

CERVICAL DYSPLASIA AND CANCER

Worldwide, cervical cancer is the most common cause of death from cancer in women, with 80% of cases occurring in developing countries. In developed countries, regular screening with Papanicolaou smears has markedly decreased the incidence of the disease, and most cases now occur in women who have not had regular smears. The incidence, and mortality, of cervical cancer in Australia have decreased markedly since the introduction of the National Cervical Cancer Screening Program in 1992.

ETIOLOGY AND EPIDEMIOLOGY

Cervical cancer is rare before 20 years of age; the average age at onset is 47 years of age.

Almost all cases of cervical cancer are caused by exposure to a high-risk human papilloma virus (HPV), such as type 16, 18, 31, 33, or 35. Types 6 and 11 have been associated with cervical warts and low-grade cervical intraepithelial neoplasia (CIN) (precancer).

CIN represents a spectrum of disease, ranging from CIN I (mild dysplasia) to CIN III (severe dysplasia and carcinoma in situ). At least 35% of patients with CIN III will develop invasive cancer within 10 years, whereas lower grades of CIN may spontaneously regress.

PREVENTION OF CERVICAL CANCER

Primary prevention is now possible with the development of a vaccine against two high risk HPV types (16 & 18). These two viral types are together responsible for 70% of cervical cancers. Two vaccines are available in Australia. Gardasil (16, 18, 6, 11) is available for females from 9 to 26 years. A free immunisation program is currently available for schoolgirls aged 12 & 13 years. Cervarix is available for females from 10 to 45 years.

SCREENING OF ASYMPTOMATIC WOMEN

All women, once they have become sexually active, should undergo cervical screening. In Australia, the National Cervical Screening Program provides free pap smears for all women aged 19 to 69 years. The recommended screening interval is every 2 years.

The false-negative rate for conventional pap smears for high-grade intraepithelial lesions (CIN 2 – 3) is generally reported to be about 20%, but it is higher for glandular lesions and for invasive cancers.

New technologies have been developed to decrease the false negative rate. Liquid-based cytology eg Thin Prep, decreases the number of unsatisfactory smears, and gives some improvement in accuracy, particularly for glandular lesions. The spatula or brush taking the smear is placed into a fixative solution, instead of smearing the cells directly onto a glass slide. Although commonly used in Australia, it is not yet approved for Medicare funding.

COLPOSCOPY

The colposcope is a stereoscopic binocular microscope of low magnification used to visualise the cervix to evaluate patients with an abnormal Pap smear. A biopsy is taken of abnormal looking areas on the cervix.

To perform a colposcopic examination, an appropriately-sized speculum is inserted to expose the cervix, which is cleansed with a cotton pledget soaked in 3% acetic acid to remove adherent mucus and cellular debris.

TREATMENT OF INTRAEPITHELIAL NEOPLASIA (PRECANCER)

LOOP EXCISION OF THE TRANSFORMATION ZONE

Large loop excision of the transformation zone (LLETZ) has gained popularity because it is simple and cheap, it can be performed on an outpatient basis under local anaesthesia, and tissue is obtained for pathological evaluation.

LASER

Destruction of the precancer by carbon dioxide laser (*light amplification by stimulated emission of radiation*) can be performed as an outpatient procedure, under local anaesthesia. Bleeding may sometimes occur, but scarring is minimal and large lesions may be destroyed with low failure rates (in the order of 5% to 10%). The equipment is expensive, so laser has lost favour in most centres.

CRYOSURGERY (Freezing)

The cryosurgery technique is a relatively painless outpatient procedure that can be performed without anaesthesia. There is no bleeding, and the equipment is cheap. However, there is a high failure rate for large lesions and for lesions extending down glands. The major side effect is a rather copious vaginal discharge that persists for several weeks.

CONE BIOPSY

This is mainly a diagnostic technique, when the abnormal area extends up the endocervical canal, but it may be used for treatment. Provided that the margins of resection are clear, cure rates are as high as those with hysterectomy for intraepithelial lesions. Bleeding, infection, cervical stenosis, and cervical incompetence are the major complications.

Hysterectomy is rarely necessary for the treatment of CIN. It may be applicable when sterilization is desired for other reasons in a patient with CIN III or when there is concomitant uterine or ovarian disease.

INVASIVE CANCER

SYMPTOMS

Invasive cancer usually presents with postcoital, intermenstrual, or postmenopausal vaginal bleeding. In patients who are not sexually active, bleeding from cervical cancer usually does not occur until the disease is quite advanced (unlike patients with endometrial cancer, who almost always bleed early). Persistent vaginal discharge, pelvic pain, leg swelling, and urinary frequency are usually seen with advanced disease.

PATHOLOGIC FEATURES

Most uterine cervical cancers are squamous in origin. Adenocarcinomas and adenosquamous carcinomas are increasing in incidence and account for about 20% to 25% of cases.

PATTERNS OF SPREAD

Invasive cervical cancer spreads by direct invasion of cervical stroma, body of the uterus, vagina, and parametrium and by lymphatic spread to pelvic and then paraaortic lymph nodes. Spread via the blood stream is usually a late phenomenon, particularly to the lungs, liver, and bone.

PREOPERATIVE INVESTIGATIONS

CLINICAL STAGING

The FIGO staging of cervical cancers is shown in Table 1

Table 1. The International Federation of Gynaecology and Obstetrics (FIGO) staging of cervical carcinoma

Stage	
PREINVASIVE CARCINOMA	
Stage 0	Carcinoma in situ, intraepithelial carcinoma (cases of stage 0 should not be included in any therapeutic statistics).
INVASIVE CARCINOMA	
Stage I	The carcinoma is strictly confined to the cervix.
Stage Ia	Invasive cancer is identified only microscopically. All gross lesions even with superficial invasion are Ib cancers. Invasion is limited to a measured stromal invasion, with a maximal depth of 5mm and a horizontal extension of not more than 7mm.
Stage Ia1	Measured invasion of stroma not greater than 3mm in depth and 7mm in width.
Stage Ia2	Measured invasion of stroma greater than 3mm and not greater than 5mm and width not greater than 7mm.
Stage Ib	Clinical lesions confined to the cervix or preclinical lesions greater than stage Ia.
Stage Ib1	Clinical lesions not greater than 4cm in size.
Stage Ib2	Clinical lesions greater than 4cm in size.
Stage II	The carcinoma extends beyond the cervix but has not extended to the pelvic wall or to the lower third of the vagina.
Stage IIa	No obvious parametrial involvement.
Stage IIb	Obvious parametrial involvement.
Stage III	The carcinoma has extended to the pelvic wall. On rectal examination there is no cancer-free space between the tumour and the pelvic wall. The tumour involves the lower third of the vagina. All cases with hydronephrosis or non-functioning kidney should be included, unless they are known to be due to another cause.
Stage IIIa	Tumour involves lower third of the vagina with no extension to the pelvic wall.
Stage IIIb	Extension onto the pelvic wall and/or hydronephrosis or non-functioning kidney.
Stage IV	The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to stage IV.
Stage IVa	Spread of the growth to adjacent organs.
Stage IVb	Spread to distant organs.

TREATMENT OF INVASIVE CANCER

STAGE IA (MICROINVASIVE CARCINOMA)

A preoperative diagnosis of microinvasive carcinoma can be made only on the basis of a cone biopsy of the cervix.

When the depth of invasion on cone biopsy is 3mm or less, horizontal dimension is 7mm or less (stage Ia1), and there is no lymphatic or vascular space involvement, an abdominal or vaginal hysterectomy is appropriate treatment. Cervical conization alone may suffice if the patient desires to maintain her fertility, as long as the cone margins are free of disease. For stage Ia2 disease, or if there is lymphatic or vascular space involvement, most gynaecologic oncologists recommend modified radical hysterectomy and pelvic lymph node dissection. If childbearing is desired, large-cone biopsy or radical trachelectomy combined with pelvic lymphadenectomy may be offered.

STAGE Ib

Stage Ib disease may be treated by either radical hysterectomy and bilateral pelvic lymphadenectomy or radiation therapy. The advantage of surgery is that the ovaries may be spared in younger women, surgical staging may be carried out, and chronic radiation complications may be avoided, particularly vaginal stenosis, radiation proctitis, and radiation cystitis.

The survival rate by either method is similar when both the surgeon and the radiotherapist are knowledgeable and skilled.

Radical Hysterectomy

In this procedure, the uterus is removed along with adjacent portions of the vagina and surrounding ligaments.

The most common complication of radical hysterectomy is bladder dysfunction, which occurs as a result of interruption of the autonomic nerves to the bladder. Normal bladder function is usually restored within 1 to 3 weeks, but 1% to 2% of patients have permanent dysfunction necessitating lifelong self-catheterisation.

A less common but life-threatening complication is deep venous thrombosis, with or without pulmonary embolism. The incidence of pulmonary embolism can be reduced with the use of early ambulation, together with prophylactic low-dose subcutaneous heparin and external pneumatic calf compression at the time of surgery and before adequate postoperative mobilization. Some degree of lymphedema occurs in 15% to 20% of patients having a pelvic lymphadenectomy.

The most serious complication of radical hysterectomy is ureteric fistula or stricture, which occurs in 1% to 2% of cases.

Radiation Therapy

For patients with stage Ib2 disease, radical hysterectomy with adjuvant radiation as necessary or primary chemoradiation, may be used.

External radiation may also be used postoperatively for patients with lymph node metastases or inadequate surgical margins. The addition of weekly cisplatin during external beam therapy has been shown to improve survival.

STAGE IIa

In patients with minimal involvement of the upper vagina, radical surgery or chemoradiation therapy may be employed. With more extensive involvement of the upper vagina, chemoradiation therapy alone is the treatment of choice.

STAGE IIb

Most patients with stage IIb lesions are treated with a combination of external beam chemoradiation and intracavitary brachytherapy. If positive para-aortic or high common iliac lymph nodes are detected by preoperative scanning, extended-field radiation may be employed to treat all of the para-aortic lymph nodes up to the diaphragm.

STAGES IIIa AND IIIb

Patients with stage IIIa and stage IIIb disease are treated with chemoradiation therapy, usually external beam followed by intracavitary brachytherapy.

STAGE IVa

Pelvic chemoradiation therapy is used in most patients with stage IVa lesions. If radiation therapy results in only partial tumour regression, a “salvage” pelvic exenteration may be performed. Primary pelvic exenteration is performed only rarely, usually when the patient presents with a rectovaginal or vesicovaginal fistula.

STAGE IVb

Patients with stage IVb disease may receive some pelvic radiation therapy to palliate bleeding from the vagina, bladder, or rectum. Because distant metastases are present, however, chemotherapy is often employed but is only palliative.

RECURRENT OR METASTATIC DISEASE

Chemotherapy

The effectiveness of chemotherapy is limited for metastatic cervical cancer.

Several drugs have been tested and found to be active in up to 35% of cases. Most responses are partial, and the patients usually progress within 12 months. The most active agents are cisplatin, bleomycin, mitomycin C, methotrexate, and cyclophosphamide.

Pelvic Exenteration

Pelvic exenteration is generally reserved for patients who have a central recurrence following pelvic irradiation. A PET scan is usually done to exclude any metastatic disease. Total exenteration involves removal of the pelvic viscera, including the uterus, tubes, vagina, ovaries, bladder, and rectum (Figure 2). Depending on the site and extent of the disease, the operation may be limited to an anterior exenteration, which spares the rectum, or a posterior exenteration, which spares the bladder.

Following the removal of the organs, pelvic reconstruction is necessary. If the bladder is removed, the ureters must be implanted into a portion of the small or large bowel that has been isolated from the remainder of the gastrointestinal tract to form a conduit. A continent conduit may be created, particularly in younger patients. When the disease is confined to the upper vagina and rectovaginal septum, the lower rectum and anal canal may be preserved and reanastomosed to the sigmoid colon. A temporary colostomy is

often required to protect the reanastomosis because of the prior irradiation. Vaginal reconstruction can be performed using a split-thickness skin graft, a rectus abdominus myocutaneous flap, or a segment of large intestine.

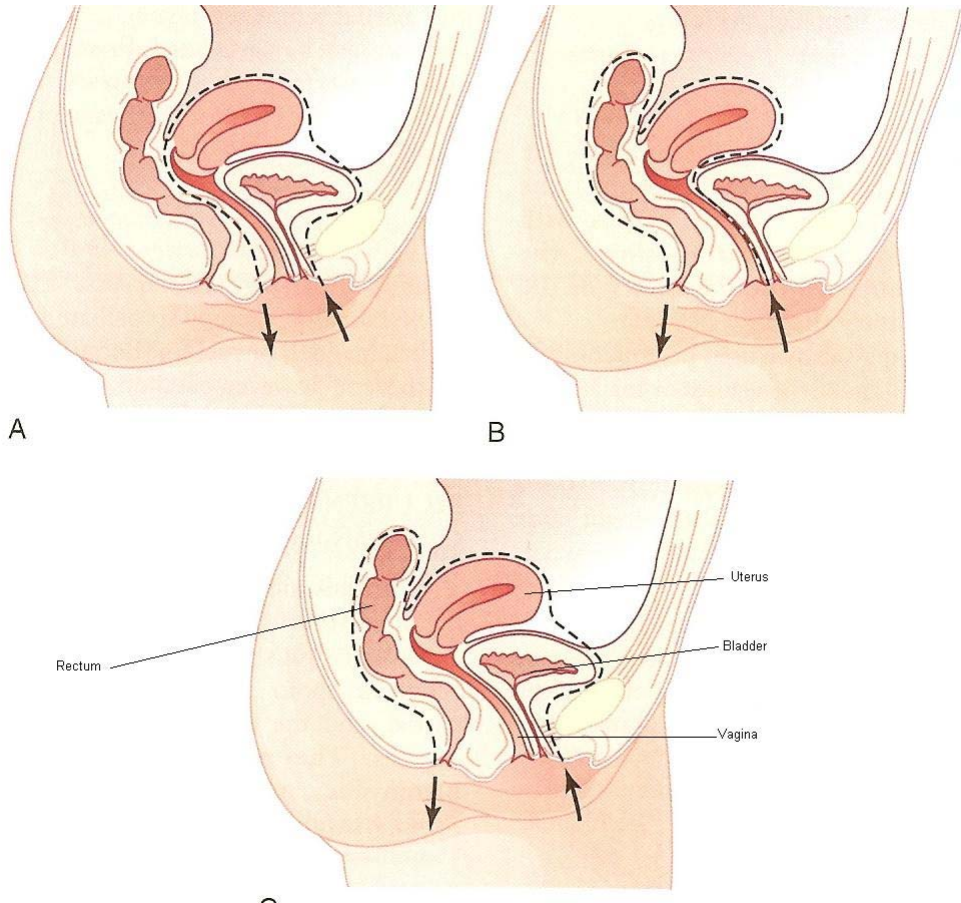


Figure 2. Organs removed in anterior exenteration (A), posterior exenteration (B), and total pelvic exenteration (C).

Prognosis for Cervical Cancer

Prognosis is related directly to clinical stage (Table 2). With higher stage disease, the frequency of nodal metastasis escalates, and the 5-year survival rate diminishes. (Survival rates are approximate only)

Table 2. Carcinoma of the cervix: survival by FIGO stage

Stage	5-Year Survival (%)
Ia	95.0
Ib	80.0
II	65.0
III	35.0
IV	20.0