GROOTE SCHUUR HOSPITAL
and
TYGERBERG HOSPITAL

GYNAECOLOGICAL ONCOLOGY UNITS

DEPARTMENTS OF

OBSTETRICS AND GYNAECOLOGY AND RADIOTHERAPY

ONCOLOGY GROUP

Protocol for the

Treatment of Gynaecological Malignancies

2026 Edition

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INTRODUCTION

This is the 14th edition of the booklet, “Protocol for Treatment of Gynaecological Malignancies”.
Members (which include gynaecological surgeons, a pathologist and radiation oncologists) of the gynaecological oncology units of Groote Schuur Hospital, Tygerberg Hospital and colleagues from private practice, contributed to the booklet. All are actively involved in the treatment of women with a gynaecological malignancy.

It should be remembered that, as with previous editions, this edition represents current views on the management of gynaecological cancer and should be used as a guide to staging and treatment and NOT as a comprehensive reference work. These views are evidence based, but are not prescriptive. It may be of value to under- and postgraduate students, interns, and registrars in training and practicing gynaecologists.

We are convinced that the best interests of our patients are served by a multi-disciplinary approach involving the medical profession including radiologists, but also oncologically trained nursing sisters, radiographers, social workers, dieticians, occupational therapists and volunteers. This approach can only be put into practice in a specialised multi-disciplinary unit and we would urge that all patients with gynaecological malignancies be referred to such a unit.

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INDEX

CHAPTER 1.

CARCINOMA OF THE VAGINA

A. FIGO STAGING

Stage I	Confined to vaginal wall
Stage II	Confined to sub-vaginal tissue
Stage III	Extension to pelvic sidewall
Stage IVa	Bladder or rectum involved
Stage IVb	Distant metastases

B. INVESTIGATIONS

- As for Carcinoma of the Cervix.
- In potentially resectable disease consider imaging (MRI/CT) for depth of invasion, involvement of underlying structures, and for suspicious nodes.

C. TREATMENT

1. **Stage I:**
   Radical Wide Local Excision with or without vaginal reconstruction
   Aim for a margin of ≥ 5mm of disease-free tissue in all directions.
   - If on pathology specimen < 1mm invasion – no further treatment.
   - If >1mm invasion – do lymphadenectomy and consider adjuvant intracavitary brachytherapy.

If lesion in the upper vagina do pelvic lymphadenectomy (treat similarly to cervical cancer), and if in the lower vagina do groin dissection.

2. **Stage II + III:**
   Concurrent chemoradiation + intracavitary brachytherapy (include pelvic and/or inguinal nodes).

Note: To make the diagnosis of primary vaginal carcinoma, the cervix must not be involved.

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CHAPTER 2.

CARCINOMA OF THE VULVA

A. FIGO staging for carcinoma of the vulva (2021)

Stage I - tumour confined to the vulva.
IA - ≤2 cm and stromal invasion ≤1 mm.
IB - >2 cm or stromal invasion > 1 mm.

Stage II - tumour of any size with extension to lower third of the urethra, lower third of the vagina, lower third of the anus with negative nodes.

Stage III tumour of any size with extension to upper part of adjacent perineal structures, or with any number of non-fixed, non-ulcerated lymph nodes.
IIIA Tumour of any size with disease extension to the upper two-thirds of the urethra, upper two-thirds of the vagina, bladder mucosa, rectal mucosa, or regional lymph node metastases ≤ 5 mm.
IIIB Regional lymph node metastases >5 mm.
IIIC Regional lymph node metastases with extra capsular spread.

Stage IV Tumor of any size fixed to bone, or fixed, ulcerated lymph node metastases, or distant metastases.
IVA Disease fixed to pelvic bone, or fixed or ulcerated regional lymph node metastases.
IVB Distant metastases.

Depth of invasion is measured from the basement membrane of the deepest, adjacent, dysplastic, tumour-free rete ridge (or nearest dysplastic rete peg) to the deepest point of invasion. Regional lymph nodes refer to inguinal and femoral lymph nodes.

B. INVESTIGATIONS histological/cytological:

- Diagnostic incisional biopsy, report to include p16/p53 IHC status and depth of invasion measurement.
- Fine-needle aspirate (FNA) of suspicious inguinal nodes.
- Cervical screening where possible.
- Radiological:
  - Chest imaging (CXR/CT)
  - Abdominal plus pelvic CT
  - MRI may be indicated in select patients
- Laboratory:
  FBC, renal function tests, liver function tests, syphilis serology, HIV (CD4 count and Viral Load if positive).

C. TREATMENT

Treatment of vulval cancer must be individualised. Treatment should be approached as two distinct pathways.

1. The vulval lesion.
2. The inguino-femoral lymph nodes (IFLN).

1. The vulval lesion

a) Superficially invasive lesions (≤ 1mm depth of invasion): radical wide local excision only.
b) Early disease with depth > 1mm but confined to the vulva without clinically suspicious lymph nodes: radical wide local excision and groin node assessment.

HPV-mediated squamous carcinoma
Aim for a surgical excision margin of 1 cm to achieve a > 2 mm pathological tumour-free margin.

Differentiated-VIN/lichen sclerosus mediated squamous carcinoma. Aim for a surgical excision margin of 2 cm to achieve a >8 mm pathological tumour-free margin.

If excision margins of the vulval primary are inadequate, re-operation is the preferred treatment where feasible. It is important to treat surrounding areas of dysplasia/field-change.

c) Advanced disease – Tumour excision compromises sphincter/s, FIGO stage 3 or 4 tumours, or bulky positive groin nodes:

- Resectable primary tumours with irresectable nodes: radical vulvectomy followed by inguinal and pelvic radiotherapy. The vulva is included in the RT field if the excision margins are inadequate and further surgery is not possible.
- Irresectable primary tumours are treated with concomitant chemo-radiotherapy. If the nodes are clinically negative, consider groin node assessment first and if negative, omit radiotherapy to the groins and pelvis.
- If the vulva excision would compromise a sphincter, consider NACT; then proceed to surgery or radiotherapy. Reassess at 6 weeks. Every attempt should be made to excise residual tumour.
- If both vulva and nodes are irresectable, treat with concomitant chemo-radiotherapy first. Reassess 6 weeks after completion of chemo-radiotherapy.
- Every attempt should be made to excise residual tumour.
- Patients with advanced disease and poor performance status – treat with palliative intent, radiation may be considered.

2. Inguino-femoral lymph node assessment.

Criteria for sentinel lymph node procedure:

- Squamous cell carcinoma.
- Unifocal tumour confined to the vulva.
- Tumour size < 4 cm and/or stromal invasion >1 mm.
- Clinically and radiologically negative inguinal-femoral nodes.
- Adequately trained surgeon & pathologist & nuclear medicine service.

Criteria for full inguino-femoral lymph node dissection:

- Sentinel lymph node criteria not met.
- Macro-metastases (>2mm) on histology of sentinel lymph nodes.

Ipsilateral inguino-femoral lymph node assessment is adequate, provided:

- The tumour is > 1cm away from the midline,
- The labia minora are not involved.
- Bilateral groin node assessment is indicated in all other scenarios, including where the ipsilateral node assessment is positive for metastases.
- Superficial/inguinal node dissection (without removing the deep/femoral nodes) is associated with a higher incidence of groin recurrence.
- Intra-operative frozen section of suspicious inguinal nodes may be useful to decide whether immediate contralateral node dissection should be performed in lateral tumours.
- Large mobile malignant nodes (e.g. positive cytology/histology) may be surgically debulked prior to radiotherapy

Indications for Adjuvant Radiotherapy after IFLN assessment:

- Micro metastases (≤ 2mm) at Sentinel node procedure.
- Single node metastasis > 5mm
- Two or more nodes positive

3. Recurrent vulval carcinoma

- Biopsy and imaging (CXR & CT or PET/CT) to delineate extent of disease.
- Individualise according to extent of disease.
- Vulvar recurrence only where possible, excision of the vulvar tumour.
- Treat surrounding areas of dysplasia/field-change.
- Chemoradiation if irresectable and no previous radiation treatment.
- Groin recurrence:
  - ► Chemoradiation if not received before.
  - ► Chemotherapy, if fit, for all other scenarios

POINTS TO REMEMBER

- In planning the management of patients, adopt a multi-disciplinary
- approach consulting with plastic surgeons, colorectal surgeons, urologists and sexual medicine specialists.
- DVT and peri-operative antibiotic prophylaxis are mandatory.
- Drainage of the inguinal area following complete lymphadenectomy should be considered.
- If adenocarcinoma of the vulva is diagnosed, exclude other primary sites.
- Melanoma and basal cell carcinoma should be managed as per standard protocols for melanoma and basal cell carcinoma.
- Paget's disease of the vulva must prompt a search for another primary site. Surgical excision margins should be ≥ 2 cm.

- For extensive Paget's disease, Imiquimod or radiation are alternative treatment options.

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CHAPTER 3.

CARCINOMA OF THE CERVIX

A. FIGO STAGING 2018

Stage I: The carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded).

IA Invasive carcinoma identified only microscopically (all gross lesions even with microscopic invasion are stage 1B cancers). Invasion is limited to measured stromal invasion with a maximum ≤ 5mm.
IA1 Measured stromal invasion < 3mm in depth.
IA2 Measured stromal invasion ≥ 3mm and ≤ 5mm in depth.

IB Invasive carcinoma with measured deepest invasion ≥ 5mm (greater than stage 1A), lesion limited to the cervix.
IB1 Invasive carcinoma < 2cm in greatest dimension.
IB2 Invasive carcinoma ≥ 2cm and < 4cm in greatest dimension.
IB3 Invasive carcinoma ≥ 4cm in greatest dimension.

Stage II: The carcinoma extends beyond the cervix, but has not extended onto the lower third of the vagina or to the pelvic sidewall.

IIA1 Involvement limited to the upper 2/3 of the vagina without parametrial involvement. Invasive carcinoma < 4cm in greatest dimension

IIA2 Invasive carcinoma > 4cm in greatest dimension.

IIB Parametrial involvement but not up to the pelvic sidewall.

Stage III: The carcinoma involves the lower third of the vagina and/or extend to the pelvic sidewall and/or causes hydronephrosis or non-functioning kidney and/or involves pelvic and/or para-aortic lymph nodes.

IIIA Involvement of the lower third of the vagina, but no extension to the pelvic sidewall.

IIIB Extension to the pelvic sidewall, and/or hydronephrosis or non-functioning kidney (unless known to be due to another cause).

IIIC Involvement of pelvic and/or para-aortic lymph nodes (including micro metastases), irrespective of tumour size and extent (with r and p notations).

IIIC1 Pelvic lymph node metastasis only.

IIIC2 Para-aortic metastasis.

Stage IV: The carcinoma has extended beyond the true pelvis or has involved (biopsy-proven) the mucosa of the bladder and/or rectum (bullous oedema does not permit a patient to be allotted to stage IV).

IVA Spread to adjacent pelvic organs.

IVB Spread to distant organs.

B. ADDITIONAL NOTES ON STAGING OF CARCINOMA OF THE CERVIX.

- Stage IA carcinoma should include minimal microscopically-evident stromal invasion as well as small tumours of measurable size. The diagnosis of stages IA1 and IA2 should be based on microscopic examination of removed tissue, preferably by a type 2 or 3 loop electrosurgical excision (LEEP or cone biopsy), which must include the entire lesion.
- Extension to the corpus should be disregarded, as it does not alter stage, prognosis or management.

- A patient with a tumour fixed to the pelvic sidewall by a short and indurated, but not nodular parametrium should be allotted to Stage IIB. It is impossible, at clinical examination, to decide whether a smooth and indurated parametrium is truly cancerous or only inflammatory. Therefore, the patient should be placed in stage IIIB only if the parametrium is nodular onto the pelvic sidewall or if the tumour extends to the pelvic sidewall.
- Malignant cells in cytological washings from the bladder require further examination and biopsy of the bladder. The presence of bullous oedema of the bladder mucosa should not permit a patient to be allocated to stage IV. If there is doubt about the staging, an examination under anaesthetic (EUA) may be appropriate.
- Stage should be allocated after all imaging and pathology reports are available, and should not be altered later e.g. after surgery or at the time of recurrence.

Considerations

a. Imaging and pathology can be used in all stages, when available, to supplement clinical findings with respect to tumour size and extent. Pathological findings supersede clinical and radiological findings.
b. The involvement of vascular/lymphatic spaces should not change the staging. The lateral extent of the lesion is no longer considered.
c. Isolated tumour cells do not change the stage, but their presence should be recorded.
d. Adding notation of r (radiology) and p (pathology) to indicate the findings
that are used to allocate the patient to stage IIIC. The type of imaging or pathology technique should be documented.

When in doubt, the lower staging should be used.

C. INVESTIGATIONS.

1. Colposcopy and excisional biopsy for Stage IA suspected micro-invasive disease (e.g. LLETZ/cone biopsy), or
2. Cervical biopsy of a macroscopically visible lesion.
3. Laboratory tests: FBC, U&E, ALP and GGT, and VDRL. HIV with informed consent and CD4 count & viral load if positive.
4. Cystoscopy: Only for stages II, III, IV, with biopsy of any suspicious lesions.If patient is asymptomatic and has no haematuria this is not compulsory in the revised staging. Cystoscopy is recommended in cases of a barrel-shaped endocervical tumour, and where the tumour has extended to the anterior vaginal wall.
5. Suspected bladder or rectal involvement should be confirmed by biopsy/ histological evidence.
6. Radiological: The revised staging permits the use of any of the imaging modalities e.g.:

- Ultrasound, CT, MRI, PET, according to available resources, to provide information about tumour size, nodal status, and local or systemic spread.
- CXR and abdominal ultrasound (with special reference to renal tract and liver).
- Selected skeletal X-Rays and/or bone scan where indicated (suspected skeletal metastases).
- MRI scans are optional for early stage disease and if available, are particularly useful for measurement of size of lesion and parametrial involvement.
- CT assessment of pelvic/para-aortic nodal areas.
- Consider radiologically-directed FNAB or biopsy of enlarged nodes or suspicious lesions if findings will alter management.

- PET-CT (if available) is more accurate than CT and MRI in detecting nodal metastases ≤10mm in size. Surgical assessment (e.g. laparoscopic lymph node dissection) may be used to tailor treatment according to extent of disease, if resources allow. The false negative rate of PET – CT is reported to be 4 – 15%. Not all enlarged lymph nodes are metastatic (particularly in HIV/TB endemic areas) and fine needle aspiration or biopsy may enable metastatic disease to be excluded.
- Pre-treatment para-aortic LN staging in women with stage IB - IVA will detect up to 18% of patients with PA lymph node involvement by cancer.
- Lymphocyst formation is the most common complication.
- If only pelvic nodes are positive the patient is assigned to stage IIIC1 and if para-aortic nodes are involved they are stage IIIC2.

D. TREATMENT.

Stage IA:

Squamous carcinoma:

(a) **Stage IA1** – options:

- Total hysterectomy (TH) only (abdominal/vaginal/laparoscopic) provided cone margins are negative and there is no lymph vascular space invasion (LVSI).
- Conization only, provided cone margins are negative for cancer, there is no LVSI, patient wishes to preserve fertility, is available/prepared to return for regular follow up, and cervix is amenable to evaluation/ examination (See Chapter 12 Fertility Sparing section).
- TH + Pelvic Lymphadenectomy (PL) or Sentinel Node Procedure (SLN) if LVSI present. Lymph node dissection may be considered if positive LVSI.
- Radical hysterectomy + SLN/PL if cone margins are involved with cancer (perceived to be stage IB1).
- Intracavitary brachytherapy if not a surgical candidate.

(b) **Stage IA2** – options:

- Total hysterectomy (abdominal/vaginal/laparoscopic) + SLN/PL if cone margins clear.
- Radical hysterectomy + SLN/PL if cone margins are involved with cancer (perceived to be stage IB1).Radical trachelectomy (+/- cervical cerclage) + SLN/PL where preservation of fertility is desired (this can be done laparoscopically if possible). (See Fertility Sparing section chapter 12).
- Chemo-radiation if not a surgical candidate.

Adenocarcinoma and Adenosquamous carcinoma:

- Where depth of invasion can be accurately assessed, treatment should be the same as for squamous carcinoma.

- Where in doubt, radical hysterectomy + PL should be performed. Consider BSO in view of higher risk of ovarian metastases.

Stage IB:
(a) **Stage IB1 and IB2:**

- Radical hysterectomy + SLN + PL. Individualise for age, obesity and co-existing medical conditions. If there is a suspicion of involved lymph nodes frozen section should be obtained. If positive, consider abandoning the hysterectomy. Discontinue hysterectomy if extra-cervical extension could compromise resection lines, in order to avoid two radical therapies i.e. surgery and adjuvant radiation.
- Radical trachelectomy (+/- cervical cerclage suture) + PL for tumours ≤ 2cm where preservation of fertility is desired. (See Fertility Sparing section Chapter 12).
- Pelvic nerve sparing surgical procedures are recommended in patients undergoing radical hysterectomy as long as curability is maintained. Intrapelvic injuries to autonomic nerves e.g. hypogastric, splanchnic nerves and pelvic plexus may lead to impairment of urination, defaecation and sexual function leading to a diminished QOL.
- Chemo-radiation + intracavitary brachytherapy if medically unfit for surgery.

Sentinel Lymph node (SLN) mapping plays an increasingly important role in the surgical management of early stage cervical cancers (stage IA, IB1 and IB2).

The LACC trial showed that hysterectomy by a minimally invasive route was associated with higher rates of recurrence compared to the open approach in early-stage cervical cancers. Further studies are on-going to confirm these findings.

(b) **Stage IB3:**

- Chemo-radiation + intracavitary brachytherapy (See Chapter 9 Principles of Radiotherapy).
- Radical hysterectomy and PL maybe an option in selected cases.
- Consider salvage hysterectomy if persistent central tumour can be histologically demonstrated 3 months post chemo-radiation treatment.
- In situations where definitive treatment may be delayed (long surgery/ radiotherapy waiting time or pregnancy), consider neo-adjuvant chemotherapy.

Stage II:

(a) **Stage IIA1:**

- Radical hysterectomy + PL if minimal involvement of upper vagina.

Chemo-radiation (CRT) + intracavitary brachytherapy.

(b) **Stage IIA2:**

- Chemo-radiation + intracavitary brachytherapy.

(c) **Stage IIB:**

- Chemo-radiation + intracavitary brachytherapy.

Indications for post-operative chemo-radiation:

- High risk criteria:
- Positive pelvic node(s).
- Positive resection line(s).
- Parametrial invasion.
- Intermediate criteria in node-negative patients: if ≥ 2 out of 4 consider RT in case of:
    - ▸ LVSI.
    - ▸ ≥ 2/3 Depth of Invasion (or >10 mm DOI).
    - ▸ ≥ 4 cm tumour size.
    - ▸ Adeno-/Adenosquamous carcinoma histology.

Notes:

- Either RT or Chemo-radiation can be used.
- Small central pelvic volume RT is an option.
- Consider RT if resection lines <5 mm.
- Add vault brachytherapy boost if cuff resection line is involved or resection lines <5 mm.

Stage III:

- Chemo-radiation + intracavitary brachytherapy.
- Palliative radiotherapy should be considered if massive tumour with bilateral hydronephrosis, severe wasting/poor performance status, or for patients with life threatening co-morbid conditions.

Stage IV:

(a) **Stage IVA:**

- Fit patients with low volume tumour: chemo-radiation + intracavitary brachytherapy.
- Patients with a bladder or rectal fistula should be referred for a surgical diversion and may receive palliative radiotherapy thereafter.
  It is essential to evaluate the patient's ability to manage stoma and -ostomy sites prior to surgery.
  Palliative radiotherapy should be considered for: massive tumours with bilateral hydronephrosis, severe wasting/poor performance status, or patients with life threatening co-morbid conditions.

(b) **Stage IVB:**

- Best supportive care.
- Palliative radiotherapy and/or trial of chemotherapy (See Chemotherapy protocols).

E. OTHER HISTOLOGICAL SUBTYPES:

- **Small cell/Neuroendocrine tumours.**
  Treat with neoadjuvant chemotherapy (Carboplatin/ Etoposide) prior to surgery or radiotherapy.

- **Adenoid cystic carcinoma.**
  Poor prognosis, treat as for SCC, stage for stage.
- **Adenoid basal carcinoma.**
  Good prognosis and negligible risk of nodal metastases.

F. RECURRENT DISEASE.

Options include:

- If recurrence confined to pelvis and no previous RT: Chemo-radiation.
- Small central recurrence and prior RT: Consider exenteration or salvage hysterectomy.
- Large recurrence in radiation field: Consider chemotherapy and best supportive care.Distant recurrence: Individualise to chemotherapy, tumour-directed RT or best supportive care.
  Carboplatin/Paclitaxel and Cisplatin/Paclitaxel , both +/- Bevacizumab (if available) are the recommended treatment regimens for fit patients with recurrent/metastatic disease.
- It is recommended that Pembrolizumab be added to platinum-based chemotherapy in patients with PDL1 positive tumours, if available. (see Targeted Therapy chapter)NB: all patients who are considered for salvage chemo-radiation or surgery must have a comprehensive metastatic work-up. PET/CT (where available) may be useful to exclude occult metastases.Pelvic exenteration may be feasible in some patients where there is no evidence of intraperitoneal or extra-pelvic spread and there is a clear tumour-free space between the recurrent disease and the pelvic sidewall.
- This approach should be reserved for those with expected curative potential and requires careful patient selection regarding physical and psychological demands.

- PET-CT is the most sensitive non-invasive test to determine any sites of distant disease and should be performed before any exenteration procedure.

G. CARCINOMA OF THE CERVIX IN ASSOCIATION WITH PREGNANCY.

(See Chapter 10).

H. POST-TREATMENT FOLLOW-UP.

- Median time to recurrence ranges from 7 – 36 months after primary treatment
- Routine follow-up visits are recommended every 3-4 months for the first 2-3 years, then 6-monthly until 5 years, then annually for life.
- At each visit, history taking and clinical examination are carried out with the aim of detecting recurrent disease, as well as complications of treatment and psychosexual morbidity.
- Colposcopy and yearly HPV testing should be done in all women who have had surgical treatment for early cervical cancer.

  Imaging as part of follow-up maybe considered in higher treated stages, but routine imaging is not recommended.
- Asymptomatic recurrent disease is detected in 30 – 70% cases by physical examination, by CXR in 20 – 50%, by CT scan in 0 – 34% and by vaginal vault cytology in 0 – 17% (vaginal vault cytology does not significantly improve the detection of early disease recurrence). Women under the age of 50 years who have lost ovarian function as a result of their treatment, should be offered hormone therapy and bone mineral densitometry (as well as thyroid and renal function surveillance).

Palliative care

Patients may present with a wide range of symptoms and signs, which include:

- Pain.
- Ureteric obstruction and renal failure.
- Haemorrhage.
- Malodorous vaginal discharge.
- Lymphoedema.
- Fistulae.
- Symptoms related to metastatic disease.

Palliative RT and/or surgery or chemotherapy should be considered in selected patients. A multi-disciplinary team and home support are strongly recommended.

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CHAPTER 4.

CARCINOMA OF THE UTERINE CORPUS

I. EPITHELIAL ENDOMETRIAL CARCINOMA

A. FIGO STAGING 2023.

Stage I: Tumour confined to the uterine corpus and ovary.
IA Disease limited to the endometrium OR non-aggressive histological type with < 50% myometrial invasion; no or focal LVSI.

IA1 Non-aggressive histological type limited to polyp or endometrium

IA2 Non-aggressive histological type; < 50% myometrial invasion, focal LVSI.

IA3 Low grade endometrioid carcinoma limited to uterus and ovary.

IB Non-aggressive histological type; Invasion ≥ 50% myometrium; no or focal LVSI.
IC Aggressive histological type limited to a polyp or endometrium.

Stage II: Tumour invades cervical stroma, without extrauterine extension OR with substantial LVSI** OR aggressive type with myometrial invasion.
IIA Invasion of cervical stroma of non-aggressive type.
IIB Substantial LVSI of non-aggressive type.
IIC Aggressive histological type with any myometrial invasion.

Stage III: Local and/or regional spread of the tumour of any histological type
IIIA Tumour invades serosa and/or adnexa by direct extension or metastasis.

IIIA1 Spread to the ovary of fallopian tube.

IIIA2 Involvement of the subserosa or spread through the serosa.

IIIB Involvement of vagina and/or parametria and/or pelvic peritoneum.

IIIB1 Metastasis/direct spread to the vagina or parametria.

IIIB2 Metastasis to the pelvic peritoneum.

IIIC Metastasis to pelvic or para-aortic lymph nodes below the renal vessels.

IIIC1 Metastases to pelvic lymph nodes.

IIIC2 Metastases to para-aortic lymph nodes.

Stage IV: Tumour invades bladder and/or intestinal mucosa, and/or distant metastasis.

IVA Tumour invasion of bladder and/or intestinal mucosa.

IVB Abdominal peritoneal metastasis beyond the pelvis.

IVC Distant metastases including extra- or intra-abdominal lymph nodes above the renal vessels.

* low grade EEC with < 50% invasion; absence of substantial LVSI, limited to the ovary without capsule involvement or rupture.

** Substantial LVSI ≥ 5 vessels.

Histopathology.

In all stages the grade of the lesion, the histological type and LVSI must be recorded as substantial or focal/absent.

Molecular classification (POLEmut, MMRd, NSMP, p53) should be included where feasible.

Serous papillary adenocarcinoma, clear cell adenocarcinoma and carcinosarcoma are by definition high grade (aggressive types).

Rules related to staging.
Endometrial cancer is surgically staged. A small number of patients with endometrial cancer, who are treated with primary radiation therapy only, should be clinically staged.

B. INVESTIGATIONS

- Histological diagnosis should be made by: Sampling of the endometrium. If feasible this should be reported with molecular profiling.
- Laboratory: FBC, LFT, RFT, baseline Ca125 and random glucose.
- X-ray chest.
- Ultrasound, or
- CT Abdomen as pre-operative investigation for high-grade uterine cancers (clear cell, serous cancer and carcinosarcoma).
- MRI can be used pre-operatively (EEC Gr1 and 2) for assessment of depth of myometrial invasion and cervical invasion. This may influence surgical approach (inclusion of lymphadenectomy).

C.TREATMENT

1. Surgical:

- Laparotomy or Laparoscopic or Robotic surgery depending on the skill of the surgeon.
- Careful exploration of abdominal cavity.
- If tumour resectable: extra-fascial total hysterectomy and bilateral salpingo-oophorectomy (TH-BSO); where indicated pelvic lymphadenectomy (PL), including common iliac nodes.

Note A: Sentinel lymph node biopsy can be considered for staging purposes in patients with low/intermediate risk disease depending on available equipment and skill of the surgeon. Indocyanine green with cervical injection is the preferred detection technique.

Side-specific systematic lymphadenectomy should be performed if sentinel lymph node is not detected on either pelvic side. Pathological ultra-staging of sentinel lymph nodes is recommended.

- Pelvic lymphadenectomy – Indications in case of high-risk factors:
  - ► Grade 3, with or without myometrial invasion.
  - ► High-grade (aggressive) histology.
  - ► Involvement of the cervix.
  - ► ≥ 50% myometrial invasion.

Note B: Indication for Frozen Section where available:

- Grades 1 and 2 endometrioid adenocarcinoma.
- Pathologist to assess (frozen section):
  - ► histological type.
  - ► grade.
  - ► depth of myometrial invasion.
  - ► cervical involvement.
  - ► if frozen section indicates > 50% myometrial invasion, grade 3, high-grade histology or cervical stromal involvement, proceed to pelvic lymphadenectomy).

- Omentectomy is recommended in patients with high-grade tumours.
- Locally advanced stage disease: Cytoreductive surgery including TAH-BSO should be attempted if deemed operable.
- Debulking of enlarged pelvic and para-aortic lymph nodes should be attempted.

2. Special circumstances.

- Simple vaginal hysterectomy +/- BSO in medically compromised patients may be considered and followed by radiation if indicated.

- In pre-menopausal patients diagnosed with low grade endometrial cancers, and < 50% myometrial invasion, ovarian preservation may be considered if the ovaries appear macroscopically normal.

This approach can help avoid the long-term sequelae of surgical menopause. Ovarian preservation is not recommended in patients with known or suspected hereditary cancer syndromes (Lynch Syndrome or BRCA mutations) due to increased risk of synchronous or metachronous ovarian malignancy.

3. Adjuvant treatment.
After histological evaluation of the uterus and adnexae (and lymph nodes) with respect to depth of myometrial invasion, grade of differentiation, cervical involvement and adnexal involvement, proceed with adjuvant treatment where indicated following current ESGO guidelines.

Table 1a
ESGO Guidelines for epithelial endometrial cancer

2023 FIGO staging			Molecular classification				
			*POLE*mut	MMRd	NSMP low-grade and ER positive	NSMP high-grade or ER neg (or both)	p53abn
I	**Confined to the uterine corpus**						
IA	IA1	Low-grade endometrioid, confined to polyp or endometrium (no myoinvasion)	Low Risk	Low Risk	Low Risk		
	IA2	Low-grade endometrioid, myoinvasion <50%, no or focal LVSI	Low Risk	Low Risk	Low Risk		
	IA3	Low-grade endometrioid carcinoma of the endometrium and ovary	Low Risk	Low Risk	Low Risk		
IB		Low-grade endometrioid, myoinvasion ≥50%, no or focal LVSI	Low Risk	Intermediate risk	Intermediate risk		
IC		High-grade histologies, limited to polyp or endometrium	Low Risk	Low Risk	NA	Uncertain risk	Uncertain risk
II	**Confined to the uterus**						
IIA		Low-grade endometrioid, invasion of the cervical stroma	Low Risk	High Intermediate risk	Intermediate risk		
IIB		Low-grade endometrioid, substantial LVSI	Low Risk	High Intermediate risk	High Intermediate risk		
IIC		High-grade histologies, any myoinvasion	Low Risk	Invasion < 50%, focal LVSI Intermediate risk	NA	High risk	High risk
			Low Risk	Invasion ≥ 50%, focal LVSI Intermediate risk			
IIC		High-grade histologies, any myoinvasion	Low Risk	Cervical stromal invasion, focal LVSI High intermediate risk	NA	High risk	High risk
			Low Risk	Substantial LVSI High intermediate risk			
III	**Local spread, regional spread, or both**						
III		Spread to ovary or fallopian tube or lymph nodes	Uncertain risk	High risk	High risk	High risk	High risk
IV	**Locally advanced disease, metastatic disease, or both**						
IVA		Invasion of the mucosa and/or the intestinal mucosa	Uncertain	High risk	High risk	High risk	High risk

Table 3

2023 FIGO staging			Molecular classification				
			*POLE*mut	MMRd	NSMP low-grade and ER positive	NSMP high-grade or ER neg (or both)	p53abn
I	**Confined to the uterine corpus**						
IA	IA1	Low-grade endometrioid, confined to polyp or endometrium (no myoinvasion)	Low Risk	Low Risk	Low Risk		
	IA2	Low-grade endometrioid, myoinvasion<50%, no or focal LVSI	Low Risk	Low Risk	Low Risk		
	IA3	Low-grade endometrioid carcinoma of the endometrium and ovary	Low Risk	Low Risk	Low Risk		
IB		Low-grade endometrioid, myoinvasion≥50%, no or focal LVSI	Low Risk	Intermediate risk	Intermediate risk		
IC		High-grade histologies, limited to polyp or endometrium	Low Risk	Low Risk	NA	Uncertain risk	Uncertai risk
II	**Confined to the uterus**						
IIA		Low-grade endometrioid, invasion of the cervical stroma	Low Risk	High Intermediate risk	Intermediate risk		
IIB		Low-grade endometrioid, substantial LVSI	Low Risk	High Intermediate risk	High Intermediate risk		
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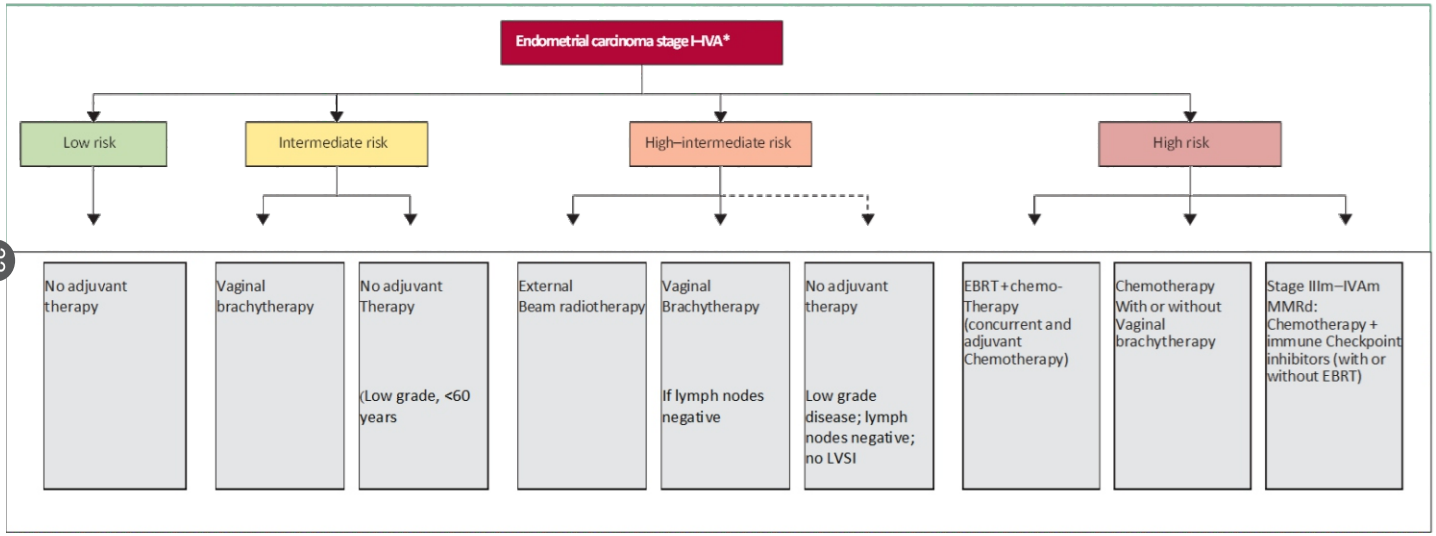
			Low Risk	Cervical stromal invasion, focal LVSI High intermediate risk			
			Low Risk	Substantial LVSI High intermediate risk			
III	**Local spread, regional spread, or both**						
III		Spread to ovary or fallopian tube or lymph nodes	Uncertain risk	High risk	High risk	High risk	High ris
IV	**Locally advanced disease, metastatic disease, or both**						
IVA		Invasion of the mucosa and/or the intestinal mucosa	Uncertain	High risk	High risk	High risk	High ris

Table 3


Endometrial carcinoma stage I–IVA*
Low risk
Intermediate risk
High–intermediate risk
High risk
No adjuvant therapy
Vaginal brachytherapy
No adjuvant Therapy
(Low grade, <60 years
External Beam radiotherapy
Vaginal Brachytherapy
If lymph nodes negative
No adjuvant therapy
Low grade disease; lymph nodes negative; no LVSI
EBRT + chemo-Therapy (concurrent and adjuvant Chemotherapy)
Chemotherapy With or without Vaginal brachytherapy
Stage IIIm–IVAm MMRd: Chemotherapy + immune Checkpoint inhibitors (with or without EBRT)

D. RECURRENT DISEASE

- Consider surgery in selected cases. PET-CT may be an option to exclude other metastases before embarking on surgery.
- Salvage whole pelvis radiotherapy, if no previous external beam given and if recurrence confirmed and confined to the pelvis.
- Chemotherapy; hormonal therapy or checkpoint inhibitors may have a role to play.
- Low-grade, slowly progressing, hormone receptor positive tumours may benefit from progestogens or aromatase inhibitors.

E. PATIENTS DEEMED UNFIT FOR SURGERY

- Patients with a reasonable prognosis from co-morbid condition: whole pelvic radiotherapy plus intracavitary brachytherapy and/or chemotherapy.
- In some cases: Intra-cavitary brachytherapy only.

II.UTERINE SARCOMAS.

This group includes:

- Leiomyosarcoma [uLMS] – Most common.
- Low Grade Endometrial Stromal Sarcomas [HG-ESS].
- High Grade Endometrial Stromal Sarcomas [LG-ESS].
- Undifferentiated uterine sarcomas [UUS].
- Adenosarcoma.
- Perivascular epithelioid cell tumours [PEComas] and neurotropic tropomysin-receptor kinase [NTRK].

FIGO STAGING OF UTERINE SARCOMAS 2009
(Leiomyosarcoma, Endometrial Stromal Sarcoma, and Adenosarcoma).

IA Tumour limited to uterus ≤ 5 cm.
IB Tumour limited to uterus ≥ 5 cm.
IIA Tumour extends to the pelvis, adnexal involvement.
IIB Tumour extends to extra-uterine pelvic tissue.
IIIA Tumour invades abdominal tissues, one site.
IIIB More than one site.
IIIC Metastasis to pelvic and/or para-aortic lymph nodes.
IVA Tumour invades bladder and/or rectum.
IVB Distant metastases.

Note: Adenosarcoma Stage I (Differs from Other Uterine Sarcomas).
IA Tumor limited to endometrium/endocervix.
IB Invasion to ≤ ½ myometrium or cervical stroma.
IC Invasion to ≥ ½ myometrium or cervical stroma.

Management

- TAH and BSO. Consider leaving ovaries for young women with early-stage disease. For young patients with low-grade (LG-ESS) and adenosarcomas without sarcomatous overgrowth remove ovaries to decrease hormonal stimulation.
- Aim for complete surgical resection. Lymph node involvement is a poor prognostic factor. Remove enlarged / palpable nodes. No therapeutic or survival benefit.

  Special situations.
  - Incidental diagnosis of uterine sarcoma after hysterectomy:
  - Pathology review.
  - Consider re-exploration if uterus was morcellated during removal.

- CT Scan chest, abdomen and pelvis.
- MRI of pelvis to evaluate tumour extension.
- Consider endocrine therapy if oestrogen or progesterone receptor positive. Note that Tamoxifen is contra-indicated.
- Following a myomectomy: TAH ±BSO is recommended.
- Consider removal of the cervix with thorough exploration and excision of any suspicious tumour where a sub-total hysterectomy had been performed.
- Adjuvant treatment

a. Leiomyosarcoma

Early Stage I/II:	Role of adjuvant treatment remains unclear.
Stage III:	Systemic therapy - Goal of chemotherapy is palliation, not cure. Options are delaying chemotherapy until progression or offer chemo after surgery.
Stage IV:	Chemotherapy: See chemotherapy chapter 8.
Radiotherapy:	Consider in HG LMS- with involvement of cervix/parametria or positive surgical margins.

b. Endometrial stromal sarcoma

Late recurrences occur in this disease thus long-term follow-up is recommended. In cases of incomplete resection and recurrence, consider hormonal therapy, especially for low-grade tumours.

c. Adenosarcoma
Low grade Adenosarcoma: / LG Stromal Sarcomas
Stage I – Follow-up only.
Stage II/IV/morcellated uterus: Consider Endocrine therapy if Oestrogen or progesterone receptor positive.
Metastatic or Relapsed Adeno-sarcoma: Endocrine Therapy.
NB: Tamoxifen is contra-indicated.

High Grade Adenosarcoma / Sarcomatous overgrowth.
Chemotherapy: Stages II-IV. (see chemotherapy chapter).
Relapsed or metastatic HG Adeno-sarcoma: Chemotherapy.
Radiotherapy for palliation / local control only.

d. Undifferentiated uterine sarcoma (endometrial sarcoma).
Adjuvant chemotherapy and radiotherapy may be considered though prognosis remains extremely poor.

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CHAPTER 5.

CARCINOMA OF THE OVARY, FALLOPIAN TUBE, AND PERITONEUM

A. FIGO STAGING (2014)

I: Growth limited to the ovaries or fallopian tube(s).
- IA Growth limited to one ovary (capsule intact) or fallopian tube(s); no tumour on ovarian or fallopian surface; no malignant cells in the ascites or peritoneal washings.
- IB Tumour limited to both ovaries (capsule intact) and fallopian tubes; no tumour on ovarian or fallopian tube surfaces; no malignant cells in ascites or peritoneal washings.
- IC Tumour limited to one or both ovaries or fallopian tubes with any of the following:
  - IC1 Surgical spill (intra-operative rupture).
  - IC2 Pre-operative rupture or tumour on the ovary or fallopian tube surface.
  - IC3 Malignant cells in ascites or peritoneal washings.

II: Tumour involves one/both ovaries or fallopian tube(s) with pelvic extension.
- IIA Extension and/or implants of uterus and/ or fallopian tube(s) and /or ovaries.
- IIB: Extension to other pelvic intraperitoneal tissues.

III: Tumour involves one or both ovaries or fallopian tubes or primary peritoneal cancer with cytological or histological confirmed spread to the peritoneum and/or metastases to the retroperitoneal nodes.
- IIIA1: Positive retroperitoneal lymph nodes (cytological/histological confirmation).
- IIIA1 (i) Metastasis less than 10mm in greatest dimension.
- IIIA1 (ii) Metastasis greater than 10mm in greatest dimension.

IIIA2 Microscopic extra-pelvic peritoneal involvement with/without retroperitoneal lymph nodes.

IIIB Macroscopic peritoneal metastases beyond the pelvis up to 2cm with/without metastases to retroperitoneal lymph nodes.

IIIC Macroscopic peritoneal metastases>; 2cm with/without metastases to retroperitoneal lymph nodes (includes extension to capsule of liver and spleen without parenchymal involvement of either organ).

IV: Distant metastases 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 the abdominal cavity).

Points to add regarding staging:

1. Staging is surgical and assists to prognosticate and allows standar- dization.
2. The primary should be stated viz. ovary, fallopian tube, peritoneal cancer or undesignated (X).
3. There is no stage I peritoneal cancer.
4. Histological subtype should be mentioned: High-grade serous (HGS), Low-grade serous (LGS), endometrioid, clear cell or mucinous are epithelial subtypes; germ cell ovarian cancer; sex cord stromal, other.
5. Note that tumour on bowel surface – stage II versus intramural lesion of bowel is stage IV.
6. If surgery is not possible due to medical co-morbidities or tumour bulk, it is recommended that histology is attained via interventional radiology and that imaging supports the presumed staging.

B. Pathology and genetics of Epithelial Ovarian Cancer (EOC)

- Epithelial ovarian cancer (EOC) is the most lethal gynaecological cancer as most women (70-80%) present late with advanced stage 3 and 4 disease. EOC predominates, as 90% of all ovarian cancers are epithelial in origin. There are currently 5 different histological subtypes of which high-grade serous represents 75% of all EOC. The management of all remains the same (see below). Understanding the different pathological subtypes allows insight into traditional and targeted treatments and prognosis.
- High grade serous (HGS): commonest and 15-20% contains germ line BRCA1 and BRCA2 mutations. There may also be homologous recombination defects. High proliferative rate and hence initially chemo-sensitive but progressive acquisition of chemo-resistance. The BRCA mutations enable the use of targeted treatments such as PARP-inhibitors (not always available to patients in limited resource settings due to high cost).
- Low grade serous (LGS): low proliferative rate and hence relatively chemo-resistant.
- Mucinous: relatively large sized tumours filled with mucinous material: only comprise 3% of primary ovarian EOC, and important to exclude colorectal origin especially if bilateral. Relatively Chemo-resistant.
- Clear cell: often associated with endometriosis. Chemo-resistant and poor prognosis.
- Endometrioid: often associated with endometriosis. Low grade shares the same profile as LGS ovarian cancer, whereas high grade shares similarities with HGS ovarian cancer.

- The importance of pathology review by ideally an expert pathologist and histological subtype, coupled with genetic testing (germ line and somatic) where appropriate, available and affordable, allows important management decisions.

C. Screening

Randomized controlled trials have not shown any benefit for screening for ovarian cancer in the general population (ref for this). Women identified as high risk due to a family history (BRCA positive etc.) may benefit with screening prior to offering Risk-reducing surgery (RRS) at an appropriate age (40 years) to balance the risk of menopause with RRS

D. Management

Epithelial ovarian tumours

Note: All women with suspected ovarian cancer should be offered a maximal surgical effort wherever possible by a gynaecological oncologist to avoid an unnecessary second laparotomy.

Standard work up includes a detailed history and clinical examination with relevant laboratory and imaging tests.

E. Standard of care for patients able to undergo surgery

I. Medically fit patients

1. Pre-operative work-up:
    - FBC, RFT, LFT.
    - Nutritional assessment, including albumin: if low, consider referral to dietician.
    - Tumour markers: CA125, CEA.
    - If significant upper or lower gastro-intestinal bowel symptoms or occult blood positive:
        - ► Gastroscopy/colonoscopy .
        - ► Also consider Gastroscopy/colonoscopy if CA125/CEA ratio ≤ 25.

- Breast palpation (mammography if indicated).
- CXR (All pleural effusions should be tapped and sent for cytology/cell block to confirm possible stage IV disease). Also consider sending for chemistry: exudate may be either malignancy or TB, transudate organ failure.
- Transvaginal Pelvic ultrasound may be useful: using the IOTA simple rules to assess B (benign) versus M (malignant) features.
- Abdominal/pelvic U/S as a minimum in limited resource settings.
- CT scan of the abdomen and pelvis is ideal to detect peritoneal metastases and upper abdominal disease. CT scans can also be used as a baseline to assess response after definitive treatment.
- MRI may be performed on an individualized basis.
- Diagnostic ascitic tap – fluid for micro/cytology/chemistry should not be done routinely unless for a diagnosis in advanced disease or if the patient is distressed due to diaphragmatic splinting.
- Refer gynaecological oncology consultant if workup and imaging support a possible malignancy.

2. Pre-operative procedures:
    - Inform stoma therapist for counselling and stoma markings if bowel involvement suspected and colostomy anticipated.
    - Frozen section (FS) is not used routinely. Consider only if it impacts on the radicality of surgical management and in young patients. The limitations of frozen section accuracy must be noted especially with borderline ovarian tumours (BOT) and sex cord stromal tumours.
    - If fertility is an issue, see chapter 12 Fertility Sparing and Gynaecological Cancer.

- Start anti-coagulative measures: thrombo-embolic stockings/calf compressors and Clexane® 1 day prior to surgery.

3. Laparotomy:
    - Skin incision: vertical.
4. Staging procedure:
    - Aspiration of fluid from POD, para-colic gutters and diaphragm for cytology (or random peritoneal biopsies from the same sites) in early-stage disease.
    - Full exploratory laparotomy, including palpation and, if indicated, excision of enlarged pelvic and para-aortic nodes.
5. Surgical treatment:
    - Primary surgery is the 1st choice for adequate diagnosis, staging and treatment. TAH, BSO and infra-colic omentectomy. Include appendectomy with mucinous tumour or macroscopic involvement.
    - Bulk reduction whenever possible of macroscopic tumour to no residual tumour, including enlarged lymph nodes in pelvis or para-aortic area. A multidisciplinary surgical team and intensive care facilities may be required if significant tumour bulk and cytoreductive surgery is planned.
    - Consider laparoscopic diagnosis and biopsy or image guided biopsy if patient has poor performance status, is medically unfit for surgery, very low albumin or extensive tumour burden not amenable to cytoreduction.
    - Terminology:
        - ► Complete cytoreduction: complete resection of tumour with no visible disease left.
        - ► Optimal cytoreduction: less than 1cm of residual disease left.
        - ► Suboptimal cytoreduction: ≥ 1 cm of residual tumour left.

- Careful documentation of size and site of residual disease.
- In apparent early-stage disease, there may be a role for systematic pelvic and para-aortic lymph node dissection for accurate surgical staging.
- There is no role for routine pelvic/para-aortic lymphadenectomy in locally advanced ovarian cancer as recent evidence has shown no therapeutic benefit.

6. Post-operative management:
   Patients who have been properly staged:
   - Refer to multidisciplinary team. (Histology review is mandatory).
   - Stage IA + B (grade 1+2) – no further treatment – careful clinical follow-up.
   - Stage IA + B (grade 3) + stage 1C – Postoperative chemotherapy. (See chapter 8 Chemotherapy Protocols).
   - Stage II – IV – Optimally debulked (no macroscopic disease):

7. Postoperative Chemotherapy. (See chapter 8 Chemotherapy Protocols).
   - Stage II – IV – Sub-optimally debulked i.e.: >1cm residual disease after primary surgery:
     - ► Consider baseline CT-scan immediately after primary surgery.
     - ► Postoperative chemotherapy. See chemotherapy protocols.
     - ► Consider Interval debulking surgery after 3 cycles if good response to chemotherapy.
   - Stages II - III where surgery was abandoned and biopsies taken only.
     - ► Consider baseline CT scan if not done pre-operatively.
     - ► Treat with 3 cycles of chemotherapy:

- ► If evidence of response to 3 cycles of chemotherapy (i.e. one log drop in level of CA 125 and/or clinical/radiological response if CA 125 not a marker), proceed to Interval Cytoreductive Surgery (i.e. TAH/ BSO/infra-colic omentectomy and debulking of macroscopic tumour). After surgery continue with at least 3 more cycles of chemotherapy.
- ► If partial response i.e.; one log drop CA 125 after first 3 cycles or minimal clinical/radiological response, no surgery, but continue chemotherapy or consider alternative chemotherapy.
- ► If no response to chemotherapy:
  - ■ Alternative chemotherapy.
  - ■ Radiation to localised symptomatic disease.
  - ■ Palliative care.

II. Unstaged (i.e. patients operated on elsewhere and no full staging performed).
Options:

- Restaging Laparotomy.
- If chemotherapy considered inevitable (i.e. grade 3 tumour on histological review or surgeon reports intra-operative evidence of extra-ovarian disease) treat with 3 cycles of chemotherapy followed by Delayed Definitive Cytoreductive Surgery (i.e.TAH/BSO/infra-colic omentectomy/maximum debulking of macroscopic tumour) and if evidence of response after surgery, continue with at least 3 more cycles of chemotherapy.
- If suboptimal response to chemotherapy, no surgery, but individualise:
  - ► Alternative chemotherapy.
  - ► Radiation to localised symptomatic disease.
  - ► Palliative care.

III. Medically fit patients but significantly impaired by the ovarian cancer. (e.g. respiratory embarrassment due to atelectasis/large pleural effusion or tense ascites with renal impairment) so that primary cytoreductive surgery is deemed hazardous.

- Make presumptive diagnosis of ovarian cancer based on:
  - ► Clinical symptoms (e.g. a clinically palpable pelvi-abdominal mass or abdominal or pelvic imaging suggestive of ovarian cancer).
    Histological or cytological cancer diagnosis either via ascitic tap or Trucut® biopsy or
  - ► laparoscopically directed biopsies.
- Elevated CA 125 >; 500 or CA 125/CEA ratio > 25.
  - ► Gastroscopy/colonoscopy/mammography where appropriate.

1. Work-up as in epithelial ovarian carcinoma.
   See before (C.I.1)
2. Management:
   - Treat with Neo-adjuvant chemotherapy (i.e. 3 cycles prior to surgery).
   - If response to chemotherapy evident (i.e. > one log drop of CA 125 or good clinical and/or radiological response) proceed to Delayed Primary Cytoreductive Surgery (i.e. TAH/BSO/infra-colic omentectomy and maximum debulking of macroscopic tumour).
   - After surgery complete at least an additional 3 cycles of chemotherapy.
   - If progressive disease after first 3 cycles, no surgery, but individualise i.e., either stop chemotherapy or change to alternative chemotherapy.
   - If stable disease after first 3 cycles, individualise i.e., 'maintenance' chemotherapy,
   - Change chemotherapy regimen or palliative care.

Unable to make presumptive diagnosis of Cancer of Ovary.

Options:

- Laparoscopy is ideal to assess extent of disease and to take biopsies for histology/immunohistochemistry.
- Laparotomy can be considered if laparoscopy facilities or skills not available.
- Consider referring to Unknown Primary Clinic if above surgery is not possible or if histology is not in keeping with ovarian cancer.

IV. Medically unfit patients

E.g. massive DVT or recent myocardial infarct so that surgery is deemed hazardous:

- Make presumptive diagnosis of Ovarian Cancer (as above).
- Consult with ICU and anaesthetists if necessary and document extent of risk.
- Treat with neo-adjuvant chemotherapy.
- Review after three cycles:

A] If significant reduction in surgical risk AND evidence of response to chemotherapy, proceed to Delayed Primary Cytoreductive Surgery. After surgery, complete at least an additional three cycles of chemotherapy.

B] No improvement in surgical risk after 3 cycles chemotherapy:

- Complete 6 cycles of chemotherapy.
- Consider post-chemotherapy surgery in selected patients.

C] No response to chemotherapy:

- Reconsider diagnosis.
- Alternative or palliative chemotherapy.
- Palliative care.

V Stage IV disease

- If stage IV by virtue of malignant pleural effusion only, proceed as for advanced disease i.e. stages II – III.
- If stage IV by virtue of other metastatic disease, treat with primary chemotherapy and consider surgery in selected cases.

D] Follow up guidelines

- No evidence about timing of follow up.
- Fair recommendation: 3 monthly for 1 year after treatment, 6 monthly for 2 further years, then yearly.
- Generally surveillance is mostly undertaken for at least 5 years after the most recent remission. Longer follow-up is a consideration in BRCA positive women.
- Clinical examination including a pelvic examination is crucial as 26 -50% of recurrences are in the pelvis.
- Routine CA 125 surveillance has not been shown to affect long-term outcome and is therefore NOT recommended.
- Routine imaging is not indicated.
- Investigations should be requested if any new symptoms or new clinical findings.

E] Special circumstances

- Inadvertent diagnosis of Carcinoma of the Ovary during surgery:
- call gynaecological oncologist to theatre or proceed with surgery as defined above.
- Unexpected histological diagnosis, management on a case-by-case basis, restaging may be deemed necessary.
- In young girls/women with a surgical suspicion of ovarian cancer, it is preferable to do conservative, ovarian and uterine sparing surgery until histology is available. (See Chapter 12 Fertility Sparing and Gynaecological cancer).

F] Controversial/new

- HIPEC (hyperthermic intraperitoneal chemotherapy after cytoreduction): may provide benefit in terms of progression free and overall survival. It is not standard of care and should only be offered in centres where experience and management of complications is available.
- IPC (intraperitoneal chemotherapy): not standard of care. Toxicity is high with poor quality of life, as compared to intravenous chemotherapy.
- The role of targeted agents in ovarian cancers. In particular PARP -inhibitors where BRCA mutations (germ line and somatic, and HRD status) can inform systemic management decisions and impact on both disease free and overall survival (see chapter 8 chemotherapy protocol/targeted agents).

G] Persistent and Refractory disease

- Platinum Refractory Disease i.e., progressive disease while on chemotherapy. Consider alternative chemotherapy or supportive/ palliative care.
- Persistent disease: partial response to chemotherapy. Either continue to maintain stable disease or consider alternative chemotherapy or supportive/palliative care.

H] Recurrent Disease

- Platinum resistant disease i.e., complete clinical response or no evidence of disease after 1st line chemotherapy and relapse within 6 months: supportive care/Consider alternative chemotherapy (not platinum-based) or radiation if symptomatic localised disease.
- Supportive care if not fit for chemotherapy.

- Platinum sensitive disease i.e., relapse 6 months after stopping chemotherapy: re-start original chemotherapy for 6 cycles. If no response, supportive care/alternative chemotherapy, or radiation if symptomatic localised disease or surgery in selected patients.
- In a patient with an elevated CA125 serum level, only start chemotherapy if there are clinical signs and/or symptoms of disease or radiological evidence of disease.
- Patients with a disease-free interval > 2 years and the following criteria may benefit from secondary cytoreduction and further chemotherapy:
  - ► Good performance status.
  - ► Clinically and radiologically resectable disease.
  - ► Ascites less than 500 ml.
  - ► Macroscopically complete resection at first surgery.
- See Chapter 13 Palliative care.

Borderline Ovarian Tumours (BOT) also called Tumours of Low Malignant Potential (LMP)

Follow the same histological subtypes as invasive epithelial ovarian cancers. The most common histological subtype is serous adenocarcinoma followed by mucinous adenocarcinoma. Tends to affect a younger population (30-40's) and the majority of BOT are stage I.

- The diagnosis should rely on the histopathology of the primary lesion.
- The tumour must be extensively sampled by histo-pathologist to exclude the presence of invasive carcinoma.

- Patients with invasive implants in the omentum or other distant locations are at higher risk for earlier recurrence, and the benefit of cytotoxic chemotherapy is uncertain given the generally low response rates.

Management:

Operative

- The primary treatment approach is surgical staging and tumour debulking as surgery remains the cornerstone of management for borderline tumours at all stages.
- In Stage I cases where fertility preservation is desired, a unilateral salpingo-oophorectomy may be performed, provided the opposite ovary is thoroughly inspected during surgery to rule out disease.
- If the patient has a single ovary or both ovaries are affected by cysts, options like partial oophorectomy or cystectomy may be considered to maintain fertility.
- For all other cases, the standard recommendation is total hysterectomy with bilateral salpingo-oophorectomy, omentectomy and maximal cytoreduction if the disease has spread.
- Laparotomy route preferred, surgery as for invasive epithelial tumours and pre-, intra- and post operative management as for invasive tumours except:
  - ► An appendectomy should be performed (even if macroscopically normal) in the following cases:
    - Mucinous tumours with peritoneal implants.
    - Mixed histology.
    - Suspected metastatic GIT neoplasm.
- Completion surgery (re-laparotomy) may be considered if a high risk of recurrence (invasive implants, micro-invasion, micro-papillary pattern on pathology review or intra-cystic carcinoma).
- Alternatively, one can consider waiting for a recurrence to occur before radical surgery.

Comments

- Adjuvant chemotherapy and hormonal treatment is not indicated for BOT.
- Consider addressing completion surgery after completion of family.
- Long-term follow-up is the same as for those with invasive cancers, but at less frequent intervals. If the contralateral ovary has been retained, it should be monitored by annual transvaginal ultrasonography.

Non-epithelial tumours of the ovary
A. Sex-cord Stromal Tumours
(Granulosa Cell Tumours, Sertoli-Leydig Tumours).

Management:
Pre-operative investigations:

- Same as for EOC. (MRI preferred to CT in adolescents/young adults to reduce radiation exposure)
- Consider endometrial sampling if suspected Granulosa cell tumour (pelvic mass and abnormal bleeding in any age group) to rule out a concomitant uterine cancer – especially in women of reproductive age where fertility sparing surgery is considered.

Note:

- ► Anti-müllerian hormone and Inhibin B (preferred in postmenopausal women) are tumour markers produced by Granulosa cell tumours. If available, consider pre-operatively serum levels. If elevated it can be used as a marker in surveillance of patients post-treatment.
- ► Sertoli-Leydig tumours: Clinical virilization may be present and androgens levels can be used as a tumour marker. Rarely, oestrogen levels can also be raised.

Operative:

- Conservative surgery for the young patient with disease confined to one ovary- USO and full staging laparotomy.
- Other- as for EOC.
- Systematic pelvic lymph node dissection is not indicated, unless clinically suspicious lymph nodes.

Postoperative management:

- Early stage disease:
  (A, B, C) Granulosa cell tumours: observation only.
- Consider adjuvant chemotherapy in high risk Stage 1 Granulosa cell disease (size >10cm, high mitotic activity or stage IC) and Stage 1 Sertoli-Leydig tumours with retiform patterns, heterologous elements or poorly differentiated.
  - ► 3-4 cycles of Cisplatin-based chemotherapy.
  - ► The optimal chemotherapy regimen is to be determined; it seems carboplatin and Paclitaxel has a similar response rate and less toxicity than BEP.

- Advanced / recurrent disease:
  - ► Debulking surgery remains the most effective treatment of metastatic or recurrent disease.
  - ► Chemotherapy for stage II - IV disease with or without residual disease.
    In case of incomplete initial cytoreduction in Stage III disease and residual disease after chemotherapy, delayed surgical attempt should be considered following NACT.
    Localized radiation and chemotherapy may be useful for recurrent disease.
  - ► If not suitable for surgery or chemotherapy, hormonal treatment (Progestin, Tamoxifen, Aromatase inhibitor or GnRH-agonist) may be considered.

- ► Bevacizumab- not indicated as no difference in PFS at recurrence.
- ► Follow up is clinical. Sex cord stromal tumours have indolent course and may require long-term follow-up; may recur 15-20+ years later.

B. Germ Cell Tumours

Management:

- Pre-operative:
  - ► If diagnosis of germ cell tumour is suspected: tumour markers (α-feto-protein, ß-HCG, LDH, Ca125) is suspected:
  - ► If gonadoblastoma is suspected, obtain karyotype on all premenarchal girls.

- Operative:
  - ► Diagnostic laparotomy or consider laparoscopy with endo-bag.
  - ► Early disease: conservative staging surgery as chemotherapy has high cure rate.
  - ► Unilateral mass: USO, omentectomy and full staging. If contralateral ovary normal, no biopsy. (see fertility sparing management).
  - ► Bilateral masses (in young patients): attempt ovarian cystectomy or biopsy of other ovary to preserve some normal ovarian tissue.
  - ► Lymph node dissection only when macroscopically suspicious nodes.
  - ► Advanced disease:
    Consider fertility-sparing surgery in women in their reproductive years – remove as much macroscopic tumour as possible.
    Full cytoreduction in postmenopausal women as in EOC.

- Post-operative:
  - ► Stage IA Dysgerminoma or stage IA grade 1 immature teratoma: after adequate surgical staging (or apparent Stage IAG1 with negative postoperative CT scan or MRI observation only
  - ► Stage IA-IC G2-G3 immature teratoma, stage IA-IB Yolk Sac Tumour with negative postoperative tumour markers and IB-IC dysgerminomas: 3 adjuvant chemotherapy (cycles are recommended BUT active surveillance is an option.
  - ► All other patients receive 4 cycles of chemotherapy (See chapter 8 chemotherapy protocols).
  - ► Repeat laparotomy after 4 cycles of chemotherapy in patients with residual tumour on imaging (particularly those with normal tumour markers) and for patients with immature teratoma is recommended.
  - ► Surgery, radiation and chemotherapy are all options for recurrent disease.
  - ► Follow up guidelines for non-epithelial malignancies: As for EOC.

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CHAPTER 6.

GESTATIONAL TROPHOBLASTIC DISEASE

DEFINITION:
All forms of premalignant or malignant neoplasia arising from the cytotrophoblast, syncytiotrophoblast, or intermediate trophoblast.

CLASSIFICATION

A. HYDATIDIFORM MOLE:

- Complete.
- Partial.

B. GESTATIONAL TROPHOBLASTIC NEOPLASIA/ TUMOUR:

- Post molar GTN
- Invasive mole.
- Choriocarcinoma (abortion, term, ectopic).
- Placental site trophoblastic tumour (PSTT – origin non-villous trophoblast).
- Epithelioid Trophoblastic Tumour (ETT – origin intermediate trophoblast).
- Atypical placental site nodule (APSN).

A. HYDATIDIFORM MOLE (Complete or Partial)
1. Investigations:

- Pelvic ultrasound, CXR, Serum β-HCG, Rhesus factor, TSH, FBC, HIV, Blood Group and screen to blood bank.

2. Management:

- Suction curettage of uterus under U/S guidance.
- 12-14mm suction cannula should be used.
- IV Oxytocin infusion may be started at the onset of suction curettage and may be continued for several hours post operatively.
- There is no consensus on cervical priming prior to the procedure and no literature for or against it.
- Medical induction and hysterotomy is not recommended except with fetus in situ or confirmed partial mole.
- Anti-D prophylaxis if indicated.
- Tissue MUST be sent for histological evaluation.
- Hysterectomy is an option if child bearing is complete.

3. Follow Up:

- β-HCG should be repeated every 2 weeks until normalisation.
- PHM: one more normal β-HCG over 1 month and then discharge.
- CHM: if β-HCG is normal within 56 days of the pregnancy event then follow up will be for 6 months from normalisation of the β-HCG level. If HCG has not reverted to normal within 56 days of the pregancy event then follow-up will before 6 months from normalisation of the β-HCG level.
- Follow-up for partial molar pregnancyis concluded once the β-HCG has returned to normal on 2 samples, at least 4 weeks apart..
- Contraception for at least 6 months.
- IUCD/Mirena is not recommended because of possible perforation until β-HCG undetectable.
- Follow-up is of utmost importance and should be done by specialized GTD clinic.
- Routine second evacuation is not indicated.

- Second evacuation may be considered in individualised cases in discussion with gynaecological oncologist.
- It is recommended that β-HCG result is plotted on a graph.
- Women with a normal pregnancy following a previous molar pregnancy do not need histology of the placenta nor a post-pregnancy β-HCG.

B. GESTATIONAL TROPHOBLASTIC NEOPLASIA/ TUMOUR

1. FIGO diagnostic criteria for POST MOLAR GTN:

- Plateau of β-HCG lasts for four measurements over a period of 3 weeks or longer; ie. Days 1, 7, 14, 21 or
- When there is a rise in β-HCG for three consecutive weekly measurements over at least a period of 2 weeks or β-HCG more; ie. Days 1, 7, 14 or
- If there is a histologic diagnosis of choriocarcinoma.

2. FIGO classification for GTN staging (2000)

Stage I: Disease confined to the uterus.
Stage II: GTN extends outside of the uterus, but is limited to the genital structures (adnexae, vagina, broad ligament).
Stage III: GTN extends to the lungs, with or without known genital involvement.
Stage IV: All other metastatic sites.

3. Investigations:

Repeat clinical examination specifically excluding vaginal metastasis

- Serum β-HCG levels.
- FBC, renal and liver function tests, TSH, VDRL, HIV.
- CXR, Pelvic U/S.
- If CXR normal: no further imaging required.

- If lung metastasis on CXR: do CT Chest.
- If lung metastasis is <1cm on CT chest: no further imaging required.
- If lung metastasis is ≥1cm on CT Chest: do MRI/contrasted CT Brain and contrast CT/MRI of abdomen/ pelvis.
- Ideally, imaging and β-HCG levels to calculate FIGO score, should be performed just before initiating treatment.
- PET/CT may be useful to locate primary source of unexplained raised β HCG if not detected by other imaging, but is not routinely performed.
- If very high β-HCG concentrations (>400,000 IU/L), even in the absence of metastases on CXR or histology of choriocarcinoma additional imaging could be considered.

FIGO/WHO PROGNOSTIC SCORING SYSTEM:

	Score			
Prognostic factors	0	1	2	4
Age (years)	<40	≥40	-	-
Antecedent pregnancy	Mole	Miscarriage	Term	-
Interval (months)	<4	4-6	7-12	>12
β-HCG (iu/liter)	<1000	1000 - 10 000	10 000-100 000	>100 000
Largest tumour (incl. Uterine)	<3cm	3-4cm	≥5	-
Site of metastases	Lung	Spleen/ Kidney	GIT	Liver, Brain
Number of metastases	-	1-4	5-8	>8
Previous chemotherapy	-	-	1 drug	≥2 drugs

A patient's diagnosis is allocated to a stage AND score e.g. stage II: 4 or stage IV: 9.

4. Management:

- Patients should ideally be managed in a specialised unit.
- Definition of chemo resistance:

Primary resistance ie no response to treatment upfront:

► β-HCG increases despite 2 courses of systemic agent .
or
► β-HCG plateau (<10% decrease over 2 weeks) despite 3 courses of systemic treatment.

Acquired resistance ie. Initial response and then plateau/rise:

► β-HCG plateau (<10% decrease over 2 courses [4 weeks]).
or
► Increase in β-HCG (at least 2 values over 2 weeks) after initial response.

Low Risk Patients (WHO/FIGO score 0-6):

- Single agent chemotherapy i.e. Methotrexate(MTX) with folinic acid rescue or Actinomycin D (see chemotherapy chapter 8 for regimens).
- Give 2 consolidation cycles of chemotherapy post normalisation of β-HCG.
- If there is resistance (see definition above) to single agent and β-HCG is ≤1000 IU/L: switch to single agent chemotherapy that was not used previously.
- If there is resistance to single agent and β-HCG is >1000IU/L: change to Multi agent chemotherapy (eg. EMA-CO)
- Hysterectomy is an alternate treatment in women with completed families and disease confined to the uterus.

- If WHO prognostic score is 5-6 AND 1 of the 3 criteria below: Treat with multi agent chemotherapy upfront.
    - ► Histology of Choriocarcinoma with metastatic disease.
    - ► No metastatic disease or Choriocarcinoma but with pre-treatment β-HCG >410 000 IU/L.
    - ► Metastasis or choriocarcinoma and pretreatment β-HCG>150 000 IU/L.

High Risk Patients (WHO/FIGO score 7-12):

- Multi-agent chemotherapy is advised: EMA-CO or EMA-EP or TP/TE (see chapter 8 for regimens).
- If there are concerns of tumour lysis syndrome (TLS) or high risk of bleeding: start with low dose induction Cisplatin/Etoposide for 1-3 cycles (see Chapter 8 chemotherapy protocols).
- Give at least 2-3 cycles consolidation chemotherapy post normalisation of β-HCG.

Ultra High Risk (WHO/FIGO score ≥13

- 1-3 cycles induction Cisplatin/Etoposide frequently used to prevent TLS and haemorrhage.
- Give at least 3-4 cycles consolidation chemotherapy post normalisation of β-HCG.

5. Special considerations:

- If brain metastasis present:
    - ► increase MTX dose in EMA-CO (see Chapter 8 Chemotherapy protocol).
    - ► Consider adding intrathecal MTX to the CO.
    - ► Neurosurgery may be considered for control of raised intra-cranial pressure, bleeding metastasis and insertion of Omaya reservoir.
    - ► Stereotactic radiotherapy can be considered for inoperable vital brain lesions at the end of treatment.

6. Surgery

- Hysterectomy (under chemotherapy cover is an option) and may be indicated in the following circumstances:
  - ► Poor response to chemotherapy (drug resistance) and disease seemingly confined to uterus.
  - ► Emergency procedure where there is uncontrollable haemorrhage.
  - ► Completed family.
- Local resection of easily accessible or chemo-resistant solitary metastases.

7. Radiotherapy: where indicated and typically for persistent symptomatic disease.

8. Pelvic artery embolization: in cases of intractable haemorrhage.

9. Follow up:

- Low Risk: β-HCG monthly for 12 months.
- High Risk/ Ultra High risk: β-HCG weekly till normal for 4 consecutive weeks, then monthly for 12 months.
- Ensure reliable contraception for at least one year.

C. ATYPICAL PLACENTAL SITE NODULE (APSN)

- Transitional stage between Placental site nodule (PST) and ETT.
- Investigations: Pelvic U/S and MRI, and consider hysteroscopy.
- May need to repeat hysteroscopy to exclude remaining lesion/ETT.
- Management:
  - ► Fertility preservation: follow up hysteroscopy, β-HCG, imaging
  - ► Completed family: hysterectomy → if no residual ETT/PSTT/APSN or just APSN → discharge

- ► Completed family: hysterectomy → residual ETT/PSTT manage as below.

D. PSTT/ETT

- Investigations: MRI brain/pelvis and CT chest/abdomen/pelvis.
- Stage as per FIGO 2000 staging classification and not the FIGO/WHO scoring system.
- Management:
  - ► **Stage 1 and interval from antecedent pregnancy <48 months:** Hysterectomy and salpingectomy.
  - ► **Stage 1 and antecedent pregnancy 48months or Stage 2 - Stage 4:** Hysterectomy and salpingectomy PLUS 12-16 weeks platinum based combination chemotherapy (EMA-EP or TP/TE).
  - ► Consider Pembrolizumab if interval from antecedent pregnancy 48 months or Stage 4 (under investigation)
- Follow-up:
  - ► Once weekly β-HCG for 6 weeks after normalization, then at least once monthly for 12 months, then reducing frequency up to 10 years.
  - ► Stage 1 and interval from antecedent pregnancy <48 months: physical exam and β-HCG adequate.
  - ► Rest: Physical exam, β-HCG and Imaging (MRI of pelvis and abdomen, chest X-ray or CT of chest (and any other previous localization of disease) once every 6 months for 2 years, then once a year for a minimum of 5 years).

E. POINTS TO REMEMBER

- Do not forget to look for vaginal metastases.
- Do not biopsy any metastases in patients with GTN because of the risk of catastrophic bleeding.
- Histology is not required for the diagnosis of choriocarcinoma/GTN.
- In patients who have had an evacuation of a molar pregnancy and are at high risk of persistent trophoblastic disease (Complete Hydatidiform Mole), β-HCG >100 000 pre-evacuation, excessive uterine size, and/or maternal age >35 and who cannot attend for serial β-HCG surveillance, consider a single dose of Methotrexate 50 mg IMI as prophylaxis against developing persistent trophoblastic disease (PTD).
- If evidence of resistance to chemotherapy, see Chemotherapy Protocols for alternative management and chemotherapy regimes.

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CHAPTER 7.
HISTO-PATHOLOGICAL GUIDELINES

The guidelines are designed to assist anatomical pathologists in the comprehensive reporting of gynaecologic cancer specimens, incorporating key elements from CAP (College of American Pathologists), RCP (Royal College of Pathologists), and FIGO (International Federation of Gynaecology and Obstetrics) guidelines.

General notes on Ultrastaging of Sentinel lymph Nodes:
In gynaecologic cancers, particularly endometrial, vulva and cervical cancer, sentinel lymph node (SLN) ultrastaging has become a standard pathological technique used to detect low-volume metastases that are often missed by standard histology. This intensive method increases the detection rate of metastases by approximately 10–15% in cervical cancer and 37–43% in endometrial cancer, often leading to a change in the patient's cancer stage (upstaging).

While a single universal protocol does not exist, major oncology bodies such as the NCCN and ESGO-ESTRO-ESP endorse the following components:

- Macroscopic Slicing: Nodes are typically sliced at 2 mm intervals; "bread-loaf" slicing (perpendicular to the long axis) is preferred over longitudinal slicing for a higher detection rate (53% vs. 33%).
- Serial Microscopic Sectioning: The paraffin-embedded node is cut into multiple levels, often 50–250 µm apart.
- Immunohistochemistry (IHC): Staining with anti-cytokeratin antibodies (e.g., AE1/AE3) is performed on at least one level to identify tumour cells.

Vulval Carcinoma
Protocol for Anatomical Pathology Grossing and Reporting.
Essential Microscopic Features to Report

- **Specimen Dimensions:** Overall length, width, and thickness of the resected specimen.
- **Macroscopic tumour size:** The tumour should be accurately measured to determine if its maximum dimension is ≤2 cm or >2 cm.
- **Histological Tumour Type:** Classification per WHO 2020 (Squamous cell carcinoma (HPV-associated, HPV-independent, NOS), Basal cell carcinoma, Adenocarcinoma, Bartholin gland carcinoma, Neuroendocrine neoplasm, other).
- **Tumour Grade:** G1:
  - ► Well differentiated;
  - ► G2: Moderately differentiated;
  - ► G3: Poorly differentiated;
  - ► G4: Undifferentiated
- **Tumour Border:** Pushing; Infiltrating*
  *Infiltrating invasion is associated with a higher frequency of regional lymph node metastasis and should be noted in the report.
- **Extension to Adjacent Structures**: Document involvement of vagina, urethra, anal/perianal region, or other specified sites.
- Tumour Dimensions: Maximum horizontal dimension and depth of invasion (DOI)#.
  - ► **Tumour thickness and depth of invasion are separate measurements:** Tumour thickness of a squamous cell carcinoma is measured in millimetres from the surface of the tumour or, if there is surface keratinization, from the bottom of the granular layer to the deepest point of invasion. Tumour thickness is NOT a parameter used in staging.

- ► **Depth of Invasion (DOI).** The depth of invasion of squamous cell carcinoma is defined as the measurement in millimetres from the epithelial-stromal junction of the adjacent, most superficial dermal papillae to the deepest point of invasion. This parameter is important for tumour staging, especially for small tumours.

- Margin Status:
  - ► Measure distance (in millimetres) from tumour to closest skin/mucosal margin and to deep margin.
  - ► Explicitly state if invasive carcinoma / high grade dysplasia (VIN 2-3) or dVIN) is present at any margin and specify which margin(s).
- Lymphovascular Invasion (LVI): Present; Not Identified; Indeterminate
- Perineural Invasion (PNI): Present; Not Identified.
- Lymph Node Status: Ultrastaging done: Yes /No.
- Number of positive nodes, size of metastases, presence of extracapsular extension.
  - ► **FIGO 2021 Criteria:**
  - ► **Size of Metastasis:** ≤5 mm (Stage IIIA); >5 mm (Stage IIIB).
  - ► **Extracapsular Spread (ECS):** Leads to upstaging to Stage IIIC.
  - ► **Isolated Tumour Cells (ITC):** Do not result in upstaging **Fixed or**
    Ulcerated Lymph Nodes: Indicates Stage IVA disease.
- Coexistent Pathology/Precursor Lesions: Identify LSIL (HPV-associated), HSIL (HPV-associated), Vulval Intraepithelial Neoplasia (VIN, HPV-independent), Lichen Sclerosis, or state "None identified".
- Ancillary Studies: Document p16 immunohistochemistry, HPV testing (if performed), and p53 immunohistochemistry.ally as HPVA or HPVI

(HPV associated or HPV independent).

Cervical Carcinoma
Protocol for Anatomical Pathology Grossing and Reporting.
Essential Microscopic Features to Report.

A. Tumour Type and Classification (WHO 5th Edition).

- **Classification:** According to WHO 5th edition, distinguishing HPV-associated (HPVA) and HPV-independent (HPVI) carcinomas.
- **Squamous Cell Carcinoma (SCC):** Most are HPVA. Use p16 immunostaining or HPV testing for HPVA/HPVI distinction.
- **Adenocarcinoma:** Separated into HPVA and HPVI types.
  - ► **HPVA Adenocarcinomas:** Usual type, mucinous types (NOS, intestinal, signet-ring cell, stratified mucin-producing p16 IHC is helpful.
  - ► **HPVI Adenocarcinomas:** Gastric type, clear cell, mesonephric, endometrioid type.
- Precursor Lesions:
  - ► **HPV-associated:** CIN (CIN1, CIN2, CIN3). CGIN (AIS/high-grade CGIN). SMILE (subtype of high-grade CGIN).
  - ► **HPV-independent:** AIS HPVI (cuboidal to columnar cells, distinct cell borders, eosinophilic/pale/foamy vacuolated cytoplasm).

B. Histologic Grade.

G1: Well differentiated.
G2: Moderately differentiated.
G3: Poorly differentiated.
GX: Cannot be assessed.

C. Tumour Dimensions.

- **Measurements:** Measure in millimetres. Report largest horizontal dimension and invasive depth/thickness.
- **Stromal Invasion #**
  - ► Depth of Stromal Invasion (millimetres): Specify mm
  - ► Depth of Stromal Invasion: Superficial one-third / Middle one-third / Deep one-third
  - ► Horizontal Extent of Stromal Invasion: Not applicable; Specify mm;
    - Estimated as less than or equal to 7 mm Estimated as greater than 7 mm
    - Specify Number of Block(s) Involved:
    - Not applicable in larger tumours that can be measured grossly.
  - ► Pattern of Invasion: Pattern A /Pattern B /Pattern C (Silva System- applicable only to invasive endocervical adenocarcinoma).
  - ► **#Depth of Invasion (DOI):** Measured from the base of the epithelium (surface or glandular) to the deepest focus of invasion. If no obvious origin, measure from deepest invasion to base of nearest non-neoplastic surface epithelium.
  - ► **#Unmeasurable DOI:** If impossible (e.g., ulcerated, polypoid), measure overall tumour thickness and explain why DOI was not assessed.
  - ► **#Hysterectomy/Trachelectomy:** Report maximum depth across all blocks. Horizontal dimension is sum of horizontal dimensions from relevant sections.
  - ► **Terminology:** Discourage "microinvasive carcinoma"; use precise FIGO stage (e.g., Ia1, Ia2).

D. Lymphovascular Space Invasion (LVSI).

- **Microscopic Criteria:** Tumour cells in endothelial-lined space, adhering to vessel, contouring to lumen, adherent fibrin, association with other vessels. Differentiate from artifact. IHC (D2-40, CD31, CD34) can confirm but is not routine.

E. Resection Margins:

- **Margin Status:** Margins must be classified as involved, negative, or indeterminate.
- **Specify Involved or Indeterminate Margins:** If a margin is involved (e.g., endocervical, ectocervical, deep) or indeterminate, the specific location and reason (e.g., cautery artifact) must be clearly stated.
- **Precursor Lesions:** The severity and extent (focal or diffuse) of any precursor lesions involving a margin must be specified.
- **Distance Measurement:** If an invasive tumour is close to, but not directly involving, a margin, the distance in millimetres must be recorded.

- **Hysterectomy/Trachelectomy Specimens:**
  - ► The lateral radial margin may include parametrial soft tissue, which should be measured if present.
  - ► If a formal parametricity was performed, the measurement from the side of the uterus to the lateral edge of the unstretched parametrium must be recorded and included in the margin evaluation. Careful microscopic examination of the parametria is crucial in these cases.
  - ► Anterior and posterior deep margins will consist of cervical stromal tissue.

F. Lymph Node Status

- **Regional vs. Non-Regional:** Regional (pelvic, para-aortic) contribute to N category. Non-regional (inguinal, supraclavicular) are distant metastasis (M1), Stage IVB.
- **FIGO 2018 Staging:** Nodal involvement leads to Stage IIIC (IIIC1 for pelvic, IIIC2 for para-aortic).
- **Micrometastases (0.2-2 mm):** Regarded as true lymph node involvement (pN1(mi) or pN2(mi) in TNM8/FIGO 2018) and lead to upstaging.
- **Isolated Tumour Cells (ITCs ≤0.2 mm):** Not considered nodal metastases; regarded as node negative (pN0(i+)).
- **Extracapsular Spread:** Important adverse prognostic factor correlates with lower survival.
- Ultrastaging to be performed if Sentinel Lymph Node sample is done.

Endometrial Carcinoma

Protocol for Anatomical Pathology Grossing and Reporting.

Essential Macroscopic and Microscopic Features to Report.

Gross Description
Hysterectomy Specimen

- S**pecimen Integrity:** Intact / Fragmented.
- **Tumour Description:**
  - ► **Location:** Fundus / Anterior wall / Posterior wall / Lateral wall / Isthmus / Diffuse.
  - ► **Size:** mm.
- **Other Uterine Findings.**

- **Adnexa:**
  - **Ovaries:** Presence of tumour: Yes / No
  - **Fallopian Tubes:** Presence of tumour: Yes / No
- **Lymph Nodes (if submitted):**
  - Pelvic: Right __ nodes, Left __ nodes
  - Para-aortic: __ nodes
- **Other Tissues (if submitted).**

Microscopic Description

A. Tumour Histology

- **Histologic Type (WHO 2020):**
  - Endometrioid adenocarcinoma (specify grade: G1, G2, G3)
  - Serous carcinoma.
  - Clear cell carcinoma.
  - Mucinous adenocarcinoma.
  - Undifferentiated carcinoma.
  - Mixed carcinoma (specify components and percentages).
  - Carcinosarcoma (MMMT) (Specify % of carcinoma and sarcoma).
  - Other (specify).
- Tumour Grade (Endometrioid type, FIGO 2023):
  - **Grade 1:** Non-squamous or morular solid growth ≤ 5%.
  - **Grade 2:** Non-squamous or morular solid growth 6-50%.
  - **Grade 3:** Non-squamous or morular solid growth > 50%.
  - Note: Serous, Clear Cell, Undifferentiated are considered high-grade (FIGO Grade 3) regardless of architectural pattern.
- **Aggressive Histologic Types:** Serous, clear cell, undifferentiated, carcinosarcoma.
- **Non-aggressive Histologic Types:** Low-grade (G1/G2) endometrioid, mucinous.

B. Tumour Invasion

- Myometrial Invasion:
  - ► Depth of invasion: (e.g., Superficial, inner half, outer half).
  - ► Percentage of myometrial thickness invaded: __ % (< 50% / ≥ 50%).
  - ► Invasion of uterine serosa: Yes / No.
  - ► Adenomyosis: Not identified / Present, uninvolved by carcinoma / Present, involved by carcinoma.
- **Cervical Involvement:**
  - ► Endocervical glandular involvement: Yes / No.
  - ► Cervical stromal invasion: Yes / No.
- **Isthmic Involvement:** Yes / No.
- **Lower Uterine Segment Involvement:** Yes* / No.
  The prevalence of Lynch syndrome in patients with LUS endometrial carcinoma (29%) has been reported to be much greater than that of the general endometrial cancer patient population (1.8%) or in endometrial cancer patients younger than age 50 years (8% to 9%).
- **Lymphovascular Space Invasion (LVSI):** Present (Focal vs Substantial >5)/ Absent.
- Peritoneal Involvement: Present / Absent (specify type: implants, ascites).
- Adnexal Involvement:
  - ► Ovarian involvement: Yes / No (specify laterality, type of involvement - direct extension, metastasis, surface, parenchymal).
  - ► Fallopian tube involvement: Yes / No (specify laterality, type of involvement).

Surgical Margins (required only if cervix and/or parametrium/paracervix is involved by carcinoma):

- ► Cervical margin: Free / Involved by tumour / Dysplasia / Other.
- ► Vaginal cuff margin: Free / Involved by tumour / Dysplasia / Other.

- **Lymph Node Examination (required only if lymph nodes are present in the specimen):**
  - ► All lymph nodes negative for tumour cells.
  - ► Positive for tumour cells (select all that apply).
- Number of Pelvic Nodes with Macrometastases.
- Number of Pelvic Nodes with Micrometastases.
- Number of Pelvic Nodes with Isolated Tumour Cells (if applicable).
- Number of Para-aortic Nodes with Macrometastases.
- Number of Para-aortic Nodes with Micrometastases.
- Number of Para-aortic Nodes with Isolated Tumour Cells (if applicable).

Note: Macrometastases (>2 mm), Micrometastases (>0.2 mm to 2 mm and/or >200 cells), Isolated Tumor Cells (≤0.2 mm and ≤200 cells). Reporting the number of nodes with or without macrometastases and micrometastases is required If pelvic and/or para-aortic lymph nodes are submitted and either are positive for tumour cell. Reporting isolated tumour cells is required only in the absence of macrometastasis or micrometastasis.

C. Other Findings

- **Endometrial Background:** Hyperplasia (specify type, with/without atypia), atrophy, polyps, chronic endometritis.
- **Associated Lesions:** (e.g., Endometriosis, adenomyosis, leiomyomas)

D. Special Studies

- Immunohistochemistry (IHC):
  - ► **Mismatch Repair (MMR) Status:** Proficient (pMMR) / Deficient (dMMR) (specify protein loss).
  - ► **p53 Status:** Wild-type / Aberrant (mutant pattern).
  - ► **ER:** Intensity and proportion of staining.
- Molecular Studies: (e.g., POLE mutation, MSI status, CTNNB1, FGFR2, KRAS, PTEN).

E. Pathologic Staging

- State if using FIGO 2018 / FIGO 2023 / FIGO molecular.

F. Molecular Classification.

- POLEmut: (POLE-mutated).
- MSI-H: (Mismatch repair deficient).
- NSMP: (No specific molecular profile / p53 wild-type – ER positive vs ER negative).
- p53abn: (p53 aberrant).

MYOMETRIAL TUMOURS

Protocol for Anatomical Pathology Grossing and Reporting.

Essential Macroscopic and Microscopic Features to Report.

A. GROSS DESCRIPTION

- Specimen weight (gr):
- Specimen dimensions (cm):
- Cervix present: Yes / No.
- Adnexa present: Yes / No.
- Uterus:
  - ► Endometrial thickness (mm).
  - ► Myometrial thickness (mm).
  - ► Serosa: Smooth / Adhesions / Tumour involvement.
- Tumour:
  - ► Number of nodules:
  - ► Site(s): Intramural / Subserosal / Submucosal.
  - ► Largest tumour
  - ► Size (cm).
  - ► Location within uterus.
  - ► Capsule: Intact / Infiltrative.

► Relationship to endometrium / serosa.

B. MICROSCOPIC DESCRIPTION.

- **Tumour type:**
  - ► Leiomyosarcoma.
  - ► Leiomyosarcoma, epithelioid type .
  - ► Leiomyosarcoma, myxoid type.
  - ► Endometrial stromal sarcoma, low grade#.
  - ► Endometrial stromal sarcoma, high grade.
  - ► Undifferentiated uterine/endometrial sarcoma.
  - ► Adenosarcoma.
  - ► Rhabdomyosarcoma.
  - ► Malignant perivascular epithelioid cell tumour.
  - ► Other histologic type not listed (specify).

Low-grade endometrial stromal sarcoma is distinguished from benign endometrial stromal nodule by depth of myometrial invasion ≥3 mm, lymphovascular invasion, or ≥3 foci of myometrial invasion of any depth.

- Histologic Grade (required only for adenosarcoma) *
  - ► Low grade.
  - ► High grade.
  - ► With sarcomatous overgrowth.

* Even a small focus of “high grade” sarcoma may result in an adverse behaviour. It is suggested that the parameter of nuclear atypia be used to distinguish between low grade and high-grade neoplasms. In low-grade neoplasms, the atypia should be akin to that seen in low-grade endometrial stromal sarcoma. Sarcomatous overgrowth in adenosarcoma is defined as the presence of pure sarcoma, usually high grade and without an epithelial component, occupying at least 25% of the tumour.

- **Myometrial Invasion (required only for adenosarcoma)**
  - ► Not identified.
  - ► Present Depth of invasion (millimeters): ___ mm.
  - ► Myometrial thickness (millimeters): ___ mm.
  - ► Percentage of myometrial invasion: ____%.

- **Histological features:**
  - ► Cellularity: Low / Moderate / High.
  - ► Cytological atypia: Absent / Mild / Moderate / Severe.
  - ► Mitotic count: __ per 10 HPF.
  - ► Coagulative tumour necrosis: Present / Absent.
  - ► Other necrosis: Hyaline / Ischaemic / Absent.

- **Margins:**
  - ► Myometrial interface: Well-circumscribed / Infiltrative.
  - ► Serosal involvement: Yes / No.

- **Lymphovascular invasion:** Present / Absent.

- **Lymph Node Examination (required only if lymph nodes are present in the specimen).**
  - ► All lymph nodes negative for tumour cells.
  - ► Positive for tumour cells (select all that apply).
  - ► Number of Nodes with Metastasis (excludes isolated tumour cells).
  - ► Number of Nodes with Isolated Tumour Cells (0.2 mm or less).

Note: Reporting the number of lymph nodes with isolated tumour cells is required only in the absence of metastasis greater than 0.2 mm in other lymph nodes.

- Nodal Site(s) with Tumour Cells (specify):
- Number of Lymph Nodes Examined:

WHO Essential diagnostic criteria for uterine leiomyosarcomaConventional (spindle cell) uterine leiomyosarcoma.

- Two or more of the following:
  - ► Marked cytological atypia (2+/3+ nuclear atypia)
  - ► Tumour cell necrosis.
  - ► ≥ 4 mitoses/mm2 (equating to ≥ 10 mitoses/10 . HPF of 0.55 mm in diameter).Epithelioid uterine leiomyosarcoma.
- One or more of the following:
  - ► Moderate to severe cytological atypia (2+/3+ atypia).
  - ► Tumour cell necrosis.
  - ► ≥ 1.6 mitoses/mm2 (equating to ≥ 4 mitoses/10 HPF of 0.55 mm in diameter).

Myxoid uterine leiomyosarcoma.

- One or more of the following:
  - ► Moderate to severe cytological atypia (2+/3+ atypia)
  - ► Tumour cell necrosis
  - ► 0.4 mitoses/mm2 (equating to > 1 mitosis/10 HPF of 0.55 mm in diameter)
  - ► Infiltrative borders / irregular margins.

VI. ANCILLARY STUDIES (if performed)

IHC markers: Desmin / SMA / Ki67 / p16 / p53 / H-caldesmon / ER / PR

Molecular studies: if evaluated*.

*Molecular testing is diagnostically unnecessary in conventional ESS and in USS but is useful in confirming the diagnosis of HG-ESS in tumours with a round cell-epithelioid appearance that can be associated with areas that have the appearance of the fibroblastic variant of conventional LG-ESS.

TUMOURS OF THE OVARY AND FALLOPIAN TUBE

Protocol for Anatomical Pathology Grossing and Reporting.
Essential Macroscopic and Microscopic Features to Report.

A. Preparation of the specimen before dissection:

- Inking of the capsular surface can be helpful at possible sites of involvement or capsular defect.
- Inking and slicing of the neoplasm only be undertaken following careful examination of the capsular surface of the ovary for adhesions that may indicate foci of capsular rupture.

B. MACROSCOPIC DESCRIPTION

SPECIMEN INTEGRITY:

- Right ovary: Ovarian capsule intact.
- Ovarian capsule ruptured.
- Tumour on surface.
- Fragmented specimen.

- Left ovary: Ovarian capsule intact.
- Ovarian capsule ruptured.
- Tumour on surface.
- Fragmented specimen.

- Right fallopian tube: Serosa intact.
- Serosa ruptured.
- Tumour on serosal surface.
- Fragmented specimen.
- Left fallopian tube: Serosa intact.
- Serosa ruptured.
- Tumour on serosal surface.
- Fragmented specimen.

C. MACROSCOPIC TUMOUR SITE:

- Right ovary.
- Left ovary.
- Peritoneum.
- Omentum.
- Right fallopian tube.
- Fimbrial.
- Non-fimbrial.
- Left fallopian tube.
- Fimbrial.
- Non-fimbrial.

MACROSCOPIC DESCRIPTION OF OMENTUM:

- Omentum dimensions:
- Omental involvemen: Involved/Not involved.
- Maximum dimension of largest deposit …… mm.

D. MICROSCOPIC DESCRIPTION

HISTOLOGICAL TUMOUR TYPE AND GRADE:

(Note: If chemotherapy has been administered the grading may need to be based on the pre-chemotherapy biopsy).

- Serous carcinomas: Low grade/High grade/Cannot be graded.
- Endometrioid carcinomas:
  - ► G1: Well differentiated.
  - ► G2: Moderately differentiated.
  - ► G3: Poorly differentiated.
  - ► GX: Cannot be graded.
- Clear cell carcinomas: High grade.
- Carcinosarcoma: High grade.
- Undifferentiated carcinomas: High grade .
- Mucinous carcinomas:
  - ► G1: Well differentiated

- ► G2: Moderately differentiated.
- ► G3: Poorly differentiated.
- ► GX: Cannot be graded.

- Mixed epithelial/other types:
  - ► Specify (if Other or Mixed epithelial types).

BORDERLINE TUMOUR:

- Present.
- Absent.
- Histological tumour type.

SEROUS TUBAL INTRAEPITHELIAL CARCINOMA (STIC):
(Required only if fallopian tube(s) are submitted and applicable to high-grade serous carcinoma only)

- Right fallopian tube:
  - ► Present – fimbrial.
  - ► Present – non-fimbrial.
  - ► Not identified.
  - ► Cannot be assessed.

- Left fallopian tube:
  - ► Present – fimbrial
  - ► Present – non-fimbrial
  - ► Not identified.
  - ► Cannot be assessed.

PERITONEAL CYTOLOGY:
Negative/Positive/Indeterminate/Not received.

LYMPH NODE STATUS:

- Not submitted/Not involved/Involved.
- Regional.
- Left pelvic:
  - ► Number of lymph nodes examined.
  - ► Number of positive lymph nodes.

- Right pelvic:
  - ► Number of lymph nodes examined.
  - ► Number of positive lymph nodes.
- Para-aortic:
  - ► Number of lymph nodes examined.
  - ► Number of positive lymph nodes.
  - ► Maximum dimension of largest deposit in regional node: mm.
- Non-regional
  - ► Number of lymph nodes examined.
  - ► Number of positive lymph nodes.

SITE OF TUMOUR:

- Primary tumour, ovary.
- Primary tumour, fallopian tube.
- Primary tumour, peritoneum.
- Undesignated: site of primary tumour cannot be assessed.

ANCILLARY STUDIES

IHC (e.g. WT1, p53, napsin A, inhibin, calretinin, SALL4, PLAP, glypican-3) – specify markers performed and interpretation.

Molecular studies if applicable: (e.g. BRCA status, HRD testing).

CHAPTER 8.

SYSTEMIC ANTI-CANCER TREATMENT (SACT) PROTOCOLS

The protocols in the following sections are guidelines and are largely based on those used at Groote Schuur Hospital, Tygerberg Hospital (Cape Town) and private practice. Administration of SACT should take place in specialised units where expertise is available to deal with patients with gynaecological malignancies. These specialised units also require a multidisciplinary approach.

GENERAL CHEMOTHERAPY CONSIDERATIONS

1. FBC including differential count to be checked prior to chemotherapy administration.
   Delay chemotherapy if:
   - WCC < 3.000 if neutrophils count not available.
   - Absolute neutrophils count < 1.5.
   - Platelets < 100.000.

   Low Hb should not cause chemotherapy delay – (transfuse if symptomatic anaemia).
2. Renal function and LFTs to be checked prior to each cycle.
3. Height and weight required for nomogram to estimate body surface area. (This must be double-checked each cycle).
4. Serum Magnesium to be checked regularly with Cisplatin therapy. Give supplemental Magnesium (1g bd po for 5 days after each cycle of Cisplatin).
5. The person administering SACT is to remain with the patient until the infusion of drugs is completed in order to detect allergic reactions or I.V. line problems.
6. Many cytotoxics are vesicants and highly toxic to tissue if extravasated, a well-placed fast running I.V. line with no leaks is essential.

This is especially true of the anthracylines, the Vinca alkaloids, Actinomycin D.

7. I.V. line to be replaced immediately if blocked to ensure administration of SACT and post-hydration fluid.
8. Warn staff that Bleomycin may cause a raised temperature, rigors or anaphylactic reaction (have emergency trolley available). 1 gr paracetamol should be used as a pre-medication to counteract this.
9. In general, do not reduce dose for obese patients; use actual mass in dose calculations. BSA should not be capped, especially in the case of patients being treated with curative intent.
10. Take note of cumulative doses of chemotherapeutic agents, especially Adriamycin, Epirubicin and Bleomycin.
11. When using Methotrexate, be aware that it can accumulate in effusions and ascitic fluid, which may give rise to a slow release and cause a severe neutropenia.
12. Always check for possible coexistent pregnancy in patients.
13. Never administer more than 2 mg Vincristine per dose.
14. Allergic reactions are common with carboplatin (and cisplatin) occurring in up to 20% of patients and are most often seen later on e.g.: after cycle 5.
15. Allergic reactions are common with the taxanes [paclitaxel and docetaxel], and these agents are always given with extensive steroid and anti-histamine premedication. Reactions are usually seen at the second or later cycle and occur within the first 15 minutes of the infusion. Any person administering these agents must be familiar with the current standard premedication (and post medication) protocols in use.
16. Premedication: Promethazine 25mg IVI 30 min before drug infusion, Dexamethasone 8 - 20 mg IVI, Ondansetron 8mg IVI, Ranitidine 50mg IVI (or Cimetidine 200mg IVI).
    With Docetaxel, the patients are given oral steroids to be taken for 3 days, starting the evening before the chemo.

17. All patients receiving anthracyclines must have their LVEF checked prior to starting chemotherapy. Repeat LVEF during chemotherapy if initial borderline result.
    Calculated creatinine clearance (Cockcroft – Gault formula) before each cycle: (140-age) x mass (kg) x 1.05/ Serum creatinine = clearance in ml/min.
    Carboplatin absolute dose based on Calvert formula (calculated clearance + 25 X AUC = dose of Carboplatin in mg.
18. Follow specific guidelines for the delivery of targeted agents/immunotherapy including baseline bloods, ECG, blood pressure, urine dipstix and cardiac evaluation.

A. GESTATIONAL TROPHOBLASTIC NEOPLASM

1. Low risk (FIGO score 0-6) - Single agent chemotherapy:
    - Methotrexate 50mg/m2 IM every 48hrs X 4 (repeat every 2 weeks)
      Leucovorin, 15 mg P.O. 30hrs after each injection of Methotrexate.
      or
    - Actinomycin D 1.25 mg/m2 IV every second week.
        - ► Continue cytotoxics until β-HCG normal (<5 IU/ml) then administer at least 2 additional cycles. (for low risk disease).
        - ► If serum β-HCG level “plateaus” or rises:
            - If > 1000 on either regime change to multiple agent chemotherapy.
            - If < 1000 on methotrexate change to Actinomycin D.

    Note: Chest x-ray signs may take 6 months to return to normal.

After complete remission is obtained 3 cycles of consolidation chemotherapy should be given-the same regimen, which was effective to reach remission. (for high-risk disease).

2. High-risk (FIGO score ≥ 7).
EMA-CO: This regimen consists of two parts:

- **EMA** (Etoposide, methotrexate & Actinomycin D) is given on days 1 and 2;
- **CO** (Cyclophosphamide & Vincristine) is given on day 8.
  EMA requires overnight admission, CO does not.
- Next **EMA-CO** cycle starts at day 15.

Additional notes:

- **EMA**
  - ► Day 1 Etoposide 100 mg/m2 IV infusion in 200 ml saline over 30 minutes; Actinomycin D, 0,5 mg, iv stat; Methotrexate, 300 mg/m2 in 1 litre saline over 12 hours.
  - ► Day 2 Etoposide 100 mg/m2 IV infusion in 200 ml saline over 30 min.; Actinomycin D, 0.5 mg IV stat.; Folinic acid, 15 mg, IM or orally every 12 hours for 4 doses beginning 24 hours after starting methotrexate.
- **CO**
  - ► Day 8 Vincristine, 1.0 mg/m2, (maximum 2.0 mg) IV stat.; Cyclophosphamide, 600 mg/m2 IV in 250 ml saline over 30 minutes.

Repeat cycles until serum β-HCG level is ≤ 5 i.u./ml and administer 6 weeks additional cycles (“insurance cycles”) but 8 weeks for WHO score > 12.

Special considerations:

- Failure to respond to EMA-CO: modify regimen as follows: omit Actinomycin D and Etoposide on day 2 of EMA. On day 8, replace CO with Cisplatin 75mg/m2 and Etoposide 120 mg/m2 alternating weekly with EMA. Consider alternative chemotherapy e.g. taxane-etoposide, taxane-platinum in case of on-going failure.
- CNS metastases:
  - ► Methotrexate is the drug of critical importance.
  - ► The Methotrexate dosage in the EMA-CO regimen is increased to 1 g/m2 to each an effective drug concentration in the CSF. Folinic acid dosage is increased to 30mg, 8 hourly x12, starting 24 hours after commencement of methotrexate. Intra-thecal methotrexate 12.5 mg is given with each dose of CO. (physicians choice)
  - ► Consider radiotherapy, surgery or alternative chemotherapy if indicated.

**If patients fail chemotherapy with high-risk disease consider pembrolizumab.

B. UTERINE MALIGNANCIES

1. High risk endometrial adenocarcinoma (see Chapter 4 Carcinoma of the Uterine Corpus).
   Options:
   - As per PORTEC-3: Cisplatin 50mg/m2 x 2 cycles q3weekly while on radiotherapy followed by Carboplatin AUC5 and Paclitaxel 175mg/m2 q 3 weekly x 4 cycles

- Carboplatin (AUC 5) IV & Paclitaxel IV175mg/m2 x 4 - 6 cycles.
  - ► (In Stage III/IV patients: For non-carcinosarcoma - Add pembrolizumab independent of PDL1, or durvalumab (for dMMR only) to chemotherapy and continue as maintenance if funding available) - most data is to continue for 2 yrs.
  - ► (In Stage III/IV patients: Add trastuzumab for HER2 positive tumours – including carcinosarcoma).
  - ► In recurrent uterine cancer: Can re-challenge or offer above if not used in adjuvant setting or if funding available: Lenvatinib/Pembrolizumab for MMR-proficient tumours or Pembrolizumab alone for MMR-deficient tumours.
- For dMMR/MSI-H metastatic tumours: consider pembrolizumab 200mg ivi q 3 weekly.
- Other drugs to consider in recurrent uterine adenocarcinoma: gemcitabine, single agent paclitaxel, cisplatin-doxorubicin, liposomal doxorubicin, addition of bevacizumab to chemotherapy regimens.
- In ER positive, recurrent uterine cancer: consider maintenance aromatase inhibitors, tamoxifen, fulvestrant, and presentational agents.

2. Leiomyosarcoma, endometrial stromal sarcoma (ESS) and undifferentiated sarcoma.
   - Adriamycin: 50 mg/m2 IV (Or Epirubicin 100 mg/m2) 3 weekly x 4 - 6 cycles.
     Note: ERNA or Cardiac Echogram prior to Epirubicin or Adriamycin.
   - Leiomyosarcoma: can consider gemcitabine-docetaxel in adjuvant setting: gemcitabine (900 mg/m2 over 90 minutes on days 1 and 8) plus docetaxel (75 mg/m2 on day 8), G-CSF D9 must be prescribed.

- High dose Provera/aromatase-inhibitors may be considered in low-grade, irresectable ESS. (ER+).

C. CARCINOMA OF THE CERVIX

For locally advanced disease consider neoadjuvant chemotherapy as per the INTERLACE study:

- Weekly Carboplatin AUC2 and Paclitaxel 80mg/m2 for 6 weeks, to start CRT in week 7- do not use as 'holding chemo'. (Planning scan in week 3).
- Improves 5-year OS by 8% compared to CRT alone.
- Concomitant chemoradiation:
  Weekly Cisplatin 40mg/m2.
- (Consider FIGO Stage III and IVA - with pembrolizumab 200mg 3 weekly x 5, followed by 15 more cycles of pembrolizumab 400mg q 6 weekly, if funding available, as per the ENGOT cxII study improves PFS, mature OS data awaited.)
- Premedication: Dexamethasone 8mg IV + 5HT3 antagonist.
- 1L N-Saline (+ 2 amps MgSO4) over 2 hours.
- Cisplatin in 200ml NS x 1 hour.
- Post-hydration 200-1000ml.
- During course of chemoradiation:
  - ► Slow-Mag 1g bd po continuously.
  - ► Metoclopramide 10mg tds as needed.
- If renal function affected, consider Carboplatin AUC 2 weekly as alternative, which is safe in the GFR range 30-90ml/min. If GFR <30ml/min do not use any chemotherapy.
- Calculate the GFR (using Cockroft-Gault equation) prior to each weekly IV dose of Cisplatin. GFR must be >60ml/min for use of Cisplatin.

Advanced disease/Metastatic disease/Recurrent disease:

- Cisplatin 50mg/m2 3 weekly IV (prescribed as above) for 3 - 6 cycles or cisplatin 50 mg/m2 and paclitaxel 135 mg/m2. Review after third cycle.
- Carboplatin AUC 5/Paclitaxel 135mg 3 weekly IV. (if unable to deliver cisplatin).
- For metastatic stage IVB cervical cancer cisplatin 50 mg/m2 + paclitaxel 175 mg/m2 q 3 weeks (or cisplatin 50 mg/m2+paclitaxel 135mg/m2 if pre-treated with chemotherapy or radiotherapy) - can add bevacizumab 15mg/kg q 3 weekly ivi – for PDL1 positive tumours add Pembrolizumab 200mg IV q3weekly or Atezolizumab 1200mg IVI q 3 weekly (if funding available).
- If progress on cisplatin/carboplatin-paclitaxel, consider gemcitabine, topotecan, vinorelbine, docetaxel.
- For dMMR/MSI-H tumours: consider pembrolizumab 200mg ivi q 3-weekly (if funding available).

D. CARCINOMA OF THE VULVA

Chemotherapy and radiotherapy concomitant:

- Weekly cisplatin 40mg/m2 (treatment of choice).
- Alternative - Day 1 - Mitomycin C (10mg/m2) in 200ml 5% Dextrose is given over 30 minutes (or alternatively Cisplatin 75mg/m2 with adequate hydration).
- Day 1- 4 (inclusive) 24-hour constant infusion of 5-Fluorouracil (1 gr/m2) in N. saline.
- The 4-day infusion of 5FU and Mitomycin is repeated on day 28 of the radiotherapy.
- If available, consider capecitabine 825mg/m2 daily on every radiation day instead of 5FU.

Consider neo-adjuvant (or palliative chemotherapy in advanced disease):

- Cisplatin 50mg/m2 or Carboplatin AUC 5 and Paclitaxel 135mg/m2.
- Cisplatin 75mg/m2 or Carboplatin AUC 5 day 1 + 5-FU 1gr/m2 constant in-fusion day 1 – 4.
- Carboplatin AUC 6 & Bleomycin 15 IU IM.
- Palliative chemotherapy options if progressed on carboplatin-paclitaxel:

Gemcitabine, capecitabine, mitomycin, immunotherapy.

E. TUMOURS OF THE OVARY

a.Epithelial Tumours.

1.First line treatment:

- Carboplatin AUC 5 + Paclitaxel 175mg/m2 q 21 days IV for 6 cycles depending on response. (Patients to have interval debulking after 3-4 cycles of chemotherapy, provided there is 1 log drop in CA125).
- Or single agent Carboplatin AUC 6 - 7.5. (Mostly reserved for elderly patients or patients with lower risk disease unwilling to lose their hair).
- Anti-emetic premedication: Dexamethasone 20mg IV + 5HT3 antagonist IV
- Cycles repeated 3 weekly; 6 cycles.
- Bevacizumab (in combination with Carboplatin and Paclitaxel) is recommended in the first line treatment for patients with advanced ovarian cancer with poor prognostic features such as stage IV or suboptimal debulking as defined in the ICON-7 trial (7.5 mg/kg complete 1 year of treatment) or as per GOG218 in patients with ascites or Stage IV disease (15 mg/kg complete 15 months of maintenance treatment).

- NB: Patients on bevacizumab MUST have a 4-week break prior to interval debulking surgery and a 6 week wait post-surgery, continue chemotherapy without it for these cycles prn.
- Maintenance treatment with bevacizumab should be offered if bevacizumab is started with chemotherapy and be continued for a total of 15/12 of treatment.
- For BRCA+ and HR deficient patients: maintenance PARP inhibitor (Olaparib®) should be offered to patients within 8 weeks post-platinum based chemotherapy: Olaparib® 300 mg po bd continuously for 2 years or Olaparib®/Bevacizumab: best data for HR deficient patients. (If funding available).

2. Second line treatment (platinum sensitive):

- Re-challenge with carboplatin-paclitaxel if recurrence > 6/12 and good response.
- Carboplatin/cisplatin-gemcitabine.
- Carboplatin-liposomal doxorubicin.

3. Second line treatment (platinum resistant/refractory):

- Paclitaxel 80mg/m2 q7 days for three weeks and then 1 week break (cycle 1). For 3-6 cycles depending on response. If patient tolerates Cycle 1, dose may be increased to 90mg/m2. Dexamethasone dosage should be decreased to 8 mg.
- Paclitaxel 175mg/m2 q21 for 3-6 cycles IV.
- Pegylated liposomal doxorubicin if paclitaxel not an option: 50mg/m2 q4weekly IVI.
- Other second-line options Docetaxel, Gemcitabine, Etoposide, Topotecan. (All as single agent or as part of multi-agent chemotherapy).
- Bevacizumab (in combination with chemo) may also be used in platinum sensitive relapsed disease (OCEANS TRIAL) and platinum resistant/refractory disease (AURELIA TRIAL).
- In BRCA+ patients: PARP inhibitor can be used in second-line post platinum-based chemotherapy as maintenance.

- For dMMR/MSI-H tumours: consider pembrolizumab 200mg ivi q 2weekly if progressed on all other treatments.
- If patients have HER2+ disease: consider HER2-blocking agents
- Oral agents as second line or poor performance, elderly patients:
  - ► Cyclophosphamide = 100mg daily PO. Repeat FBC monthly.
  - ► Tamoxifen = 20 mg BD (some evidence to use letrozole/fulvestrant in ER+ disease).

b. Germ Cell Tumours.

1. BEP: (3 or 5 day regimens may be used, but 3 day regimen considered more toxic.)
   Five-day regimen: given 3 weekly

- Cisplatin 20 mg/m2 D1-5 daily IVI-dilute in 250ml N/Saline and run in over 2hrs.
- VP16/Etoposide 1oomg/m2 D1-5 daily IVI dilute in 500ml N/Saline and run in over 1hr.
- Bleomycin 30units in 50ml N/Saline D1, 8, 15 (max 10 doses) run in over 10 minutes.
  - ► Pre-treatment audiometry, calculated creatinine clearance, pulmonary function tests.
  - ► On day 1, Pre-hydration with 1L N-Saline (+ 2 amps MgS04) over 2 hours.
  - ► Anti-emetic: Dexamethasone 8 mg IV D1-5. 5HT3 antagonist 1 vial IV.
    Cisplatin is given in 200ml N-Saline over 2 hours, “piggy bagged”.
  - ► Treatment is given with curative intent; any delay or dose reduction may have a significant detrimental effect on outcome. Dose intensity should be maintained regardless of counts. Growth factors may be required.

► Supplemental Oxygen may precipitate/aggravate Bleomycin pulmonary toxicity. FIO2 should not exceed 30-40% unless absolutely necessary.

2. Impaired audiometry initially, or during BEP or calculated creatinine clearance < 60ml/min:

- Day 1 only Carboplatin AUC 5. Day 1-2-3: Etoposide + Bleomycin.

3. Resistant and recurrent Germ Cell tumours **Modified VeIP.**

- Vinblastine 0.11mg/kg ivi push day 1 and 2 only.
- Ifosfamide 1.2 mg/m2 days 1-5 with mesna protection.
- Cisplatin 20 mg/m2 days 1-5.

F. PHARMACOLOGICAL MANAGEMENT OF NAUSEA AND VOMITING

Nausea and vomiting are common accompaniments of cytotoxic treatment. They are amongst the most distressing side-effects to the patients.
Current anti-emetics regimens greatly ameliorate these side effects:

- Dexamethasone 8-20mg IV. PLUS High emetic risk regimens (incl. Carboplatin, cisplatin, ifosfamide) add a NK1 receptor antagonist if funding available: Aprepitant D1-3 po (125/80/80mg) + 5HT3 antagonist IV and oral post-chemotherapy for 3-5 days.
- Moderate emetic risk regimens: intravenous 5HT3 antagonist followed by oral 5HT3 antagonist post chemotherapy 3-5 days – or Palonosetron (Onicit®) 0.25mg only IV (lasts 5 days) if funding available.
- Post-chemotherapy: Metoclopramide 10mg QDS PO and cyclizine suppositories 100 mg for up to 5 days. Can also add betanoid/dexamethasone 4mg-8mg po bd for up to 3 days.

- Specific anti-emetic regimens for specific chemotherapy drugs can be found: at https://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf.

G. PRE-EXISTING MEDICAL CONDITIONS AND CHEMOTHERAPY

Certain pre-existing medical conditions may have an influence on the efficacy and on the side-effect profile of chemotherapeutic agents (Table 1).

TABLE 1 Pre-existing medical conditions and chemotherapy.

Pre-existing condition	Special care with the following drugs
Abnormal liver functions	Methotrexate Vincristine/blastine Epirubicin 5FU Taxanes
Abnormal liver functions	Methotrexate Actinomycin D Bleomycin Cisplatinum Carboplatinum Etoposide
Hearing impairment	Cisplatinum
Neurological abnormalities	Vincristine Paclitaxel

Pre-existing condition	Special care with the following drugs
Cardiac insufficiency	Epirubicin Doxorubicin
HER2-blocking agents	
Bone marrow depression	All except: Vincristine Bleomycin Cisplatinum
Drug therapy:	
• NSAID's:	Methotrexate
• Warfarin	all (esp. 5FU)
• Anti-malarials:	Methotrexate
• Irradiation:	Methotrexate 5-FU Mitomycin-C Bleomycin Epirubicin/doxorubicin Actinomycin D

Note:Radiation “recall” may occur with subsequent treatment with Actinomycin D or Epirubicin.

H. PREPARATION AND HANDLING OF CYTOTOXIC AGENTS

Many drugs used in the treatment of cancer are toxic to normal tissues, and extreme care is therefore necessary to ensure that the appropriate dose and route of drug administration are employed.

Three potential hazards have been recognised:
1. An irritant or vesicant effect on the skin or other tissues.
2. A carcinogenic effect.
3. A mutagenic effect.

The dangers of carcinogenic and mutagenic effects for doctors, nurses, and others involved are minimal. However, the dangers of irritant or vesicant effects are present. Care should be taken, particularly when drawing up vesicant drugs, to ensure that:
1. Aerosols of the agent are not produced.
2. The drug does not contaminate the skin or other mucosal surfaces.
3. Residual drug is disposed of in such a way that it minimizes the risk of exposure to other personnel.
4. The vesicant properties of commonly used cytotoxic agents are outlined in Table 2.

TABLE 2. Vesicant properties of cytotoxic drugs

Highly vesicant	Irritant	Non-irritant
Actinomycin D	Bleomycin	Methotrexate Paclitaxel 5FU
Epirubicin/Doxorubicin Vinblastine Vincristine	Cisplatin Cyclophosphamide Etoposide Carboplatin	

Note: Immediate treatment:

1. Disconnect the infusion set. Leave the cannula in situ and gently aspirate as much of the drug as possible. Remove cannula thereafter. Record amount aspirated.
2. Administer pain relief as required and elevate limb.
3. Anthracycline, Alkalyting agent or Antibiotic: LOCALISE and NEUTRALISE. Ie: apply cold pack for 20min every 4 x daily for 3 days. Neutralise with specific antidote if available.
4. Vinca alkaloids, Platins, Taxanes: DISPERSE and DILUTE. I.e.: apply warm compress for 20min 4 x daily. Administer antidote if available.
5. Document incident.
6. Refer to Plastic surgery or Hand Clinic.

I. SIDE-EFFECTS

Chemotherapeutic agents may have a variety of side-effects. Please refer to package inserts of drugs.

Figure 1 Chemotherapeutic agents and incidence of side effects.

	Methotrexate	5-Fluorouracil	Cyclophosphamide	Paclitaxel	Melphalan	Actinomycin D	Adriamycin	Bleomycin	Mitomycin C	Vincristine	Etoposide	Cisplatinum	Carboplatinum	Docetaxel	Olaparib toxicity
Bone	**	**	**	*	**	**	**	*	**	*	**	*	**	**	**
Sclerosant						*	**		*	*	*				
Neurological	*	*		**		*		**		**		*	*		*
Skin	*	*	*			*		**							*
Pulmonary	*							**							
Renal	*											**	*		
Hepatic	**		*	*				*		*				*	*
Cardiac			*				**								
Endocrine			*												
Bladder			**												
GIT	**	**	**		*	**	**		*						**
Allergic								*							
Alopecia	*	*	**	**		**	**			*				**	*
Metabolic			*			*				*					
Nausea/ Vomiting	*	*	**	*	**	**	**	**	**			**	*	**	*
Stomatitis	***	**				*	**	*					*		

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CHAPTER 9.

PRINCIPLES OF RADIATION THERAPY (RT)

- Aim of RT is to achieve loco-regional control of the cancer while preserving normal tissue functions.
- Radiation damages DNA which interferes with cell division resulting in the cell dying a “reproductive death”. It damages cancer cells relatively more efficiently than normal cells, provided the radiation is given in many small fractions. Normal cells can repair most sub-lethal DNA damage between fractions, while tumour cells do not repair efficiently, accumulate damage, then die from apoptosis during cell division.
- RT is administered from outside the body (teletherapy) with photon beams which can be gamma rays (cobalt machine) or X-rays (linear accelerator). Teletherapy is also called External Beam Radiotherapy (EBRT). Radiation can also be given in close proximity to a tumour, using an isotope (brachytherapy = BT). A combination of the above methods is commonly used.
- The unit of radiation is the Gray (Gy).
- Total radiation dose is limited by the surrounding “organs at risk” (OAR), such as the bladder, rectum, small bowel, femoral heads, etc.
- Intra-tumoral hypoxia makes cancer cells less radiosensitive, hence anaemia (Hb<10) during EBRT should be reversed by transfusion.

<u>CERVIX:</u>

- See indications in Chapter 3 Carcinoma of the Cervix.
- Radical (curative intent) RT consists of EBRT to the pelvis, encompassing the cervix, uterus, suspensory ligaments, upper vagina and pelvic lymph nodes. This is followed by BT to the tumour.

EBRT:

- 1.8-2Gy/fraction to a total of 46-50.4 Gy (Mon-Fri). Use of VMAT/advanced planning techniques are preferable where possible.
- If there are bulky or PET-CT positive nodes, a boost to the nodes are advised. Simultaneous intergrated boost (SIB) technique is preferred to sequential boost as it still maintains the same overall treatment time. PTV node boost to 60Gy.

Brachytherapy:

- 5-7Gy/fraction in 2-4 fractions. Depends on applicator used and the residual tumour size.Brachytherapy is an essential component of potentially curative RT for LACC.
- Started towards the end or immediately after of a course of EBRT to allow for tumour shrinkage first.
- It is applied under anaesthesia as a high dose boost treatment to the primary cancer.
- Brachytherapy is now planned with advanced planning techniques.
- Systemic AntiCancer Treatment (SACT):
- Radiation-sensitising SACT with cisplatin, given in small weekly doses concurrently with EBRT in cervical cancer, improves survival by 5-10% at 5 years.

<u>UTERINE CANCERS:</u>

- RT mostly used in the post-operative setting (see Chapter 4 Carcinoma of the Uterine Corpus).
- Depending on the indication for RT, EBRT or Vault BT or a combination of the two is used.
- VBT only: 7Gy in 3 fractions, weekly prescribed to 5mm from the vaginal surface with specific length and diameter cylinder.

- EBRT: 1.8Gy/fractions in 25-28 fractions (Mon-Fri) to a total of 45Gy-50.4Gy. If VBT added (cervix +): 10-11Gy/2 fractions.
- RT (EBRT/BT/Combo) may also be used if patient is clinically or medically inoperable.

VULVA CANCER:

- RT may be used in the adjuvant,definitive and palliative setting.

INDICATION	DOSE & FRACTIONATION
ADJUVANT	All: PTV-elective nodes & PTV vulva 45 - 50 Gy in 25# RESECTION MARGIN FOR VULVAL TUMOUR • 1mm: PTV vulva boost at least 60Gy. • 1-3mm: PTV vulva boost 56Gy. • >3mm: PTV vulva 45 - 50.4Ggy. LYMPH NODE INVOLVEMENT • Micrometastatic positive sentinel LN ≤2 mm: 50Gy to PTV elective nodes (as per GROINSS_VII). • Fully resected, no ECE: Boost involved nodal bed to 56 Gy. • ECE +: Boost involved nodal bed to atleast 60 Gy.

INDICATION	DOSE & FRACTIONATION
RADICAL TREATMENT (INOPERABLE)	PTV Elective node and PTV vulva: 45–50.4 Gy. PTV vulva boost and PTV node boost: 60–68 Gy.
PALLIATIVE	Dose/fractionation selected according to performance status and co-morbidity. 8 Gy in 1 fraction. 20 Gy in 5 fractions daily over 1 week. 30 Gy in 10 fractions over 2 weeks.

- Boost can be given as a sequential boost or as simultaneous integrated boost (SIB).
- It is preferable to use VMAT for these patients.

VAGINAL CANCERS:

- RT used for larger, inoperable lesions or in patients not medically fit for surgery.
- Treatment technique is broadly similar to cervix cancer and involves concomittant chemoradiation. In unfit patients, radiation alone may be used.
- Brachytherapy using a cyclinder or ring and tandem may be used for upper vaginal lesions and interstitial brachytherapy may be considered for lower vaginal lesions.

OVARIAN CANCER:

- No evidence for use of radiation treatment in the curative setting.
- Justifiable in patients with relapsed disease who have pain, bleeding or a discharge which cannot be controlled by other means
- The combination of PARP inhibitors with radiation is currently being investigated.

PALLIATION:

- An important indication for EBRT is for symptom-relieving palliation, for pain, bleeding etc.
- The decision to use palliative vs curative RT is usually taken at the Combined Clinic, depending on tumour extent, co-morbidities, and physical status.
- Because such patients do not generally survive for long enough to develop radiation complications, palliative RT is given at higher dose per fraction than 2 Gy, over 1- 2 weeks (3Gy x10#'s or 4Gy x 5#'s).
- Occasionally urgent RT is used for uncontrolled bleeding not responding to packing etc. It has a haemostatic effect on the tumour though it is uncertain by which mechanism.

SIDE EFFECTS:

- Side effects from RT can be Early/Acute (during, or <6months after treatment), or late(>6 months to years later).
- Early/acute effects are related to epithelial irritation, eg skin changes in skin folds or on the perineum, bladder (dysuria, frequency), or rectum (tenesmus, diarrhoea). These are treated symptomatically and heal completely within weeks.
- Late/Chronic morbidity relates to microvascular damage caused by radiation, which leads to tissue hypoxia, then fibrosis (strictures) or necrosis (eg recto-vaginal fistula). Majority of these effects are mild, though rectal bleeding from chronic ulceration, stenosis and fistulae, or macroscopic haematuria from bladder damage, are amongst the more severe complications. Small bowel complications include chronic enteritis, subacute intestinal obstruction, perforation or strictures.

- Most patients may experience vaginal fibrosis and vaginal shortening, which lead to decreased sexual satisfaction and painful intercourse. Regular sexual activity and oil based lubricants are encouraged.
- Patients should also be counselled about menopausal symptoms and loss of fertility. Young patients should be referred for possible fertility sparing procedures.

CHAPTER 10.

MALIGNANCY IN PREGNANCY

A. INCIDENCE:

- Breast, cervical cancer most common.
- Leukaemia and lymphoma ± 25% of cases.
- Others include melanoma, thyroid cancer, ovarian cancer and colon cancer.
- Prognosis potentially similar as in non-pregnant state.

B. MANAGEMENT:

- Termination of pregnancy should be considered if appropriate gestation and patient wishes.

Surgery during pregnancy:

- Ideal time 16 – 18 weeks.
- Abdominal surgery may increase risk of premature delivery.
- Laparoscopic surgery (open entry) safe in experienced hands.

Chemotherapy during pregnancy:

- Wait until after 14 weeks gestation to start chemotherapy
- Folic acid antagonists (e.g. methotrexate) and idarubicin are contra-indicated.
- Pharmaco-dynamics and pharmaco-kinetics of chemotherapy may change due to increased GFR and liver metabolization.
- Interval of 3 to 4 weeks between last chemotherapy and delivery
  (generally: no chemotherapy administered after 35 weeks of pregnancy with main concern being fetal thromobocytopaenia at the time of delivery).

- No obvious increased risk for congenital malformations after intra-uterine exposure to chemotherapy during second and third trimesters.

Radiotherapy during pregnancy:
- Radiotherapy is a relative contra-indication.
- Radiotherapy (with proper shielding of uterus) may be applied to the upper body during pregnancy with relative safety if unavoidable.
- Upper body radiotherapy should preferably be given with the fetus in the cephalic position after 28 weeks (to protect fetal neurological system).
- If chemotherapy and radiotherapy are needed as adjuvant treatment, radiotherapy will be postponed until after delivery.

C. INVASIVE CERVICAL CANCER:
- If micro-invasive carcinoma is suspected, a cone biopsy should be considered under general anaesthesia.
- Prophylactic cerclage may decrease bleeding and premature labour.
- Conservative approach only if firm desire to continue the pregnancy.
- Neo-adjuvant chemotherapy is an option.
- Caesarean section delivery route of choice in bulky tumours.

Management:
- Stage-related, as for non-pregnant patients.

Timing of intervention:
- <24 weeks – immediate.
- 24-34 weeks – delay until >34 weeks
- >34 weeks – delivery and treatment.

Stages IB/IIA:

- <24 weeks – radical hysterectomy + pelvic lymphadenectomy with fetus in-situ.
- 24-34 weeks – delay until >34 weeks, then classical C/section plus radical hysterectomy + pelvic lymphadenectomy. (This approach may require individualisation – tumour size, patient's wishes etc.).
- >34 or more weeks – classical C/section plus radical hysterectomy + pelvic lymphadenectomy.

Stages IIB, III and IV:

- ≤ 12 weeks – start chemo-radiation. Medical termination of pregnancy an option.
- 12 to 24 weeks: Terminate pregnancy – start chemoradiation. Alternatively, consider neo-adjuvant chemotherapy if patient wishes to continue pregnancy.
- ≥ 24 weeks – Neo-adjuvant chemotherapy while awaiting fetal maturity before delivering by classical C/section. Start chemo-radiation + intracavitary brachytherapy post-operatively.

D. VULVAL CANCERS:

- Surgery possible during pregnancy – individualise.

E. ENDOMETRIAL CANCER:

- Rare malignancy in pregnancy and is often associated with miscarriage

F. OVARIAN CANCER:

- Proper surgical staging procedure with diagnostic aim.
- Chemotherapy during pregnancy not contra-indicated.
- Completion surgery may be delayed until after the pregnancy.

G. ADNEXAL MASSES:

- Ideal time for surgery during second trimester.
- Individualized care based on ultrasound and clinical features.
- Torsion, rupture, and bleeding potential complications.
- Laparoscopy contra-indicated in masses suspicious of malignancy.

H. GENERAL COMMENTS:

- Malignant melanoma may metastasize to the placenta and fetus – placenta must be sent for histological assessment. If positive, examine fetus for possible metastases.

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CHAPTER 11.

FAMILIAL GYNAECOLOGICAL MALIGNANCIES

5-15% of gynaecological cancers are related to a known pathogenic mutation. The most common are: BRCA1, BRCA2 and Lynch (HNPCC) syndromes. There also exist clinical hereditary cancer syndromes, i.e. where there is no known pathogenic mutation, and the diagnosis is made via clinical history in consultation with a genetic counsellor.

All women with a suggestive family history, or who are closely related to a person with a known pathogenic mutation for one of the hereditary gynaecological cancer syndromes must be referred to a genetic counsellor before any genetic testing is performed. Risk assessment, medical and psychological implications, fertility implications, implications for other family members, life insurance implications and risk-reducing interventions must be discussed.

It is best practice to test the individual with the cancer diagnosis to determine the exact mutation, rather than test for multiple possible mutations in unaffected family members. Once the specific mutation is identified in the affected person, further testing of family members is then both easier and less expensive.

A. AFFECTED INDIVIDUALS WITH NO FAMILY CANCER HISTORY (Perform multi-gene/full gene testing)

- All women with a personal history of high-grade non-mucinous epithelial ovarian/fallopian tube /primary peritoneal cancer regardless of age.
- A personal history of breast cancer before age 40.
- A personal history or triple-negative breast cancer at any age.
- A personal history of both breast and ovarian cancer.

- Recurrent breast cancer in the contralateral breast, especially if the primary cancer was diagnosed before age 50.
- Synchronous endometrial/colorectal cancer before age 50.
- As we start to incorporate molecular profiling of all endometrial cancers, all tumours are subject to MSI/MMR protein testing. Patients with tumours expressing mutations in these proteins should undergo Lynch (HNPCC) syndrome testing.
- In sites not yet integrating MSI/MMR protein testing in endometrial cancers, endometrial cancers in women < 50 years old should all be tested for MMR gene mutations.

B. INDIVIDUALS WITH A FAMILY HISTORY SUGGESTIVE OF A HEREDITARY CANCER SYNDROME (typically require full genetic screening)

1. Based upon family history
   - First-degree relatives with any of the high-risk cancers above.
   - Clustered cancers: multiple members (2–3+) affected by breast, ovarian, colorectal, or endometrial cancers on the same side of a family.
   - Known mutations within a family: any person where a known inherited mutation (like BRCA1/2 or Lynch Syndrome genes) has been identified in a family member.
2. Based upon ancestry (i.e. founder mutations, need only to test for the pre-identified mutation):
   - Ashkenazi Jews.
   - Afrikaner descent.

There is no good quality evidence that supports ovarian cancer screening in high-risk individuals, using modalities such as serum CA-125 levels or 6-monthly pelvic ultrasound.

The UKFOCS study showed no decrease in mortality. False positive screen results lead to unnecessary or premature surgical intervention affecting childbearing potential and quality of life.

In women who choose not to undergo risk-reducing bilateral salpingo-oophorectomy (RRBSO) at the recommended age, screening using ultrasound and serum CA-125 starting from the recommended age onwards may be considered. However, the benefit hereof remains uncertain.

Prophylaxis/interventions in mutation carriers to reduce risk of gynaecological cancers should begin 5 years before the age of cancer onset of the youngest affected family member, or latest at age 30.

1. Epithelial ovarian/fallopian tube cancer prevention strategies are recommended in women with these mutations: BRCA1/2, RAD51C/D, BRIP1, Lynch syndrome with mutated MLH1, MSH2 or MSH6 genes. (In women with PALB2 mutation, RRBSO is recommended only once post-menopausal)

    a) Medical Intervention
    - "Ever use" of the combined oral contraceptive has been shown to reduce ovarian cancer risk in mutation carriers. Continuous COC use for 5 years affords a 50% risk reduction and the risk reduction increases for every further 5 years of use. Data interrogating the potential of COC-use increasing breast cancer risk is conflicting.

    b) Surgical Intervention:
    - Prophylactic RRBSO in BRCA1/2 mutation carriers offers an 80-90% reduction in ovarian cancer risk, and a variable level of breast cancer risk reduction.

It also offers a 77% reduction in all-cause mortality.

- Women who desire children should be offered consult with a fertility specialist regarding oocyte/embryo.
- The optimal timing of RRBSO is recommended at 35-40 years for BRCA1 carriers; and 40-45 years for BRCA2 carriers.
- Specific laboratory sectioning (SEE-FIM protocol) (cutting at 3 mm sections) must be specified on the laboratory request form of RRBSO specimens.
- Prophylactic salpingectomy and delayed oophorectomy (PSDO) are not recommended outside of a clinical trial.
- In patients who chose PSDO, delaying oophorectomy reduces the benefit offered by optimally timed RRBSO by 1-2%. This increase in ovarian cancer risk must be measured against the benefits of delaying menopause, and against the substantial decrease in all-cause mortality offered by optimally timed RRBSO.
- Hysterectomy at the time of RRBSO should not be recommended, unless other indications for hysterectomy exist.
- There are conflicting opinions on the role of menopause hormonal therapy (MHT) post-RRBSO. MHT in unaffected women may be offered until 45 years old. Longer use beyond 45 years may be considered in women who have undergone risk reducing bilateral mastectomy.
- Consider combining Mirena IUS with oestrogen-only HRT to avoid the need of systemic progesterone. Hysterectomy at the time of RRBSO has been performed as another strategy to avoid the need for combined MHT.
- Following RRBSO, there are no data to support ongoing gynae- cological screening though the risk of developing primary peritoneal cancer remains between 1-3%.

2. Lynch Syndrome (previously known as hereditary non-polyposis colorectal cancer - HNPCC) is characterised by mutations in mismatch repair genes MLH1, MSH2, MSH6 and PMS2. The clinical manifestations of Lynch syndrome include:
    - 30-73% increased lifetime risk of colo-rectal cancer
    - 30-51% increased lifetime risk of endometrial cancer
    - 4-15% increased lifetime risk of ovarian cancer
    - Plus to a lesser extent: gastric, small bowel, urinary tract, pancreas, brain and cutaneous gland tumours.

- The risk of endometrial cancer appears higher in MLH1, MSH2 and MSH6 mutation carriers.
- Counsel patients early about warning signs, earlier child bearing and explain future risk-reducing (RR) strategies.
- Surveillance methods for gynaecological cancers in Lynch carriers remain controversial and are not supported by evidence.
- Offer RR hysterectomy for Lynch carriers at completion of childbearing, or at 35 years for MLH1 and MSH2 carriers, and at 40 years for MSH6 mutation carriers.
- The role of additional BSO at hysterectomy must be discussed as Lynch mutation carriers have a 4-15% risk of developing ovarian cancer.
- Menopausal hormonal therapy is acceptable following surgical menopause.
- Mirena-IUS and healthy weight maintenance are recommended, but their value as a RR intervention remains unproven.

- Surveillance is considered acceptable in a patient who declines RR hysterectomy and has been educated on the significance of immediate reporting and investigation of AUB/PMB.
- Invasive screening via 6 monthly/yearly endometrial biopsies may be considered, but rather counselling women with Lynch syndrome to seek immediate assessment where there is AUB/PMB may be more acceptable to the patient and does not alter disease-specific mortality.
- Refer to a gastro-enterologist for colonoscopy-based screening. The starting age and frequency of scopes dependent on the exact gene mutation.

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CHAPTER 12.

FERTILITY SPARING OPTIONS AND GYNAECOLOGICAL CANCER

A. CERVICAL CANCER

- Ensure a realistic evaluation of reproductive potential is completed.
- SCC or usual-type HPV-associated adenocarcinomas are the only tumour histology with reasonable evidence.
- Stage 1A2 – 1B2 always require histological nodal assessment before managing the cervical tumour, while stage 1A1 tumours without LVSI do not require histological assessment of pelvic lymph nodes.
- Stage 1A2 tumours (no LVSI) can be managed with cone biopsy or simple trachelectomy.
- Stage 1B tumours that are ≤ 2 cm are best suited to fertility sparing options and can be managed with radical trachelectomy.
- Tumours between 2 – 4 cm can be considered in select cases.
- Tumours > 4 cm are not suited to fertility sparing options.
- Surgical management of adenocarcinomas requires either excision of the entire endocervical canal, or endocervical curettage to exclude skip lesions.
- Deeply invasive tumours ≥ 10 mm are not suited to fertility sparing.
- Pre-operative MRI is essential in assessing local disease and possible spread to pelvic nodes. There needs to be at least 1 cm of radio-
- logically clear tissue between the upper margin of the tumour and the internal cervical os.
- Where available, intra-operative frozen section is recommended to confirm complete excision margins.

- The safety of neo-adjuvant chemotherapy to avoid radical trachelectomy for tumours between 2 – 4 cm remains undetermined; trials are ongoing.
- Endocrine ovarian function may be preserved in more advanced cases by surgical ovarian transposition during radical surgery or before planned radiotherapy. There is a wide variation in success rates of preserving ovarian function, ranging between 50 and 90%.
- Completion surgery in the absence of disease once childbearing is complete is not mandatory.

B. ENDOMETRIAL CANCER

5% of endometrial cancers occur in women younger than 40 years of age. There are a number of RCTs of reasonable quality that support combined hormonal treatment with oral/local progestins with or without hysteroscopic tumour resection to preserve fertility. The highest complete response rates and live birth rates seem to be supported where hysteroscopic tumour resection is combined with progestin therapy. GnRH analogues should not be considered first-line.

- Ensure a realistic evaluation of reproductive potential is completed.
- Essential to have a fertility specialist at MDT discussion with adequate counselling balancing fertility against oncological safety.
- Only women with well-differentiated (grade 1) endometrioid carcinoma without myometrial invasion or extra-uterine spread should be considered for fertility sparing options.

- Lynch-syndrome related endometrial cancers must be discussed case-by-case. Exclude/prevent other Lynch-associated tumours. Lynch-related endometrial cancers have a different molecular tumour pathogenesis and there are no RCTs to support fertility sparing options in this group, therefore application of the rules assigned to sporadic G1 EEC is not possible.
- Hysteroscopic biopsy yields better specimen quality than blind sampling, therefore avoiding under-grading. Specialist gynaecological pathologist review of all histology is essential.
- Expert transvaginal ultrasonography or MRI is essential to exclude myometrial invasion and radiological suggestion of extra-uterine/pelvic nodal spread.
- Molecular profiling is essential in all endometrial tumours. Tumours with mutations in p53 or MMR genes are not suited to fertility-sparing options.
- Treatment is 3 – 12 months with oral progestin therapy and/or a levonorgestrel-releasing intrauterine system before commencing fertility treatment or conception.
- Endometrial sampling to assess treatment response every 3-6 months. Complete response is defined as 2 normal biopsies 3 months apart before attempting conception.
- Re-evaluate case-by-case if no response by 6 months and abandon if no on only partial response by 15 months.
- Completion hysterectomy is recommended once fertility is no longer desired. Oophorectomy to be individualised.

C. OVARIAN CANCER

General guidelines

- Ensure there is a fertility specialist in all MDT discussions.
- The primary aim of fertility sparing surgery (FSS) is to preserve the uterus and at least one ovary.
- Ovarian stimulation cycles and egg/embryo preservation should be considered if surgical preservation of an ovary is not possible.
- If BSO is indicated at surgery, the uterus can be preserved provided the endometrium is benign following hysteroscopic evaluation, and that the serosa is unaffected.
- Minimally invasive surgery is suitable in selected cases.

1. Borderline tumours:

- Unilateral Borderline Ovarian Tumour (BOT): offer unilateral salpingo-oophorectomy (USO) or cystectomy.
  Bilateral BOT: USO with contralateral ovarian cystectomy.
  Pelvic washings, multiple peritoneal biopsies, omental biopsy or omentectomy, and biopsy of any visible peritoneal lesions should be performed (complete surgical staging).
- Review histology at multidisciplinary meeting to ensure that an invasive tumour is not missed.
- The presence of micro-invasion in the ovarian tumour does not preclude fertility sparing options.
- The presence of non-invasive peritoneal/omental implants in BOT's do not preclude fertility sparing options.
- Completion surgery once childbearing is complete remains controversial for BOT's.

2. Malignant epithelial tumours

- Seven % of epithelial ovarian cancers (EOC) occur in women below 40 years of age, and 1% occur in women below 30 years.
- Generally, only stages 1A (grade 1 & 2) and 1C1 (grade 1 & 2) are eligible for fertility sparing surgery (FSS).
- FSS is not appropriate in the presence of malignant washings/ascites.
- Complete surgical staging (as previously described) remains paramount, even while preserving the uterus and one ovary. Ipsilateral pelvic ± para-aortic lymphadenectomy is recommended to exclude occult lymphatic spread when FSS is performed.
- FSS in stage 1C2 low-grade serous or low-grade endometrioid can be considered in selected cases but recurrence rates are higher.
- FSS for early-stage HG serous or clear cell carcinomas is not recommended.
- Routine completion surgery is not recommended, except in patients with a hereditary predisposition to ovarian cancer.

3. Non-epithelial tumours:

- Most patients with germ cell and sex-cord-stromal tumours have good outcomes with surgery alone or a combination of surgery and platinum-based chemotherapy.
- Surgery for non-epithelial ovarian cancer should be individualized, but fertility sparing surgery remains a realistic goal in most cases. This applies especially to germ cell tumours due to their excellent chemo-sensitivity.
- The only Sertoli-Leydig cell tumour that is eligible for FSS is a G1 or G2 stage 1A or 1C1.

- Even with FSS, complete surgical staging should still be performed.
- Management after final histological diagnosis will depend on the particular histological type.
- Where there is visible bilateral ovarian involvement at time of surgery, perform a USO and then attempt ovarian cystectomy or partial oophorectomy/tumour shaving of the less-affected ovary.

D. OVARIAN PRESERVATION IN NON-GYNAECOLOGICAL MALIGNANCIES

Surgery, systemic chemotherapy and radiotherapy for non-gynaecological malignancies may compromise ovarian function. The following options can be considered:

- Historically, cryopreservation of oocytes had poor outcomes, but modern vitrification techniques are leading to improved live birth rates from frozen oocytes, negating the need to freeze embryos instead.
- Must be safe for oncological treatment to be delayed.
- Oocyte stimulation cycles have not been shown to worsen oncological outcomes, specifically in breast cancer.
- Adoption, surrogacy and donor oocytes should always be discussed.

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CHAPTER 13.

MINIMALLY INVASIVE SURGERY (MIS) IN GYNAECOLOGIC ONCOLOGY

MIS includes conventional laparoscopy and robotic surgery.

The aim of laparoscopy in oncology is to obtain equivalent survival and recurrence outcomes to laparotomy without compromising staging or resection quality, while improving peri-operative recovery.

Compared with open surgery, MIS usually achieves:

- Less blood loss and post-operative pain, fewer wound complications, shorter length of hospital stay, faster return to normal function.
- Similar lymph node yield for staging procedures when performed by experienced teams.
- Better quality sentinel lymph node mapping.

Oncological risks to consider:

- Tumour manipulation/spillage (especially where uterine manipulators, intracorporeal colpotomy, or morcellation are involved).
- CO2 pneumoperitoneum and potential tumour cell dissemination.
- Port site metastases.

A. MIS in endometrial cancer:

- MIS has become the gold standard for the management of low-risk and high-risk endometrial cancer, including total hysterectomy (TH) / bilateral salpingo-oophorectomy (BSO) and Lymph Node (LN) assessment.

- MIS are preferred in the appropriate patient due to a lower rate of surgical site infection, transfusion, venous thromboembolism, decreased hospital stay, and lower cost of care, without compromise in oncological outcome.
- Clinical trials (including LAP2) demonstrated that approximately 25% of patients needed conversion to laparotomy because of poor visibility, metastatic cancer, bleeding, increased age, or increased body mass index (BMI).
- Robotic surgery in experienced hands, may result in less frequent conversion to laparotomy when compared to laparoscopy, especially for patients who have an increased BMI and may be safer in patients at higher anaesthetic risk, while resulting in comparable perioperative and oncological outcomes.
- Any intraperitoneal tumour spillage, including tumour rupture or morcellation (including in a bag), should be avoided.
- If vaginal extraction risks uterine rupture, other measures should be taken (mini laparotomy or use of endobag).
- A preoperative or intraoperative finding of metastatic spread outside the uterus (excluding lymph node metastases) is a relative contraindication for minimally invasive surgery.

B. MIS in cervical cancer:

Stages: 1A1/1A2:

- MIS route is acceptable.
- Oncological outcomes are the same as non--MIS surgery.

Stages: 1B1/1B2/IIA1:

- Minimally invasive radical hysterectomy is associated with poorer oncological outcomes (reduced disease free survival and overall survival) than open abdominal radical hysterectomy and is not currently recommended.

C. MIS in Ovarian Cancer:

- Specific risks include:
  - ► Potential rupture of the ovarian capsule with spillage.
  - ► Risk of port site metastases, more with larger masses and concomitant ascites.
  - ► Difficulty in the manual assessment and palpation of lymph nodes.
- MIS in ovarian cancer requires a high level of expertise and should only be performed in high-volume oncological centres with adequate experience in advanced surgical procedures.
- In early-stage disease, MIS to achieve the surgical goals may be considered in selected patients if performed by an experienced gynaecologic oncologist.
- MIS may be used for interval debulking surgery (IDS), provided that optimal debulking can be achieved (e.g. assessment with the Fagotti score).
- If the patient cannot be optimally debulked using MIS, either in the primary debulking surgery (PDS) or interval debulking surgery setting, then they should be converted to an open procedure
- In selected patients with advanced-stage disease, MIS may be used to assess whether optimal cytoreduction is likely to be achieved by PDS. If PDS is not possible then a histological diagnosis can be made followed by neoadjuvant chemotherapy and delayed primary surgery.

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CHAPTER 14

PALLIATIVE CARE

Palliative Care in Gynecologic Oncology. Quick-Reference & Protocol Guide: Palliative Care in Gynecologic Oncology

When to Refer to Palliative Care

- Stage III/IV gynecologic cancer.
- Poor response to treatment.
- Uncontrolled symptoms: Pain ≥ 5/10, fatigue, nausea, dyspnoea, constipation, bleeding.
- Psychological distress (patient or caregiver).
- Functional decline (ECOG ≥ 2).
- Need for advance care planning or end-of-life discussions.

Tips for Using SPIKES effectively:

Letter	Step	Description
S	**Setting up the interview**	Prepare the environment and yourself.
P	**Perception**	Assess the patient's understanding.
I	**Invitation**	Ask how much the patient wants to know.
K	**Knowledge**	Share information in small, clear chunks.
E	**Empathy/Emotions**	Respond empathetically to emotions.
S	**Strategy and Summary**	Outline next steps and ensure understanding.

Tips for Using SPIKES effectively:

- **Practice active listening** and let silence do some of the work.
- **Avoid false reassurance.**
- **Normalize reactions:** Fear, anger, denial are common.
- **Document the discussion** for continuity of care.

Table 2 Symptom Management Snapshot

Symptom	First-line Management
Pain	WHO ladder: 1. Paracetamol/NSAIDs 2. Weak opioids (tramadol) 3. Strong opioids/oral morphine.
Nausea/Vomiting	Metoclopramide; haloperidol or ondansetron if severe.
Constipation	Senna + docusate; lactulose; rectal measures if needed.
Dyspnea	Low-dose oral morphine; fan to face; oxygen if hypoxic.
Fatigue	Energy conservation, naps, dexamethasone if tumor-related.
Bleeding	Tranexamic acid; vaginal packing; palliative radiation if feasible.
Vaginal discharge/ foul odor	Vaginal douche, metronidazole gel or systemic.
Anorexia/cachexia	Dietician consultation Appetite stimulants (e.g., megestrol acetate or corticosteroids) and treat reversible causes of anorexia including xerostomia, nausea, mucositis, and depression. It may improve intake and reduce the rate of weight loss.
Delirium	Evaluate severity and cause (hypo or hyperactive). Screen for and treat underlying reversible causes, infections, metabolic e.g., hypercalcaemia, medication E.g., opiate toxicity, brain metastases should be excluded.

Symptom	First-line Management
Delirium	Patient nursed in a quiet environment. Sedation may require haloperidol, benzodiazepines oral/IV/IM/sub-cutaneous route.
Bone Metastases	Bisphosphonates e.g., zoledronic acid reduce the morbidity of metastatic bone disease by decreasing skeletal related events such as fractures. Consider palliative radiotherapy to symptomatic area. Recent data has shown that 3 monthly dosing is as effective as monthly bisphosphonates.

Palliative Care Protocol Template

1. **Initial Palliative Assessment:**
- Symptom review.
- Psychosocial screening.
- Spiritual needs.
- Caregiver strain.
- Preferred site of care (home, hospice, hospital).

2. **Care Plan:**
- Symptom control goals (e.g., pain < 3/10).
- Medications from WHO list.
- Identify caregiver.
- Regular reassessments (every 2–4 weeks).

3. **Team Involvement:**
- Oncologist: directs care.
- Nurse: symptom tracking, patient education.
- Social worker: financial/emotional support.
- Spiritual care: if available.
- Palliative specialist: for complex cases.

4. End-of-Life Planning:

- Advance directives.
- Do not resuscitate discussions.
- Ensure home supply of medication for symptom control.
- Hospice referral when appropriate.

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