Management of cervical cancer

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BACKGROUND
Australia now has one of the lowest incidence and mortality rates for cervical cancer worldwide. Women who develop the disease frequently have underutilised cervical screening opportunities and commonly present with symptoms such as abnormal vaginal bleeding.

OBJECTIVE
This article reviews the management of women presenting with cervical cancer in Australia today.

DISCUSSION
Although fertility sparing options of management are emerging, these options are only available for women presenting with early stage disease. For women presenting with substantial disease, radical surgery and/or chemoradiation is required. These women face the rigors of radical therapy as well as challenges to their sexual identity with loss of fertility, loss of ovarian function, and vaginal shortening and stenosis. Health care providers need to be cognitive and sensitive to these issues.

Australia boasts one of the lowest incidence and mortality rates for invasive cervical cancer worldwide (*Table 1*). However, despite the success of the Australian National Cervical Screening Program, 649 women developed invasive cervical cancer in Australia in 2002 and over 200 women will succumb to the disease annually. Cervical cancer is the second most common cancer affecting women worldwide with over 400 000 cases annually. Women in underdeveloped countries commonly present with advanced disease, and this, coupled with inadequate access to appropriate radiotherapy and support, has devastating consequences for both the woman and her family.

The age distribution for cervical cancer in Australia has two peaks observed for women aged 35–49 years and 60–69 years (*Figure 1*). The diagnosis of invasive cervical cancer in women of reproductive age is particularly challenging as preservation of fertility may not be possible.

Presentation

Women with early cervical carcinoma may be asymptomatic and have the diagnosis suggested only by abnormal cytology and subsequent colposcopy and biopsy. However, many women presenting with invasive cervical cancer will have significant symptoms. Over 80% of women diagnosed with invasive squamous cervical cancer will not have had regular Pap test screening.[1] In this group, it is frequently symptoms that lead the woman to seek an opinion from a general practitioner or gynaecologist.

The most common symptoms of cervical cancer are abnormal vaginal bleeding and vaginal discharge. Sexually active women experience postcoital bleeding, but for women who are not sexually active, intermenstrual and postmenopausal bleeding may eventually occur. Large tumours can become infected and cause an offensive serous discharge. Rarely women presenting with advanced disease will experience pelvic pain and discomfort, pressure symptoms, vaginal passage of faeces or urine (due to fistulae) and anuria from ureteric obstruction.

The frequency of the main histological subtypes of cervical carcinoma in Australia is illustrated in *Figure 2*.

Pap smears effectively identify squamous preinvasive disease but are unreliable at detecting preinvasive glandular disease, adenocarcinoma in situ. Women undergoing a Pap test should be informed that the test assists in the prevention of the majority of cervical cancers (excluding adenocarcinoma). Cervical screening programs result in a falling incidence of invasive squamous disease but not adenocarcinomas to any major extent (*Figure 2*). It is also extremely important to inspect the cervix carefully when taking a Pap smear. The presence of abnormal contact

bleeding or an abnormal appearance is a valid reason for colposcopic referral. It is important to be aware that in the presence of invasive cancer cervical smears are unreliable as a diagnostic tool. This is due to two factors: individual cancer cells are obscured by inflammatory exudate and necrotic debris (tumour diathesis); and the common cytological criteria used by cytologists are aimed at identifying preinvasive abnormalities. These often differ significantly from the features of frankly malignant cancer cells. A recent report suggested that invasive carcinoma was suggested in only 23 out of 71 cervical cytology reports of women presenting with invasive disease.[2] Cytology results in this situation can be falsely reassuring. If an invasive cervical cancer is suspected, direct referral to a gynaecological oncologist is appropriate.

Prevention of squamous cervical cancer via secondary measures such as organised screening programs is effective. Primary prevention measures are now available in the form of prophylactic vaccines against high risk human papillomavirus (HPV) subtypes. Both these topics are covered elsewhere in this issue of *Australian Family Physician*.

Management

Women diagnosed with invasive cervical cancer should be managed by a multidisciplinary team that includes a gynaecologic oncologist, radiation oncologist, and pathologist. Initial assessment defining the extent and stage of the disease is essential as the choice of treatment modality is defined according to the stage of disease. Cervical cancer is staged according to the FIGO (Federation Internationale des Gynaecologistes et Obstetristes) staging system (*Table 2*) which is based on a system originally developed by the Radiological Sub-Commission of the Cancer Commission of the Health Organisation of the League of Nations.[3,4] For microinvasive lesions, staging is dependant upon the dimensions of the invasive component. However, for the majority of substantial cancers the staging system is based on clinical examination and imaging of the renal tract. Vaginal and rectovaginal examination allows assessment of the extent of pelvic disease. It is acknowledged that assessment based on clinical findings is often inaccurate. The system remains to allow comparisons to be made worldwide, remembering that cervical cancer is particularly common in the developing world. In the past, full examination under anaesthesia (EUA) including cytoscopy and sigmoidoscopy was undertaken. Now more sophisticated imaging such as computerised tomography (CT) scanning and magnetic resonance imaging (MRI) has meant little additional information is gained from formal EUA. MRI has been shown to be particularly useful for determining tumour size, degree of stromal penetration, uterine body involvement, parametrial extension and lymph node status as well as invasion of adjacent structures (ie. bladder and rectum). It is argued that most clinicians allow information obtained from modern medical imaging, surgical techniques, and FIGO staging to influence management decisions, and there is now debate about the need for a revised staging system.[3]

Early cervical cancers can be treated with either surgery or radiation, with equal efficacy, although surgery allows one to delineate the exact extent of the disease, results in fewer longer term bowel, bladder and vaginal complications and allows for preservation of ovarian function. Microinvasive disease (<3 mm depth of invasion without lymph vascular space invasion) can be treated by simple hysterectomy or cone biopsy if fertility is desired. For more extensive invasive carcinomas with less than 5 mm cervical stromal invasion, surgical assessment of pelvic nodes in order to exclude metastatic disease may also be justified.[5] Five year survival for women with Ia disease is excellent – in the order of 95% (*Figure 3*).

Table 1. Incidence of cervical cancer and mortality rate, selected countries, 2002

Country	Incidence per 100 000 women (ASR)	Mortality per 100 000 women (ASR)
South Africa	38.2	22.6
Central America	30.6	15.0
South East Asia	18.7	10.2
New Zealand	10.0	3.2
United Kingdom	8.3	3.1
United States	7.7	2.3
Canada	7.7	2.5
Australia	6.9	1.7
Finland	4.3	1.8

Source: GLOBOCAN 2002 [www-depdb.iarc.fr/globocan/GLOBOframe.htm]

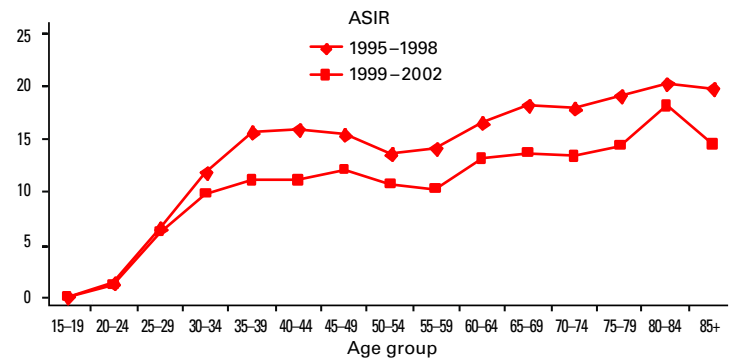

Figure 1. Age standardised incidence rates of invasive cervical cancer for women diagnosed in 3 year periods: 1999–2002 and 1995–1998. Rates are expressed per 100 000 women (age standardised to the 2001 Australian standard population)
Source: National Cancer Statistics Clearing House. AIHW Cervical screening in Australia 2001–2002

Surgical management is also an option for women with stage IB or IIA disease less than 4 cm in diameter. This usually takes the form of a radical hysterectomy and bilateral pelvic lymphadenectomy. Results from a phase III randomised trial demonstrated that primary radiotherapy gave equivalent results in this situation.[6] Primary radiotherapy for cervical cancer involves a pelvic field using external beam radiotherapy (45–50 Gy) and brachytherapy (80–85 Gy to point A). For premenopausal women this leads to ovarian failure, unless ovarian transposition is undertaken, and vaginal stenosis and dysparunia. For women undergoing surgery adjuvant radiotherapy is also advised when surgical pathology suggests positive pelvic nodes, close or involved margins or large tumour volume. The Landoni[6] study conclusively demonstrated that the combination of surgery and radiotherapy resulted in the severe morbidity for 28% of women treated and it is now strongly recommended that the planned use of both radical surgery and radiotherapy should be avoided. Current management will therefore depend on a number of factors including: age, menopausal status, comorbidities, histological subtype, tumour size, results of imaging and the availability of local resources.

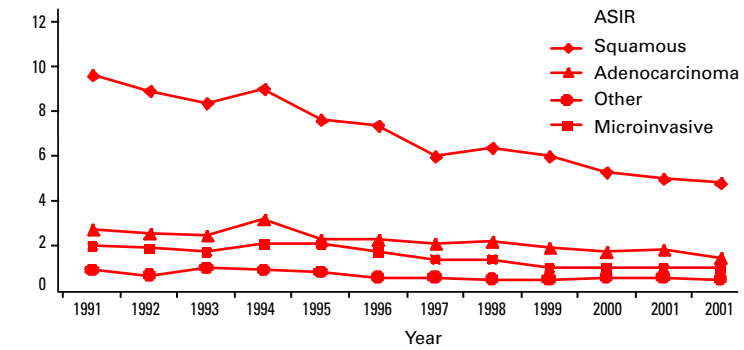

Figure 2. Age standardised incidence rates for cervical cancer by histological type for women, all ages 0–85+ years Australia 1990–2001. Rates are expressed per 100 000 women (age standardised to the 2001 Australian standard population)
Source: National Cancer Statistics Clearing House. AIHW Cervical screening in Australia 2001–2002

Table 2. Carcinoma of the cervix uteri: FIGO nomenclature[1,15]

Stage 0	Carcinoma in situ, cervical intraepithelial neoplasia grade III
Stage I	Carcinoma strictly confined to the cervix (extension to the corpus would be disregarded)
Stage IA	Invasive carcinoma that can be diagnosed only by microscopy
Stage IA1	Measured stromal invasion of not >3.0 mm in depth and extension of not >7.0 mm
Stage IA2	Measured stromal invasion of >3.0 mm and not >5.0 mm with an extension of not >7.0 mm
Stage IB	Clinically visible lesions limited to the cervix uteri or preclinical cancers greater than stage Ia
Stage IB1	Clinically visible lesions not >4.0 cm
Stage IB2	Clinically visible lesions >4.0 cm
Stage II	Cervical carcinoma invades beyond uterus, but not to the pelvic wall or lower third of vagina
Stage IIA	No obvious parametrial involvement
Stage IIB	Obvious parametrial involvement
Stage III	Carcinoma has extended to pelvic wall. The tumour involves the lower third of the vagina. All cases with hydronephrosis or nonfunctioning kidney are included
Stage IV	Carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum
Stage IVA	Spread of the growth to adjacent organs
Stage IVB	Spread to distant organs

Source: GLOBOCAN 2002 [www-depdb.iarc.fr/globocan/GLOBOframe.htm]

For women with FIGO stage IB2-IIA greater than 4 cm diameter and for women with more advanced carcinomas (FIGO stage IIB-IVA) radiotherapy is the treatment of choice. This should be accompanied by concurrent platinum base chemotherapy which has been shown to improve survival.[7–9] Five year survival for women by FIGO stage is illustrated in *Figure 3*. For women with positive common iliac or para-aortic nodes or high risk disease (ie. uterine body involvement) extended field radiation may be considered.[3] Unfortunately overall survival of these high risk women remains poor (*Figure 3*).

Recent advances in management

Radical trachelectomy

One of the most important advances in recent years is the development of fertility preserving procedures for women with early cervical carcinomas. Radical trachelectomy involves pelvic lymph node dissection usually via a laparoscopic route, radical removal of the upper vagina and most or all of the cervix and parametrium but preservation of the uterus. Most patients will have a suture placed around the lower uterine segment to prevent pregnancy loss due to cervical incompetence. Delivery of subsequent pregnancies should be by caesarean section. With increasing worldwide experience, this procedure appears safe for selected patients under 40 years of age who wish to preserve fertility with carcinomas less than 2 cm diameter.[10,11] Surprisingly only around 43% of women undergoing this procedure try to conceive and of these, 70% will achieve a pregnancy.[12] Premature delivery and mid trimester losses are significant risks.

New and novel surgical approaches

Minimally invasive surgery has major advantages to patients in terms of cosmesis and recovery time. Laparoscopic approaches to radical cancer surgery are being developed,

but the efficacy and safety of these approaches are seldom assessed in a randomised manner. Laparoscopic pelvic and para-aortic lymphadenectomy has been demonstrated as feasible via either a transperitoneal or extraperitoneal approach and appears safe in the hands of an experienced surgeon.[13] This allowed the development of alternate approaches to radical hysterectomy such as radical vaginal hysterectomy and total laparoscopic radical hysterectomy.

There are advocates for laparoscopic assessment of pelvic and para-aortic nodal status in women presenting with advanced cervical carcinoma allowing radiotherapy fields to be accurately tailored to individual disease. This approach is of no proven benefit; indeed the only randomised trial suggested poorer outcomes for surgically staged patients.[14]

Management of advanced and recurrent disease

Women presenting with distant metastatic disease (FIGO stage IVb) require palliative treatment. Chemotherapy may be considered for symptom control only. The majority of women presenting with recurrent disease do so within 2 years of diagnosis and subsequent prognosis is poor with most patients dying from uncontrolled disease. Uncontrolled pelvic disease is particularly challenging leading to neuropathic pain, fistulae and renal failure. Involvement of the expertise of a palliative care team is optimal in the management of this group of women.

Psychosexual issues

Women with cervical carcinoma face many challenging issues. Some feel let down by the cervical screening program; others perceive guilt because they neglected to have regular Pap tests. Most perceive the stigma that continues to be attached to this disease. The causal agent, HPV is sexually transmitted and most women enquire at some stage as to the cause of their cancer. Along with physical challenges such as vaginal shortening and stenosis, these issues can lead to major psychosexual morbidity. The caring physician needs to be sensitive to all of these issues.

Summary of important points

- Over 80% of women presenting with invasive cervical cancer will not have had regular Pap tests.
- Women undergoing a Pap test should be informed that the test can assist in the prevention of the majority of cervical cancers (excluding adenocarcinoma).
- Women with invasive cervical carcinoma commonly present with symptoms including abnormal vaginal discharge and bleeding.
- When taking a Pap smear inspect the cervix carefully. An abnormal appearing cervix or brisk contact bleeding is a valid reason for colposcopic referral.

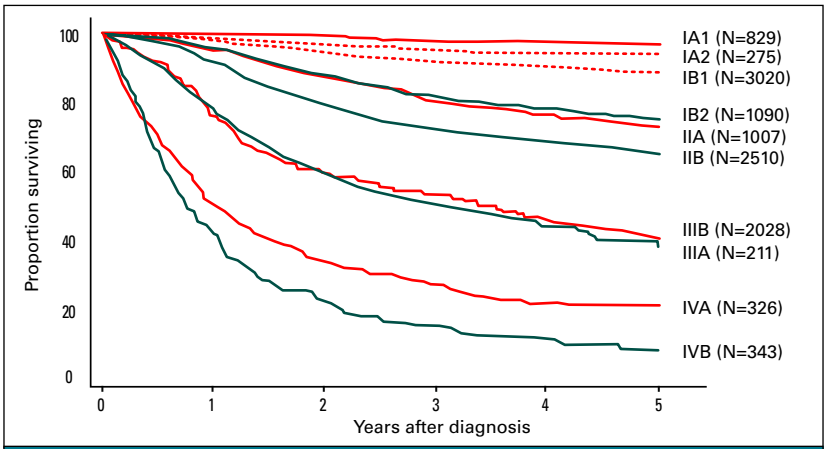

Figure 3. Five year survival of cervical cancer patients according to FIGO stage. Reproduced with permission: Quinn M, Benedet J, Odicino F, et al. Carcinoma of the cervix uteri. Int J Gynaecol Obstet 2006

Conflict of interest: none declared.

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