SCAN Gynaecological Group

Clinical Management Protocols:
Cancer of the Cervix

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THE MANAGEMENT OF CANCER OF THE CERVIX

All patients, following a diagnosis of invasive carcinoma of the cervix, should be referred to the Gynaecological Multi-disciplinary Meeting (MDM) for discussion regarding their further management. In general patients with early stage disease (FIGO Stage IB) will be seen by either or both the gynaecological oncologist and the clinical oncologist to discuss possible treatment options.

When a LETZ or biopsy is reported as showing invasive or micro invasive carcinoma, the pathology should be reviewed at the Gynaecological MDM 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, advice, and information throughout the cancer journey.
**DIAGNOSIS**

**Asymptomatic patients with abnormal cervical cytology**
(See Guidelines for Referral for Colposcopy)

**Symptomatic patients**
Cancer of the cervix is rare in women with history of adequate attendance for cervical screening and negative smears. The symptoms associated with cervical cancer are non-specific, and common to many benign gynaecological conditions – intermenstrual bleeding, postcoital bleeding, postmenopausal bleeding (PMB), vaginal discharge and pelvic pain. Women presenting with PMB should have a pelvic examination during the course of their clinical assessment to exclude cancer of the cervix (SIGN 61 Investigation of postmenopausal bleeding). The probability of a woman with postcoital bleeding having cervical cancer is low (1:44,000 in women under 24, 1:2,400 in women over 45, SIGN 99 Management of cervical cancer). The National Cancer Referral criteria for urgent referral are post-coital bleeding age > 35 years that persists for more than 4 weeks, and for non-urgent referral, repeated unexplained post-coital bleeding (NB Chlamydia infection should be excluded prior to referral). Unless the cervix appears suspicious of cancer on examination, referral should be to gynaecology in the first instance, or as dictated by local pathways.

**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 gynaecology MDM for discussion regarding further management.

**Colposcopy**

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

ii) Symptomatic patients with postcoital or intermenstrual bleeding should be referred to the general gynaecology clinic for assessment with onward referral to colposcopy thereafter, only if indicated.
STAGING AND SPREAD OF DISEASE

FIGO Staging

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.

Stage 0  Carcinoma in situ (CIN3).

Stage I  Cervical carcinoma confined to uterus

   Ia1  \leq 3\text{mm stromal invasion}, \leq 7\text{mm surface extent.}
   Ia2  > 3\text{mm and} \leq 5\text{mm stromal invasion,} \leq 7\text{mm surface extent.}
   Ib1  Tumour larger than Ia2 but \leq 4\text{cm diameter.}
   Ib2  Tumour larger than Ia2 and > 4\text{cm diameter.}

Stage II  Cervical carcinoma invading beyond uterus, but not to pelvic side wall, or lower one third of vagina

   IIA  Without parametrial invasion.
   IIB  With parametrial invasion.

Stage III  Carcinoma extending to pelvic wall and/ or involving lower third of vagina and / or causing hydrenephrosis or non-functioning kidney

   IIIA  Tumour involving lower ⅓ of vagina; no extension to pelvic side wall.
   IIIB  Tumour extending to the pelvic side wall and/ or causing hydrenephrosis or non-functioning kidney
Stage IV  Tumour invading bladder or rectum and/ or extending beyond true pelvis

IVa  Mucosa of bladder or rectum involved (not bullous oedema only).
IVb  Distant metastases.

Spread of disease

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

ii) Lymphatic:
   - Paracervical
   - Obturator, external & common iliac,
   - Para-aortic nodes (occasionally direct)
   - Internal iliac and pre-sacral nodes

iii) Dissemination:
   - usually late
STAGING INVESTIGATIONS

- MRI scan of pelvis/abdomen to assess primary tumour volume and extension into adjacent tissues – parametrium, vagina, bowel, and bladder and to assess liver. (NOT INDICATED IN IA DISEASE)

- Post contrast CT scan of pelvis in women with contraindications to MRI scan.

- Non contrast CT chest to detect presence of visceral metastatic disease. (NOT INDICATED IN IA DISEASE)

- Indications for PET CT scan

  1. Following staging MRI of pelvis and lower abdomen, cases with stage 1B or IIA cervix cancer (greater than 2 cm) who are being considered for radical hysterectomy and pelvic lymph node dissection (RHND) are advised to undergo PET/ CT to exclude any occult metastases.

  2. Following staging MRI of pelvis in patients being considered for concomitant Chemo-Radiation Therapy (CCRT) for localised disease to detect presence of involved pelvic and para aortic lymph nodes.
HISTOPATHOLOGY

All tissue specimens removed at surgery are submitted for histopathological examination. Specimens are handled according to 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).

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)
  - Histological size
  - Extent of tumour (e.g. involvement of vaginal wall or parametrium)
  - Grade
  - Presence or absence of lymphatic/vascular space invasion
  - Depth of invasion
  - Pattern of invasion (infiltrative or cohesive invasive front)
  - Horizontal extent (measured in mm by ocular micrometer) of microinvasive or early invasive squamous carcinomas
  - Status of resection margins (presence of tumour and distance from margin)
  - FIGO stage

All cases are reviewed by consultant pathologists with a special interest in gynaecological pathology, and presented at the Combined Gynaecological Oncology Multi Disciplinary Meeting prior to decision making about post-surgical management.
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. For some patients, a laparoscopic (key-hole) approach might be considered.

Micro invasive carcinoma

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

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. A vaginal hysterectomy, simple total abdominal (TAH) or laparoscopic (TLH) hysterectomy (+/- BSO) may be appropriate in the presence of gynaecological symptoms if, childbearing is complete, or there are specific high risk factors and/ or a history of poor compliance with follow up, and/ or if the patient prefers.

Stage Ia2

Usually treated more radically than stage Ia1 with a 'modified' radical hysterectomy and pelvic lymphadenectomy/ sampling, or radical total laparoscopic hysterectomy with laparoscopic pelvic lymph node sampling.
Surgery for Stage IB1 disease

Radical (Wertheim's) hysterectomy with pelvic lymphadenectomy is comparable to radical radiotherapy and concurrent Cisplatin chemotherapy in Stage IB1 tumours (<4cm) although there have been no clinical trials directly comparing the two treatment modalities. For women with stage IB1 tumours, radical total laparoscopic hysterectomy and laparoscopic pelvic lymphadenectomy may be considered.

Fertility sparing surgery

In patients wishing and eligible for fertility sparing surgery (tumour ≤2cm), consideration will be given to referral to a national centre (usually London) with experience in radical trachelectomy and laparoscopic pelvic lymphadenectomy. It is envisaged that this service will be offered in a Scottish centre in the future.

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
Primary radical radiotherapy for IB-IVA disease

Treatment regime

- 4500cGy in 25 fractions over 5 weeks (15MeV photons for most patients)
- Haemoglobin to be maintained above 12g/dl
- MRI scan repeated in 4th/5th week of treatment to assess response to treatment and assist in planning of brachytherapy
- Image guided HDR cervical brachytherapy (3 insertions)

Concurrent radical / adjuvant chemoradiotherapy:

Single agent cisplatin chemotherapy is used as a radiation sensitizer and has been shown in several trials and meta-analyses that it contributes to a significant improvement in overall survival. It is also associated with increased toxicity in the long term.

Indications:
- Radical or adjuvant treatment with radiotherapy
- WHO PS 0 or 1
- Adequate renal function (creatinine clearance >50ml/min)

Chemotherapy:
- Weekly concurrent cisplatin chemotherapy (40mg/m²)
- Cisplatin dose capped at 40mg stat or omitted if PS=/>2 or creatinine clearance <50ml/min

Neoadjuvant chemotherapy:

This is not routine practice in the management of cervical cancer but in certain exceptional circumstances that will need to be discussed at the gynae-oncology MDT neoadjuvant chemotherapy can be considered e.g. in the management of patients presenting during pregnancy.
Post-operative chemo radiotherapy following radical hysterectomy

Indications:

- Positive lymph nodes
- Positive margins ($\leq 5$mm)
- $\geq 2$ of the following
  - $>1/3$ stromal invasion
  - LVSI
  - tumour diameter $>4$cm

Treatment regime

- 4500cGy in 25 fractions over 5 weeks (15MeV photons for most patients)
- Weekly concurrent cisplatin chemotherapy ($40$mg/m$^2$)
- Chemotherapy dose capped at 40mg stat or omitted if PS$>$2 or creatinine clearance $<50$ml/min
- Haemoglobin to be maintained above 12g/dl
- HDR Vaginal Vault Brachytherapy if close/positive margins ($\leq 5$mm):
  - 2100cGy in 3 fractions over 3 weeks to top 2cm of vagina at 0.5cm depth

Palliative radiotherapy

Indications:

- Control pelvic symptoms eg pain, bleeding, discharge, in pts presenting with:
  - metastatic disease
  - local recurrence

Treatment regime

- 3000cGy in 10 fractions
- 2000cGy in 5 fractions
- 800cGy single fraction
- Brachytherapy insertion (ring & tandem or a line source may be appropriate)
FOLLOW-UP POLICY AFTER RADICAL TREATMENT

After surgery

3-monthly for 1 year, 6-monthly for 1 year, then yearly to 5 years. Vault cytology will be performed at 6 and 18 months following hysterectomy and discontinued thereafter if cytology is negative. Discharge at 5 years, if well, with normal cytology. No further smears will be required.

Patients treated by radical trachelectomy will have 6-monthly smears for 1 year and yearly smears thereafter for 9 years. Discharge at 10 years if well, to routine recall at the Practice, to age 60. Completion surgery is not advised.

After radiotherapy

Follow-up 8 weeks post treatment with MRI to assess response, then 3-monthly to 18 months, then 6-monthly to 3 years then annually to 5 years.

On completion of radiotherapy patients are provided with a patient information leaflet ‘After radiotherapy to the pelvis’. This details the use of vaginal dilators and pelvic floor exercises post treatment. Vaginal dilators minimize vaginal vault stenosis post treatment. It is recommended that the dilators are used three times weekly for at least twelve months starting two weeks following completion of treatment. In addition regular pelvic floor exercises help strengthen the muscles in the pelvic floor post treatment.

Pre-menopausal patients are offered HRT on completion of treatment to reduce post menopausal symptoms. A combined preparation of HRT is required.

Referral to a menopause clinic or a pelvic dysfunction clinic may be required for selected patients.
TREATMENT OF RECURRENT/ METASTATIC DISEASE

Central recurrence

- Consider pelvic exenteration. When exenteration is proposed for locally relapsed disease PET/CT is recommended to identify those patients who are not suitable surgical candidates.
  - Consider XRT if not previously treated.

Side wall recurrence

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

Metastatic disease

- Palliative chemotherapy
- Palliative XRT for para-aortic nodes, skeletal and brain metastases
- Consider entry into clinical trial
Palliative chemotherapy:

Indications:
- patients who relapse or present with metastatic disease
- WHO PS 0 or 1
- Adequate renal function (creatinine clearance >50ml/min)

1\textsuperscript{st} line chemotherapy: Cisplatin & topotecan combination has been shown to have a survival advantage over single agent cisplatin. Topotecan requires prior approval by MMC.
- Cisplatin 50mg/m\textsuperscript{2} day 1
- Topotecan 0.75mg/m\textsuperscript{2} day 1,2,3
- Repeated every 21 days for maximum of 6 cycles with CT scan to assess response after 3\textsuperscript{rd} and 6\textsuperscript{th} cycles

In patients who cannot have topotecan then single agent cisplatin is the first line treatment.
- Cisplatin 100mg/ m\textsuperscript{2} day 1
- Repeated every 21 days for maximum of 6 cycles with CT scan to assess response after 3\textsuperscript{rd} and 6\textsuperscript{th} cycles

2\textsuperscript{nd} line chemotherapy: Carboplatin & paclitaxel. This combination can be considered in first line for patients who relapse within less than 6 months after radical treatment with cisplatin chemoradiotherapy.
- Carboplatin AUC 6 (use Chateleut formula) day 1
- Paclitaxel 175mg/ m\textsuperscript{2} day 1
- Repeated every 21 days for maximum of 6 cycles with CT scan to assess response after 3\textsuperscript{rd} and 6\textsuperscript{th} cycles
Additional information can be found at the following websites:

http://www.cancerhelp.org.uk>
