# Invasive cervical cancer

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## Abstract

Cervical cancer is the second most common cancer in women worldwide and is the leading cause of death in women in sub-Saharan Africa. In this review, the aetiology of cervical cancer is discussed plus HPV vaccination, diagnosis, imaging techniques, FIGO staging and management with surgical options for stage 1a1–1b1 and non-surgical options for stage 1b2–3b cervical cancer. Palliative treatments and exenterative surgery are included.

**Keywords** cervix cancer; chemoradiation; cone biopsy; radical hysterectomy; trachelectomy

## Introduction

Cervical cancer is the second most common cancer in women worldwide. In developed countries, the incidence of cervical cancer is low due to screening programmes. In the UK, approximately 2800 women are diagnosed with and 1000 women die from cervical cancer each year, with screening estimated to save up to 5000 lives per year.

## Aetiology

The cause of cervical cancer is persistent human papilloma virus infection. Human papilloma virus (HPV) is detected in 99% of cervical tumours, in particular the oncogenic subtypes such as HPV 16 and 18 which account for 70% of all cervical tumours. Other oncogenic subtypes of HPV are 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 82.

Newly acquired genital HPV infections are usually eliminated by the immune system. If this does not occur, the longer an oncogenic HPV subtype is present and the greater the viral load, the higher the chance of developing a precancerous lesion on the cervix. A precancerous lesion can progress to invasive cancer, but may also regress if the HPV is eliminated. Human immunodeficiency virus (HIV) infection and other immune deficiency states such as transplant rejection drug usage and smoking act as cofactors to stop the elimination of HPV by the immune system.

Cervical cancer is more common than other HPV derived cancers (vagina, vulva, penile, anal, and laryngeal) due to the transformation zone on the cervix. The area of exposed columnar tissue on the cervix known as the ectropion, under goes squamous metaplasia and transforms into squamous tissue – hence the label transformation zone. This area is susceptible to the effects of oncogenic HPV.

## Vaccination

Most people who come into contact with HPV can clear the virus from their bodies. In some women the HPV persists and can cause abnormal cells to develop in the cervix, vulva, vagina and anus. It is estimated that vaccinating girls against HPV could save up to 400 lives per year.

There are currently three vaccines available:

- Cervarix a bivalent vaccine active against HPV 16 and 18.
- Gardasil, quadrivalent vaccine active against HPV 6, 11 plus 16 and 18.
- Gardasil 9, nonavalent vaccine against 6,11 plus 16, 18, 31, 33, 45, 52 and 58

At present Gardasil quadrivalent vaccine is being used in the UK to vaccinate young girls aged 12 to 13 as part of the childhood vaccination programme. This vaccine is protective for cervical cancer and genital warts. The vaccine is given as a series of two injections 6–24 months apart. The vaccine is preventative rather than therapeutic and is best given before the onset of sexually activity prior to exposure of HPV. Girls can have the HPV vaccine up to aged 18 on the NHS but if they are over 14 they need a series of three injections because the immune response to the vaccinations are not as good in older girls.

In Australia where the quadrivalent vaccine has been used since 2007 there has been a 90% reduction in genital warts in heterosexual men and women under the age of 21 years.

Women should attend for cervical screening from the age of 25 even if they have been vaccinated. Vaccination will reduce the risk of cervical cancer by 70%.

## Diagnosis

Diagnosis is made by history, examination and biopsy.

### History

The symptoms associated with cervical cancer are very common and non-specific (see list below). Many are associated with *Chlamydia trachomatis* infection and therefore it is important to test for this infection particularly in young women where it is highly prevalent.

Signs and symptoms suggestive of cervical cancer are:

- Postcoital bleeding – the most common symptom
- Intermenstrual bleeding
- Postmenopausal bleeding
- Vaginal discharge (blood stained)
- Pelvic pain
- Suspicious cervix on examination

In later stages of cervical cancer:

- Loin pain from hydronephrosis due to obstruction of the ureters from lateral spread
- Sciatica as the cancer compresses nerve roots
- Swollen leg from deep vein thrombosis

The prevalence of post-coital bleeding in the community is thought to be between 0.7 and 9%. Post-coital bleeding is known to be a warning sign for cervical cancer and is the presenting symptom in 6–10% of such patients. The NHS Cervical Screening Programme suggests referral to a gynaecologist if a

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woman presents with post-coital bleeding and is over 40 years old or if their cervix looks abnormal. NHS suspected cancer guidelines suggest that post-coital bleeding for more than 4 weeks in women older than 35 years should be referred urgently to be seen within 2 weeks, and for all other cases of repeated unexplained PCB, referral should be early, within 4–6 weeks.

Post-menopausal bleeding can herald an endometrial cancer and therefore these women need an ultrasound to measure the endometrial thickness and an endometrial biopsy if the endometrial thickness is ≥4 mm.

### Examination

Examination of the cervix with a speculum is mandatory.

A suspicious cervix, or a woman with persistent symptoms is referred to colposcopy for a more detailed examination and biopsies. Figure 1 shows cervical cancer.

### Investigations

**Pathology:**

The common types of cervical cancer are:

- Squamous cell carcinoma (approximately 75%)
- Adenocarcinoma (approximately 20%)

Small cell and large cell neuroendocrine tumours, sarcoma, lymphoma and melanoma are possible but rare.

Squamous cell carcinomas arise from the precursor cervical intraepithelial neoplasia (CIN) in squamous cells and adenocarcinomas arise from the precursor cervical glandular intraepithelial neoplasia (CGIN) in glandular cells.

Spread of cervical cancer is usually direct to parametrium (the tissue to the side of the cervix), then the pelvic side wall (causing ureteric obstruction), bladder and bowel. It can also spread via lymphatics to pelvic and paraaortic lymph nodes. Spread via the blood to the lungs and liver occurs late.

There are risk factors that determine if the patient is high risk or low risk for metastatic disease and they are:

- Tumour grade
- Tumour size
- Depth of invasion
- Lymphovascular space invasion
- Status of lymph nodes

**Imaging:** all patients with a diagnosis of cervical cancer > stage 1a1 have an MRI cervix (Figure 2) to define local spread and a CT of abdomen and chest to look for signs of distant spread. MRI is used for the cervix as it is able to detect spread to the parametria. CT is not able to confidently demonstrate this. MRI is more accurate than clinical staging.

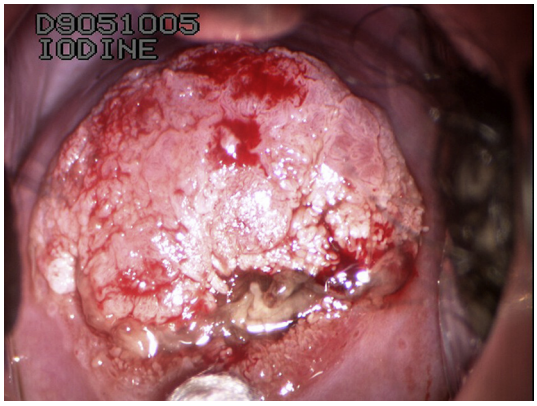


**Figure 1** Cervical cancer.

Criteria for lymph-node involvement on CT and MRI are based on size and morphology. A node is judged suspicious when shape is spherical and the shortest diameter is greater than 10 mm. More recently, positron emission tomography (PET/CT) has been seen to have the potential to accurately delineate the extent of disease and the disease in distant sites, with high sensitivity and specificity. PET/CT is especially useful in detecting lymph node involvement and is more sensitive than CT alone or MRI especially in detecting paraaortic lymph node involvement.

A new technique called diffusion-weighted imaging (DWI) is a form of MR based imaging that assesses the water diffusion properties of tissue. Generally densely cellular tissues or those with cellular swelling exhibit lower diffusion coefficients and this difference has helped to differentiate between normal tissue and cancer. This can be helpful to determine if lymph nodes are involved with disease, or if there is residual tumour or recurrence following treatment.

**Learning points**

- Anyone with irregular vaginal bleeding should have a speculum examination to examine the cervix
- Pre-menopausal women with irregular vaginal bleeding should be tested for *C. trachomatis*
- Women with postmenopausal bleeding should have an ultrasound scan to measure endometrial thickness and have a biopsy if the endometrial thickness is ≥4 mm

## Staging (Figure 3)

Since most cases of cervical cancer occur in developing countries with poor resources, and in order to allow comparisons of data between different countries, FIGO (Féderation Internationale de Gynécologie et d'Obstétrique) staging does not include information from pelvic MRI, CT and PET/CT. Lymph node status does not alter FIGO staging, as nodal spread is not confirmed if treatment is with chemoradiation (see section 6).

FIGO staging is based on clinical examination performed under anaesthetic in order to determinate tumour size, vaginal and/or parametrial involvement and bladder/rectum tumour spread. Chest radiography, intravenous pyelography, cystoscopy and proctoscopy (if apparent bladder or rectal involvement) are permitted.

Determining parametrial involvement is important because the treatment modality changes from surgery with no parametrial involvement to chemoradiotherapy if parametrial involvement exists. An examination under anaesthesia allows a more accurate assessment of the parametrium as the patient is more relaxed than in clinic, but MRI is more accurate than clinical assessment.




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