Protocol for Planning and Treatment

The process to be followed when a course of chemotherapy is required to treat:

CANCER OF THE CERVIX including vagina/vulva

Patient information given at each stage following agreed information pathway

1. DIAGNOSIS

All patients, following a diagnosis of invasive carcinoma of the cervix, should be referred to the Combined Gynaecological Oncology Clinic for discussion regarding their further management. Patients with early stage disease will be seen by both the gynaecological oncologist and the clinical oncologist to discuss possible treatment options.

When a LETZ or biopsy has been carried out following an abnormal smear suggestive of CIN3 /invasive carcinoma, the pathology should be reviewed at the Combined Gynaecological Oncology Clinic for discussion of whether further assessment or treatment is indicated.

It is well recognised that women with cervical cancer have a variety of psychosocial, psychosexual and informational needs. Patients will be provided with the opportunity to discuss their concerns and questions confidentially in a private area at all stages of the disease process. Written literature will be available to support verbal information. Referral to a Clinical Nurse Specialist will ensure continued support throughout the cancer journey.

1.1 Asymptomatic patients with abnormal cervical cytology
(see Guidelines for Referral for Colposcopy)

1.2 Symptomatic patients
There may be local guidelines for “fast-tracking”, which should be followed, but in general, patients with symptoms such as post-coital or inter-menstrual bleeding, post-menopausal bleeding, or offensive blood-stained vaginal discharge, with or without a suspicious cervix, and irrespective of smear result, should be referred to the gynaecologist for further investigations: which may include colposcopy or EUA with D&C and cervical biopsies.

1.3 Advanced disease
Patients with advanced disease may present with ureteric obstruction or bowel complications and be seen initially by the urologist or general surgeon. These patients should be referred to the locally designated gynaecologist or gynaecological oncology team for further management.

1.4 Colposcopy
i) Asymptomatic patients following an abnormal smear or suspicious-looking cervix should be referred for colposcopy.

ii) Symptomatic patients with a suspicious-looking cervix should be sent for a biopsy.

2. STAGING AND SPREAD OF DISEASE

2.1 FIGO 2009

Stage I The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded)
IA Invasive carcinoma which can be diagnosed only by microscopy, with deepest invasion ≤5 mm and largest extension ≥7 mm
IA1 Measured stromal invasion of ≤3.0 mm in depth and extension of ≤7.0 mm
IA2 Measured stromal invasion of N3.0 mm and not N5.0 mm with an extension of not N7.0 mm
IB Clinically visible lesions limited to the cervix uteri or pre-clinical cancers greater than stage IA □
IB1 Clinically visible lesion ≤4.0 cm in greatest dimension
IB2 Clinically visible lesion N4.0 cm in greatest dimension
Stage II Cervical carcinoma invades beyond the uterus, but not to the pelvic wall or to the lower third of the vagina
IIA Without parametrial invasion
IIA1 Clinically visible lesion ≤4.0 cm in greatest dimension
IIA2 Clinically visible lesion N4 cm in greatest dimension
IIB With obvious parametrial invasion
Stage III The tumour extends to the pelvic wall and/or involves lower third of the vagina and/or causes hydronephrosis or non-functioning kidney
IIIA Tumour involves lower third of the vagina, with no extension to the pelvic wall
IIIB Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney
Stage IV The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to Stage IV
IVA Spread of the growth to adjacent organs
IVB Spread to distant organs
N.B. Staging for carcinoma of the cervix is a clinical (not surgical) system of staging and is therefore inherently imprecise in terms of tumour volume and lymphatic spread

2.2 Spread of disease

i) Direct:
vagina
myometrium
parametrium
bladder, rectum (less common)

ii) Lymphatic:
paracervical
obturator, external & common iliac, para-aortic nodes (occ. direct)
internal iliac and pre-sacral nodes

iii) Dissemination:
usually late (lung/liver)

3. HISTOPATHOLOGY

Introduction

All tissue specimens removed at laparotomy are submitted for histopathological examination. Specimens are handled according to Standard Operating Procedures (SOPs) of the Department of Pathology, which cover fixation, dissection, block taking and reporting, and conform to national guidelines and minimum data sets (where available).

All cases are reviewed by consultant pathologists with a special interest in gynaecological pathology, and presented at the Combined Gynaecological Oncology Clinic Meeting prior to decision making about post-surgical management.

Ovarian Cancer

Histopathology reports on ovarian cancer cases include the following:

Summary of clinical history

Macroscopic description of all specimens including dimensions of ovarian tumours, status of capsule, cyst contents

Microscopic description (synoptic report available) including:

- Histological tumour type (WHO classification)
- Grade
- Status of capsule
- FIGO stage

Endometrial Cancer

Histopathology reports on endometrial biopsy specimens (Pipelle or curettage) will include:

- Histological tumour type. If the tumour type is one recognised to have an aggressive clinical course (such as papillary serous carcinoma or clear cell carcinoma), a comment to this effect will be made in the report.
- Grade

Histopathology reports on cases of hysterectomy for endometrial carcinoma will include the following:

- Summary of clinical history

Macroscopic description of specimens including:

- Dimensions of tumour
- Apparent extent, including depth of myometrial invasion, cervical involvement, adnexal involvement

Microscopic description (synoptic report available) including:
- Histological tumour type (WHO classification)
- Grade
- Extent of myometrial invasion
- Presence or absence of lymphatic/vascular space invasion
- Presence or absence of cervical mucosal or stromal involvement
- Presence or absence of adnexal involvement including fallopian tubes and ovaries
- FIGO stage

Cervical Cancer

LETZ specimens showing microinvasive carcinoma are reported using a template format, which will include the following:
- Depth of invasion in mm (measured by ocular micrometer)
- Horizontal extent of invasive lesion (measured by ocular micrometer)
- Focality of invasive lesion(s)
- Presence or absence of lymphatic invasion
- Status of excision margins
- Presence of concurrent CIN or CGIN. In early invasive adenocarcinoma, it is recognised that measurement of depth of invasion may be difficult or impossible.

Reports on diagnostic biopsy specimens of frankly invasive carcinoma will include:
- Histological tumour type
- Grade
- Presence or absence of lymphatic invasion.

Histopathology reports on Wertheim's hysterectomy cases include the following:
- Summary of clinical history
  Macroscopic description of specimens, including dimensions of tumour, extent of local spread, distance from vaginal resection margin

Microscopic description (synoptic report available) including:
- Histological tumour type (WHO classification)
- Grade
- Presence or absence of lymphatic/vascular space invasion
- Depth of invasion and horizontal extent (measured in mm by ocular micrometer) of microinvasive or early invasive squamous carcinomas
- Status of original and paracervical surgical excision margins
- FIGO stage

Vaginal cancer

The histopathological report will include the following:
- Summary of clinical information provided, including reasons for biopsy
- Specimen type
- Macroscopic description, including accurate measurement of specimen, tumour and distance from resection margins

Microscopic report including:
Histological tumour type
- Accurate measurement (optical micrometer) of depth and lateral extent of early invasive tumours
- Proximity to lateral and deep excision margins
- Presence or absence of lymphatic/vascular space invasion

Vulval cancer

The histopathological report will include the following:
- Summary of clinical information provided, including indications for biopsy
- Specimen type
- Macroscopic description, including accurate measurement of specimen, tumour and distance from resection margins

Microscopic report including:
- Histological tumour type
- Accurate measurement (optical micrometer) of depth and lateral extent of early invasive tumours
- Proximity to lateral and deep resection margins
- Presence or absence of lymphatic/vascular space invasion
- Description of adjacent vulval skin
- Total number of lymph nodes in each submitted group
- Total number of involved lymph nodes in each submitted group

4. INVESTIGATIONS

(may not be required in patients with early stage disease)

i) EUA and cervical biopsies +/- D&C
ii) FBC, U&E, Creatinine, LFTs
iii) MRI scan abdomen and pelvis for assessment of local spread and measurement of tumour volume. MRI is probably more helpful than CT for the demonstration of lymph node enlargement, but is not always reliable.
iv) CT thorax and abdomen
v) consider CT PET

5. TREATMENT

All patients will have an opportunity to discuss their condition and will be given a full explanation of the aims and possible side effects of treatment, before giving their written informed consent to treatment. In early stage disease, management may be modified according to the fertility requirements of the patient.

5.1 Microinvasive carcinoma

NB This diagnosis must never be made solely by punch biopsy. An adequate loop biopsy is mandatory for this diagnosis.

5.1.1 Stage Ia1
Usually no further treatment is required after an adequate LETZ, in which the resection margins are clear. A further LETZ may be required if the margins of the first LETZ specimen are involved. Simple hysterectomy may be appropriate in the presence of gynaecological symptoms, if childbearing is complete, and/ or if the patient prefers.

5.1.2 Stage Ia2
Usually treated more radically than stage Ia1 with a 'modified' radical hysterectomy and pelvic lymphadenectomy.

5.2 Stage Ib and IIa

Wertheim's hysterectomy with pelvic lymphadenectomy or radical radiotherapy. Results of both treatments are comparable but there have been no randomised studies.

5.2.1 Advantages of surgery

- Defines stage of disease and lymph node histology
- Probably fewer late complications, particularly in patients with a previous history of pelvic inflammatory disease and/ or previous pelvic surgery
- In patients with co-existing benign pathology (e.g. fibroids) or anatomical anomalies (e.g. bicornuate uterus) which compromises satisfactory intra-cavitary radiotherapy
- Ovarian conservation in pre-menopausal patients, although combined HRT can be given safely following radiotherapy
- Less sexual dysfunction, although this should not be a problem with the routine use of vaginal dilators following radiotherapy
- Patient choice if suitable for surgery

5.2.2 Indications for primary radiotherapy for stages Ib and IIa

- Patient unfit for radical surgery (obesity, associated medical conditions, age)
- Large primary tumours (> 4cm)
- High risk of lymph node involvement e.g. poorly differentiated tumour, lymphatic permeation
- Patient preference

5.2.3 Indications for pelvic XRT following hysterectomy

- Tumour close to resection margins and/ or parametrial extension (i.e. tumour upstaged)

Three or more positive lymph nodes following pelvic lymphadenectomy

- 1 - 3 positive lymph nodes, deep stromal invasion, lymphatic or vascular permeation: cases must be discussed individually
- Diagnosis made after simple hysterectomy

5.2.4
a) Non-bulky Ib consider 2 insertions 6750cGy to point a.
b) Bulky tumours > 3cm and/ or evidence of lymphatic/ vascular permeation, and/ or lymph node enlargement on MRI scan, require external beam radiotherapy to the whole pelvis and weekly chemotherapy (see para 5.3.1) plus intracavitary caesium 2700cGy to point A single insertion.

5.3 Stage IIb and III
5.3.1 External beam therapy
3 or 4 field 'brick' technique using 6 or 10MV photons:
- CT planned

If there is evidence of lymph node enlargement on MRI or CT scan, the fields may be extended to cover the lower para-aortic nodes:

Dose:
Stage Ib to IV: 4500 cGy in 25 daily fractions over 5 weeks with weekly cisplatin 40mg/m2
If nodal involvement may give 50.4 Gy in 28 fractions

Post-operative : 4500 cGy in 25 daily fractions over 5 weeks with weekly cisplatin

5.3.2 Intracavitary caesium
27 Gy to point A. Note we will soon be moving to MRI planned brachytherapy using an Iridium source

5.3.3 Synchronous chemotherapy
Cisplatin 40mg/m2 iv infusion over 3 hr weekly x 4 or 5 during external beam therapy

5.4 Stage IV
Therapy must be individualised. Some patients with central disease involving the bladder/ bowel may be suitable for pelvic exenteration. Treatment is usually palliative. Palliative XRT is often helpful to control symptoms (see Para.5.6)

5.5 Radiotherapy for nodal disease
5.5.1 Stage Ib and IIa with positive pelvic nodes
Patients with early stage disease who have histologically positive nodes, and who are receiving standard post-operative pelvic XRT (as Para 5.3.1 above), should be considered for a 'boost' to the involved nodes: 1500cGy in 8 fractions

5.5.2 Para-aortic nodes
Para-aortic nodes are not routinely irradiated in advanced disease, but it may be helpful in patients with symptoms from enlarged nodes (see Para.5.6).

5.6 Palliative radiotherapy

5.6.1 A single intra-cavitary treatment prescribing 3500cGy to 'Point A' will often control bleeding in advanced disease.

5.6.2 External beam therapy using parallel opposed fields (A-P) to the whole pelvis or para-aortic nodes will often improve pain control from advanced disease.

6. CHEMOTHERAPY

6.1 Indications

- Primary treatment of patients presenting with metastatic disease
- Treatment of recurrent or disseminated disease not amenable to exenteration or further XRT

6.2 Regimes

Carboplatin/Palliate
Cisplatin /Topotecan

7. FOLLOW UP

7.1 After surgery

4-monthly for 1 year, 6-monthly for 1 year, then yearly to 5 years. Discharge at 5 years, if well.

7.2 After radiotherapy

On completion of radiotherapy, all patients will be given a vaginal dilator to use until the vaginal epithelium is healed (usually 1st month post-treatment) to prevent vaginal stenosis.

Pre-menopausal patients are commenced on HRT, the preferred option being a continuous combined therapy. (NB patients who have not had a hysterectomy must be given combined HRT).

Follow-up 1 month post treatment, 3-monthly for 2 years, 6-monthly for up to 5 years, then written follow-up by GP, if well with no treatment-related morbidity. All patients should expect a follow-up MRI scan about 6 months after completing treatment & sometimes a re-assessment EUA.

8. TREATMENT OF RECURRENT/METASTATIC DISEASE

8.1 Central recurrence

- Consider pelvic exenteration
- XRT following primary surgery if no previous radiotherapy

8.2 Side wall recurrence

- XRT if not previously treated
- Consider chemotherapy, but response not high if previous XRT

8.3 Metastatic disease

- Chemotherapy response up to 60% with pulmonary metastases
- Palliative XRT for para-aortic nodes, skeletal and brain metastases

9. TREATMENT DEFINITIONS

CISPLATIN
40mg/m² IV Infusion Days 1, 8, 15, 22 and 29
Weekly for 5 weeks

100mg/m² IV Infusion Day 1
Repeated every 21 days

80mg/m² IV Infusion Day 1
5-Fluorouracil 1000mg/m²/day IV Infusion Days 2-5 via pump
Repeated every 21 days for up to 6 cycles

Carboplatin/Paclitaxel
Carboplatin AUC 5-6, Paclitaxel 175 mg/m2

Author: …… Signature: …….. Date: ……

Chair: …… Signature: …….. Date: ……
(on behalf of OHMMG)

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