EPITHELIAL OVARIAN CANCER (LEVELS OF EVIDENCE IN PARENTHESES)

Clinical Suspicion of Ovarian Cancer

- Symptoms of bloating, dyspepsia, nausea, constipation, distension, abdominal or pelvic pain, urinary frequency or urgency
- Palpable pelvic or abdominal mass
- Ascites/pleural effusion

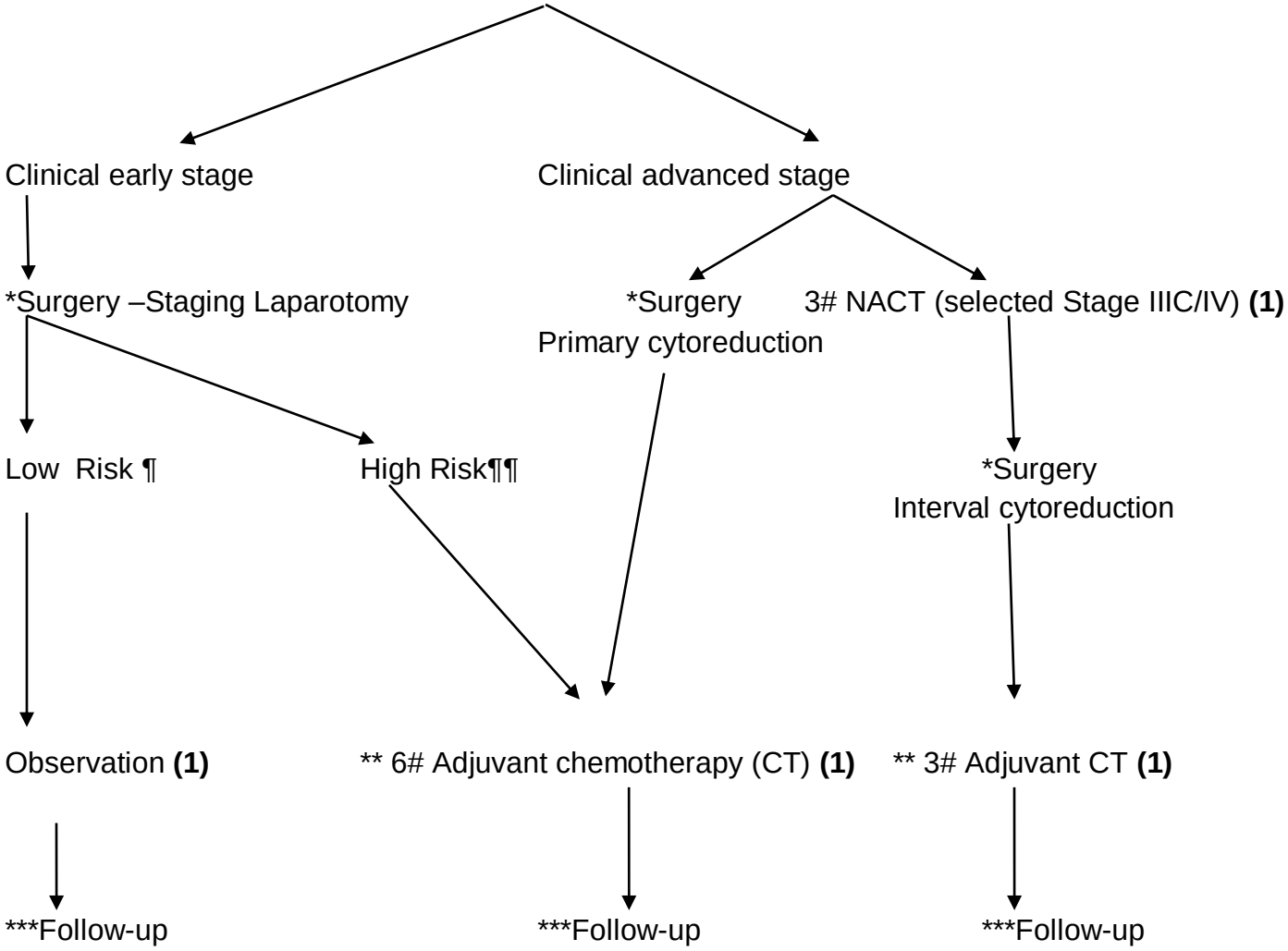
WORK UP

- Personal and family history
- Complete History including
  - Change of bowel habits, bleeding per rectum, weight loss or jaundice - Any breast lump
  - Menstrual History -In young women history of primary amenorrhea.
- Thorough clinical examination including pelvic and per rectal examination. To also do clinical breast examination and especially look for any supraclavicular lymph node.
- Haematological and biochemical investigations
- Serum tumor markers: CA-125, CEA, CA 19.9 (Ca 19.9-optional)
  (In patients <40 years to also do AFP, βHCG, S LDH, S Inhibin B if indicated)
- Contrast CT scan of abdomen and pelvis and chest Xray. CT scan of the chest if clinically indicated or Germ Cell tumor is suspected.
- Upper and Lower GI endoscopy if clinically indicated eg.
  - If History /examination suggestive of GI involvement
  - If there is only ascites and no adnexal mass seen on imaging
  - Bilateral solid adnexal masses
  - CA 125 : CEA <25
- Ascitic fluid/ pleural fluid cytology (if present).
- Cell block preparation for IHC may be done (IHC Optional)
- If disease is confined to the ovary and /or primary surgery is planned FNAC/ Biopsy of the mass if primary surgery **not** indicated. Biopsy or FNAC to be done only in advanced disease where primary surgery not planned.

- Genetic Testing for BRCA 1 and 2 in case family history suggestive. Consider in all high grade serous carcinoma (Optional)

PRIMARY TREATMENT

PRIMARY TREATMENT (Levels of evidence in parentheses)



¶ Low Risk- Stage IA/IB , Grade 1, Non-Clear cell Histology

¶¶ High Risk – Stage IA/IB, Grade 2/3, Clear cell histology, Stage IC, Stage II

NOTES

I. FIGO (International Federation of Gynaecology & Obstetrics) Staging for Ovarian Cancer 2013[2]

Ovarian malignancies are staged surgico-pathologically. Patients with stage I and II are considered early stage disease, whereas stage III and IV fall into the category of advanced stage disease. Stage IIIc is the most common stage of presentation

Stage I: Tumor confined to ovaries or fallopian tube(s) **T1-N0-M0**

IA: Tumor limited to 1 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 1 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-M

Stage II: Tumor involves 1 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 1 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 10mm in greatest dimension
- IIIA1(ii) Metastasis more than 10mm 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 2cm 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

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

Extension of tumor from omentum to spleen or liver (stage IIIC) should be differentiated from isolated parenchymal metastases (stage IVB).

II. * SURGERY

Early Stage Disease

- Primary surgery for diagnosis, staging and treatment is the mainstay.
- The surgery should entail peritoneal fluid cytology, systematic exploration of the abdomen and pelvis, multiple peritoneal biopsies, total abdominal hysterectomy with bilateral salpingo-oophorectomy, omentectomy. Systematic pelvic and para-aortic lymphadenectomy to be done for staging. Conservative surgery i.e. unilateral salpingo-oophorectomy with preservation of the normal contralateral ovary and uterus may be considered in young patients desirous of child bearing with stage IA, low grade disease or borderline tumours. Close observation is essential in these cases.

Advanced Stage Disease

- Interval cytoreductive surgery after neoadjuvant chemotherapy is associated with less surgical morbidity and morbidity and no difference in disease free or overall survival.
- Cytoreductive surgery includes systematic exploration of the abdomen and pelvis, total abdominal hysterectomy with bilateral salpingo-oophorectomy, omentectomy and removal of all metastatic disease Pelvic and para-aortic lymphadenectomy has not shown to have any survival advantage.
- In advanced disease upfront surgery should be considered in those with omental metastasis <5 cm or low grade tumors.

The optimal goal of cytoreductive surgery is to leave behind no visible or palpable residual disease but the minimum goal is to leave behind less than 1cm (preferably less than 0.5 cm) residual disease at any given site.

** Pathology- Grossing and complete reporting of the surgical specimen should be done.

III. ** **CHEMOTHERAPY**

- Six cycles of paclitaxel and carboplatin every 3 weekly is the standard adjuvant chemotherapy. [1,3]

  In early stage ovarian cancer where chemotherapy is indicated, can consider 6 cycles single agent carboplatin or 3 cycles of paclitaxel and carboplatin. (However in high grade serous carcinoma consider 6 cycles of Paclitaxel and Carboplatin)

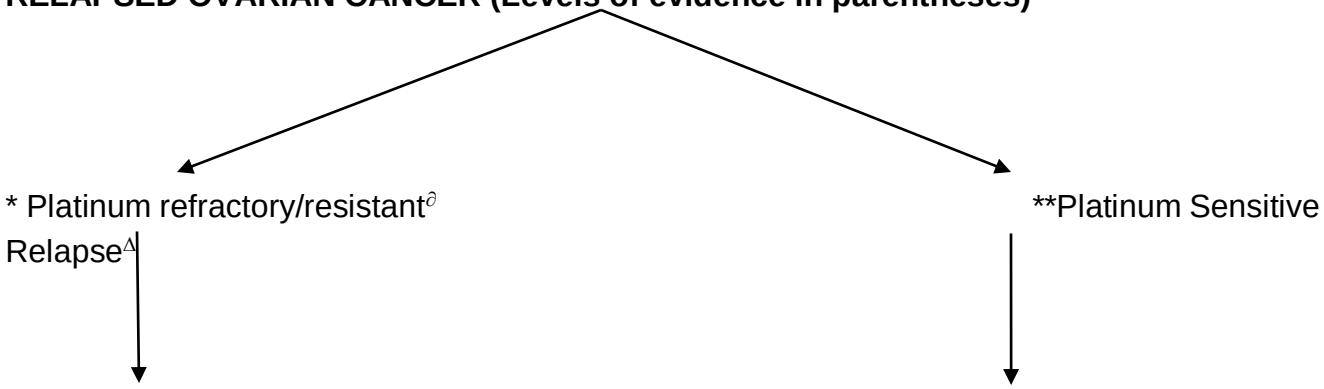
- Three cycles of neoadjuvant chemotherapy followed by interval debulking surgery and 3 cycles of adjuvant platinum based chemotherapy is an appropriate option for patients with bulky stage IIIC or IV ovarian carcinoma.[4]
- In patients with poor performance status or elderly patients Single agent Carboplatin may be considered.[5]

- Intraperitoneal chemotherapy may be considered in patients with optimal cytoreduction in centres with experience.[6](Optional)
- Bevacizumab – This is approved for adjuvant use with adjuvant chemotherapy followed by maintenance .However in view of a DFS benefit of 2 months, cost, toxicity and no OS advantage in the overall population, the magnitude of clinical benefit needs to discussed. It may be considered in high risk population ie those with stage IV disease or those without optimal cytoreduction (Optional).(1)
- PARP inhibitors (Optional)- The use of PARP inhibitors in first line after treatment with platinum has shown to improve progression free survival especially in those with germ line BRCA 1/2 mutation , estimated freedom from disease progression or death at 3 years ,60% versus 27%. (Ref 15 , 16)

IV. ***FOLLOW UP

- History and clinical examination every 3 monthly for 2 years, 6 monthly for 5 years and then yearly life long
- Ca-125 at every visit if initially elevated
- Imaging as clinically indicated(ultrasound / CT / Chest X ray)
- Hematological and biochemical investigations as clinically indicated

RELAPSED OVARIAN CANCER (Levels of evidence in parentheses)



*Single agent CT/Best supportive care **(1)** ** Platinum based combination CT **(1)**
***Consider addition of bevacizumab (Optional) **(1)**

PARP inhibitors (Optional)

∂No response or progression on previous platinum therapy or progression within 6 months of its completion
∆Progression more than 6 months after completion of previous platinum chemotherapy

RECURRENT OVARIAN CANCER

Treatment of recurrent disease to be initiated at symptomatic or *significant radiological progression.* CA 125 rise alone may not need systemic chemotherapy.(2)

Treatment of Relapsed disease (3)

Platinum Sensitive Relapse – Relapse after 6 months

- Treatment Platinum based doublet ie a combination of platinum with paclitaxel, Gemcitabine or liposomal doxorubicin. Similar efficacy, difference in toxicity profile.
- May consider liposomal doxorubicin and platinum in those with partial platinum sensitive disease (i.e. those relapsing within 6-12 months).

Platinum Resistant Relapse – Relapse within 6 months

- Single agent-Oral Etoposide,
- Liposomal doxorubicin, Weekly Paclitaxel, topotecan, single agent Gemcitabine
- In those with poor performance status palliative care alone should also be considered

Other Agents in Relapsed Ovarian Cancers (Optional)

- Bevacizumab-In patients with advanced ovarian cancer bevacizumab with chemotherapy and then as maintenance in the adjuvant setting is approved. There is however a PFS advantage with OS benefit only in the high risk subgroup of those with stage IV disease, inoperable stage III and those who are suboptimally debulked. It has also been approved with chemotherapy in those with both platinum sensitive and relapsed ovarian cancers where it has shown a PFS benefit. The cost, toxicity and magnitude of benefit needs to be discussed.

- PARP inhibitors - In patients with relapsed ovarian cancer with response to platinum based chemotherapy maintenance with PARP inhibitors (niraparib, rucaparib, olaparib) is an option irrespective of their BRCA status. In those with germ line BRCA mutation PARP inhibitors have been approved after 2 (rucaparib) or 3 (olaparib) or more lines of therapy. Olaparib has recently been approved in patients with advanced ovarian cancer with germline or somatic mutation who achieve a partial or complete response to first line platinum based chemotherapy. There is however yet proven progression free survival benefit. The magnitude of benefit with PARP inhibitors need to be weighed against cost and toxicity.

Secondary Cytoreduction

The jury on secondary cytoreduction is still out. The Desktop III trial has shown a PFS benefit in patients who relapsed after 6 months of a platinum free interval, had an ECOG performance status of 0 to 1, complete resection at initial surgery and minimal ascites (<500ml). The OS results are still awaited. In the GOG 213 study did not show a benefit in PFS or OS, the majority of patients in this trial had received bevacizumab.

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