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

2009 Edition

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INTRODUCTION

This is the 10th edition of the booklet, “Protocol for Treatment of Gynaecological Malignancies”. For the first time members of gynaecological oncology units of both Groote Schuur Hospital as well as Tygerberg Hospital contributed to the booklet. Moreover radiotherapist in private practice, who are actively involved in the treatment of patients with a gynaecological malignancy also contributed. Judy Whittaker edited the histology section.

It should be remembered that, as with previous editions, this edition represents current views on the treatment of gynaecological cancer and should be used as a guide to staging and treatment and NOT as a comprehensive reference work. It nevertheless will be of value to under- and postgraduate students, interns, registrars in training and practising gynaecologists. This booklet may serve as a guideline to standardize the management of patients with a gynaecologic malignancy.

We are convinced that the interests of our patients are served by a multi-disciplinary approach involving, not only the medical profession, 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 unit and we would urge that patients with gynaecological malignancies be referred to such a unit.

This 10th edition contains for the first time guidelines on the management of familial cancers as well as the management of gynaecological cancer in pregnancy.

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CARCINOMA OF THE VULVA

A. TNM CLASSIFICATION

T Primary tumour.
Tis Pre-invasive carcinoma (carcinoma in situ).
T1 Tumour confined to the vulva and/or perineum, ≤2cm in greatest dimension.
T2 Tumour confined to the vulva and/or perineum, >2cm in greatest dimension.
T3 Tumour of any size with adjacent spread to the urethra and/or vagina and/or the anus.
T4 Tumour of any size infiltrating the bladder mucosa and/or the rectal mucosa including the upper part of the urethral mucosa and/or fixed to the bone.
N Regional lymph nodes.
N0 No nodes palpable.
N1 Unilateral inguinal lymph node metastasis.
N2 Bilateral inguinal lymph node metastases.
M Distant metastasis.
M0 No clinical metastasis.
M1 Distant metastasis (including pelvic lymph node metastasis).

B. FIGO STAGING (CLINICAL AND SURGICAL)

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Stage IA	Lesions ≤ 2cm in size confined to the vulva or perineum with stromal invasion ≤1mm. Nodes are not palpable/no nodal metastases.
Stage IB	Tumour of any size confined to vulva, negative nodes.
Stage II	Tumour confined to the vulva and/or perineum, >2cm in greatest dimension. No nodal metastases.
Stage III	Tumour of any size with: (1) Adjacent spread to the lower urethra and/or vagina or anus, (2) and/or unilateral inguinal lymph node metastases.
Stage IVA	Tumour invades any of the following: (1) Upper urethra, bladder mucosa, rectal mucosa, pelvic bone, (2) and/or bilateral inguinal node metastases.
Stage IVB	Any distant metastasis including pelvic lymph nodes.

C. INVESTIGATIONS

Histological/cytological:

- Diagnostic biopsy.
- Fine-needle aspirate (FNA) of suspicious inguinal nodes.
- Pap smear of cervix.

Radiological:

- CXR.
- X-ray pelvis if bone involvement suspected.
- Ultrasound of abdomen (liver, spleen)

Laboratory:

- FBC, RFT, LFT, VDRL.
- HIV with informed consent.

D. TREATMENT

1. **Superficially invasive**: < 1 mm invasion (<3mm full thickness), wide local excision.
2. **Early disease**: central location - see flow chart 1.
3. **Early disease**: lateral location - see flow chart 2.
4. **Advanced (or recurrent) vulval carcinoma**:
   (a) If nodes are irresectable but primary tumour is resectable, give pelvic radiotherapy after radical vulvectomy. Vulva included in field if excision margins <1cm.
   (b) Irresectable primary tumour is treated with concomitant chemo-radiotherapy. If nodes are clinically negative, consider groin node dissection first. No inguinal or pelvic radiotherapy (RT) is necessary if nodes are histologically not involved. Large mobile malignant nodes (positive cytology on FNA) may be debulked by simple resection prior to radiotherapy. ***Individualisation*** (according to age, obesity etc) is mandatory under these circumstances. Nodal areas, where necessary, are included in the radiation fields.
   (c) If both vulva and nodes are irresectable, treat with concomitant chemo-radiotherapy first.
   Chemotherapy including Mitomycin C and 5-Fluorouracil (See page 48).

Radiotherapy:
Commences on day 1, at least 1 hour after chemotherapy has started. The target volume is individualised but includes the vulva, groin and pelvic nodes. A pair of AP-PA parallel-opposed portals is used (e.g. 20 x 20 cm with appropriate shielding). 2.5 Gy daily, 5 times per week for 2 weeks is administered (25 Gy midplane dose).
Re-assess 2 weeks later to allow settling of perineal skin reaction and regression of tumour. If nodal disease is not present, and sufficient regression of the primary tumour has occurred, wide local excision is performed. If regression of primary tumour is insufficient, repeat chemo-radiation but reduce RT to 20Gy in 10 fractions. Reassess 2-3 weeks later. Every attempt should be made to excise residual tumour. If regression is complete, biopsy of tumour bed. If surgery is not possible, or extensive residual nodal disease is present, small volume booster doses of 15-20 Gy are applied to any residual tumour (for chemotherapy see page 48)

An alternative approach to fractionation would be: 45 Gy in 25 fractions to the larger volume and a booster dose of 15 – 20 Gy in 1.8 – 2 Gy fractions as appropriate over 6 week period. (chemotherapy see page 48)

(d) Patients with advanced disease and poor Performance Status – palliative RT is given (30 Gy in 10 fractions).

POINTS TO REMEMBER

- In planning the management of individual patients, adopt a multi-disciplinary approach consulting with plastic surgeons, colorectal surgeons and urologists.
- If excision margins of the vulval primary are inadequate (<1cm), re-operation is an option.
- Frozen section of inguinal nodes, if suspicious, may be useful to decide whether immediate contralateral node dissection should be performed in lateral tumours.
- Steps for inguinal node dissection: remove superficial nodes; open fascia into femoral triangle, palpate and remove nodes medial to the femoral vein.
- DVT- and antibiotic prophylaxis are mandatory.
- Drainage of the inguinal area after surgery is essential.
- If adenocarcinoma of vulva, look for underlying primary.
- Melanoma – treat as for melanoma elsewhere.
- Basal cell carcinoma – wide local excision.
- Paget's disease of the vulva must prompt search for underlying cancer. Excision margins should be > 2 cms of disease-free tissue. For extensive Paget's disease

- Chemo-radiation is an option
- Where adequately trained, sentinel node dissection should be considered.

Key References:

Van der Velden J, Hacker NF. Prognostic factors in squamous cell cancer of the vulva and the implications for treatment. Curr Opin Obstet Gynecol 8 (1): 3-7 (1996).

Tyring, S.K. Vulvar squamous cell carcinoma: guidelines for early diagnosis and treatment. Am J Gyn Obstet 189 (3 suppl) S 17-23 (2003).

Van der Zee A et al, Sentinel node dissection is safe in the treatment of early-tage vulvar cancer. J Clin Oncol 2008;26:884-9.

Brown R.S.D. Radiotherapy for Perianal Paget's Disease. Clin Onc. 2002 14: 272-284.

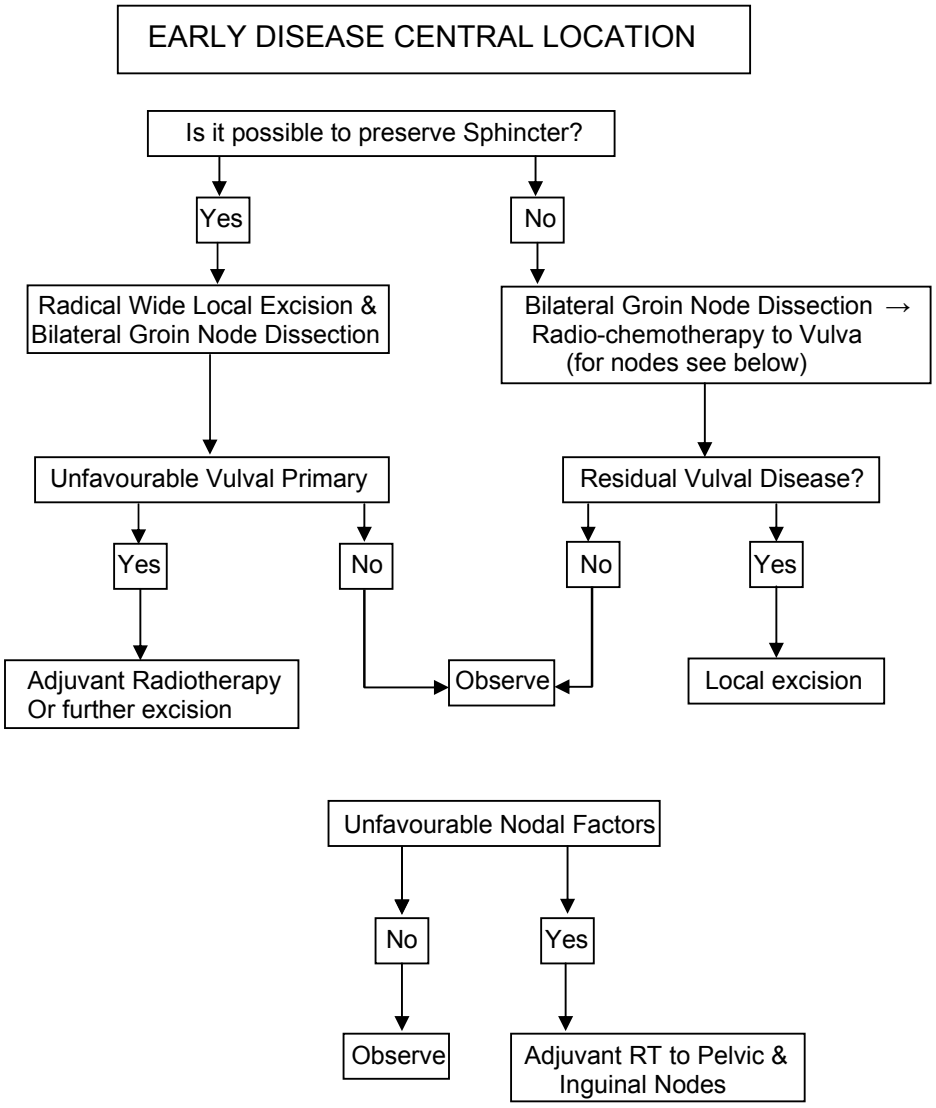
DEFINITIONS FOR FLOWCHART 1 and 2

Central lesion:
Involves a midline structure or is too close to the midline to be cleared by a surgical margin of 1cm.
Lateral lesion:
Excision with a surgical margin of 1cm, which does not encroach on midline structures
Early favourable disease:
Impalpable inguinal LN's or mobile resectable groin nodes and radical excision of vulval lesion can be accomplished without sphincter sacrifice.
Advanced disease:
Suspicious lymph nodes e.g. immobile, matted nodes are present and/or radical excision of the vulval tumour will require sphincter sacrifice.
Unfavourable vulval primary:
Excision margins <1cm free of tumour.
Unfavourable nodal factors:
≥2 nodes positive, or single nodal metastasis >5mm, or extracapsular spread.
Radical wide local excision:
Excision clears the tumour by a margin of at least 1cm in ALL directions and extends down to deep perineal fascia.

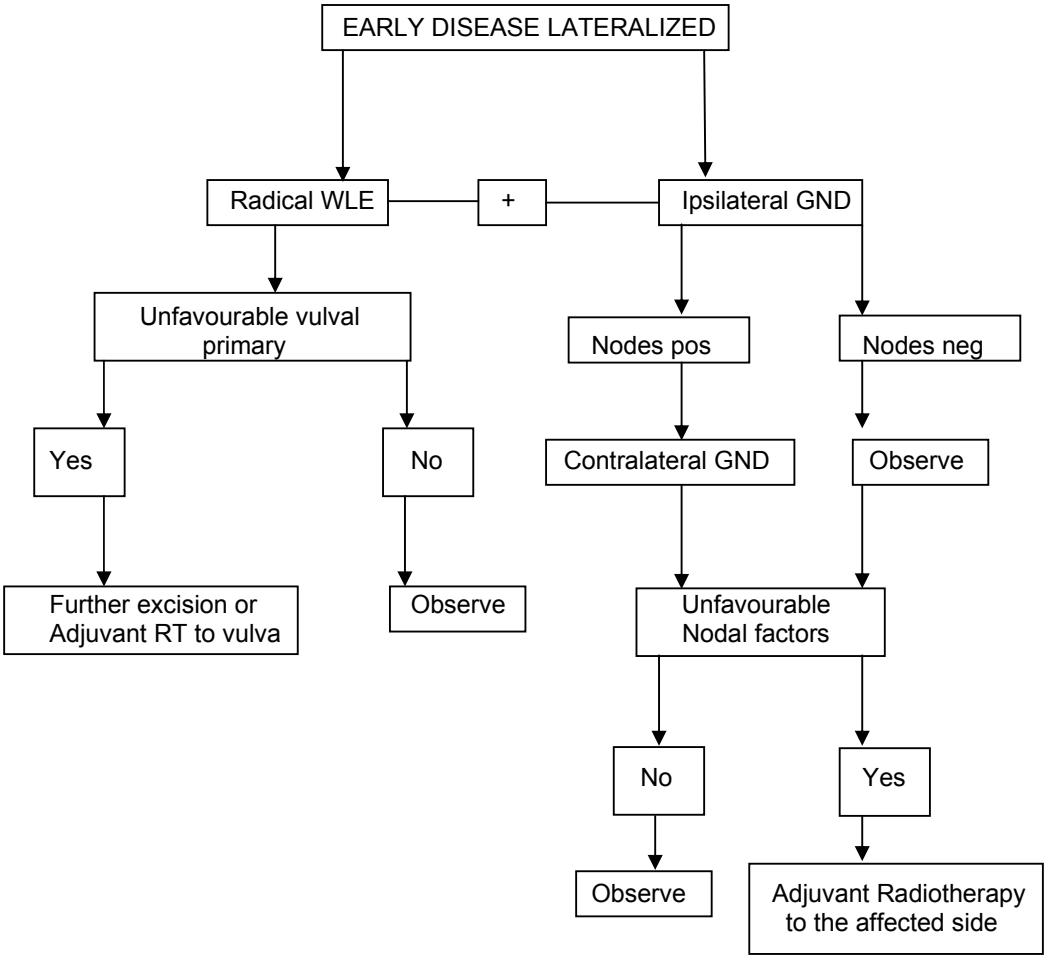
NOTE: Superficial invasion:

- <1mm depth of invasion (or <3mm full thickness) and ≤2cm in diameter.
- Patients with stage IA can be treated with wide local excision only without nodal dissection.

FLOW CHART 1


EARLY DISEASE CENTRAL LOCATION
Is it possible to preserve Sphincter?
Yes
No
Radical Wide Local Excision & Bilateral Groin Node Dissection
Bilateral Groin Node Dissection →
Radio-chemotherapy to Vulva
(for nodes see below)
Unfavourable Vulval Primary
Residual Vulval Disease?
Yes
No
No
Yes
Adjuvant Radiotherapy Or further excision
Observe
Local excision
Unfavourable Nodal Factors
No
Yes
Observe
Adjuvant RT to Pelvic & Inguinal Nodes

FLOW CHART 2



WLE: Wide local excision

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 Ca Cervix.

C. TREATMENT

1. **Stage I**:
   Radical Wide Local excision with or without vaginal reconstruction.
   Aim for margin of 5mm of disease-free tissue in all directions.
   - If on pathology specimen ≤1mm invasion – no further treatment.
   - If >1mm invasion adjuvant intracavitary brachytherapy.
2. **Stage II + III**:
   Concurrent chemo-radiation + intracavitary.
   brachytherapy (pelvic and/or to inguinal nodes).

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

Key Reference

Grigsby, P.W. Vaginal cancer. Curr Treat Options Oncol 2002 3 (2): 25-30.

Frank SJ et al. Definitive radiation therapy for squamous cell carcinoma of the vagina. Int J Radiation Oncol and Biol Physics. 2005, 62:138 - 147

CARCINOMA OF THE CERVIX

A. FIGO STAGING (CLINICAL)
(Stage I and II modified 1994, introduced 1996)

Stage 0 Carcinoma in situ, intra-epithelial carcinoma

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

- IA Invasive cancer identified only microscopically. (All gross lesions even with superficial invasion are Stage IB cancers) Invasion is limited to measured stromal invasion with a maximum depth of 5mm* and no wider than 7mm.
- IA1 Measured invasion of stroma no greater than 3mm in depth and no wider than 7mm.
- IA2 Measured invasion of stroma greater than 3mm and no greater than 5mm in depth and no wider than 7mm.

Stage IB Clinical lesions confined to the cervix or preclinical lesions greater than stage IA.

- IB1 Clinical lesions no greater than 4cm in size.
- IB2 Clinical lesions greater than 4cm in size.

Stage II The carcinoma extends beyond the cervix, but has not extended onto the pelvic wall. The carcinoma involves the vagina, but not as far as the lower third.

- IIA Involvement of up to the upper two thirds of the vagina. No obvious parametrial involvement.
- IIB Obvious parametrial involvement but not onto the pelvic sidewall.

Stage III The carcinoma has extended onto the pelvic sidewall. On rectal examination, there is no cancer free space between the tumour and pelvic sidewall. The tumour involves the lower third of the vagina. All cases of hydronephrosis or non-functioning kidney should be included unless they are known to be due to other causes.

- IIIA Involvement of the lower vagina but no extension onto pelvic sidewall.
- IIIB Extension onto the pelvic sidewall, or hydronephrosis/ non-functioning kidney.

Stage IV The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder and/or rectum.

- IVA Spread to adjacent pelvic organs.
- IVB Spread to distant organs.

(*The depth of invasion should not be more than 5mm taken from the base of the epithelium, either surface of glandular, from which it originates. Vascular space invasion should not alter the staging.)

B. ADDITIONAL NOTES ON STAGING OF CARCINOMA OF THE CERVIX

Stage IA carcinoma should include minimal microscopically evident stromal invasion as well as small cancerous tumour of measurable size. The diagnosis of stages IA1 and IA2 should be based on microscopic examination of removed tissue, preferably a cone biopsy, which must include the entire lesion. The upper limit of Stage IA2 is given by measurement of the 2 largest dimensions in any given section.

As a rule, it is impossible to estimate clinically whether a cancer of the cervix has extended to the corpus. Extension to the corpus should therefore be disregarded.

A patient with a growth fixed to the pelvic wall 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 case should be placed in stage IIIB only if the parametrium is nodular on the pelvic wall or if the growth extends to the pelvic sidewall.

The presence of bullous oedema of the bladder mucosa should not permit a case to be allotted to Stage IV. Malignant cells in cytological washings from the bladder require further examination and biopsy of the bladder.

If there is doubt of the staging an examination under anaesthetic maybe appropriate.

The clinical stage must under no circumstances be changed on the basis of subsequent findings.

C. INVESTIGATIONS

Biopsy

Colposcopy: Stage IA.

Cystoscopy: Only for stages II, III, IV. Biopsy suspicious lesions

Radiological:
- X-ray chest, abdominal ultrasound (with special reference to renal tract and liver)
- Ultrasound/intravenous pyelogram (in selected cases),
- Selected skeletal X-Rays and/or bone scan where indicated (clinical suspicion skeletal metastases) ..
- MRI/CT scans optional for early stage disease.
- CT assessment of pelvic/para-aortic nodal areas in stage IB2 or higher scheduled for curative chemo-radiotherapy.

Consider FNAB if questionable findings.

Laboratory: FBC, LFT, RFT and VDRL. HIV with informed consent.

D. TREATMENT

(Note: Radiotherapy with curative intent is administered concurrently with weekly Cisplatinum (See page 48).

Stage IA:

Squamous carcinoma:

(a) Stage IA1 (≤3mm) – options:

- Conization only, provided cone margins are negative, no vascular/lymphatic invasion, wishing to preserve fertility.
- Total hysterectomy (abdominal/vaginal/laparoscopic) provided cone margins negative and no vascular/lymphatic invasion.
- TAH + Pelvic Lymphadenectomy (PL) if vascular/lymphatic invasion present.
- Radical hysterectomy + PL if cone margins (perceived to be stage IB1) are involved with cancer.
- Intracavitary brachytherapy if not surgical candidate.

(b) Stage IA2 (>3 mm, ≤5mm) – options:

- Total hysterectomy (abdominal/vaginal/laparoscopic) + PL if cone margins clear and no vascular/lymphatic invasion.
- Radical hysterectomy + PL if cone margins (perceived to be stage IB1) are involved with cancer.
- Radical trachelectomy (+ Shirodkar suture) + PL where preservation of fertility is desired.
- Chemo-radiation if not surgical candidate.

Adenocarcinoma:

- Where depth of invasion can be accurately assessed, treatment should be the same as for squamous carcinoma. Where in doubt, radical hysterectomy + PL. (Bilateral salpingo-oophorectomy may be an option)

Stage IB:

(a) Stage IB1 (≤ 4cm):

- Radical hysterectomy + PL. Individualise for age, obesity and co-existing medical conditions.
  - Continue surgery if pelvic or limited para-aortic nodes enlarged but resectable.
  - Discontinue hysterectomy if extra-cervical extension could compromise resection lines but remove enlarged resectable nodes.
  - Discontinue surgery if multiple enlarged para-aortic nodes, or irresectable pelvic nodes.
- Radical trachelectomy (+ Shirodkar suture) + PL for tumours ≤ 2cm where preservation of fertility is desired.

- Chemo-radiation + intracavitary brachytherapy if medically unfit for surgery.

(b) Stage IB2 (>4cm):
- Chemo-radiation + intracavitary brachytherapy.
- Radical hysterectomy and PLND maybe an option in selected cases
- Consider salvage hysterectomy if persistent central tumour can be histologically demonstrated 2-3 months post-treatment.

Stage II:

(a) Stage IIA:
- Radical hysterectomy + PL if tumour ≤ 4cm and minimal involvement of upper vagina.
- Chemo-radiation + intracavitary brachytherapy if medically unfit or tumour > 4cm or extensive vaginal involvement.

(b) Stage IIB:
- Chemo-radiation + intracavitary brachytherapy.

Indications for post-operative chemo-radiation:
- Positive pelvic node(s).
- Resection lines involved or <5mm.
- Parametrial invasion.
- Unexpected histological finding of cancer after hysterectomy (except in superficially invasive cancers >3 mm and ≤5mm, adequate resection margins and no vascular invasion – consider PL).
- Patients at high risk for central recurrence after radical surgery and negative lymph nodes consider for adjuvant chemo-radiotherapy if 2 out 3 of the following are present:
  - Deeply (> 10mm) invasive tumours.
  - 4cm in diameter.
  - LVSI positive.

Stage III:
- Chemo-radiation + intracavitary brachytherapy.
- Palliative radiotherapy should be considered:
  Massive tumours with bilateral hydronephrosis, severe wasting/poor performance status, or patients with life threatening co-morbid conditions – short course palliative RT to control symptoms.

Stage IV:

(a) Stage IVA:
- Fit patients with low volume tumour – a full course of chemo- radiation + intracavitary brachytherapy is given.
- The majority of patients are given, to control symptoms, palliative radiotherapy and/or surgical diversion where indicated (urinary diversion with ileal conduit or de-functioning loop colostomy).

(b) Stage IVB:
- Palliative radiotherapy and/or trial of chemotherapy to pelvis and/or symptomatic metastatic sites.

E. 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.

F. CARCINOMA OF THE CERVIX IN ASSOCIATION WITH PREGNANCY

See page 35.

Key references

Nag S, Erickson B et al. The American Brachytherapy Society recommendations for high-dose-rate brachytherapy for carcinoma of the cervix. Int J Radiat Oncol Biol Phys 2000 48: 201 - 208.

Allen D. and Narayan K. Managing advanced-stage cervical cancer Best Pract Res Clin Obstet Gynaecol 2005 19(4): 591 - 609.

Rotman M et al. A phase III randomized trial of postoperative pelvic irradiation in Stage IB cervical carcinoma with poor prognostic features: follow-up of a Gynecologic Oncology Group study. Int J Radiat Oncol Biol Phys 2006 May 1; 65(1): 169-176.

Rose PG et al. Long-term follow-up of a randomized trial comparing concurrent single agent cisplatin, cisplatin-based combination chemotherapy, or hydroxyurea during pelvic irradiation for locally advanced cervical cancer: a Gynecologic Oncology Group Study J Clin Onc 2007 Jul 1; 25 (19): 2804-2810.

Tierney, Vale C, Symonds P. Concomitant and neoadjuvant chemotherapy for cervical cancer. Clin Onc 2008 20: 401 – 416.

CARCINOMA OF THE UTERINE CORPUS

A. FIGO STAGING (SURGICAL)

1. Stage

IA Grade 1,2,3 Tumour limited to endometrium.
IB Grade 1,2,3 Invasion to 1/2 myometrium.
IC Grade 1,2,3 Invasion to > 1/2 myometrium.
IIA Grade 1,2,3 Endocervical glandular involvement only.
IIB Grade 1,2,3 Cervical stromal invasion.
IIIA Grade 1,2,3 Tumour invades serosa and/or adnexae and/or positive peritoneal cytology.
IIIB Grade 1,2,3 Vaginal metastases.
IIIC Grade 1,2,3 Metastases to pelvic and/or para-aortic lymph nodes.
IVA Grade 1,2,3 Tumour invasion of bladder and/or bowel mucosa.
IVB Distant metastases including intra-abdominal and/or inguinal lymph nodes.

2. Histopathology

FIGO grading cases of carcinoma of the corpus should be grouped with regard to the degree of differentiation of the adenocarcinoma as follows:

G1 5% or less of a non-squamous or non-morular solid growth pattern.
G2 6-50% of a non-squamous or non-morular solid growth pattern.
G3 More than 50% of a non-squamous or non-morular solid growth pattern.

Notes on pathological grading:

(a) Notable nuclear atypia, inappropriate for the architectural grade, raises the grade of a grade I or grade II tumour by one.
(b) In serous adenocarcinoma, clear-cell adenocarcinoma and squamous-cell carcinoma, nuclear grading takes precedence.
(c) Adenocarcinoma with squamous differentiation is graded according to the nuclear grade of the glandular component.

3. Rules related to staging.

Endometrial cancer is surgically staged. A small number of patients with endometrial cancer who will be treated with primary radiation therapy should be clinically staged (FIGO 1971).

B. INVESTIGATIONS

Histological diagnosis should be made by:
Sampling of the endometrium.
Radiological: X-ray chest.
Ultrasound, or where available MRI, of abdomen and pelvis.

Laboratory: FBC, LFT, RFT, baseline Ca125 and random glucose.

C. TREATMENT

1. Surgical: (see flow diagram)

- Laparotomy.
- POD washings for cytological examination.
- Careful exploration of abdominal cavity.
- If tumour resectable: extra-fascial total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH, BSO) & where indicated pelvic lymphadenectomy (PL), including common iliac nodes.
- Pelvic lymphadenectomy – Indications:
  - High risk factors preoperatively :
    - Grade 3, with or without myometrial invasion.
    - Type of histology (UPSC-Clear cell carcinoma).
    - Stage II disease.

  Indications for Frozen Section:
  - Pre-operative complex atypical hyperplasia.
  - Grades 1 and 2 adenocarcinoma.
  - Pathologist to assess (frozen section) histological type, grade, depth of myometrial invasion, and cervical involvement. If the frozen section indicates more than 50% myometrial invasion, grade 3 or cervical stromal involvement, proceed to pelvic lymphadenectomy.

- Omentectomy is recommended in patients with grade 3 disease and with clear cell or UPSC tumours.
- Locally advanced stage disease: cytoreductive surgery including TAH-BSO should be attempted.
- Removal of bulky lymph nodes should be attempted.

Special circumstances

- Simple vaginal hysterectomy in medically compromised and/or obese patients may be considered, followed by radiation if indicated.
- Laparoscopic assisted vaginal hysterectomy (LAVH) and BSO with or without pelvic lymphadenectomy may be considered in selected patients.

2. Adjuvant treatment

After histological evaluation of the uterus and adnexae (and lymph nodes) with respect to size of the tumour, depth of myometrial invasion, grade of differentiation, angiolymphatic invasion, cervical involvement and adnexal involvement, proceed with adjuvant treatment where indicated.

Stages I & II:

- High risk stage I and stage II endometrial endometrioid carcinoma with no pelvic nodal involvement will receive postoperative vaginal vault brachytherapy (4 - 6 weeks after operation). Follow up 3 monthly x 1 year, then 6 monthly x 2 years.
- High risk stages I and stage II endometrial carcinoma but no pelvic lymphadenectomy done; postoperative whole pelvic radiotherapy + vaginal vault brachytherapy.

Stage III:

- Whole pelvic irradiation.
- Consider chemotherapy in selected case prior to radiotherapy.
- For Stage IIIC consider extended field irradiation.
- Consider additional brachytherapy in case of cervical involvement.

Stage IV:

Individualise, e.g. chemotherapy, hormonal (medroxy-progesterone acetate), palliative radiotherapy, symptomatic treatment.

D. Recurrent Disease

- Consider surgery in selected cases
- Salvage whole pelvis radiotherapy if no previous external beam given and if recurrence confirmed and confined to the pelvis
- Chemotherapy or hormonal therapy may have a role to play

E. PATIENTS DEEMED MEDICALLY UNFIT FOR SURGERY

Stage I-IV:

- Non-obese, reasonable prognosis from co-morbid condition: whole pelvis radiotherapy plus intracavitary brachytherapy (as for carcinoma of the cervix).
- Elderly, obese etc: Intracavitary brachytherapy only.

F. UTERINE PAPILLARY SEROUS CARCINOMA AND CLEAR CELL CARCINOMA.

Stages I & II:

- Mid-line vertical incision.
- TAH-BSO-Omentectomy-pelvic lymphadenectomy.
- If stage IB, IC, IIA, IIB, vaginal vault brachytherapy.
- Platinum-based chemotherapy for all stages (as for ovarian cancer).
- If only TAH-BSO (No surgical staging) individualise adjuvant treatment.

Stage III:

Surgery as in stage I & II and adjuvant platinum based chemotherapy (6 cycles), followed by pelvic radiotherapy. (See page 47).

Stage IV:

Debulking surgery followed by chemotherapy where appropriate.
(See page 47).

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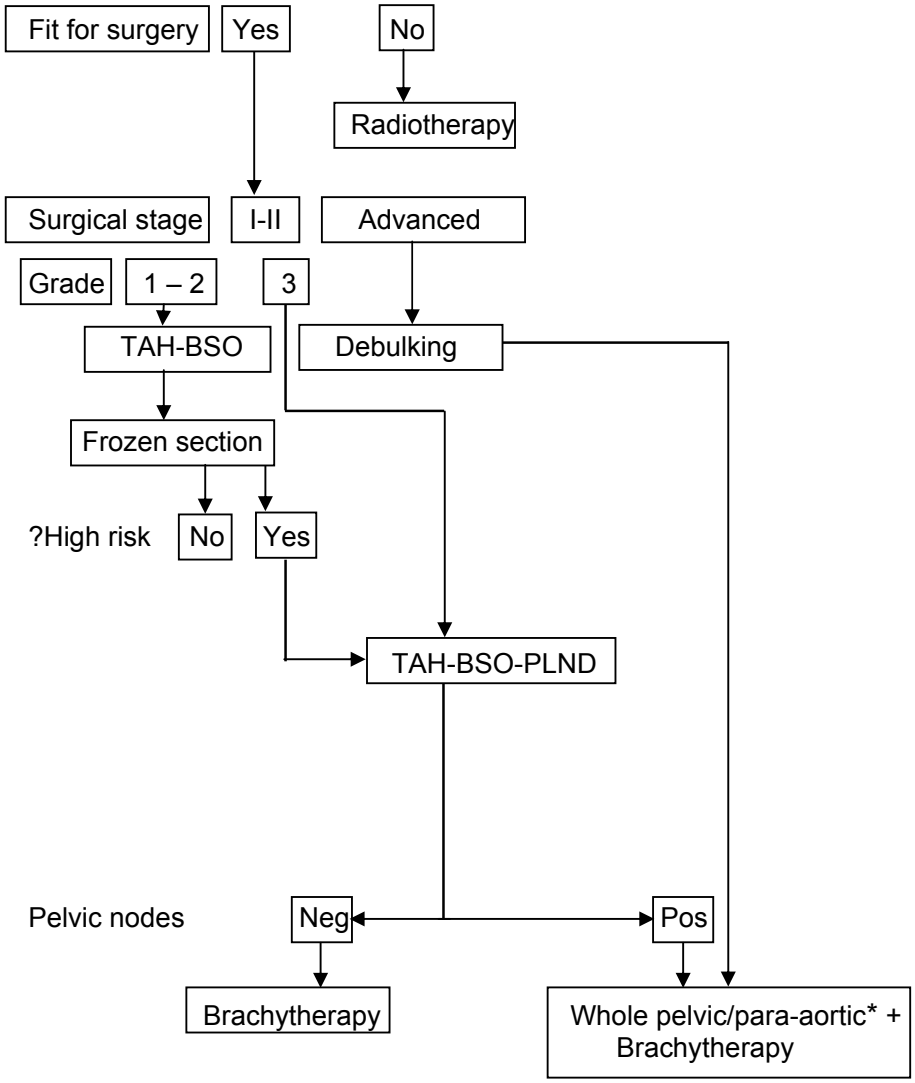
Therapeutic strategies in patients with endometrial cancer



* Include para-aortic nodal stations if 2 or more external iliac nodes and/or common iliac nodes are involved

TAH: Total Abdominal Hysterectomy
BSO: Bilateral Salpingo-Oophorectomy
PLND: Pelvic Lymph Node Dissection (Incl. Common Iliac nodal group)

G. OTHER UTERINE MALIGNANCIES

a. Leiomyosarcoma.

b. Endometrial stromal sarcoma.

c. Carcinosarcoma.

1. Investigations:

- CXR, CT chest, if indicated.
- Ultrasound, or, if available, MRI of abdomen and pelvis.
- FBC, LFT, RFT.

2. Treatment

- Laparotomy; careful exploration of abdominal cavity.
- TAH, BSO + Pouch of Douglas washings (upstaging 12-40%).
- Full pelvic lymphadenectomy only for carcinosarcoma (MMMT). (Leiomysarcoma – Risk of lymph node involvement close to 0% if confined to uterus only).
- Resection of all pelvic tumour where possible.
- Postoperative management:
  a. Leiomyosarcoma:
     - Low risk (<10 mitoses/10 HPF, no residual pelvic tumour): follow-up only.
     - High risk (≥10 mitoses/10 HPF, residual pelvic tumour, metastases): consider chemotherapy (Adriamycin) x 4 cycles (see page 48) followed by radiation therapy to whole pelvis or localised metastases.
     - Incompletely excised: Consider chemotherapy + radiation therapy.

  b. Endometrial stromal sarcoma:
     - Long-term follow-up.
     - In case of incomplete resection and recurrence: consider high dose MPA only.

  c. Carcinosarcoma (previously known as MMMT):
     - Stage I – II (Node negative): Chemotherapy (see page 47) followed by vault brachytherapy.
     - Stage III (e.g. Node positive): Chemotherapy (see page 47) followed by whole pelvic radiation.
     - Unstaged i.e no lymphadenectomy done: Chemotherapy (see page 47) followed by whole pelvic radiation.
     - Local recurrences or stage IV: Treat symptomatically and individualise.

Key references:

Creasman, W.T., Morrow, C.P., Bundy, B.N., Homesly, H.D., Graham, J.E. and Heller, P.B. Surgical pathologic spread patterns of endometrial cancer: A Gynecologic Oncology Group study, Cancer 60: 2035-2041 (1987).

Aalders J., Abeler, V., Kolstad, P., Onsrud, M. Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma: clinical and histopathologic study of 540 patients. Obstet Gynecol 56: 419-427 (1980).

Creutzberg, C.L., Van Putten, W.L., Koper, P., Lybeert, M.I., Jobsen, J., Warlam-Rodenhuis, C.C., De Winter, K.A., Lutgens, L.C., Van Den Bergh, A., Van Den Steen-Banasik, E. Beerman H., Van Lent, M. Surgery and post-operative radiotherapy versus surgery alone for patients with Stage I Endometrial carcinoma: Multicentre randomized trial. Lancet 355: 1491-1411 (2000).

Keys H.M., Roberts J.A., Brunetto V.L., Zaino R.J., Spirtos N.M., Bloss J.D., Pearlman A., Maiman M.A., Bell J.G. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. Gynecologic Oncology Group Gyn Oncol 92 (3): 744-751 (2004).

Carey M.S., Gawlik C., Fung-Kee-Fung M., Chambers A., Oliver T. Systemic review of systemic therapy for advanced or recurrent endometrial cancer. Gyn Oncol 10: 158 – 167 (2006).

Chan J.K., Kapp D.S. Role of complete lymphadenectomy in endometrioid uterine cancer. Lancet 8: 832 – 841 (2007).

Lackman, F.D., Craighead, P.S. Therapeutic dilemmas in the management of uterine papillary serous carcinoma. Curr Treat Options 4 (2): 99-104 (2003).

Manolatsas T.P., Wain G.V., Williams K.E., Friedlander M., Hacker N.F. Multimodality therapy with clinical Stage I and II malignant mixed Mullerian tumors of the uterus. Cancer.15;91(8): 1437-43(2001).

Kanjeekal S., Chambers A., Funk Kee Fung M., Verma S. Systemic therapy for advanced uterine sarcoma: A systemic review of the literature. Gynecol Oncol 97(2): 624-637 (2005).

CARCINOMA OF THE OVARY

A. FIGO CLASSIFICATION (SURGICAL)

Stage

I Growth limited to the ovaries

IA Growth limited to one ovary; no ascites. No tumour on the external surface; capsule intact.

IB Growth limited to both ovaries; no ascites. No tumour on the external surfaces; capsules intact.

IC Tumour either Stage IA or IB but with tumour on the surface of one or both ovaries; or with capsule ruptured; or with ascites present containing malignant cells or with positive peritoneal washings.

II Growth involving one or both ovaries with pelvic extension.

IIA Extension and/or metastases to uterus and/or tubes.

IIB Extension to other pelvic tissues.

IIC Tumour either IIA or IIB but with tumour on surface of one or both ovaries; or with capsule(s) ruptured; or with ascites containing malignant cells or with positive peritoneal washings.

III Tumour involving one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes. Superficial liver metastases equal Stage III. Tumour is limited to the true pelvis but with histologically verified malignant extension to small bowel or omentum.

IIIA Tumour grossly limited to the true pelvis with negative nodes but histologically confirmed microscopic seeding of abdominal peritoneal surfaces.

IIIB Tumour of one or both ovaries with histologically confirmed implants of abdominal peritoneal surfaces, none exceeding 2cm in diameter. Nodes negative.

IIIC Abdominal implants >2cm in diameter and/or positive retroperitoneal or inguinal nodes.

IV Growth involving one or both ovaries with distant metastases. If pleural effusion is present there must be a positive cytology result to allot a case to Stage IV. Parenchymal liver metastases equal Stage IV.

B. Management

Epithelial ovarian tumours

All women with suspected ovarian cancer should be offered a maximal surgical effort wherever possible by a gynaecological oncologist.

I. Standard of care for patients able to undergo surgery

1. Pre-operative work-up:
   - FBC, RFT, LFT.
   - Tumour markers: CA125, CEA.
   - If significant bowel symptoms or occult blood positive: gastroscopy/colonoscopy or barium studies.
   - Careful breast palpation (mammography if indicated).

- CXR (All pleural effusions should be tapped to confirm possible stage IV disease). U/S of liver and/or CT scan for liver metastases if suggested by radiologist. CT scan or MRI to be performed on an individualised basis.
- Diagnostic ascitic tap – fluid for micro/ cytology/ chemistry.
- Refer gynaecological oncology consultant.

2. Pre-operative procedures:
   - Inform stoma-therapists if bowel involvement suspected and colostomy anticipated.
   - Book frozen section (If indicated).
   - Start anti-coagulative measures.
3. Diagnosis made at laparotomy or laparoscopy where indicated
4. Laparotomy:
   - Intermittent pneumatic compression/ or TED stockings.
   - Incision: vertical.
   - Bloodless entry into abdominal cavity.
5. Staging procedure:
   - Immediate aspiration of fluid from POD and para-colic gutters for cytology (or random peritoneal biopsies from same sites).
   - Wipes (or biopsies) from diaphragm (right and left).
   - Full exploratory laparotomy, including palpation and, if indicated fine needle aspiration/excision of enlarged pelvic and para-aortic nodes.
6. Treatment
   - TAH, BSO and infra-colic omentectomy.
   - Bulk reduction of macroscopic tumour to ≤1cm, including enlarged lymph nodes in pelvis or para-aortic area.
   - Cytoreductive surgery only if complete resection of tumour possible.
   - Careful documentation of size and site of residual disease.
   - Serum tumour markers if not taken previously.
   - In stage 1 disease there may be a role for systematic pelvic and para-aortic lymph node dissection.

   Note 1: Where preservation of fertility is an important issue and in stage 1A disease, unilateral salpingo-oophorectomy with omentectomy and full staging may be acceptable management.

   Note 2: All patients should be operated on by a gynaecological oncologist – if not, re-laparotomy may be necessary for accurate staging and debulking.

7. Post operative management:

   - **Patients who have been properly staged (see flow diagram):**

   ➢ Immediate:
     - Book histology review

- Book Combined Assessment Clinic (multidisciplinary approach is advised).

➢ Long-term:
- **Stage 1A + B (grade 1+2)** – no further treatment – follow-up at ovary clinic.
- **Stage IA + B (grade 3) + stage 1C** – Chemotherapy with Carboplatinum X 4 cycles at 3 weekly intervals (See page 49).
- **Stage II - IV – Optimally debulked (<1cm):**
- Postoperative Chemotherapy with Carboplatinum X 6 cycles at three weekly intervals (See page 49).
- **Stages II - III Sub-optimally debulked**
  (> 1cm) residual disease after primary surgery: (Consider baseline CT-scan or MRI immediately after primary surgery). Treat with at least 3 cycles of chemotherapy:
  - ✓ If **evidence of response** to 3 cycles of chemotherapy (see page 49) (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. (See page 49).
  - ✓ If **partial response** i.e. ≤ one log drop Ca 125 after first 3 cycles, no surgery, but continue chemotherapy. (See page 49).
  - ✓ If **no response to chemotherapy:**
    - ❑ Alternative chemotherapy (See page 49).
    - ❑ Radiation to localised symptomatic disease.
    - ❑ Palliative care.

- **Unstaged (i.e. patients operated on elsewhere and full staging not 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 at least 3 cycles of chemotherapy (see page 49) followed by **Delayed Definitive Cytoreductive Surgery** (i.e. TAH/BSO/infra-colic omentectomy/maximum debulking of macroscopic tumour) if evidence of response. After surgery, continue with at least 3 more cycles of chemotherapy. (See page 49).

➢ If suboptimal response, no surgery, but individualise:
- Continue chemotherapy.
- Change to alternative chemotherapy. (See page 49).
- Radiation to localised disease.
- Palliative care.

II. Medically fit patients but significantly impaired by presence of pelvic mass and ascites (i.e. respiratory embarrassment due to atelectasis/large non-malignant pleural effusion or tense ascites with renal impairment) so that primary cytoreductive surgery is deemed hazardous.

a. Make *presumptive* diagnosis of ovarian cancer based on:

Clinical picture

Ascitic tap to confirm adenocarcinoma on cytology or Trucut® biopsy or laparoscopic directed biopsy

Other factors that support the presumptive diagnosis of ovarian cancer:

- Elevated CA 125.
- Gastroscopy/colonoscopy/mammography negative where appropriate.
- Pelvic Ultrasound, CT Scan or MRI suggestive of ovarian cancer.

1. Work-up as in epithelial ovarian carcinoma

a. See before.

2. Management:

- Treat with Neo-adjuvant chemotherapy (i.e. at least 3 cycles of chemotherapy prior to surgery).
- If response to chemotherapy evident (i.e. ≥ one log drop of CA 125 or good clinical 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 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.

b. Unable to make *presumptive* diagnosis of Cancer of Ovary

Options:

- Laparoscopy
- Laparotomy.
- Consider empirical chemotherapy.
- Individualise i.e. depends on response to empirical chemotherapy.
- Consider referring to Unknown Primary Clinic.

IIIa. 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 and document extent of risk.

- Treat with neo-adjuvant chemotherapy with at least 3 cycles of chemotherapy. (See page 49).
- 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 three cycles of chemotherapy. (See page 49).

  B] No improvement in surgical risk after 3 cycles chemotherapy:
  - Complete 6 cycles of chemotherapy. (See page 49).
  - May consider post-chemotherapy surgery in selected patients.

  C] No response to chemotherapy:
  - Reconsider diagnosis.
  - Alternative or palliative chemotherapy.
  - Palliative care.

IV 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.

C. 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.

D. Persistent and Refractory disease

- Platinum Refractory Disease i.e progressive disease on chemotherapy. Stop chemo and consider alternative chemotherapy or supportive/palliative care. (See page 49).
- Persistent disease: partial response to chemotherapy. Either continue to maintain stable disease or stop chemotherapy and consider alternative chemotherapy or supportive/palliative care.

E. Recurrent Disease

- Platinum resistant disease i.e complete clinical response or no evidence of disease after first line chemotherapy and relapse in ≤6 months. supportive care/alternative chemotherapy or radiation if symptomatic localised disease. (See page 49).
- Platinum sensitive disease i.e. relapse after 6 months after stopping chemo – restart original chemo for 6 cycles.

- If no response – supportive care/alternative chemotherapy or radiation if symptomatic localised disease or surgery in selected patients
- Rising CA125 without clinical or radiographic evidence of recurrence – assume recurrence, but only start chemotherapy if there are clinical signs and/or symptoms of disease or radiological evidence of disease

F. Epithelial Tumours of Low Malignant Potential (LMP)

Management

- Laparotomy and surgery as for invasive epithelial tumours.
- Pre-, intra- and post operative management as for invasive tumours except:
  - In cases of mucinous tumours with pseudomyxoma peritonei, appendicectomy should be performed even if macroscopically normal.
  - Conservative surgery i.e. unilateral salpingo-oophorectomy, and omentectomy may be considered in young patients with stage I disease and who wish to retain their fertility, providing they have been correctly staged according to the criteria stated above.

Comments

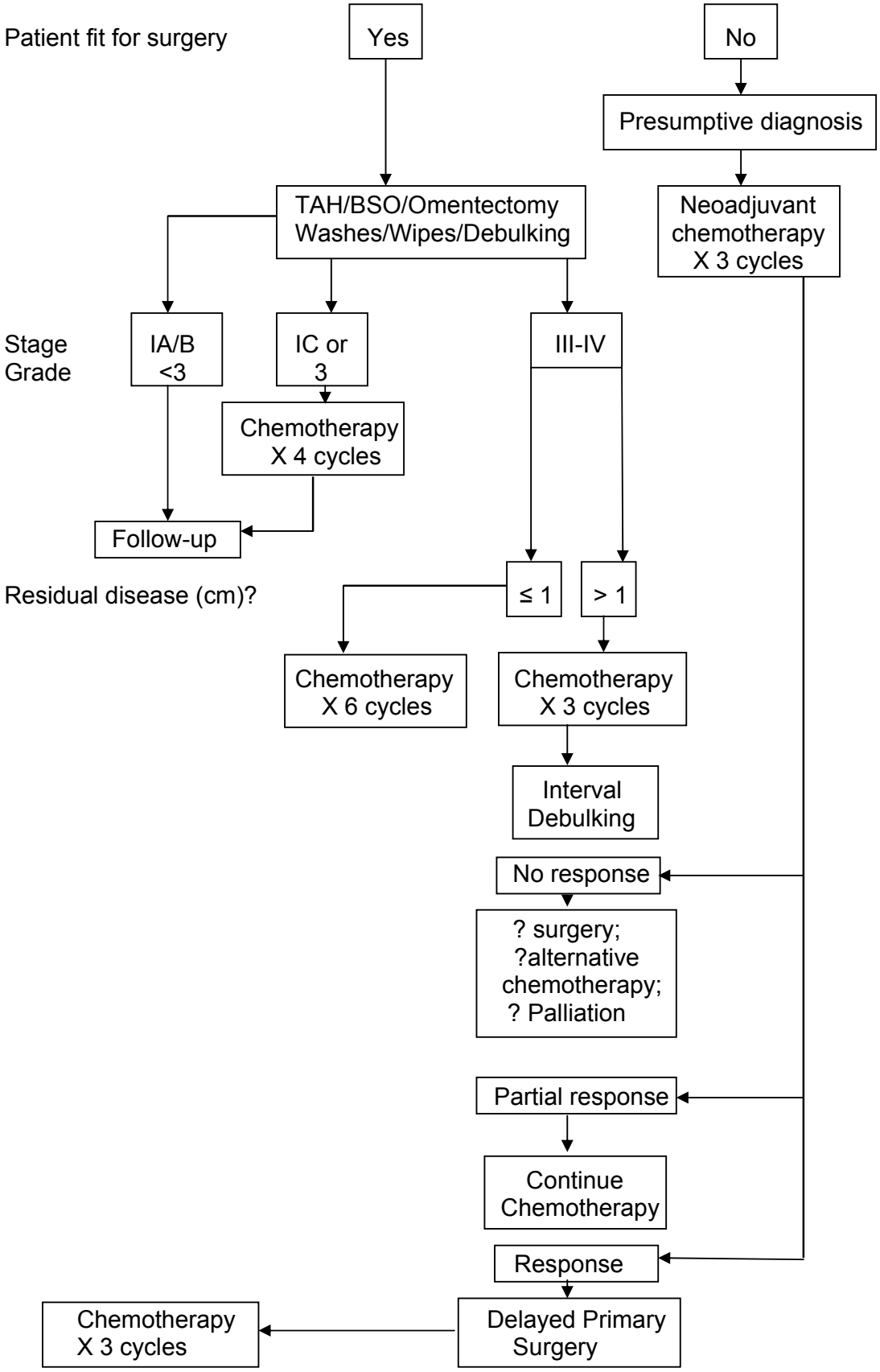
- The treatment of choice in LMP tumours is surgery. Therefore, in cases of inadequate staging re-laparotomy may be indicated.
- Chemotherapy not indicated for LMP tumours.
- Long term follow-up is essential.

G. Sex-cord Stromal Tumours

Management:

- Laparotomy
- Surgical management:
  - Women who want to preserve fertility, USO and omentectomy with full staging is acceptable.
  - If fertility not an issue, surgery as for epithelial tumours.
  - Consider chemotherapy if greater than stage 1 and where there is residual disease post surgery.
  - Surgery/localised radiation and chemotherapy may be useful for recurrent disease.

Management of Epithelial Ovarian Cancer



H. Germ Cell Tumours

Management:

- Pre-operative:
  - Tumour markers (α-Feto-protein, β-HCG, LDH, CA 125).
- Operative:
  - Diagnostic laparotomy.
  - Intra-operative frozen section if available.
  - Unilateral salpingo-oophorectomy, omentectomy and full staging, including sampling and debulking suspicious lymph nodes.
  - If bilateral ovarian involvement, attempt ovarian cystectomy of other ovary in order to preserve some normal ovary.
- Post operative:
  - Apparent Stage IA Dysgerminoma or Stage 1A, grade I Immature Teratoma with negative postoperative markers and negative CT-Scan or MRI: observation only.
  - All other patients receive 4 cycles of chemotherapy or give chemotherapy until tumour marker negative + 1 additional cycle (See pages 49).
  - Repeat laparotomy after 4 cycles of chemotherapy in patients only with immature Teratoma component and residual tumour after first operation or with radiological or clinical evidence of disease.
  - Surgery, radiation and chemotherapy are all options for recurrent disease.

References

A E Guppy, P D Nathan, GJS Rustin. Epithelial Ovarian Cancer: A review of Current Management. Clinical Oncology 2005; 17: 399 – 411.

D M Gershenson. Fertility sparing surgery for malignancies in women. J Natl Cancer Inst Monogr. 2005; 34: 43 – 47.

J Baptist Trimbos, Ignace Vergote, Giorgio Bolis, Jan B Vermorken, Constantino Mangioni, Caterina Madronal et al. Impact of Adjuvant Chemotherapy and Surgical Staging in Early-Stage Ovarian Carcinoma: European Organisation for Research and Treatment of Cancer-Adjuvant Chemotherapy in Ovarian Neoplasm Trial. J Natl Cancer Inst 2003; 95: 113 – 125.

Deborah Armstrong. Relapsed Ovarian Cancer: Challenges and Management Strategies for a Chronic Disease. The Oncologist 2002;7(suppl 5): 20 – 28.

Panici PB, Maggioni A, Hacker N, Landoni F, Ackermann S, Campagnutta E et al. Systematic aortic and pelvic lymphadenectomy versus resection of bulky nodes only in optimally debulked advanced ovarian cancer: a randomized clinical trial. J Natl Cancer Inst 2005; 8: 560 – 566.

GESTATIONAL TROPHOBLASTIC DISEASE

CLASSIFICATION

A. Hydatidiform mole:
- Complete.
- Partial.

B. Gestational trophoblastic neoplasia/tumour:
- Persistent/invasive mole
- Choriocarcinoma (abortion, term, ectopic).
- Placental site trophoblastic tumour (PSTT – origin non-villous trophoblast)
- Epithelioid Trophoblastic Tumour (ETT – origin intermediate trophoblast).

A. HYDATIDIFORM MOLE

1. Investigations:
- Pelvic ultrasound.
- Pre-operative CXR, serum β-HCG, TSH, HIV testing.

2. Management:
- Suction curettage of uterus; under U/S guidance.
- Cross match 2 units of blood to be available in theatre.
- Send tissue for histological evaluation.
- Contraception (hormonal) for at least 6 months.
- Follow-up is of utmost importance and is done by a special GTD clinic (2-weekly β-HCG until negative, then monthly for 6 months).
- It is recommended that ßHCG quantified result is plotted on a graph .A normal semi-logarithm post-molar curve for serum β-HCG is depicted in figure 1.

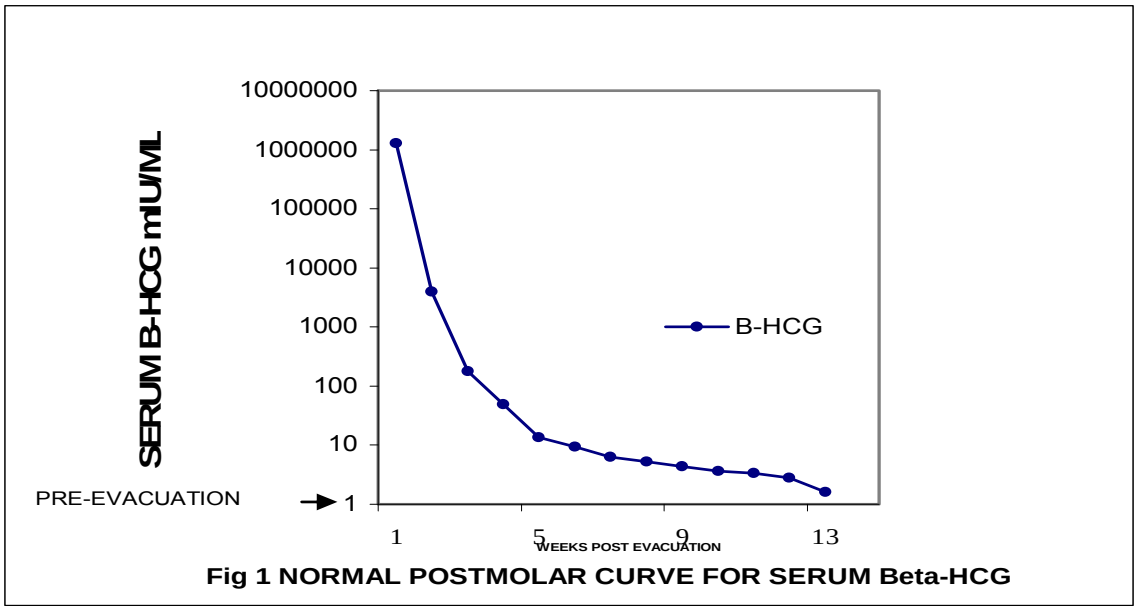


Fig 1 NORMAL POSTMOLAR CURVE FOR SERUM Beta-HCG

B. GESTATIONAL TROPHOBLASTIC NEOPLASIA/TUMOUR

1. Diagnostic criteria for persistent/invasive mole/choriocarcinoma

- Rising or static levels of serum β-HCG.
- Serum β-HCG level >20000 four weeks post-evacuation.
- Serum β-HCG elevated 6 months post-evacuation.
- Histological evidence of choriocarcinoma at any site.
- Non-pulmonary metastases.
- Persistent bleeding despite repeat evacuation.
- Lung metastases do not justify chemotherapy if the serum β-HCG levels are declining.

FIGO CLASSIFICATION FOR GTN

STAGING

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 tract involvement.

Stage IV All other metastatic sites.

SCORE

Prognostic factors	Score 0	1	2	4
Age (years)	<40	≥40		
Antecedent pregnancy	Mole	Abortion	Term	
Interval (months)	<4	4-6	7-12	>12
β̃-HCG (iu/litre)	$<10^3$	10^3-10^4	10^4-10^5	$>10^5$
Largest tumour (incl. Uterine)	<3	3-5cm	>5cm	
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.

2. Investigations

- Serum β-HCG levels.
- FBC, Renal and liver function tests
- TSH
- HIV and VDRL
- CXR, Ultrasound of abdomen, Pelvic ultrasound.
- IF CXR negative do CT Chest
- IF CXR or CT Chest positive do CT/MRI Brain

3. Management

Patients should be managed in a specialised unit (see flow diagram). The treatment of this malignancy depends on the ready availability of serum β-HCG assays.
The management decisions depend on whether the patient is **low** (0-6) or **high risk** (7 or greater) according to the modified WHO/FIGO scoring system.

a. Low Risk Patients:

Single agent chemotherapy i.e. Methotrexate or Actinomycin D (see page 46)

b. High Risk Patients:

Multi-agent chemotherapy: EMA-CO (see page 46)

- Surgery i.e.
  - Hysterectomy (under chemotherapy cover is an option) is 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.
- Radiotherapy – Use where indicated.
- Pelvic Artery Embolization: In cases of intractable haemorrhage.

Follow up after treatment

β-HCG weekly till normal for 3 consecutive weeks, then monthly for 12 months. Ensure reliable contraception for one year.

C. TREATMENT: PSTT/ETT

- Individualise.
- Surgery is the cornerstone of treatment.
  Chemo- and radiotherapy are occasionally indicated.

E. POINTS TO REMEMBER

- Do not forget to look for vaginal metastases.
- Do not biopsy any metastases in patients with GTN.
- Histology is not required for the diagnosis of choriocarcinoma.
- Prophylactic chemotherapy post-evacuation may be considered in high risk hydatidiform mole, especially where loss to follow-up is a high possibility.
- If evidence of resistance to chemotherapy, turn to page chemo for alternative management and chemotherapy regimes

Key References:

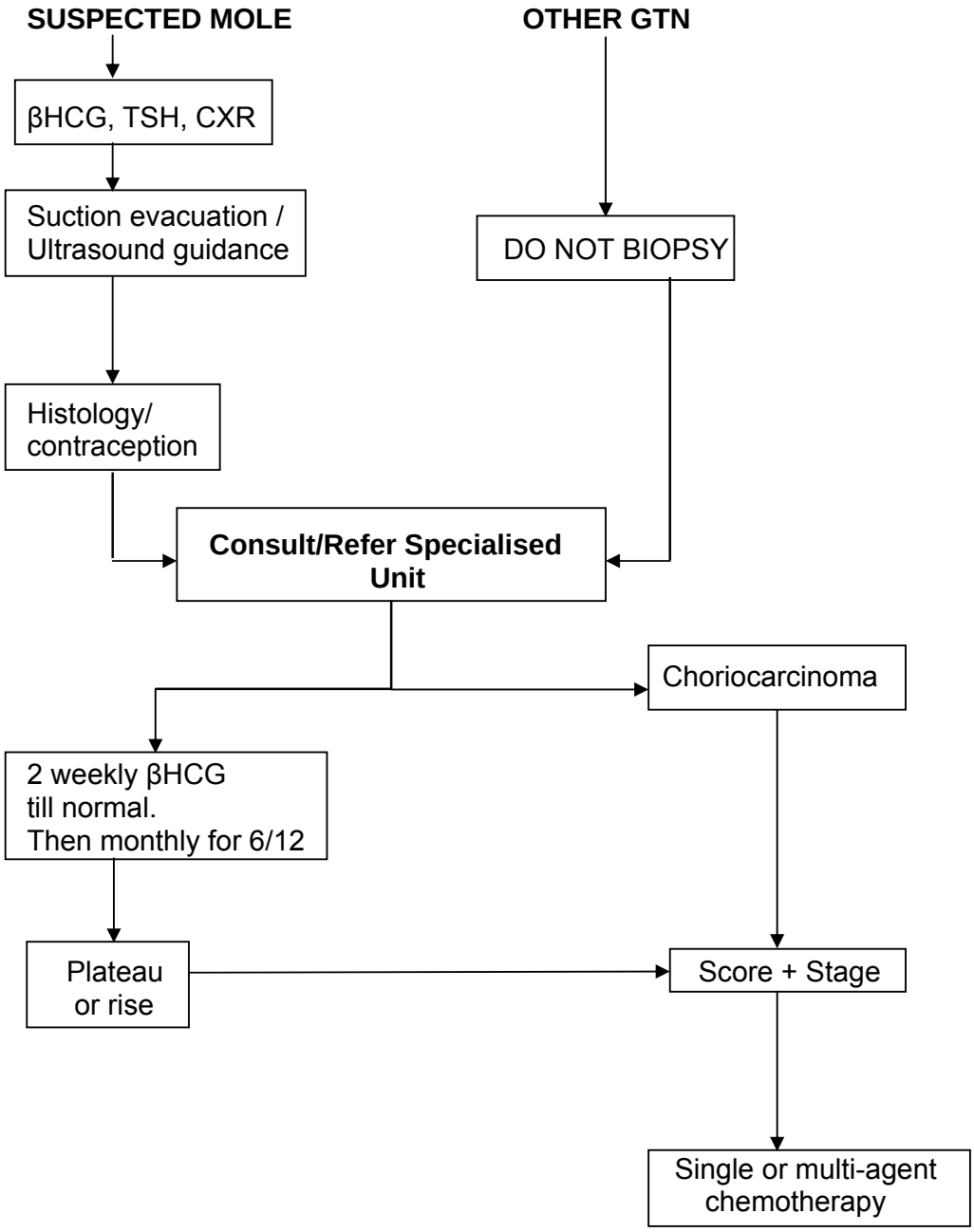
Soper JT, Mutch DG, Schink JC. Diagnosis and treatment of trophoblastic disease: ACOG Practice Bulletin No.53. Gynecol.Oncol. 93 (2004), pp 575 – 585.

Ngan HYS. The practicality of FIGO 2000 staging for gestational trophoblastic neoplasia. Int J Gynecol Cancer. 14 (2004), pp 202 – 205.

Kohorn EI. The new FIGO 2000 staging and risk factor scoring system for gestational trophoblastic disease: description and clinical assessment. Int J Gynecol Cancer. 11 (2001), pp 73 – 77.

Hextan Ngan, Karen Chan, Kar-Fai Tam. Gestational trophoblastic disease. Curr Obstet Gynecol (2006);16:93 - 99

MANAGEMENT GTN



MALIGNANCY IN PREGNANCY

A. INCIDENCE:

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

B. MANAGEMENT:

- Termination of pregnancy must be considered.

C. SURGERY DURING PREGNANCY:

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

D. CHEMOTHERAPY DURING PREGNANCY:

- Recommended to wait until 14 weeks gestation to start chemotherapy.
- Folic acid antagonists (e.g. methotrexate) and idarubicin not safe in pregnancy.
- 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 (as a general rule no chemotherapy administered after 35 weeks of pregnancy with main concern being bone-marrow suppression at the time of delivery).
- No obvious increased risk for congenital malformations after intra-uterine exposure to chemotherapy during second and third trimesters.

E. RADIOTHERAPY DURING PREGNANCY:

- Radiotherapy with proper screening of uterine cavity may be applied to the upper body during pregnancy with relative safety.
- Chest radiotherapy should preferably be given with the fetus in the cephalic position after 28 weeks (to protect fetal neurological system).
- If chemo-and radiotherapy is needed as adjuvant treatment, radiotherapy often postponed until after delivery.

F. INVASIVE CERVICAL CANCER:

- If invasive carcinoma is suspected, a flat cone biopsy (coin 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 an option.
- C/section delivery route of choice.

Management:
Stage-related, as for non-pregnant patients.
Timing of intervention:
- <24wks – immediate.
- ≤32/34wks – delay until 32 wks, then amniocentesis + steroids before delivery.
- >32/34wks – immediate +/- amnio and steroids.

Stages IB/IIA:
- <24wks – radical hysterectomy + pelvic lymphadenectomy with fetus in-situ.
- 24 - 34 wks – delay until 32/34 wks, then classical C/section plus radical hysterectomy + pelvic lymphadenectomy. (This approach may require individualisation – tumour size, patient's wishes etc.).
- >32/34wks – classical C/section plus radical hysterectomy + pelvic lymphadenectomy.

Stages IIB, III and IV:
- ≤ 12 weeks – start chemo-radiation after medical abortion.
- 12 to 24 wks – start chemoradiation (to 20 Gy) prior to hysterotomy. Restart treatment (including intracavitary brachytherapy) 7 days post-op.
- ≥ 24 wks – await fetal maturity before delivering by classical C/section. Start chemo-radiation + intracavitary brachytherapy 7 days post-op.

G. VULVAL CANCERS:
- Surgery possible during pregnancy – individualise.

H. ENDOMETRIAL CANCER:
- Rare malignancy in pregnancy and is often associated with miscarriage.

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

J. 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.

K. GENERAL COMMENTS:
Malignant melanoma may metastasize to the placenta and fetus – placenta must be sent for histological assessment. If positive, examine fetus for possible metatastases.

KEY REFERENCES:

1. Hunter, M.I., K. Tewari, and B.J. Monk, *Cervical neoplasia in pregnancy. Part 2: current treatment of invasive disease.* Am J Obstet Gynecol, 2008. 199(1): p. 10-8.
2. Amant, F., K. Van Calsteren, I. Vergote, and N. Ottevanger, *Gynecologic oncology in pregnancy.* Crit Rev Oncol Hematol, 2008. 67(3): p. 187-95.
3. Leiserowitz, G.S., G. Xing, R. Cress, B. Brahmbhatt, J.L. Dalrymple, and L.H. Smith, *Adnexal masses in pregnancy: how often are they malignant?* Gynecol Oncol, 2006. 101(2): p. 315-21.

FAMILIAL GYNAECOLOGICAL MALIGANCIES

Refer for genetic counselling when deemed high risk i.e. 20-25% chance.

- Women with a personal history of both breast and ovarian cancer.
- Women with Ovarian Carcinoma (at any age) and a close relative (male or female) with breast cancer at less than 50 years of age.
- Women with breast cancer at age less than 50 years with a close relative with ovarian or breast cancer (male or female breast cancer).
  Ashkenazi Jews with Ca. breast before age 40 or Ovarian Carcinoma at any age.
- Two or more first degree relatives with Ovarian Carcinoma at any age
- Family contains an affected individual with a pathogenic mutation in one of the known predisposition genes (BRCA or HNPCC).
- Paternal transmission i.e. male intervening between two affected women on the same side of the family.
- 3 Family members with cancer, 2 of whom have been diagnosed with colorectal cancer before age 50 and one case of Ovarian Carcinoma.
- Synchronous endometrial/colorectal cancer before age 50.

Prophylaxis:

- Combined oral contraceptives will reduce ovarian cancer, but warn about risks of breast cancer.
- Prophylactic surgery:
  - Optimal age debatable.
  - HRT post surgery unresolved.
  - Prophylactic BSO: Breast cancer reduction in 50% of BRCA + patients.
- Continued surveillance for primary peritoneal carcinoma

Key references

James P.A. et al. Optimal Selection of Individuals for BRCA Mutation Testing: A Comparison of Available Methods. J Clin On. 2006 24(4): 707-715.

Schmeler K.M. et al. Prophylactic Surgery to Reduce the Risk of Gynecologic Cancers in the Lynch Syndrome. N Engl J Med 2006 354 (3), 261-269.

GuillemJ.G. et al. ASCO/SSO Review of Current Role of Risk-Reducing Surgery in Common Hereditary Cancer Syndromes. J Clin Onc. 2006 24 (28) 4642-4660.

GUIDELINES FOR PATHOLOGISTS

These guidelines are drawn up to achieve uniformity in the reporting by pathologists, which will affect management strategies.

A. Cancer of the vulva:

1. Specimen processing:
- Draw a diagram of the specimen with any orientation markers.
- "Ink" the excision margins.
- Take sections at right angles to the excision margins and record cassette number on diagram.
- Section through centre of tumour down to deep excision.

2. Record:
- Tumour type and grade (differentiation); presence of VIN3.
- Dimensions.
- Distance from all excision margins.
- Depth of invasion from the basement membrane.
- Presence or absence of vascular space invasion.
- If lymph nodes are included:
  - The total number on each side.
  - The number with metastatic deposits and size of largest deposit.
  - Whether of not the metastases invade beyond the lymph node capsule.

Vulvectomy worksheet for vulval carcinoma

Summary

- Tumour type: _____
- Differentiation _____
- Presence of VIN 3 ☐
- Presence of Lichen Sclerosis ☐
- Size (maximum dimensions) _____ x _____ x _____ mm
- Greatest depth of invasion _____ mm Situation _____

- Distance from excision lines:
    - Superior _____ mm Inferior _____ mm
    - Left _____ mm Right _____ mm
- Vascular invasion.
- Lymph nodes: (Number +ve for metastases / number examined)
    - Left inguinal _____ Right inguinal _____
    - Others (specify) _____
- Attach annotated diagram and / or photograph.

B. Carcinoma of the uterine cervix

Wertheim's hysterectomy for cervical carcinoma. (+ Cone biopsy)

1. Specimen processing:
- Paint the anterior and posterior surfaces of the cervix with different colour markers.
- Measure the vaginal cuff anterior and posterior before dissection.
- A horizontal slice through the cervix above the transformation zone is very helpful to assess excision margins. Blocks must extend to the inked excision line. Remember to record cassette numbers for relevant sides etc.
- Para-sagittal and coronal sections through the ectocervix and vaginal cuff are required.
- Pelvic lymph nodes.

2. Record:
- The tumour type and grade (differentiation).
- The size of the tumour in three dimensions.
- The dominant site of occurrence.
- The depth of invasion and the distance to anterior, posterior, left and right parametrial excision lines.
- The length of the vaginal cuff and whether or not the fornices are involved with either invasive tumour or CIN.
- The presence or absence of vascular space invasion.
- The number of lymph nodes examined for each side and the number involved by metastases (? Extra capsular spread).

Wertheim's hysterectomy worksheet

Summary

- Tumour type: _____
- Differentiation: _____
- Dominant situation: _____

- Size (maximum dimensions) _____ x _____ x _____ mm.
- Greatest depth of invasion: _____ mm Situation: _____
- Distance from excision lines:
  - Anterior _____ mm Posterior _____ mm
  - Left _____ mm Right _____ mm
- Vaginal cuff: Anterior _____ mm Posterior _____ mm
- Vascular invasion:
- Lymph nodes: (Number +ve for metastases / number examined)
  - Left external iliac _____ Right external iliac _____
  - Left internal iliac _____ Right internal iliac _____
  - Left obturator _____ Right obturator _____
  - Others (specify) _____

C. Hysterectomy for cancer of the endometrium:

1. Specimen processing:
- Transverse (anatomical horizontal) slices through the body of the uterus and upper endocervical canal. The lower cervix should be cut in para sagittal and coronal planes.
- Identify the area of deepest myometrial invasion. Select block(s) through the full thickness to include the serosa. If too large for one cassette, bisect and record cassette numbers.

- Ensure that you can identify anterior, posterior left and right sides of uterus either by recording in report or by differential marking before dissection.
- Pelvic lymph nodes.

2. Record:
- Tumour type and, if endometrioid, FIGO grade.
- Depth of myometrial invasion (as < or > 50%), thickness of myometrium and distance of deepest invasion from the serosa.
- Presence or absence of vascular space invasion.
- The morphology of uninvolved endometrium.
- Presence or absence of endocervical involvement and whether only on surface or with cervical stromal invasion.
- If lymph nodes are included:
  - The total number on each side.
  - The number with metastatic deposits and size of largest deposit.
  - Whether of not the metastases invade beyond the lymph node capsule.

Worksheet frozen section/definitive histology

- Histology Endometrioid Clear cell Other
- Grade 1. 2. 3.
- Tumour size:_____ mm
- Myometrial invasion: None < 50% ≥ 50%
- Myometrial invasion _____mm; Myometrial thickness: _____mm
- LVSI Negative Positive
- Cervical involvement Negative Positive
- Lymph nodes: (Number +ve for metastases / number examined)
  - Left external iliac _____ Right external iliac _____
  - Left internal iliac _____ Right internal iliac _____
  - Left obturator _____ Right obturator _____
  - Left common iliac _____ Right common iliac _____
  - Others (specify) _____

D. Cancer of the ovary

1. Specimen processing:

a. Ovaries:

- Weigh and measure each in 3 dimensions.
- Describe if received intact or disrupted, and if the capsule is breached.
- Take a transverse section through the ovary, and describe solid/ cystic/ papillary areas.
- Embed at least 3 sections of any solid/papillary areas, up to a maximum of 1 section per 1 cm of solid tumour.
- Section the non neoplastic ovary and the fallopian tubes.
- Take sections of all surface adhesions.

b. Omentum:

- Weigh and measure.
- Describe macroscopic and size of nodules.
- Sample nodules, and take 8 random sections of omentum, if nodules are not seen.

c. Uterus

- As for routine hysterectomy (sample any surface adhesions).

d. Lymph Nodes:

- Describe number, size of largest and block all lymph nodes.

2. Record:

- Tumour type and Silverberg Grade.
- Involvement of capsule and/or surface of capsule.
- If 1 or 2 ovaries involved.
- Fallopian tube morphology.
- Histology of cyst lining, presence of endometriosis etc.
- Vascular invasion if present.
- Omental metastases with size.
- Number of lymph nodes found on each side, and number with metastases (record extension through the capsule if present).
- Serosal or peritoneal tumour presence.
- The morphology of all aspects of the uterus.

Ovarian Cancer Work Sheet

Summary:

- Tumour site:
  - Left Ovary: ☐
  - Right Ovary: ☐

- Both Ovaries: ☐

- Tumour Size _____ mm
- Capsule integrity: Intact/ breached
- Tumour type _____ Tumour differentiation: _____

Extent of Invasion:

- Omental involvement: Yes / No
- If Yes size of Omental metastases: _____ mm
- Presence of omental implants: Yes / No If Yes: Invasive / Non-invasive

Regional Lymph Nodes:

- Number examined _____ Number involved _____
- Lymph vascular invasion: Yes/No
- Presence of additional pathology (e.g. Endometriosis)

_____

- Attach Photograph of external and internal surface(s) of tumour.

CHEMOTHERAPY PROTOCOLS

Chemotherapeutic agents all have the common end-point of cell destruction, but without particular specificity for malignant cells and may extend their toxic effects to normal cells.
The protocols in the following sections are guidelines and are based on those mainly used at Groote Schuur Hospital and Tygerberg Hospital.
Administration of chemotherapy should take place in specialised units where expertise is available to deal with patients with gynaecological malignancies requiring chemotherapy. These specialised units also require a multidisciplinary approach.

A. GENERAL CHEMOTHERAPY CONSIDERATIONS

1. FBC including differential count to be checked prior to chemotherapy administration, viz. Ideally Hb > 10Gm%; Transfusion if necessary.
   Delay chemotherapy if:
   - WCC < 3.000 if neutrophils count not available.
   - Absolute neutrophil count < 1.5.
   - Platelets < 100.000.

   Low Hb should not cause delay; transfuse if symptomatic anaemia.

2. Height and weight required for nomogram. This must be double-checked.

3. Serum Magnesium checked regularly prior to cycles of Cisplatinum. Give supplemental Magnesium (1 Gram bd. PO for 5 days after each cycle of Cisplatinum).

4. The person administering the cytotoxics is to remain with the patient until the infusion of drugs is completed in order to detect allergic reactions or I.V. line problems.

5. 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.

6. I.V. line to be replaced immediately if blocked for any reason, to ensure administration of cytotoxics and post-hydration fluid.

7. Warn staff that Bleomycin may cause a raised temperature, rigors or anaphylactic reaction (have emergency trolley available).

8. Renal function to be checked prior to chemotherapy administration.

9. In general, do not reduce dose for obese patients, Use actual mass in dose calculations up to a maximum of 2 m^2. If bone marrow problems occur, use ideal weight for height.

10. Take note of cumulative doses of chemotherapeutic agents, especially Adriamycin, Epirubicin and Bleomycin.

11. When using Methotrexate, be aware that effusions will trap Methotrexate which may give rise to a slow release and may 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. Any person administering these agents must be familiar with the current standard premedication (and post medication) protocols in use.

16. All patients getting anthracyclines must have their LVEF checked prior to starting chemotherapy. Repeat LVEF during chemotherapy if initial borderline result

B. GESTATIONAL TROPHOBLASTIC NEOPLASM

1. Low risk (FIGO score 0-6) (Single agent chemotherapy)
   - Actinomycin D 1.2 mg/m^2 I.V. every second week.
     or
   - Methotrexate 30mg/m^2 I.M. weekly.
     Leucovorin, 7.5 mg P.O., 24 hrs after each injection of Methotrexate.
     - Continue cytotoxics β-HCG normal (<10 IU/ml) and administer at least 2 additional cycles after β -HCG level is normal.
     - If serum β-HCG level "plateaus" or rises, change to multiple agent chemotherapy.

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

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 & Oncovin = Vincristine) is given on day 8. EMA may require overnight admission, CO does not.
   - Next **EMA-CO** cycle starts at day 15.

EMA

Day 1 Etoposide, 100 mg/m^2 I.V. infusion in 200 ml saline over 30 minutes; Actinomycin D, 0,5 mg, iv stat; Methotrexate, 300 mg/m^2 in 1 litre saline over 12 hours.

Day 2 Etoposide, 100 mg/m^2 I.V. infusion in 200 ml saline over 30 min.; Actinomycin D, 0.5 mg I.V. stat.; Folinic acid, 15 mg, I.M. or orally every 12 hours for 4 doses beginning 24 hours after starting methotrexate.

CO

Day 8 Vincristine, 1.0 mg/m^2, (maximum 2.0 mg) I.V. stat.; Cyclophosphamide, 600 mg/m^2 I.V. in saline.

Repeat cycles until serum β-HCG level is ≤10 i.u./ml and administer 4 additional cycles ("insurance cycles") thereafter.

Special considerations:

- Failure to respond to EMA-CO: modify regime as follows: omit Actinomycin D and Etoposide on day 2 of EMA. Replace CO with Cis-platinum 75mg/m^2 and Etoposide 120 mg/m^2 alternating weekly with EMA. Consider alternative chemotherapy e.g. PVB, PEB in case of ongoing failure.

- CNS metastases:
  Methotrexate is the drug of critical importance.
  The Methotrexate dosage in the **EMA-CO** regimen is increased to 1 g/m^2 to reach an effective drug concentration in the CSF. Folinic acid dosage is increased to 30mg, 8 hourly x12, starting 24 hours after commencement of methotrexate. Intrathecal methotrexate 12.5 mg is given with each dose of **CO**.
  Consider radiotherapy, surgery or alternative chemotherapy if indicated.

C. UTERINE MALIGNANCIES

1. High risk uterine adenocarcinoma (including UPSC, Clear Cell, Carcinosarcoma, Stages IC – IIIC high grade endometrioid adenocarcinoma).
   Options:

   - Cisplatinum 75 mg/m^2 I.V. & Doxorubicin I.V.(Adriamycin 50 mg/m^2 or Epirubicin 100mg/m^2) 3 weekly x 4-6 cycles.
   - Carboplatinum AUC 5 I.V. & Doxorubicin I.V. (Adriamycin 50 mg/m^2) ^{3} weekly x 4-6 cycles (patients who cannot tolerate hydration regime or with impaired renal function or hearing problems).
   - Carboplatinum AUC 5 I.V. & Paclitaxel I.V. 175mg/m^2 x 4-6 cycles.

2. Leiomyosarcoma, endometrial stromal sarcoma (ESS) and undifferentiated sarcoma.
   Adriamycin: 50 mg/m^2 I.V. (Or Epirubicin 100 mg/m^2) 3 weekly x 4 – 6 cycles.
   Note:
   - ERNA or Cardiac Echogram prior to Epirubicin or Adriamycin
   - High dose Provera may be considered in ESS.

D. CARCINOMA OF THE CERVIX

Chemotherapy and radiation concomitant:
- Weekly Cisplatinum 40mg/m^2.
- Premedication: Dexamethasone 8mg I.V. + $5HT_3$ antagonist.
- 1L N-Saline (+ 2 amps $MgSO_4$) over 2 hours.
- Cisplatinum in 200ml NS x 1 hour.
- 200ml NS fast.
- During course of chemotherapy-radiation:
  - Slow-Mag1 bd P.O. continuously.
  - Metaclopramide 10mg tds as needed.
- If renal function affected, consider Carboplatinum 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 I.V. dose of Cisplatin. GFR must be >60ml/min and ideally >90ml/min for use of Cisplatinum.

E. CARCINOMA OF THE VULVA

Chemotherapy and radiotherapy concomitant:
- Day 1 – Mitomycin C (10mg/m^2) in 200ml 5% Dextrose is given over 30 minutes (or alternatively Cisplatinum 75mg/m^2 with adequate hydration).
- Day 1-4 (inclusive) – 24 hour constant infusion of 5-Fluorouracil (1 gram/m^2) in N. saline.
- The 4 day CVI of 5FU (but not the Mitomycin C) is repeated in week 4 of the radiotherapy.
- The regime is repeated on day 28 of the radiotherapy.

Consider neo-adjuvant (or palliative chemotherapy in advanced disease):
- Cisplatinum 75mg/m^2 or Carboplatinum AUC 5 day 1 + 5-FU 1 gram/m^2 constant infusion day 1 – 4.
- Carboplatinum AUC 6 & Bleomycin 15 IU I.M.

F. TUMOURS OF THE OVARY

a. Epithelial Tumours.

1. *First line treatment*

- Carboplatinum AUC 6- 7.5.
- Anti-emetic premedication: Dexamethasone 20mg I.V. + $5HT_3$ antagonist I.V.
- Carboplatinum AUC 6.
    - Calculated creatinine clearance (Cockcroft – Gault formula) before each cycle:
    - (140-age) x mass (kg) x 1.05/ Serum creatinine = clearance in ml/min.
    - Carboplatinum absolute dose based on Calvert formula (calculated clearance + 25) x AUC = dose of Carboplatinum in mg.
- Cycles repeated 3 weekly; 6 cycles.
- Cycles repeated 3 weekly; 4 cycles for high risk Stage I disease.

2. Second line treatment.

- Oral agents as second line or poor performance, elderly patients:
    - Cyclophosphamide = 100mg daily PO. Repeat FBC monthly.
    - Melphalan = weight in Kg/10 = No of tablets per day; 5 days every 4 weeks.
    - Tamoxifen = 20 mg BD.
- Other second-line options Docetaxel, Paclitaxel, Gemcitabine, Liposomal doxorubicin, Etoposide, Topotecan. All as single agent or as part of multi-agent chemotherapy.

b. Germ Cell Tumours

1. **PEB**:

- Cisplatinum 35 mg/m^2 day 1-2-3.
- VP16/Etoposide 120mg/m^2 day 1-3.
- Bleomycin 15 IU in 1 litre Belsol (or Plasmalyte B) x 8 hours day 1-2-3.
    - Pre treatment audiometry, calculated clearance.
    - On day 1, Prehydration with 1L N-Saline (+ 2 amps $MgS0_4$) over 2 hours.
    - Anti-emetic: – Dexamethasone 8 mg I.V. day 1-2-3.
      – $5HT_3$ antagonist 1 vial I.V.
    - Cisplatinum is given in 200ml N-Saline over 2 hours, “piggy bagged” with mannitol 500ml over 2 hours.
    - Bleomycin in 1L Belsol (or Plasmalyte B), then 1L N-Saline 6-8 hourly x 2.

2. Impaired audiometry initially, or during PEB or calculated creatinine clearance< 60ml/min:
   - Day 1 only Carboplatinum AUC 5.
   - Day 1-3: Etoposide + Bleomycin.

3. Resistant and Germ Cell tumours.
   Modified VIP.
   Vinblastine 6 mg/m^2 day 1 only.
   Ifosfamide 1.5 mg/m^2 days 1-2-3.
   Mesna 80% of full dose of Ifosfamide at 0-4-8 hrs for 3 days.
   Cisplatinum 35 mg/m^2 days 1-2-3 or Carboplatinum 300 mg/m^2 day 1.

G. 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 I.V.
- Standard: intravenous $5HT_3$ antagonist followed by oral $5HT_3$ antagonist post chemotherapy 3-5 days. – or Palonosetron (Onicit) 0.25mg only I.V.(lasts 5 days).
- Post-chemotherapy : Metaclopramide 10mg QDS PO and cyclizine suppositories 100 mg q & h p.c. for up to 5 days.

H. PRE-EXISTING MEDICAL CONDITIONS AND CHEMOTHERAPY

Certain pre-existing medical conditions may have an influence on the efficacy and more so on the side-effect profile of chemotherapeutic agents. (Table1.)

TABLE 1 Pre-existing medical conditions and chemotherapy.

Pre-existing condition	Special care with the following drugs
Abnormal liver functions	Methotrexate Vincristine Vinblastine Epirubicin 5FU
Abnormal Renal functions	Methotrexate Actinomycin D Bleomycin Cisplatinum Carboplatinum Etoposide
Hearing impairment	Cisplatinum
Neurological abnormalities	Vincristine Paclitaxel
Cardiac insufficiency	Epirubicin Doxorubicin
Bone marrow depression	All except: Vincristine Bleomycin Cisplatinum
Drug therapy:	
o NSAID's:	Methotrexate
o Warfarin	all (esp. 5FU)
o Anti-malarials:	Methotrexate
o Irradiation:	Methotrexate 5-FU Mitomycin-C Bleomycin Epirubicin/doxorubicin Actinomycin D

Note: Radiation "recall" may occur with subsequent treatment with Actinomycin D or Epirubicin**.**

I. 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 is 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	Cisplatin	
Vinblastine	Cyclophosphamide	
Vincristine	Etoposide	
	Carboplatin	

Note: Immediate treatment:
- Infiltrate area with Solucortef (dose 100mg = 2 ml) and/or
- Na bicarbonate, subcutaneously

J. SIDE-EFFECTS

Chemotherapeutic agents may have a variety of side-effects. The most common side-effects have been depicted in Figure 1.

		Bone marrow	Sclerosant	Neurological	Skin	Pulmonary	Renal	Hepatic	Cardiac	Endocrine	Bladder	GIT	Allergic	Alopecia	Metabolic	Nausea/ Vomiting	Stomatitis
A	Methotrexate	** *		*	*	*	*	**				** *		*		*	** *
	5-Fluorouracil	** *		*	*							**		*		*	** *
	Cyclophosphamide	** *			*			*	*	*	**	**		**	*	**	
	Leukeran	** *		*	*	*		*								*	
B	Melphalan	** *										*				**	
	Actinomycin D	** *	*	*	*							**		**	*	**	*
	Adriamycin	** *	**						**			**		**		**	**
	Bleomycin	*		**	** *	** *		*					*			**	*
C	Mitomycin C	** *	*									*				**	
	Vincristine	*	*	** *				*						*	*		
D	Etoposide	** *	*														
	Cisplatinum	*		*			** *									**	
E	Carboplatinum	** *		*			*									*	*

A = Nucleic acid and folate antimetabolites; B = Alkylating agents; C = Antibiotics;
D = Vinca alkaloids; E = miscellaneous

<u>Figure 1</u> Chemotherapeutic agents and incidence of side-effects

Consulting Pathologists

Dr Judith Whittaker & Dr Carolyn Baigrie