Invasive cancer of the cervix

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Abstract

Invasive cervical cancer remains the second commonest female malignancy worldwide. Early-stage disease may be asymptomatic. Advances in imaging techniques have improved selection of the appropriate treatment approach. Treatment options vary for each stage. An excisional cone is sufficient for treatment of micro-invasive disease (Ia1) provided the margins are clear. The management of stage Ia2 disease is more controversial. Surgery and radiation have similar survival rates for stage Ib—IIa disease, while the combination of both increases morbidity. Later stage tumours (IIb—IV) should be treated with chemoradiation as this is related to improved survival but also higher short- and medium-term toxicity in comparison to radiotherapy alone. Fertility-sparing surgical techniques such as radical trachelectomy may be appropriate in selected cases. Management of recurrent disease depends on the initial treatment, the individual characteristics and the presence of distant disease. Management of cervical cancer during pregnancy remains a challenge and appropriate counselling on individual patient basis is necessary. As the disease usually affects young women, psychological morbidity is significant and emotional support is essential.

Keywords cervical cancer; cervical screening; chemoradiation; CIN; FIGO staging; radical hysterectomy; trachelectomy

Introduction

Cervical cancer remains the second commonest female malignancy worldwide. Three-quarters of affected women live in developing countries that experience the major burden of disease. The disease primarily affects younger active women and therefore, the total years-of-life lost is proportionately higher than that for most other cancers with a later onset.

Countries with established screening programmes face different challenges; improving outcome for women with advanced disease, preserving fertility in younger women who increasingly bear the greatest burden of the disease, and incorporating advances in medical technology such as positron emission tomography (PET) and minimal access surgery are some of those challenges. The realization that persistent infection with oncogenic high-risk human papillomavirus (HPV) is causally associated with cervical cancer has been, undoubtedly, the most significant advance globally that led, more recently, to the development of prophylactic vaccines.

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Epidemiology

Cervix cancer is the seventh in frequency cancer overall worldwide, with an estimated 493,000 new cases leading to 274,000 deaths in the year 2002 (Figure 1). The mortality is substantially lower than the incidence; worldwide, the ratio of mortality to incidence is 55%. Cervical cancer still remains an important public health issue in Europe with more than 66,000 new cases and 29,000 deaths annually. The majority of these cases are diagnosed in Eastern European countries (Figure 2). In the UK in 2006, there were 2873 registrations, and 941 deaths in 2007 (Figure 3).

Screening programmes have led to both reduced incidence and down staging of the disease with around a third of cancers being diagnosed as stage I. In the UK, it is estimated that screening saves approximately 5000 lives every year. The benefits are more obvious since the reorganization of the service in 1988 and the increase in coverage (from 35% in 1988 to 85% in 1998). The incidence of cervical cancer has fallen in the UK by 44% since 1975, and mortality from 7.1 per 100,000 in 1988 to 2.4 per 100,000 in 2007 (Figure 4).

The incidence rate for cervical cancer peaks at the age range 30—40 years of age, declines in incidence for older age groups but peaks again in the early 80 years age band (Figure 5).

Pathological subtypes

The majority of cervical cancers are squamous in origin, but adenocarcinomas appear to be increasingly common, accounting for approximately 20% of all primary cervical cancers. This increase partly reflects an increased awareness of the disease. Adenocarcinoma is more likely to be diagnosed in younger women and has largely poorer prognosis in comparison to cervical squamous carcinoma, which partly reflects the delay in diagnosis. Cytology screening programmes were designed to detect squamous lesions and, as a result, the endocervical distribution of glandular abnormalities reduces their accuracy. Specific oncogenic HPV types, and in particular HPV 18, have been related to adenocarcinoma.

The rare, but aggressive small-cell neuroendocrine-type squamous carcinoma typically behaves like similar disease arising from the bronchus. Adenocarcinomas can be pure but a significant proportion (40%) has mixed adeno-squamous cells, the adenosquamous carcinoma. Adenocarcinomas include many more histological subtypes than squamous cancers. About 80% are made up of cells of the endocervical type with mucin production.

Patterns of spread

Cervical cancers spread

- by direct spread into the cervical stroma, parametria and beyond, into the vagina, the body of the uterus, the bladder and the rectum.
- by lymphatics spread into parametrial, pelvic sidewall and para-aortic nodes. The incidence of pelvic lymph node and

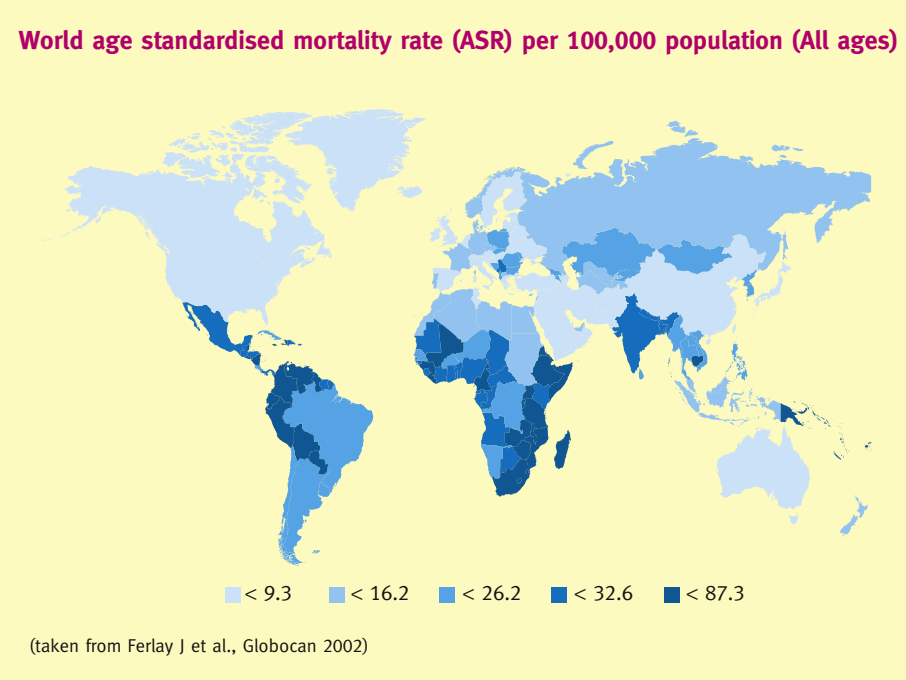

Figure 1

para-aortic disease according to stage is illustrated in Table 1.

- by blood-borne spread, although it is unusual

Clinical management

Presentation

The symptoms associated with cervical cancer are common, non-specific and usually associated with later stage disease. Early-stage disease may be asymptomatic and suspected on a cervical sample or diagnosed following treatment for cervical precancer, commonly in the form of large loop excision of the transformation zone (LLETZ). The classical signs and symptoms are irregular vaginal bleeding, especially post-coital and abnormal appearance of the cervix. Invasive cancer is rare in women with post-coital bleeding, but assessment is merited as it is much more common in this group than in the general population. Those symptoms are also common in women with *Chlamydia trachomatis* infection. Discharge and pain are often associated with more advanced disease.

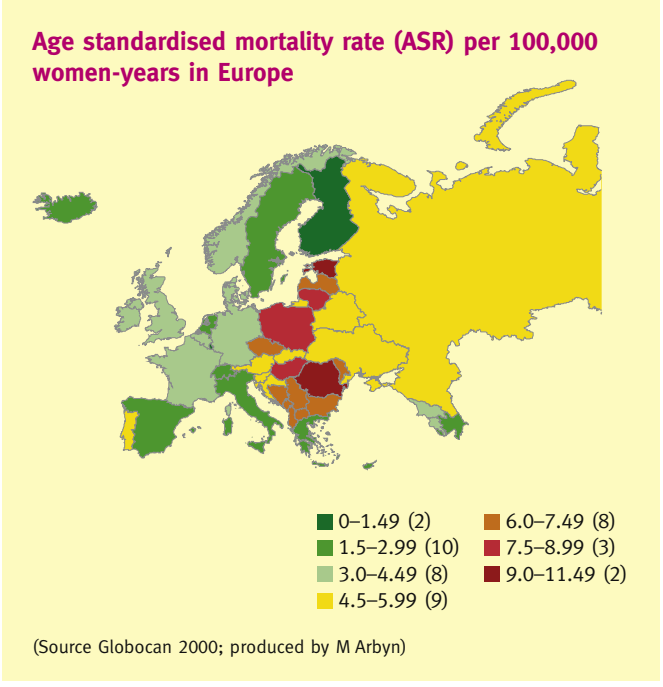

Figure 2

Diagnosis

Diagnosis requires a biopsy for histopathological review by an experienced gynaecological pathologist. The biopsy needs to be large enough to demonstrate stromal invasion and often an appropriately sized loop diathermy (LLETZ) may be used. The optimal biopsy site is often the edge of the tumour that allows assessment of the transition from invasive to non-invasive. Central biopsies may reveal only pre-malignant or necrotic material, though often there may be no alternative. The tumours may bleed briskly after a biopsy and occasionally require packing. In very early disease, a cone with loop diathermy (LLETZ), knife (cold-knife conization) or diathermy needle (NETZ) can be diagnostic but also curative. Biopsies in a pregnant patient are important if invasion is suspected, but should be performed by an experienced clinician as significant bleeding may occur.

Staging procedures

Having established the diagnosis, the next step is to stage the disease, as this determines the ongoing management, it helps to assess prognosis and exchange of information among health professionals.

Cervix cancer is still staged clinically using the International Federation of Gynaecology and Obstetrics (FIGO) system (Table