CHAPTER 15.

Non-surgical management of cervical cancer

This chapter deals with the treatment modalities used in the non-surgical management of cervical cancer. These include radiotherapy, chemotherapy, and various combinations of radiotherapy and chemotherapy.

15.1 Radiotherapy

Radiotherapy for cervical cancer usually involves a combination of external beam radiotherapy (EBRT) and brachytherapy using intracavitary radiotherapy (ICR). The goal of the treatment is to balance EBRT and ICR in a way that maximizes the likelihood of loco-regional tumour control while minimizing the risk of treatment complications.

The total radiation dose that can be delivered to the pelvis by EBRT is limited by the tolerance of normal tissues in the pelvis, such as the urinary bladder and the small and large bowels, and thus ICR is needed to deliver cancerocidal doses to the gross tumour in the cervix and parametrium.

For many patients with advanced loco-regional disease, radiotherapy may be integrated with concomitant chemotherapy to augment the prospects of a cure. The primary goals of EBRT are to sterilize regional disease and to shrink the central tumour, to facilitate subsequent ICR. Ideally, the entire course of treatment should be completed in less than 8 weeks; excessive prolongation of the overall treatment time may compromise disease control.

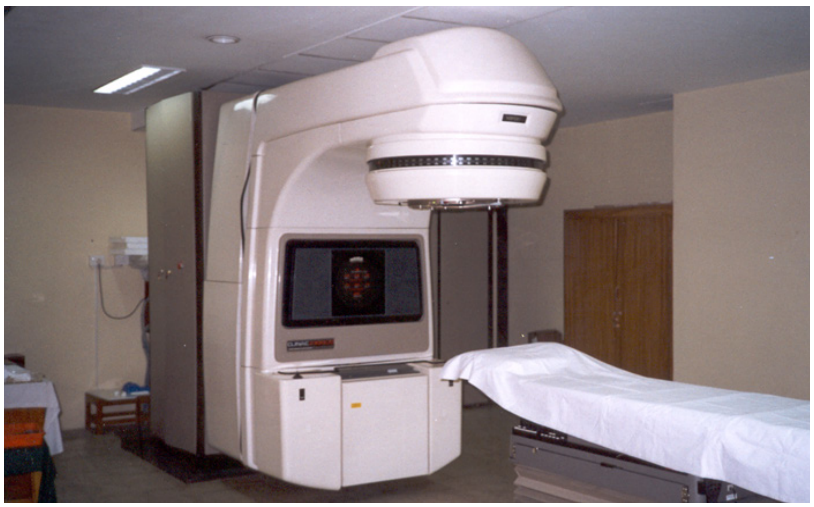
With image-based technical advances such as three-dimensional conformal radiotherapy, intensity-modulated radiotherapy, and image-guided radiotherapy, it is possible to provide more precise and accurate radiation delivery, with the potential for dose escalation, improved tumour control, and reduced toxicity by minimizing the dose to the surrounding normal tissues. However, these techniques require sophisticated equipment infrastructure and adequately trained personnel and are not feasible in low-income countries with weak health systems.

15.1.1 Radiotherapy equipment

Radiotherapy for cervical cancer involves both EBRT and ICR.

In EBRT, the radiation is delivered as a beam from a radioactive source kept at a source-to-axis distance of 100 cm or 80 cm in a teletherapy machine such as a linear accelerator (linac) (Fig. 15.1) or a telecobalt machine (Fig. 15.2). Modern teletherapy machines are

Fig. 15.1. Linear accelerator (linac).



isocentrically mounted, allowing the beam to rotate around the patient at a fixed source-to-axis distance of 100 cm (linacs) or 80 cm (telecobalt machines). Linacs use electricity to generate high-energy X-rays (15–25 MeV) and permit homogeneous delivery of radiation to deep tissues with relative sparing of superficial tissues, whereas telecobalt machines emit gamma rays from a radioactive cobalt (cobalt-60) source kept in the head of the machine.

From the 1950s onward, telecobalt machines were at the forefront of delivering EBRT for many years. However, linacs have largely replaced telecobalt machines in many high- and middle-income countries as the most widely used radiation source in modern radiotherapy. For instance, in France, there are no more functional telecobalt machines, and in Morocco, all 32 of the teletherapy machines are linacs. In India, in 2000 there were 245 telecobalt machines and 34 linacs, and in 2014 there were 238 telecobalt machines and 308 linacs.

Over the course of five increasingly sophisticated generations, linacs have become compact, versatile, efficient, and affordable, with a wide range of energies. Linacs require more sophisticated maintenance in terms of medical physics and dosimetry support; they require continuous electricity and consume large amounts of electricity. In contrast, in telecobalt machines, the cobalt-60 source is replaced after two or three half-lives (approximately 10.6 years or 15.9 years). The telecobalt machine has been the preferred teletherapy machine in low-income developing countries, because of its affordability and sturdy reliability. Finally, in many countries manual treatment planning has largely been replaced by computerized treatment planning systems.

ICR is a necessary component of radiotherapy for cervical cancer. In ICR, radioactive sources are placed into the uterine cavity and vagina to deliver a very high radiation dose to the cervix and uterus with relative sparing of surrounding tissues, such as the bladder, rectum, small bowel, and superficial soft tissues. Early ICR techniques involved the placement of sealed radioactive sources such as radium-226 or caesium-137, which is not optimal from a radiation protection perspective; automatic afterloading devices using empty applicators are now used to deliver ICR.

For ICR, the radiation source is encapsulated within a non-radioactive metallic capsule. After accurate positioning of the delivery devices (applicators) in the vagina (ovoids) and uterine cavity (tandem) with the help of X-ray, ultrasonography, or CT imaging, the radiation sources are afterloaded; after the delivery of the radiation dose, the sources are removed manually by a radiation oncologist. Alternatively, the sources may be inserted using a computer-aided remote afterloading machine (Fig. 15.3), which automatically removes them when the treatment has been completed. Precise placement of the applicator is essential for improved local control and reduced morbidity.

For treatment planning, a computer is used to calculate the amount of time required to deliver the prescribed dose of radiation to the tumour. Although low-dose-rate brachytherapy with caesium-137 has been the traditional approach, the use of high-dose-rate brachytherapy with iridium-192 is increasing. High-dose-rate brachytherapy eliminates radiation exposure to medical personnel and allows a shorter treatment time and greater patient convenience. The outcome of high-dose-rate

Fig. 15.2. Telecobalt machine.

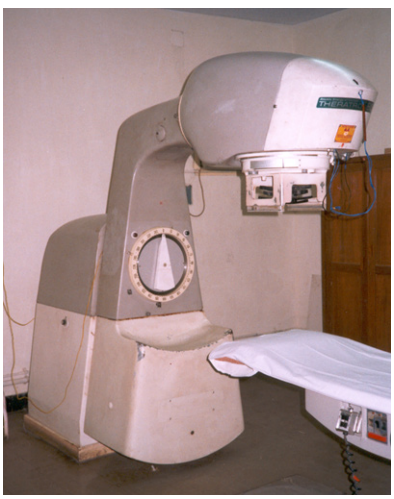
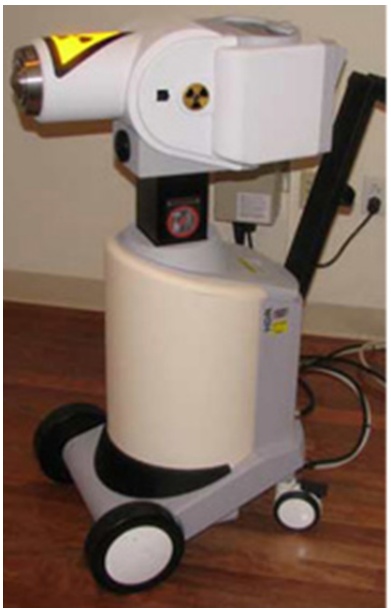


Fig. 15.3. High-dose-rate remote afterloading brachytherapy machine.



brachytherapy is similar to that of low-dose-rate brachytherapy in terms of loco-regional control and complication rates.

15.1.2 Radiotherapy dose

It is important to prescribe the optimal dose for both radical and palliative radiotherapy and to measure the dose correctly to avoid unintended damage to normal tissues. Radical treatment refers to prescription of a high dose of radiation with curative intent, while accepting a certain amount of side-effects, complications, and late sequelae and anticipating an eventual cure or long-term disease-free survival. Palliative treatment refers to the delivery of smaller doses of radiation (which by itself does not cause any toxicity or complications) to relieve symptoms, accepting that long-term survival or a cure is unlikely because of the very advanced clinical extent of disease, as in disease with distant metastases.

The choice of radiotherapy dose and delivery techniques takes into account the normal tissue/organ tolerance in the radiotherapy portals or fields and the cancerocidal dose required to destroy the cancer cells and the lesion in radical treatments. The normal tissue tolerance dose varies between tissues/organs and depends on the proportion of tissues/organs treated.

Radiotherapy dose is described in terms of grays (Gy) or centigrays (cGy = 0.01 Gy). The total radiation dose is usually divided into several small fractions of radiation (about 180 cGy or 200 cGy per fraction), which, as daily treatment progresses, gradually accumulate to the total dose prescribed. Radiation is usually delivered as one fraction per day, 5 days per week for a total period of 4–8 weeks. Fractionation of the total radiation dose over a period of 4–8 weeks leads to maximum cancer cell kill while allowing maximal recovery of and minimal damage to normal cells. During the interval between the fractions, normal cells recover much faster than tumour cells, ideally resulting in maximum tumour cell kill and minimal damage to normal tissues.

Radical radiotherapy doses are typically 35–40 Gy in 15–20 fractions over 3–4 weeks for highly radiosensitive lymphomas and germ-cell tumours, whereas the doses range from 50 Gy in 15 fractions over 3 weeks to 65–70 Gy in 30–35 fractions over 6–7 weeks for most squamous cell carcinomas. Palliative radiotherapy doses are on the order of 30 Gy in 10 fractions over 2 weeks or 20 Gy in 5 fractions over 1 week, or even a single dose of 8–10 Gy.

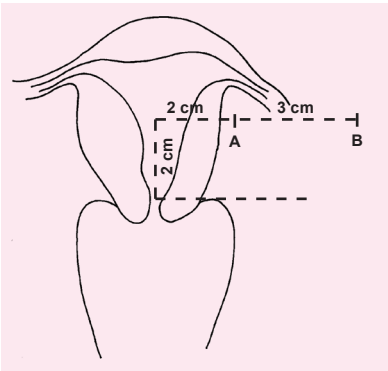
The skin may be marked to indicate the radiotherapy portal where treatment should be delivered. The patient should be immobilized so that the target region receives the intended dose. The daily treatment setup is reproduced by in-room laser alignment to either skin marks or fixation aids such as thermoplastic devices.

ICR can be given using a high dose rate over a few minutes (5–15 minutes) per session or a low dose rate over 20–60 hours. Low-dose-rate brachytherapy is delivered at a dose rate to point A (see below) of less than 0.5 Gy/hour, typically using caesium-137. Since the early 2000s, the traditional low-dose-rate brachytherapy with caesium-137 has largely been replaced by high-dose-rate brachytherapy with iridium-192. With high-dose-rate brachytherapy, a remote afterloading technology allows the iridium source attached to the end of a cable to be robotically driven through multiple channels, stopping at predetermined dwell positions for varied lengths of time. The most common fractionation schedules for high-dose-rate brachytherapy are 5–6 Gy in 5 fractions or 7 Gy in 4 fractions. High-dose-rate fractions are typically delivered 1 or 2 times per week.

15.1.3 Radiotherapy reference points and EBRT portals

The target volume for treatment of cervical cancer involves the gross tumour as defined by clinical and radiological investigations as well as the suspected subclinical disease and the parametrial, pararectal, internal iliac, external iliac, common iliac, obturator, and presacral lymph node regions. Radiotherapy protocols for patients with cervical cancer have traditionally used dosing at two anatomical points, called point A and point B (Fig. 15.4), to standardize the doses delivered. Point A is defined as a point 2 cm from the external os and 2 cm lateral to the endocervical canal. Point B is defined as a point 2 cm from the external os and 5 cm lateral to the patient's midline, relative to the bony pelvis. In general, for smaller cervical cancers, such as stage IA2 and IB1 disease, the radical (with curative intent) dose to

Fig. 15.4. Diagram showing point A and point B.



point A is about 70–75 Gy, whereas for larger cervical cancers, such as stage IB2 disease and beyond up to stage IVA, the dose to point A may be 80–90 Gy. The dose indicated is the sum of both EBRT and ICR.

The basic standardized treatment planning for EBRT is based on two-dimensional treatment planning. This process makes use of a radiotherapy X-ray simulator, a two-dimensional computerized treatment planning system used for calculation of dose distributions in a single plane or a few planes of the treatment volume, and treatment verification. The radiotherapy simulator mimics the functions and motions of a radiotherapy treatment unit. It allows the beam direction and treatment fields to be determined to encompass the target volume and spare normal structures from excessive radiation.

The EBRT portals to deliver radiation doses include the pelvis from the L5–S1 junction (so as to include the common iliac nodes) to the lower border of the obturator foramen; the lower border may be extended further to 2–3 cm down to the introitus if there is vaginal involvement. The lateral border extends to 1.5–2 cm lateral to the pelvic brim (bony pelvis). The portals usually measure 15 × 12 cm or 15 × 15 cm. A four-field box technique with an anterior portal, a posterior portal, and two lateral portals (12 × 8 cm or 15 × 8 cm) is used when the separation at mid-pelvis (or the inter-field distance between the anterior and posterior portals) is more than 20 cm. Lateral portals allow a decrease in the dose to the small bowel and the lower rectum. The anterior margin of the lateral portals is at the cortex of the symphysis pubis, and the posterior margin extends to the sacral hollow.

A 4 cm-wide divergent, wedge-shaped alloy midline block may be used (after the initial dose of 30 Gy in 15 fractions) to shield the rectum and bladder for part of the pelvic irradiation (20 Gy in 10 fractions), to allow a higher dose to be given by brachytherapy and to reduce late rectal and bladder sequelae. EBRT with midline block is followed by ICR of 30–35 Gy to point A, taking the total dose to point A to 80–90 Gy.

The use of CT and MRI has made it easier to obtain more accurate tumour localization, which has led to three-dimensional treatment planning.

In the 1990s, the treatment planning for EBRT involved three-dimensional treatment planning and conformal radiotherapy, in which the target volumes and organs at risk are delineated using CT scans or MRI. In the 2000s, modern treatment planning systems permitted the development of intensity-modulated radiotherapy. However, facilities in public health services in many low-income countries lack the equipment and human resources to deliver these advanced radiotherapy techniques.

15.1.4 Survival outcomes after radiotherapy

The 5-year survival rates after radiotherapy for cervical cancer are as follows: stage IA, 95%; stage IB1, 85%; stages IB2 and IIA, 60–65%; stage IIB, 50%; stage III, 30–40%; stage IVA, 10–15%; and stage IVB, 5%.

15.1.5 Sequelae of radiotherapy for cervical cancer

Acute side-effects during radiotherapy may include abdominal cramps, rectal discomfort, diarrhoea, occasional rectal bleeding, dysuria, increased urinary frequency, nocturia, haematuria, erythema, dry/moist desquamation of the perineum or intergluteal fold, radiation vaginitis, and superficial ulceration of the vagina. Late sequelae include proctitis/cystitis (3–10%), vaginal stenosis, vaginal atrophy, dyspareunia, anal incontinence, vesicovaginal or rectovaginal fistula, lumbosacral neuropathy, and femoral neck fracture.

15.2 Chemotherapy

Commonly used chemotherapeutic agents for treating cervical cancer include cisplatin, carboplatin, 5-fluorouracil, ifosfamide, irinotecan, and taxanes. Of these, the mostly widely used agent is cisplatin, alone or in combination with 5-fluorouracil. Administration of cancer chemotherapy is associated with considerable systemic toxicity, particularly haematological, gastrointestinal, renal, and skin toxicity, and alopecia. Chemotherapy requires careful monitoring of general health, blood counts, and liver and kidney function during and after treatment.

15.3 Concurrent chemo-radiotherapy

In 1999, after RCTs demonstrated that concurrent chemoradiotherapy (CCRT) improved survival over radiotherapy alone, the United States National Cancer Institute issued an alert recommending that cisplatin-based CCRT should be considered instead of radiotherapy alone when there is an indication of radiotherapy in cervical cancer. Since that alert, CCRT has been widely practised and has

largely replaced radiotherapy alone for locally advanced cervical cancer.

In a Cochrane review of RCTs comparing CCRT with radiotherapy for locally advanced cervical cancer, adding chemotherapy to radiotherapy seemed to offer a modest but significant additional benefit on all outcomes and for all stages of disease. However, the interpretation of the benefits was complicated by the use of different treatments in the control arms of the included studies, heterogeneity in trial results, and inconsistency in the definition of outcomes between trials (Green et al., 2005). In a meta-analysis based on 13 trials comparing chemoradiotherapy versus the same radiotherapy, there was a 6% improvement in 5-year survival with chemoradiotherapy (hazard ratio, 0.81; $P < 0.001$) (Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration, 2008; Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC), 2010). A meta-analysis of seven RCTs found insufficient evidence that hysterectomy with radiotherapy, with or without chemotherapy, improves the survival of women with locally advanced cervical cancer who are treated with radiotherapy alone or CCRT (Kokka et al., 2015).

However, acute haematological, renal, and gastrointestinal toxicities are increased with chemoradiotherapy. Serious haematological toxicity increased by approximately 2–10-fold in several individual trials. There was also a significant increase in serious gastrointestinal toxicity associated with platinum-based chemoradiotherapy (Green et al., 2005).

15.4 Neoadjuvant chemotherapy

The use of chemotherapy before the application of definitive treatments, such as surgery or radiotherapy, with the aim of decreasing tumour size and extent and improving curability, is called neoadjuvant chemotherapy. Despite significant response rates to chemotherapeutic agents such as cisplatin and paclitaxel, the role of neoadjuvant chemotherapy in the treatment of cervical cancer remains controversial. Neoadjuvant chemotherapy followed by radiotherapy is not superior to radiotherapy alone or CCRT. To date, there is no evidence that overall survival improves after neoadjuvant chemotherapy and definitive treatment, and the toxicity of chemotherapy and the delay of definitive radiotherapy could reduce overall survival.

15.5 Non-surgical options by stage

The various options for treatment of cervical cancer using radiotherapy and chemotherapy are listed in Table 15.1 and outlined below.

15.5.1 Stage IA2

Patients with stage IA2 cervical cancer who are poor surgical risk may be treated with EBRT plus brachytherapy or with brachytherapy alone. If the depth of invasion is less than 3 mm and there is no lymphovascular invasion, EBRT is not needed and these patients may be treated with ICR alone to a total dose of 65–75 Gy to point A in one or two sessions. Alternatively, patients with stage IA2 disease may be treated with EBRT

Table 15.1. Non-surgical options for treatment of cervical cancer

Stage	Treatment option
IA2	• External beam radiotherapy with intracavitary brachytherapy • Intracavitary brachytherapy alone
IB and IIA	• External beam radiotherapy with intracavitary brachytherapy • Concurrent chemoradiotherapy with external beam radiotherapy, intracavitary brachytherapy, and concurrent chemotherapy with cisplatin or cisplatin plus 5-fluorouracil • External beam radiotherapy with intracavitary brachytherapy with surgery for any residual disease • Radical hysterectomy followed by postoperative radiotherapy for cases with a high risk of recurrence
IIB and III	• Concurrent chemoradiotherapy with external beam radiotherapy, intracavitary brachytherapy, and concurrent chemotherapy with cisplatin or cisplatin plus 5-fluorouracil is the standard treatment of choice • External beam radiotherapy with intracavitary brachytherapy
IVA	• Radical or palliative treatment, based on extent of rectal/bladder involvement, renal function, parametrial involvement, general health, and performance status • If patient is in good general health, concurrent chemoradiotherapy with external beam radiotherapy, intracavitary brachytherapy, and concurrent chemotherapy with cisplatin or cisplatin plus 5-fluorouracil • If extensive rectal/bladder involvement, renal failure, bilateral, hard, fixed parametrial involvement, palliative short-course radiotherapy or palliative chemotherapy
IVB	• Palliative short-course radiotherapy • Palliative single-agent chemotherapy with cisplatin or carboplatin or ifosfamide • Palliative combination chemotherapy with cisplatin plus 5-fluorouracil or cisplatin plus ifosfamide or carboplatin plus paclitaxel or carboplatin plus gemcitabine

of 40–45 Gy in 20–25 fractions over 4–5 weeks and ICR of 30–35 Gy.

15.5.2 Stages IB and IIA

Patients with stage IB1 and stage IIA (with the length of vaginal involvement < 2 cm) cervical cancer who are poor surgical risk may be treated with a combination of EBRT and ICR, to a dose of up to 80–85 Gy to point A. Primary therapy for these stages should avoid routine use of both radical surgery and radiotherapy, in order to minimize morbidity associated with multimodality treatment.

One RCT found that there was no significant difference in the overall survival of patients treated with surgery and those treated with radiotherapy for stage IB and stage IIA cervical cancers (Landoni et al., 1997). That study also documented significantly poorer outcomes for patients with bulky cancers (> 4 cm in diameter) who underwent either surgery or radiotherapy compared with those with smaller tumours (< 4 cm in diameter).

Patients with stage IB2 and bulky stage IIA (> 4 cm) cancers and stage IIA cancers with the length of vaginal involvement exceeding 2 cm should be treated with EBRT and ICR to a total dose of 85–90 Gy to point A and concurrent chemotherapy with cisplatin or cisplatin plus 5-fluorouracil. For these patients, adjuvant pelvic irradiation may also be warranted, providing one of the following pertains:

- more than two thirds stromal invasion;
- lymphovascular invasion;
- tumour size > 4 cm.

Pelvic irradiation with concurrent cisplatin-based chemotherapy should be considered in women with positive pelvic nodes, positive surgical margin, or positive parametrium. Finally, vaginal brachytherapy may be considered where the surgical specimen reveals a positive vaginal margin.

15.5.3 Stages IIB and III

The treatment of choice for patients with stage IIB and stage III cervical cancer is CCRT with EBRT, ICR, and concurrent chemotherapy. The chemotherapy may be either

- cisplatin (e.g. 40 mg/m^2 weekly for 4–6 weeks), or
- cisplatin plus 5-fluorouracil (e.g. cisplatin 50–75 mg/m^2 intravenously on day 1 plus 5-fluorouracil 1000 mg/m^2 as a 24-hour continuous intravenous infusion on days 1–4 every 3 weeks for 2–4 cycles).

Patients with stage IIB and stage III disease who are in poor general health may still be treated with EBRT and ICR, but concurrent chemotherapy should be avoided because of the associated increased toxicity. The dose should be at most 85–90 Gy to point A. In low-income countries, many clinicians still consider radical radiotherapy alone to be an acceptable approach in view of poor socioeconomic and nutritional status, doubtful tolerance of chemotherapy due to already low haemoglobin and impaired renal function, and poor patient compliance. A large RCT comparing CCRT with radiotherapy alone at the Tata Memorial Centre, in Mumbai, India, has completed patient recruitment, and the results are awaited. The results are likely to clarify the role and utility of CCRT in developing countries.

15.5.4 Stage IVA

For patients with stage IVA cervical cancer who are in good general health with good performance status, minimal rectal and bladder involvement, and normal renal function, CCRT may be considered. However, extensive rectal or bladder involvement with fistula, impaired renal function, hard, fixed, extensive parametrial involvement on both sides, and poor performance status preclude any scope for radical CCRT, and these patients are candidates for either

- palliative short-course radiotherapy (30 Gy in 10 fractions over 2 weeks, or 20 Gy in 5 fractions over 1 week), or
- palliative chemotherapy (e.g. paclitaxel 175 mg/m^2 intravenously over 3 hours on day 1 every 3 weeks to a total of 2–4 cycles, or paclitaxel 135 mg/m^2 intravenously over 24 hours on day 1 and cisplatin 50 mg/m^2 every 3 weeks to a total of 2–4 cycles).

The management of rectovaginal or vesicovaginal fistulas requires substantial supportive care.

15.5.5 Stage IVB

Patients with stage IVB disease are candidates for palliative radiotherapy to the pelvis (30 Gy in 10 fractions or 20 Gy in 5 fractions or 8–10 Gy in 1 fraction) and to metastatic sites, such as bone and para-aortic nodes, or for management with palliative chemotherapy.

15.6 The need for cancer diagnosis and treatment infrastructure in LMICs

The wider implementation of national HPV vaccination programmes and HPV-based screening programmes has the potential to substantially decrease the burden of cervical cancer in LMICs. However, the financial and organizational difficulties faced in these countries and the lack of government policy initiatives to support resources for comprehensive and quality-assured cervical cancer prevention programmes mean that a substantial number of women will continue to be affected by cervical

cancer. Unfortunately, many LMICs have extremely limited cancer health-care services, and access to and availability of radiotherapy and chemotherapy continue to be barriers to effective treatment in many developing countries. For instance, there are no radiotherapy services available in 22 countries in sub-Saharan Africa, and access to cancer medication is meagre.

The main objective of including the chapters on management of invasive cervical cancer in this manual is to convince the reader how easy it is to prevent cervical cancer by screening and vaccination, while emphasizing the need to care for those women affected by cervical cancer now and in the future in LMICs by developing basic health infrastructure to offer much-needed and affordable cancer diagnosis and treatment services. These services will also provide care for patients with a wide range of other common cancers.

It is illustrative to read about the experience at the Tata Memorial Centre, in Mumbai, India. There, the phased development of infrastructure and skills and the adoption of new developments in management and cervical cancer care have, over time, led to substantial improvements in outcomes (Shrivastava et al., 2013). This retrospective analysis based on 6234 patients with cervical cancer treated over a 15-year period illustrates how much patient treatment and outcomes can be improved with the acquisition of new equipment, the improvement of clinical skills, the introduction of multidisciplinary tumour clinics, and the introduction of evidence-based management policies.

Cervical cancer prevention is easy and affordable, by introducing population-based screening and vaccination programmes, but there is still a need to care for the women affected by cervical cancer now and in the future in those LMICs where these proven programmes have not yet been introduced. The best way to do this is by developing basic health infrastructure to offer much-needed and affordable cancer diagnosis and treatment services. These will serve not only patients with cervical cancer but also those with a wide range of other common cancers.

Key points

- The treatment modalities used in the non-surgical management of cervical cancer include radiotherapy, chemotherapy, and various combinations of radiotherapy and chemotherapy, particularly concomitant or concurrent chemoradiotherapy.
- Adding chemotherapy to radiotherapy seems to offer a modest but significant additional benefit on all outcomes and for all stages of disease, but the combination has significant side-effects.
- The best way to care for women with cervical cancer is by developing basic health infrastructure, whereby affordable cancer diagnosis and treatment services will serve not only patients with cervical cancer but also those with a wide range of other common cancers.