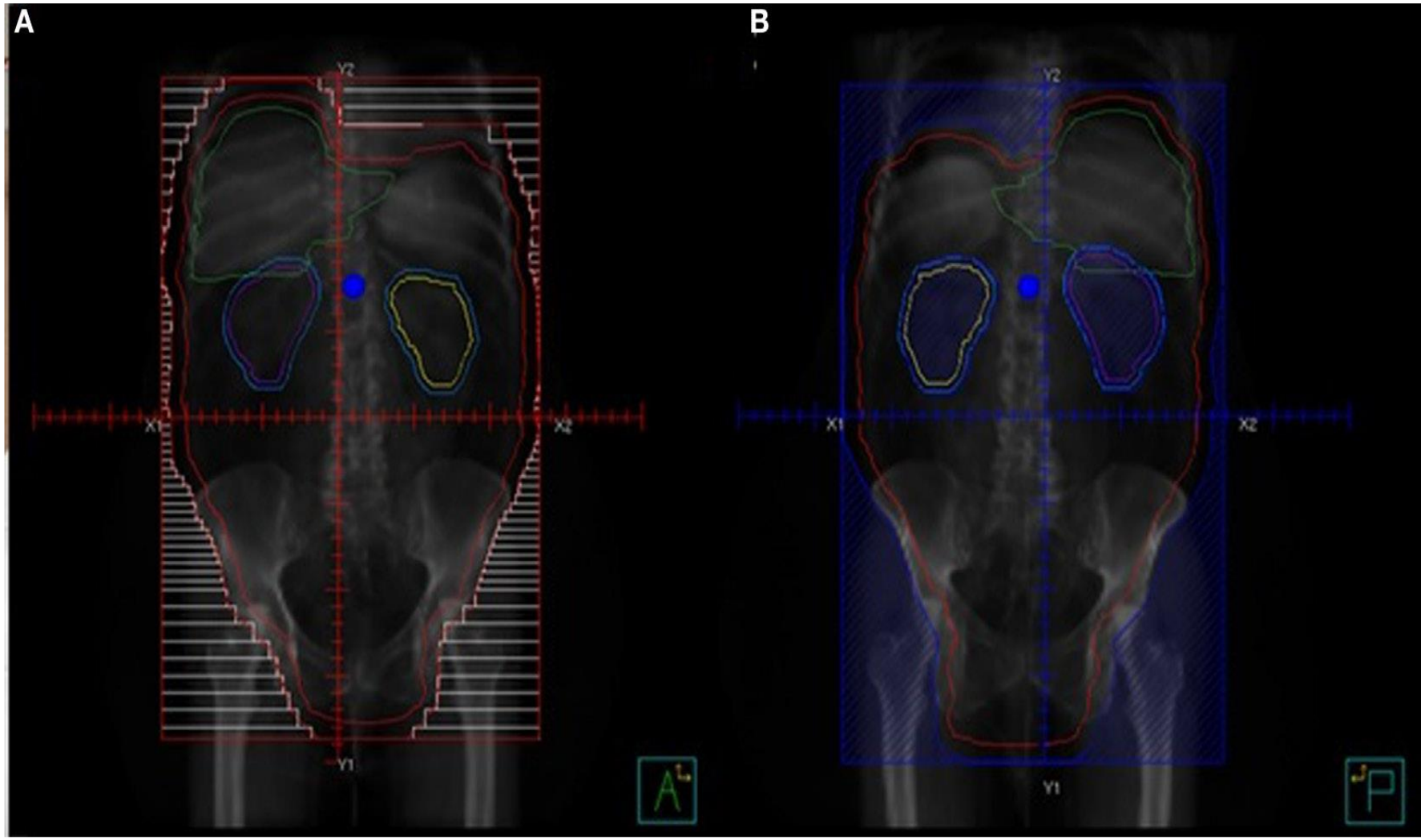
# $P^{32}$

- Pure beta emitter
  - maximum energy of 1.71 MeV
  - maximum penetration of 8 mm (average: 1 to 4 mm),
  - Half-life of 14.3 days
- No gamma contamination
- Used intraperitoneal at a dose of 10 to 20 mCi.
- Absorbed by the peritoneal surface via macrophages and then excreted through the lymphatic channel into systemic vasculature and liver.
- Mobilization of the patients in the first 6 hours is critical for homogeneous dispersion of the radio colloids on the serosal surfaces
- Dose calculations gave an estimated tissue surface dose of 30 Gy per 370 MBq of $^{32}P$ administered.
- The amount of $^{32}P$ in peripheral blood increased for 7 days after administration and was then followed by a continuous decrease.
- The estimated peripheral blood dose is 0.012 Gy, and maximum bone marrow dose is 0.06 Gy.

# Whole Abdominal Irradiation

- Used in patients in completely resected tumors
- not suitable for Macroscopic residuals.
- Advantage in comparison to 32P - homogeneous dose to all areas of the abdomen/ pelvis and the ability to encompass the pelvic and para-aortic lymph nodes.
- Disadvantage - with conventional techniques - dose-limiting acute and late toxicity predominantly hematologic and gastrointestinal.
- Target volume - Entire peritoneum,
- Borders –
  - cephalad border – encompass diaphragm
  - caudal border - Pelvic floor,
- Dose –
  - Whole abdomen - 25 to 30 Gy @ 1-1.5 Gy/#
  - Pelvis - 45 Gy.
- Dose Constraints – Liver Dmean- 25Gy, B/L kidney – D mean 18Gy (island block)

# Conventional whole abdominal radiation



# Whole Abdominal Radiation

- Acute reactions - acute toxicity included diarrhea, fatigue, nausea, and hematologic effects.

- Late Toxicity –
  - basal pneumonitis – (up to 20% of patients),
  - liver damage
  - bowel toxicity (10–15% of patients). Bowel Obstruction -8%

- Long-term complication rate using conventional radiotherapy techniques is significant.

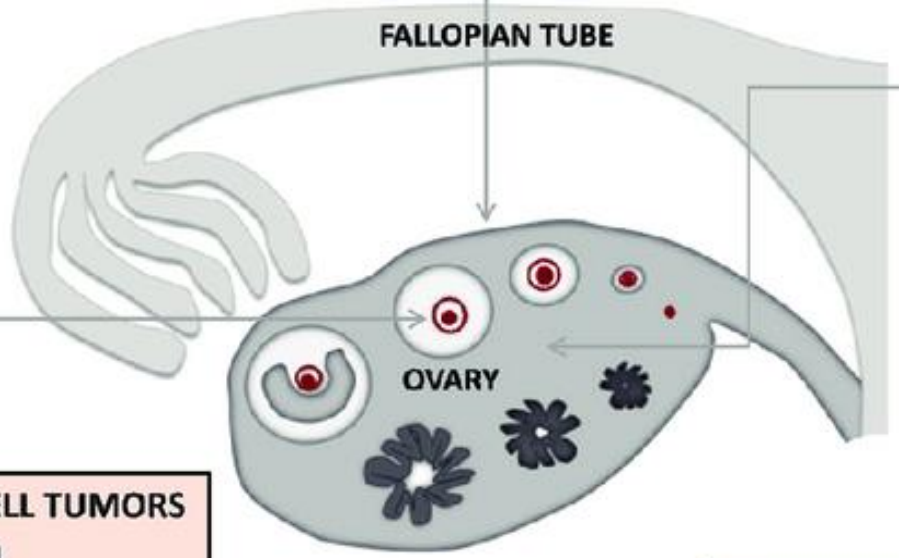
- At this time, WAI is not included in the treatment guidelines

# Non epithelial tumors of Ovary

# Types of Ovarian Cancer & Their Origin

90% of all ovarian cancer

**OVARIAN EPITHELIAL CANCER**
- High-Grade Serous Carcinomas
- Low-Grade Serous Carcinomas
- Clear cell carcinoma
- Endometrioid
- Mucinous




**OVARIAN SEX CHORD-STROMAL TUMORS**

Stromal tumors
1. Fibroma
2. Thecoma
3. Fibrosarcoma
4. Leydig cell tumor
5. Steroid cell tumor
6. Sclerosing stromal tumor

Sex chord tumors
1. Adult granulosa cell tumor
2. Juvenile granulosa tumor
3. Sertoli cell tumor
4. Sex chord tumor with annular tubules

Mixed sex chord-stromal tumors
1. Sertoli-Leydig cell tumor

90% of all hormone producing cancer

70% of all ovarian cancer in 1st 2 decades of life

**OVARIAN GERM CELL TUMORS**
1. Dysgerminoma
2. Immature teratoma
3. Yolk sac tumors
4. Mixed germ cell tumors

**SMALL CELL CARCINOMA OF THE OVARY**
1. SCCO - hypercalcemic type
2. SCCO - pulmonary type

Ravindran, Febina & Choudhary, Bibha. (2021). Ovarian Cancer: Molecular Classification and Targeted Therapy. 10.5772/intechopen.95967.

# Serum Markers

| Tumor Type | AFP | hCG | LDH |
|---|---|---|---|
| Dysgerminoma | — | +/− | + |
| Choriocarcinoma | — | + | — |
| Endodermal sinus tumor | + | — | — |
| Immature teratoma | +/− | — | — |
| Mixed germ cell tumor | +/− | +/− | +/− |
| Embryonal carcinoma | +/− | + | — |
| Polyembryoma | +/− | + | — |

- Most ovarian neoplasms diagnosed in children and adolescents are germ cell tumors, with approximately two-thirds of these tumors being malignant at the time of diagnosis.

- Germ cell tumors comprise 20% of all ovarian neoplasms and 2% to 5% of all ovarian malignancies.

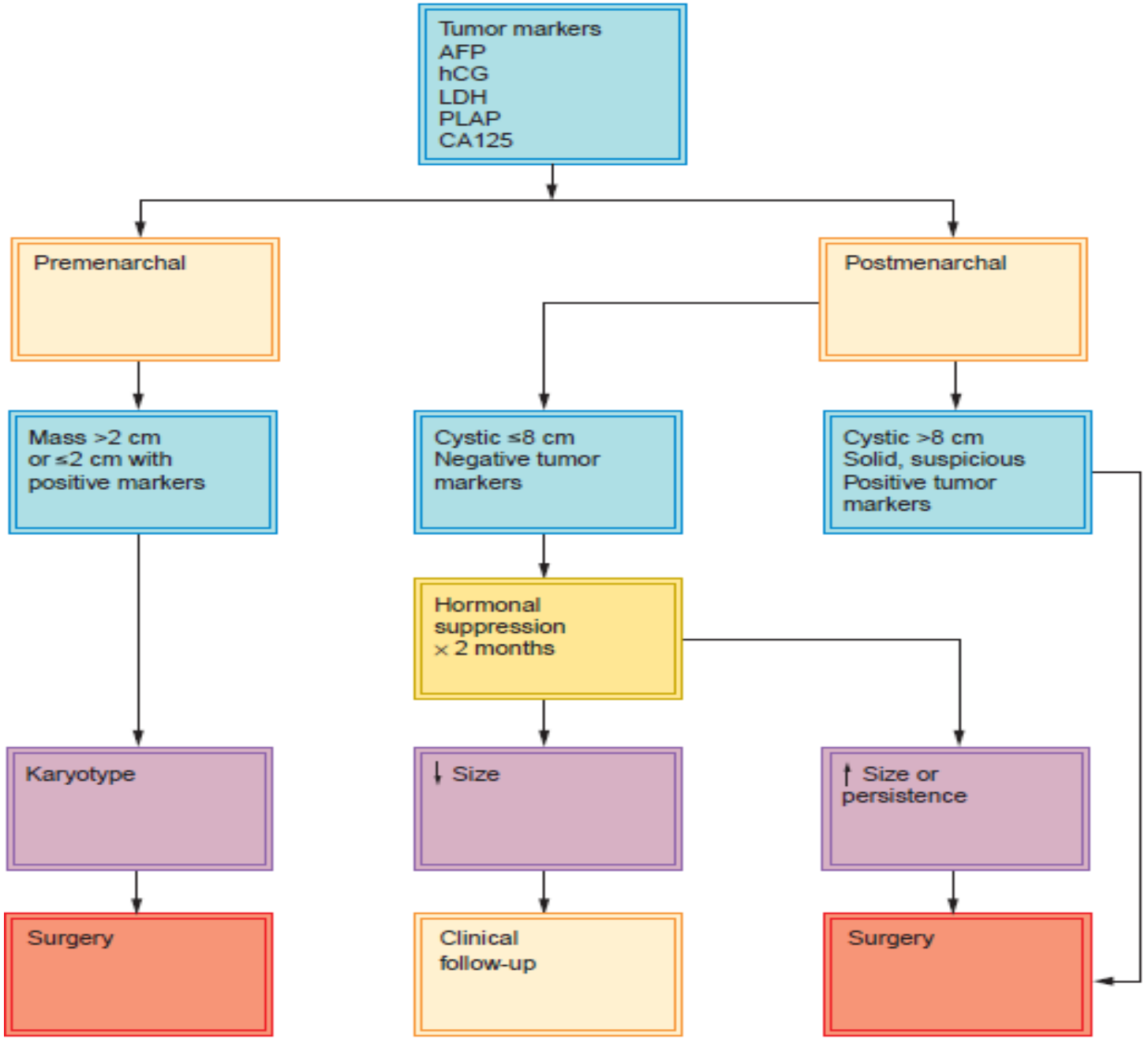
- Dysgerminoma – 40-50%

- Immature teratoma – 20%

- Yolk sac tumor 20%

- Rest are rare .

# Management of adnexal lesion in Premenopausal patient.

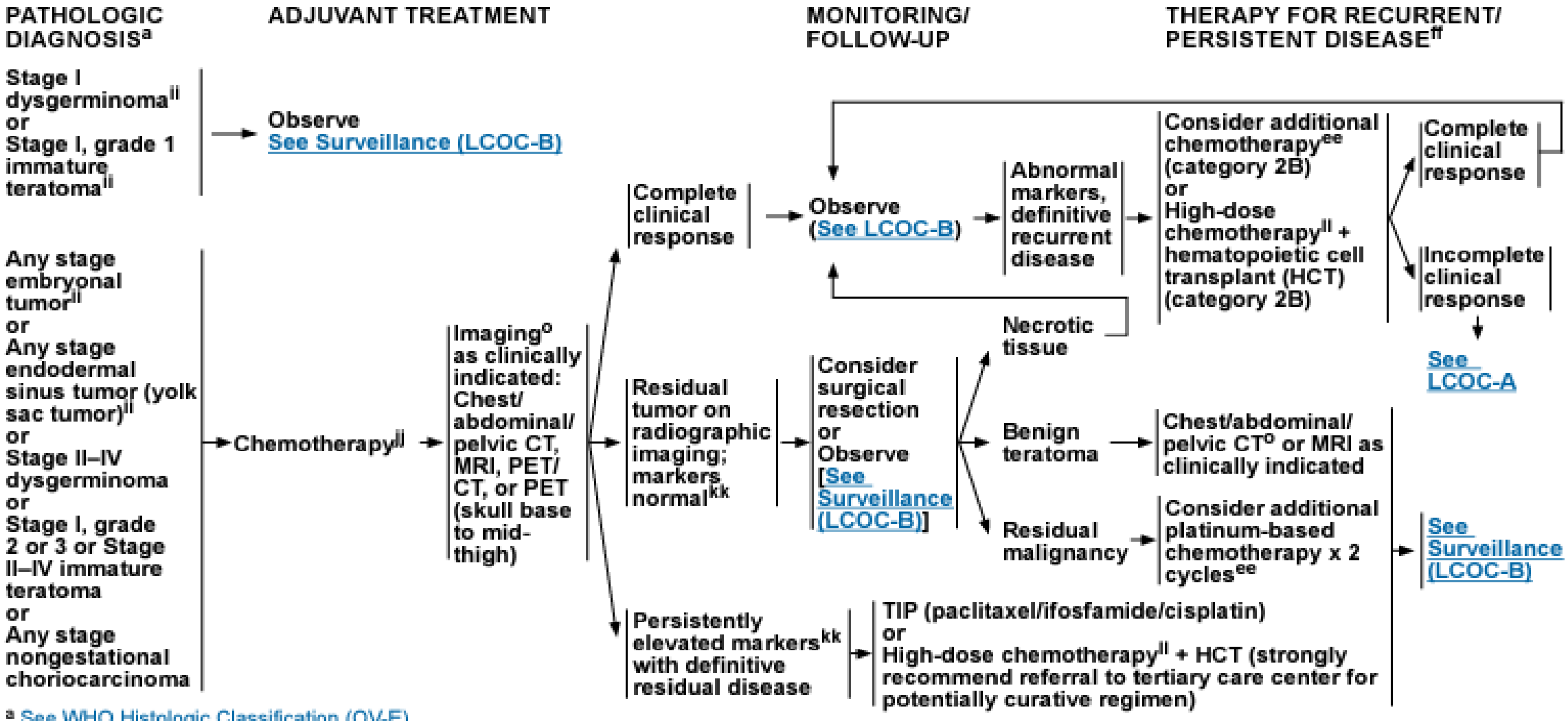



**Berek & Hacker's Gynecologic Oncology**
***Sixth Edition***

# Dysgerminoma

- Facts
  - Most common malignant germ cell tumors
  - Highest bilaterality rate (20%),
  - 10% of the ovaries being grossly involved and 10% being microscopically involved
- 80% present before the age of 30
- Comprehensive staging is recommended
- If fertility desired unilateral Sx may be done.
- stage I – Observation
- Stage II & III - three to four cycles of BEP

# Malignant Germ cell Tumors




[a] See WHO Histologic Classification (OVAE)

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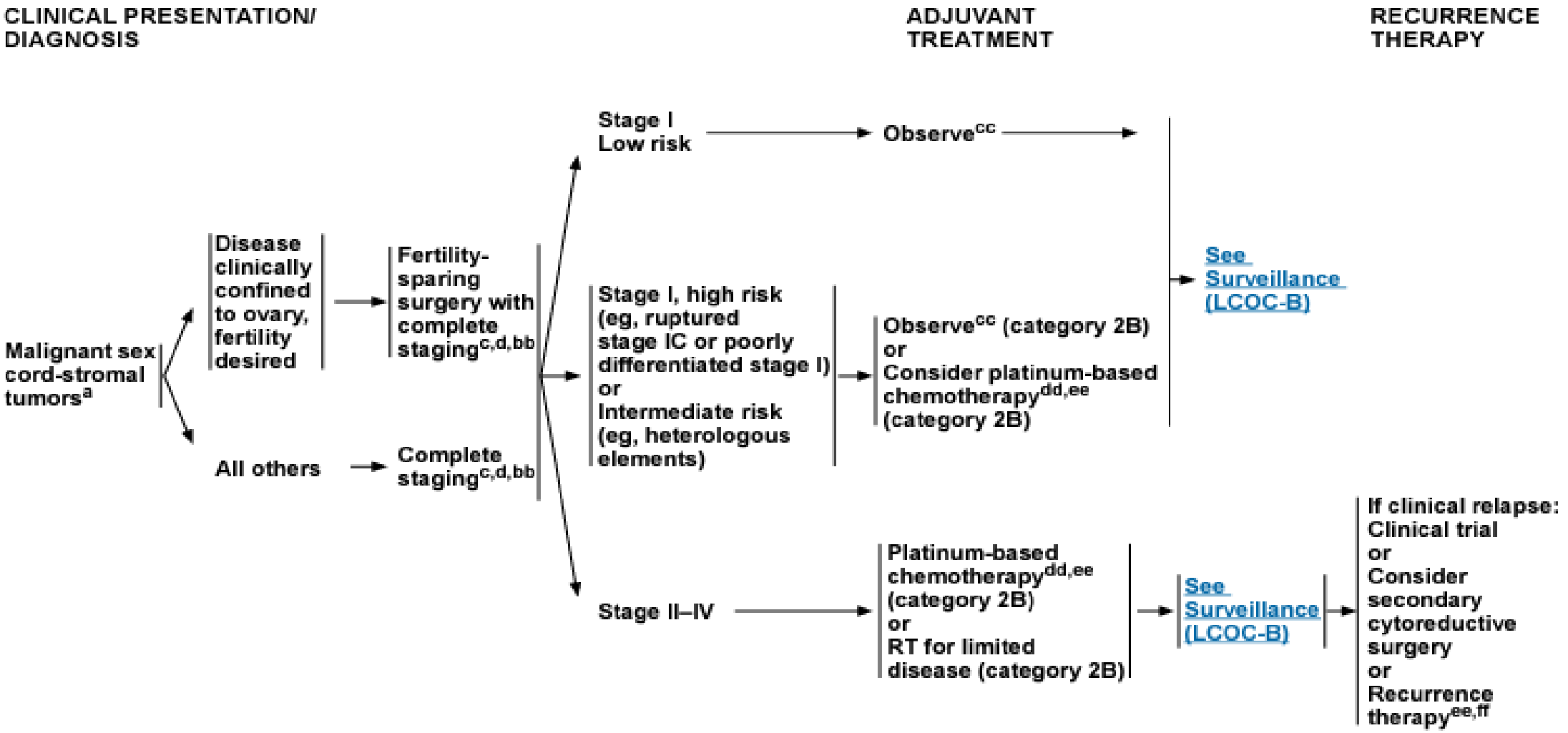
# Sex cord-stromal tumors

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THANK YOU