Advances in the management of cancer of the cervix

Cancer of the cervix remains a very common female cancer in South Africa.

JILL HARRIS, ***MB ChB, FC Rad Onc***

Senior Consultant, Department of Radiation Oncology, Tygerberg Hospital and Stellenbosch University

After internship, Jill Harris moved to Frere Hospital in East London as a medical officer in internal medicine and started her specialist training there. She completed her specialist training at Groote Schuur Hospital and did a fellowship at the National Accelerator Centre before joining Tygerberg Hospital as the radiation oncologist responsible for gynaecological and urological cancer.

HENNIE BOTHA, ***MB ChB, MMed, FCOG***

Senior Consultant, Department of Gynaecology, Tygerberg Hospital and Stellenbosch University

Hennie Botha started his medical career at a mission hospital in Malawi. A short stint in the UK preceded his specialist training at Tygerberg Hospital. Subsequently he gained experience in gynaecological oncology at the Three Counties Cancer Centre in the UK. He is currently a gynaecological oncologist at Tygerberg Hospital.

Carcinoma of the uterine cervix remains the number one cancer of women in South Africa according to the International Agency for Research on Cancer. During the last 20 years tremendous progress has been made in the understanding of the pathogenesis of cervix cancer; new technologies exist to prevent the development of cervix carcinoma and, if prevention fails, to treat cancer effectively.

Aetiology

There is an extremely strong relationship between human papillomavirus (HPV) infection and the development of cervical dysplasias and cancers. HPV16 is associated with more than 50% of all invasive carcinomas, HPV18 with 16% and HPV31 with 8%. If a woman is HPV16 DNA-positive for more than 24 months, her relative risk for developing a cervical intra-epithelial neoplasia (CIN) lesion is 100. This is 10 times the risk for the development of lung cancer because of heavy smoking.

However, other factors interact with HPV in the development of carcinoma. Immune suppression is important and, in particular, HIV infection leads to a higher incidence and more aggressive natural history of dysplasias and cancer. Cigarette smoking is an important additional risk factor for the development of cervical cancer, and other infections like herpes may also play a role.

Cancer prevention

Primary prevention entails reducing the exposure to causative agents. A programme to encourage healthy sexual behaviour will reduce the rate of HPV and HIV infection, especially during the teenage years. By introducing very strict anti-smoking legislation our previous Minister of Health has saved many lives.

A new, very promising technology that will become available in the near future is aimed at preventing HPV infection through immunisation. The first commercially available vaccine will contain the 2 most serious oncogenic types of HPV, namely 16 and 18. These vaccines performed very well in large studies with nearly 100% prevention of persistent HPV infection and may prevent up to 70% of all cervix cancer cases if the whole population is immunised. Patients need to be immunised before they are exposed to HPV infection; therefore the best age may be pre-pubertal children. Boosters may be needed 5 - 10 years after the initial dose, although this has not yet been confirmed with long-term follow-up studies.

Secondary prevention of disease encompasses different strategies, one of which one may be screening. A good screening test, in the form of cervical cytology, is available and it may reduce the incidence of cervix carcinoma dramatically if it is used effectively. In the UK a population-based programme was introduced in the 1980s that dramatically reduced the number of cervical cancer cases. Cytology can only be successful if it is used on a large population percentage (approximately 70%) before it will make any difference to the national cancer incidence. The problems with cytology in South Africa are the lack of resources and a very mobile population and difficulty in tracing cases.

Liquid-based cytology and HPV typing decrease the false negative rate of standard Pap smears. Liquid-based cytology uses the same principle as the Pap smear but the technique has a better sensitivity and specificity for the diagnosis of high-grade intra-epithelial lesions. HPV typing has the advantage of very high sensitivity but with a very low positive predictive value in young patients. A combination of cytology and human papillomavirus testing is now standard practice in the USA.

Another strategy for secondary prevention is to identify high-risk groups and to manage them very carefully with regular clinical examination and special investigations. A high-risk group in the cervical cancer scenario are those patients who are HIV positive. In a very good study from the University of KwaZulu-Natal it was found that patients with HIV infection present 15 years earlier with cervix carcinoma than their HIV-negative counterparts. From other work it is clear that patients with HIV infection are at a high risk for the development of intra-epithelial lesions and also have a high risk for progression towards cancer. These patients should therefore be followed up more closely with regular cytology screening. The

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suggestion is that all HIV-positive patients should have at least annual cytology screening.

National policy. The national policy for cervical cancer screening in the public sector was introduced in 1998. With this programme the Department of Health estimated a reduction of up to two-thirds of cervical cancer incidence if every woman in South Africa could have 3 cytology smears 10 years apart starting at the age of 30. This is based on a mathematical model taking into consideration the national cancer incidences and the age at presentation of these cases. This programme compares well with the WHO suggestion of a single smear per woman per lifetime in low-income countries.

Treatment

Early cervical cancer

Cervical cancer is a disease with a wide variety of symptoms that may include an offensive vaginal discharge, abnormal menstrual bleeding or postmenopausal bleeding and particularly post-coital bleeding. Other symptoms may include recto- and/or vesico-vaginal fistulae and it may also be completely asymptomatic. When a patient is examined and a suspicious lesion on the cervix is diagnosed, it is important to take a biopsy and a cytology smear and refer the patient for immediate further attention.

Staging of cervical cancer is important so as to select the most appropriate treatment. Staging is done according to FIGO guidelines and relies on clinical findings, simple radiological investigations (plain film chest X-ray, IVP or ultrasound) and cystoscopy and proctoscopy. Improved imaging modalities such as CT and MRI scans have improved the ability to detect lymphadenopathy and better delineate local spread. Position emission tomography (PET) scanning furthermore allows better determination of lymphadenopathy in cervical cancer, but these modalities have not been incorporated into the FIGO staging guidelines as they are not routinely available in developing countries, where the main burden of this disease falls.

Treatment for cervical cancer is best decided by multidisciplinary teams represented by gynaecologists, oncologists and radiologists. Early cervical carcinoma (up to stage IIa) may be treated with surgery. The aim of surgery is to be conservative enough to preserve normal function but also to be radical enough to remove tumour with adequate margins. New developments in the surgical management of cervical carcinoma include conservative surgery that may preserve fertility in young patients, such as a cold knife cone biopsy in very early lesions or more complex operations like radical trachelectomy, which entails removal of the cervix while maintaining the uterine body in selected patients.

The standard surgery for visible early cervical carcinoma is a radical hysterectomy with pelvic lymph node dissection. It is very important that these patients should be operated on at a tertiary referral centre because inappropriate management may necessitate postoperative radiotherapy, with its associated complications.

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Advanced cervical cancer

More advanced cancers (stages 2B or greater) are treated by means of radiotherapy and chemotherapy. Radical radiotherapy lasting 6 - 7 weeks is appropriate for many of these patients, with 5-year survival outcomes after treatment of 35 - 65%. Unfortunately there is a subset of stage 3B patients with bulky disease, bilateral hydronephrosis or impaired renal failure who will have a poor outcome after radiotherapy and may be palliated rather by short-course radiotherapy. Stage 4A or B patients are considered generally to be incurable and the aim of palliative RT is to control symptoms such as bleeding or pain. Patients who present with or subsequently develop fistulae (to bowel or bladder) are best palliated by means of surgical bypass procedures if their functional status allows.

In order to cure cervical cancer, it is necessary to achieve loco-regional and systemic control. Unfortunately most patients who relapse have isolated pelvic or combined pelvic and systemic relapse. Any improvements in the survival of patients with locally advanced cervical cancer will first necessitate improvements in the dose delivered to the high clonogenic burden at the primary site, while sparing the surrounding normal tissues. Once this has been addressed further attention can be focused on control of micro-metastatic disease.

Radical radiotherapy technique

External beam radiotherapy

Advances in the delivery of external beam radiotherapy have contributed to improved survival in cervical carcinoma, with a randomised control trial (RCT) showing improved survival utilising higher energy photons from a linear accelerator compared with those from a cobalt unit. Technology has continued to develop since that early innovation and new (but expensive) techniques and equipment are available that enable an increase in the dose to the tumour volume while sparing normal tissues. This is accomplished by conformal three-dimensional radiotherapy in which CT-based planning allows accurate delineation of the tumour and normal tissues and each beam is shaped to conform to the tumour volume excluding normal tissues. Furthermore, intensity-modulated radiotherapy allows each beam to be broken up into a number of smaller beams (in a simplified understanding) each with a different intensity. Multiple beams from different angles are utilised further, allowing full or escalated dose to tumour while limiting dose to normal structures. Unfortunately these techniques are not

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standard therapy in this disease and currently are in practice in a few selected indications in developed countries. Even if RCTs were to show an improvement in survival using these techniques, the majority of patients presenting with locally advanced cervical cancer would not benefit due to associated prohibitive costs and resource restrictions in the developing world. However, it is possible to achieve a great deal with a standard linear accelerator or even a cobalt unit in a thin patient. High-energy photons are utilised in a 4- or 2-field arrangement (Figs 1 - 3). The target volume consists of the primary tumour and uterus, parametria and vagina and the regional nodal drainage areas. This requires the whole pelvis to be treated and the dose that can be delivered is determined by the tolerance of the small bowel, bladder and rectum.

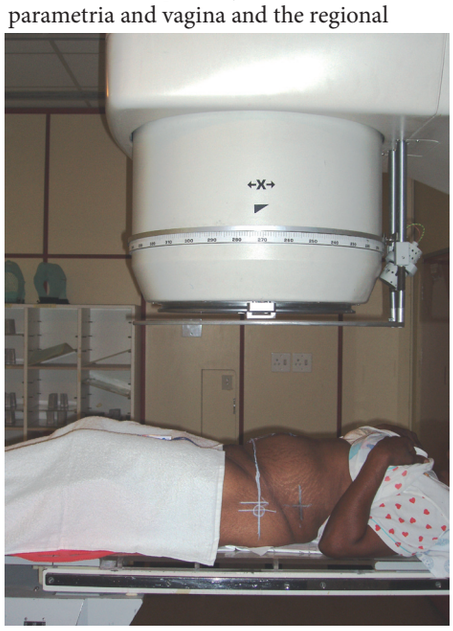

Fig. 1. Set-up of anterior field with localising marks visible on patient's skin and the linear accelerator head visible above the patient.

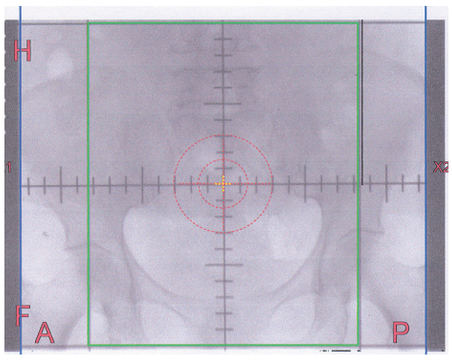

Fig. 2. A simulator verification film of the anterior field showing the field boundaries and the underlying bony anatomy. The field covers the whole pelvis and the common iliac lymph nodes.

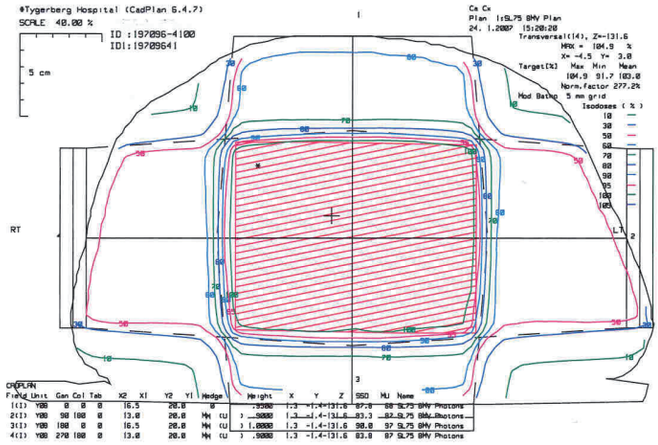

Fig. 3. A single transverse plot of the dose distribution of a 4-field box plan using anteroposterior and two lateral fields.

Concomitant chemosensitisation

Multiple RCTs and a meta-analysis of the combined data have shown an absolute improvement in survival of 12% with chemosensitisation given concomitantly with radiotherapy compared with radiotherapy alone. Controversy exists as to the magnitude of the benefit in locally advanced disease as the majority of the patients accrued to these trials in the developed world represented surgically staged patients with earlier disease. However, a RCT undertaken in India in stage 2B - 3B patients showed an overall survival advantage at approximately 3 years when concomitant cisplatin was given together with radiotherapy. The RCTs employed various chemotherapeutic agents and regimens and the best approach is unknown. However the authors of the meta-analysis conclude that a reasonable approach in the developing world is weekly cisplatin administration, which is cheap and easily administered on an outpatient basis.

Intracavitary brachytherapy

Intracavitary radium treatment has long been used in the treatment of cervical cancer and predates improvements in external beam delivery. The techniques have evolved over time but improvements have largely occurred as a result of our understanding of fractionation and radiobiology. The applicators available are still similar in principle to the initial applicators used by the pioneers of this technique, allowing the radioactive source to be introduced into the uterine canal and vaginal fornices (Fig. 4) with rapid dose fall-off sparing surrounding normal structures. Major advances have occurred in the radiation exposure to patients and staff and remote afterloading (Fig. 5) and use of new, safer radio-isotopes is standard. Further improvements in the planning of the intracavitary therapy continue and sophisticated CT scan imaging and complicated dose algorithms are currently being developed.

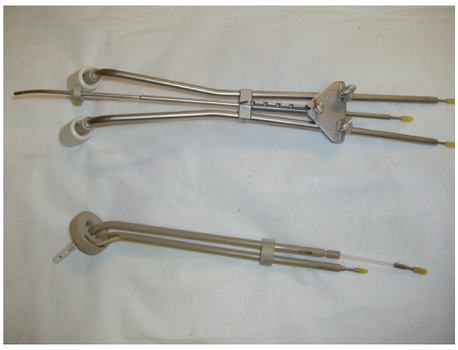

Fig. 4. Applicators used in intracavitary brachytherapy to guide the radioactive source into the uterine cavity and the vaginal fornices.

Fig. 5. An example of a remote afterloader used to deliver intracavitary brachytherapy.

More advanced cancers (stages 2B or greater) are treated by means of radiotherapy and chemotherapy.

Conclusion

Although there have been encouraging improvements in the treatment of cervical cancer and survival gains have been achieved, these are modest compared with the effect on morbidity and mortality that preventive measures might have. It is of fundamental importance that effective HPV vaccination (and screening) programmes are instituted as soon as possible as the delay between the roll-out of these interventions and a decrease in the mortality from cervical cancer will be up to 2 decades. The burden of this preventable disease on the women of developing countries necessitates that evidence-based medical practice not be stalled at the level of publication but rather be promptly implemented into standard practice.

A programme to encourage healthy sexual behaviour will reduce the rate of HPV and HIV infection, especially during the teenage years.

Further reading

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Mahdavi A, Monk BJ. Vaccines against human papillomavirus and cervical cancer: promises and challenges. *Oncologist* 2005; 10: 528-538.

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In a nutshell

- Human papillomavirus infection is the primary aetiological agent in cervical cancer.
- HPV vaccinations have decreased persistent HPV infection in 2 large RCTs.
- Cervical cytology is an effective screening tool in preventing cervical carcinoma.
- The National Screening Programme in SA, if effective, should reduce the rate of cervical cancer by two-thirds.
- Radical hysterectomy and pelvic lymph node dissection is standard surgical therapy for early invasive cancer.
- Most recurrences after radiotherapy in locally advanced cervical cancer have a local component.
- Concomitant cisplatin chemoradiation improves survival in cervical cancer.
- Intracavitary brachytherapy is an integral part of radiotherapy for cervical cancer.

single suture

Do not leave infants unattended in car seats

Infant car seats are known to be vital to protect infants from injury and death in motor vehicle accidents. But research from New Zealand suggests that young infants should not be left to sleep unattended in car seats. Studies have shown that pre-term and term infants with pre-existing health conditions are at risk of oxygen desaturation and secondary apnoea while restrained in a semi-reclining infant car seat. Shirley Tonkin and colleagues looked at 43 consecutive, otherwise healthy, infants presenting after an acute life-threatening event and found that 9 had been asleep in car seats at the time of the event – a perceived change in colour and breathing. They suggest that car seats may cause forward flexion of the neck and lead to impaired airway function and oxygen desaturation.

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