IAEA HUMAN HEALTH REPORTS No. 6

Management of Cervical Cancer: Strategies for Limited-resource Centres — A Guide for Radiation Oncologists

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MANAGEMENT OF CERVICAL CANCER: STRATEGIES FOR LIMITED-RESOURCE CENTRES — A GUIDE FOR RADIATION ONCOLOGISTS

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FOREWORD

Cervical cancer remains a significant cause of morbidity and mortality among women globally, even though it is the cancer with the greatest demonstrated potential for secondary prevention. In some regions of the world the incidence is alarmingly high, such as in sub-Saharan Africa, some countries in Latin America, India and South-East Asia. This disease is highly preventable and curable at a relatively low risk and low cost when screening of asymptomatic women is available, together with appropriate diagnosis, treatment and follow-up.

In developing clinical guidelines, the International Atomic Energy Agency (IAEA) has selected forms of cancer or clinical situations that are very common in low and middle income Member States and for which radiation oncologists consistently express a need for guidance. Clinical guidelines for the management of cervical cancer do exist in the published literature. However, these guidelines have usually been developed in and for affluent environments where all modern diagnosis and treatment modalities are available for the practitioner. In limited resource environments, the radiation oncologist is faced with the question, what would be the minimally acceptable line of action with the limited resources available? Clinical guidelines focusing on low and middle income countries provide a practical tool to these practitioners.

This publication is aimed at the radiation oncologist working in centres with limited resources and treating a large number of patients with cervical cancer on a daily basis. The approach and techniques are intended to be simple, feasible and resource sparing to the extent that this is possible when dealing with a complex treatment modality. The Division of Human Health is placing special emphasis on the subject of cervical cancer, which is addressed not only in this guide but also in regional training courses and coordinated research projects on the subject.

The IAEA officer responsible for this publication was E. Rosenblatt of the Division of Human Health.

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1. INTRODUCTION

1.1. GENERAL CONSIDERATIONS

In 2008 it was estimated that 529 000 incident cases and 275 000 deaths due to carcinoma of the uterine cervix (cervical cancer) occurred annually worldwide. About 88% of this burden is borne by low and middle income (LMI) countries where cervical cancer is the leading malignancy among women [1, 2].

A number of guideline documents are available for the management of common cancers in the published literature. Large academic institutions typically produce their own local guidelines and use them on a daily basis. In the telecommunications era, a wealth of information is available 'a click away' for those who have access to a computer and a broadband Internet connection. One may then ask why the Division of Human Health of the International Atomic Energy Agency (IAEA) has embarked on the preparation of guidelines addressed to limited resource Member States.

The IAEA has a mandate in the application of nuclear techniques in human health including radiotherapy. A long tradition of support to radiotherapy centres worldwide derives from Article II of the IAEA Statute: "The Agency shall seek to accelerate and enlarge the contribution of atomic energy to peace, health and prosperity throughout the world."

As opposed to large academic institutions or private centres in affluent environments, the radiation oncologist in a resource limited setting is faced with a different reality. The paucity of resources is reflected in the limited availability of treatment equipment and quality assurance (QA) equipment. The shortage of trained staff in sufficient numbers is a chronic problem in the developing world. There is limited, if any, access to the published literature, and in many regions an additional problem is the language barrier.

Professionals having Internet access are faced with an enormous amount of information, making it difficult to prioritize what is acceptable care and what is feasible with the resources available. In addition, the transition from conventional two-dimensional (2-D) treatment planning to three-dimensional conformal radiotherapy (3-D CRT) is creating the need for technical guidance for professionals working in smaller, resource limited centres.

In work with LMI countries, we are regularly faced with the need for concise, clear and evidence based guidelines on the treatment of common cancers with radiotherapy. Ideally these guidelines should be available in the local languages.

IAEA guidelines on the treatment of cancers and commonly encountered clinical situations (e.g. painful bone metastasis, radiotherapy for palliation) are directed to the radiation oncologist practicing in an environment with relatively limited resources, who is usually confronted with a large number of patients requiring and deserving adequate radiotherapy. For this target audience, IAEA guidelines aim at providing the following:

(a) Simple and concise sets of recommendations;
(b) Recommendations that are evidence based;
(c) Practical advice on how to perform procedures;
(d) Guidelines initially produced in English, to be translated into all or some of the United Nations (UN) official languages for use in non-English speaking Member States.

This publication has been conceived as a practical manual for the radiation oncologist treating large numbers of cervical cancer patients in a limited resource setting. Users are encouraged to 'adapt' the guidelines to the realities of their own region and/or culture. The methodology followed for producing these guidelines consisted of: defining the objectives and scope; preparing a work plan; forming an expert consultants group; selecting the clinical questions; identifying the published evidence; reviewing and grading the evidence; making group decisions and reaching consensus; linking the guidelines to other guidelines on the subject; creating guideline recommendations; writing the draft guidelines; consulting within and outside the experts group; and editing and final checking of the guidelines before publication.

Recognizing that the 'evidence' is in some respects dynamic and that concepts and procedures in radiation oncology change with time, these guidelines will need to be updated in the future.

1.2. UNDERLYING FRAMEWORK

The following assumptions and context underlie the presentation of material in this report:

(a) All the recommended interventions are based on scientific evidence with the level of evidence and/or grade of recommendation indicated.
(b) Comprehensive control of cervical cancer should ideally be undertaken in the context of a national cancer control programme.
(c) Cervical cancer control should, as far as possible, be integrated into existing sexual and reproductive health services at the primary health care level.
(d) Screening and early diagnosis will lead to the identification of patients with early and advanced invasive cervical cancer. Therefore, screening and early detection programmes should be coupled with appropriate treatment services that should include surgery, radiotherapy, medical oncology and palliative care.
(e) The concepts and recommendations on prevention, early detection and management of precancerous lesions are in harmony with those recommended by the World Health Organization (WHO) and follow WHO documents.

1.3. THE ROLE OF THE RADIATION ONCOLOGIST

Patients with cervical cancer are usually referred to the radiation oncologist either for definitive radiotherapy (usually in more advanced cases) or to consider post-operative radiotherapy following a radical surgical procedure. The roles of the radiation oncologist in this clinical setting include:

— Clinical and physical assessment of the patient in general and assessment of the extent of local-regional disease;
— Disease staging;
— Treatment prescription;
— Review of simulation;
— Selection of the optimal treatment plan;
— Clinical review of the patient during treatment;
— Re-evaluation of disease following external beam radiotherapy;
— Prescription of brachytherapy (BT);
— Insertion of BT applicators;
— Imaging of BT;
— Selection of treatment plan, dose and fractionation;
— Evaluation of the patient following treatment;
— Patient follow-up or return to referring physician for follow-up;
— QA programme implementation for all of the process (see Annex X).

Some of these tasks should be performed in close collaboration with the medical physicist and radiation therapy technologists. In some environments, radiation oncologists are licensed to prescribe and administer cancer chemotherapy. In other centres, chemotherapy is given only by medical oncologists. In the latter situation, close collaboration and coordination with the medical oncologist is also essential.

1.4. LEVELS OF EVIDENCE AND GRADES OF RECOMMENDATION

Recommendations in this publication are generally followed by the level of evidence available and/or the grade of recommendation. The grading scheme and hierarchy of evidence (Table 1) is the one published by Buyse [3].

In the current guidelines, levels of evidence are correlated with grades of recommendation according to the scheme in Table 2.

TABLE 1. SIMPLIFIED SCALE FOR CLASSIFICATION OF EVIDENCE BASED ON THE UNDERLYING STUDY DESIGN

Level	Study design
Level I	Adequately powered high quality randomized trial, or meta-analysis of randomized trials showing statistically consistent results
Level II	Randomized trials inadequately powered, possibly biased, or showing statistically inconsistent results
Level III	Non-randomized studies with concurrent controls
Level IV	Non-randomized studies with historical controls (e.g. typical single arm phase II studies)
Level V	Expert committee reviews, case reports, retrospective studies

TABLE 2. GRADES OF RECOMMENDATION

Grade	Evidence level
A	Directly based on level I evidence
B	Directly based on level II evidence or extrapolated recommendation from level I evidence
C	Directly based on level III evidence or extrapolated recommendation from level II evidence
D	Directly based on level IV evidence or extrapolated recommendation based on level II or III evidence
Good practice point (GPP)	The view of the guideline development group

2. PREVENTION

The risk factors for the development of carcinoma of the cervix and its intraepithelial precursor, cervical intraepithelial neoplasia (CIN), follow a pattern typical of sexually transmitted disease (STD). These include sexual intercourse at an early age, multiple sexual partners, history of other STDs and smoking [4]. Until recently the association between these risk factors was only the subject of speculation. However, the epidemiologic findings, combined with the results of molecular studies, are generally thought to be sufficient to identify human papilloma virus (HPV) infection acquired through sexual intercourse as an etiologic agent in the development of most cervical cancers [5–7]. The primary risk factor in the development of cervical cancer is prolonged infection with HPV.

2.1. MESSAGES ABOUT SEXUAL BEHAVIOUR

The following evidence based messages can lead to behavioural changes that may reduce the incidence and morbidity inflicted by cervical cancer:

(a) Delay first sexual intercourse: people who engage in early sexual activity are more likely to be infected with HPV.
(b) Delay first childbearing: the hormones of pregnancy may increase the risk of developing cervical cancer. Studies have pointed to hormonal changes during pregnancy as possibly making women more susceptible to HPV infection or cancer growth. Another thought is that the immune system of pregnant women might be weaker, allowing for HPV infection and cancer growth.

(c) Limit the number of pregnancies: women who have had five or more children have a higher chance of developing cervical cancer.
(d) Reduce the number of sexual partners: the more partners a person has, the greater the chance of becoming infected with an STD, including HPV and the human immunodeficiency virus (HIV), both of which increase the risk of cervical cancer.
(e) Avoid partners who have multiple partners.
(f) Use condoms: condoms have been shown to protect against STDs and to reduce the risk of cervical cancer.
(g) Do not smoke tobacco: women who smoke have a higher risk of almost all cancers, including cervical cancer.
(h) Seek treatment immediately if you have symptoms that suggest you may have an STD, or if you suspect you have been exposed to an STD. Prompt treatment of STDs may protect against HPV and cervical cancer.
(i) Women over 25 require screening. Almost all women who have had sexual intercourse have probably been exposed to HPV. Screening can detect early lesions that, if successfully treated, can prevent cancer progression.
(j) Message to men: reduce the number of your sexual partners, and always use a condom, especially with new partners.
(k) For a more detailed guide for health education and counselling related to cervical cancer, the reader is referred to the relevant WHO publications [8, 9].

2.2. HUMAN PAPILLOMA VIRUS AND THE HPV VACCINES

2.2.1. HPV infection

Following the discovery that HPV is responsible for cervical cancer, long time collaborators D. Lowy, chief of the US National Cancer Institute (NCI) Laboratory of Cellular Oncology (LCO), and J. Schiller, head of the LCO's Neoplastic Disease Section, began research in the early 1980s to understand how these viruses infect cells. It was not until the early 1990s that the mission was undertaken to design a vaccine that would prevent HPV infection and, thus, cancer.

Of the over 100 classified genotypes of HPV, more than 40 types can infect the upper respiratory–digestive tracts and anogenital areas [6, 10, 11]. In most cases, HPV infection is resolved or becomes undetectable, causing no disease. However, persistent infections caused by high risk HPVs may lead to genital warts and/or neoplastic transformation, which can result in cervical cancer in 10–20 years [10–12]. Over 99% of cancers of the uterine cervix are attributed to persistent infection by HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68, in that order of frequency. Among these, the causal association between infection and invasive cervical disease is strongest for HPV types 16 and 18 [10, 13]. These types cause 70% of all cervical cancers and high grade squamous intraepithelial precancerous lesions (CIN 2 and 3) [14].

Both oncogenic and non-oncogenic HPV types are associated with low grade lesions (CIN 1), and the types involved in cervical disease may also cause dysplasia and cancer in other anogenital areas, e.g. vulva, vagina, penis and anus. HPV is also associated with external genital warts, respiratory papillomatosis, and head and neck tumours [15–25].

Particularly HPV types 6 and 11 are responsible for over 90% of cases of genital warts, as well as causing around 10% of low grade cervical lesions [13, 17].

Both harmless and cancer linked HPVs pass by skin to skin contact. The high risk types of HPV need to penetrate deeply into the lining of the cervix to establish a chronic infection. A vaginal sore or sexual intercourse, which can abrade the lining, may provide a point of entry for the HPV. Once inside the cervical lining, the virus attaches to the epithelial cells. As these cells take in nutrients and other molecules normally present in their environment, they incorporate the virus as well. This sits inside the epithelial cells housed in a protective shell made of a viral protein called L1. Then the viral coat is degraded, leading to the release of the virus's genetic material into the cell and its nucleus. From the nucleus, the genes of the virus are expressed, including two genes called E6 and E7, which instruct the cell to build viral proteins called E6 and E7 [6, 17, 26–29]. Over 99% of cervical cancer cases are linked to long term infections with high risk HPVs [5, 10, 12, 17, 30, 31].

Viral oncoproteins E6 and E7 disable tumour suppressor genes, such as p53, resulting in deactivation of 'damage surveillance' for normal cervical epithelial cells. These protective proteins usually arrest cellular growth

when a serious level of unrepaired genetic damage exists. Even after these tumour suppressors are disabled, it can take more than ten years before the affected tissue becomes cancerous [5, 10, 28, 29, 31].

2.2.2. HPV vaccines

A vaccine to prevent chronic HPV infection or premalignant cervical lesions from progressing to cancer clearly offers a cost effective long term strategy to reduce the cervical cancer burden, particularly in developing countries where effective screening programmes are not available. The encouraging experimental results obtained so far have prompted both commercial and public institutions to pursue the clinical development of vaccines. Recombinant deoxyribonucleic acid (DNA) technology is being used to produce vaccines against HPV, and both prophylactic and therapeutic vaccines are under development and clinical testing [12, 29].

In 2006, Gardasil®, a vaccine against four HPV types, was licensed for market in Gabon, followed by the USA, Canada and more than 100 other countries [32]. Initial recommendations for the use of Gardasil® in Canada and the USA included 9–13 year old females prior to coitarche and 14–26 year old females, even if already sexually active, with a history of cervical abnormalities or prior HPV exposure. The vaccine was not recommended for females who were pregnant or less than 9 years of age. For women older than 26 years, immunization could be considered according to individual circumstances.

Another HPV vaccine, Cervarix™, became available in May 2007 in Australia for females aged 10 to 45, in September 2007 in the European Union (EU) and in the USA in 2009 for females aged 10 to 25 [33–35]. In 2009, the US Food and Drug Administration (FDA) licensed the use of Gardasil® for 9–26 year old males against genital warts caused by HPV 6 and 11 [36].

Gardasil® and Cervarix™ are prophylactic vaccines for the primary prevention of HPV types 16 and 18 (implicated in 70% of cervical cancers). Additionally, Gardasil® protects against HPV types 6 and 11 (implicated in genital warts, which are non-lethal but painful and difficult to treat) [37–39].

A three dose intramuscular administration at 0, 1–2 and 6 months is required [33]. The vaccines generate a relatively robust immune response against targeted HPV types in 15–25 year old females who are pre-coitarchal and/or DNA and serologically negative for the targeted HPV types [40, 41]. For both vaccines, the immune response in older women (25–45 years of age) is stronger than natural infection levels but less than that in 9–15 year olds [42, 43].

HPV vaccines have been formally recommended, although not uniformly adopted, for large scale use in the public sector health care systems and national immunization programmes of the wealthier countries of Europe, North America and Australasia [44, 45]. In developing countries, however, HPV vaccines are not available through national immunization programmes. Following the usage of the International Monetary Fund, and in the absence of other established naming conventions, we apply the term ‘developing country’ to emerging and developing economies [46].

Cost is a leading barrier to equitable delivery of HPV immunization in developing countries, where limited health budgets must address multiple contending priorities [10]. The high vaccine cost can be linked to the monopoly pricing power of vaccine manufacturers seeking to recover high development costs. Their retention of exclusive patent rights and their power to keep vaccine prices high are aided by the absence of compulsory licences, which could authorize the competitive development of cheaper biogenetics through developing country manufacturers. Public sector funding, the aid of vaccine funding consortia such as the Global Alliance for Vaccines Initiative (GAVI), and suitable technology transfer mechanisms are crucial to making HPV vaccines available at affordable prices in developing countries [47–50].

Currently, developing countries bear about 80% of the global mortality from cervical cancer, i.e., an estimated 242 000 compared to 33 000 deaths in high income countries [51, 52]. Given the gaps in secondary prevention, HPV immunization would seem to be the obvious intervention to control mortality from cervical cancer in developing countries.

It is important to recognize that vaccination protects a person from future infection by the high risk types of HPV that are carcinogenic. It is not a vaccine against the cancer itself. Once administered, the vaccine triggers a strong humoral and cellular immune response, so the vaccinated person’s body makes and stockpiles antibodies that can recognize and attack the L1 protein on the surface of HPV. If an exposure occurs, the antibodies sensitized to the L1 protein coat the virus, thus preventing release of its genetic material [5, 29].

After vaccination, it is strongly recommended that women continue to undergo routine Papanicolaou (Pap) tests or approved cervical cancer screening tests. Although the anti-HPV vaccine prevents infection by the dominant HPV types, which are responsible for 70% of cervical cancer, it does not prevent infection by other types that can also cause cervical cancer. A Pap test can detect abnormal cervical growth, regardless of the inciting HPV strain.

Studies are under way to determine if a booster, in addition to the three initial intramuscular injections, will be necessary for long term protection. The new HPV vaccine remains effective for up to four years, but additional research and time are required to determine the duration of protection. An NCI study in progress will follow vaccinated women for several more years to obtain this critical information on the vaccine's long term safety, and the extent and duration of its protection.

WHO has initiated a variety of activities aimed at accelerating the vaccine technology and at supporting vaccine development. Given the long record of prophylactic viral vaccines as a cost effective approach to preventing infection or modifying disease, an effective vaccine against oncogenic types of HPV could have a tremendous impact on the global cervical cancer burden.

3. EARLY DETECTION AND SCREENING

3.1. DEFINITION

Screening is a public health intervention consisting of testing all women at risk of cervical cancer, most of whom will be asymptomatic. Therefore, organized screening programmes designed and managed at the central level to reach most women at risk are preferable to opportunistic screening [50].

3.2. PURPOSE

Screening aims to detect precancerous changes, which if not treated may lead to cancer. In settings with a high prevalence of HPV infection, screening for cervical cancer is particularly important. HIV positive women have more persistent HPV infections and a higher incidence of cervical precancer and invasive cancer [48]. Where HIV is endemic, screening results may be positive in up to 15–20% of the target population. Cytology screening is equally effective in HIV positive and HIV negative women. Although HIV infected women are at a greater risk of precancerous and cancerous lesions, screening follow-up and treatment may not be a priority for these women, who have competing health and/or social needs.

All women, regardless of their HIV status, should be encouraged to be screened for cervical cancer, provided they have access to affordable services. Care should be taken not to link a positive cervical cancer screening test to HIV testing. However, women with precancer may benefit from knowing their HIV status, especially if antiretroviral (ARV) treatment is available. Screening criteria for women with known HIV infection should be developed at the national level with these issues in mind.

3.3. SCREENING TECHNIQUES

3.3.1. Cytology screening

Cytology based methods of screening include the conventional Pap test and liquid based cytology (LBC) tests. In the Pap test, a sample of cells is taken from the transition zone (T zone) of the cervix using an extended tip wooden spatula or brush. The sample is then smeared onto a glass slide and immediately fixed to preserve the cells. The slides are sent to a cytology laboratory where they are stained and then examined using a microscope to determine whether the cells are normal and to classify them according to the Bethesda classification [50].

The LBC test consists of transferring the specimen from a brush to a preservative solution. The specimen is then sent to a laboratory where the slide is prepared. LBC is more expensive than conventional Pap smear cytology,

and the laboratory staff require additional training to read the slides. Several studies have demonstrated that LBC has similar sensitivity to a Pap smear [7, 53, 54].

Health workers are responsible for ensuring that women are informed of results, receive appropriate follow-up, and/or are treated as indicated.

The accuracy of cytological testing depends on the quality of the services, including the sampling technique (taking and fixing the smear), and the staining and interpretation of the smears in the laboratory. Under the best conditions, conventional cytology can detect up to 87% of precancer and cancer. However, under poor conditions, the sensitivity can be as low as 30%. The specificity of the test is usually over 90% [50, 55, 56].

3.3.2. Visual inspection

Two visual methods are available: visual inspection with acetic acid (VIA) and visual inspection with Lugol's iodine (VILI). Abnormalities of the cervical mucosa are identified by inspection without magnification, after the application of dilute acetic acid (VIA) or Lugol's iodine (VILI) [16, 50, 57].

Where resources are limited, VIA and VILI are promising alternatives to cytology, since laboratory services are not required [18, 19]. In research settings, VIA has an average sensitivity of about 86% in detecting abnormal lesions, whether invasive or non-invasive [56]. One study has shown that VILI can detect 92% of lesions, a sensitivity level considered higher than that of either VIA or cytology. Its ability to identify women without disease is similar to that of VIA (85%) and lower than that of the Pap test [20, 53]. VILI can be performed in clinics and outpatient facilities, and is a relatively simple and painless procedure. Assessment is immediate, and no specimen or specimen processing is required [50].

3.3.3. HPV testing

New screening procedures are based on the detection of high risk HPV DNA in vaginal or cervical smears. The specimens collected are transported to a laboratory where they are processed. HPV DNA methods currently require sophisticated and expensive laboratory equipment. Work is under way to develop a more affordable and less complicated test that can be carried out in lower resource settings.

Detection of high risk HPV does not indicate whether or not precancer or cancer is present. It simply relates the presence of an HPV infection. HPV infections are very common in women under 35 years of age and most resolve spontaneously. When HPV detection is used as a primary screening test, the sensitivity for detecting abnormalities is quite high, over 90% [10, 50]. The combination of cytology and HPV testing has a very high sensitivity and negative predictive values approaching 100% [56].

Mexico's experience in HPV testing, self-sampling practices and other approaches that have advanced opportunities for patient screening serves as an example that warrants consideration when developing new strategies in developing countries [58].

It may be possible to increase the interval between screenings for women who are negative on both tests. Major challenges in the successful implementation of both tests, particularly for low resource settings, include the high cost and reliable transport methods.

3.3.4. Screen and treat approach

With the single visit approach, the clinician can offer immediate treatment for women with a positive VIA or VILI evaluation, without a cytologically confirmed screening test. Cryotherapy is one potential treatment approach. The Alliance for Cervical Cancer Prevention has conducted studies showing that the screen and treat approach, involving one or two visits, may offer an effective solution to the problem of follow-up visits [15, 50]. It eliminates the need to wait on a diagnosis and the additional time required to return for treatment, as well as the need for extensive tracking systems.

3.4. RECOMMENDATIONS ON SCREENING FOR CERVICAL CANCER

Repeat screening demands follow-up compliance with treatment, which is a particular challenge in remote, impoverished, rural areas, where women must schedule time away from necessary daily tasks or travel long distances to clinics to be tested. Ensuring compliance requires maintaining screening registries and establishing mechanisms for reminders and follow-ups that do not provoke anxiety or cause embarrassment for the women [4]. Inadequate networks, personnel and expertise inhibit public education, disease surveillance and follow-up monitoring in resource-poor settings [59].

The implementation of screening methods comes with challenges. Although HPV testing is less affected by subjectivity or artefact than cytology or VIA, it requires more laboratory facilities, costs more than Pap tests and can be difficult to introduce in developing countries. Furthermore, HPV testing has higher sensitivity and higher specificity than cytology, implying fewer false negatives but increased false positives and over-triaging to colposcopy. This can increase resource demands on health care and anxieties and physical burdens for patients. Although new and cheaper HPV tests are being developed, they are not yet available for widespread use in developing countries [26, 60–62].

Inexpensive visual screening procedures such as VIA and VILI are easier to implement in developing settings, and local health workers can be trained to perform them. However, the readings may be highly subjective, error prone and not easily reproducible [63].

In developing countries, the limitation of resources available to the health care system affect ‘structure’; that is, the physical capacity of the medical system to manage disease. In turn, structural limitations constrain ‘access’ and negatively impact ‘processes’ and ‘outcomes’ [64].

Criteria for age and frequency of cervical cancer screening are the following [9]:

(a) Women younger than 30 years of age should not undergo screening except for women known to be HIV infected or living in a high HIV prevalence area.
(b) At a minimum, a national programme should prioritize women who are between 30 and 49 years old for screening.
(c) The screening interval (frequency) should not be less than five years (and not less than ten years, if using an HPV test).
(d) Priority should be given to maximizing coverage within the at-risk target age group and ensuring complete follow-up of those women with abnormal screening test results rather than maximizing the number of tests performed in a woman’s lifetime.
(e) In high HIV prevalence countries, women who screen positive for cervical cancer should be offered HIV testing and counselling.

3.5. THE LINK BETWEEN SCREENING AND THE CANCER CONTROL PROGRAMME

Screening is effective only if there is a well organized system for follow-up and treatment. Potential limitations in screening programme implementation are:

— Lack of personnel adequately trained in screening methods;
— Limited access to a well organized system for follow-up and treatment of abnormal findings.

Women who are found to have abnormalities on screening require follow-up, histopathological diagnosis and possibly treatment, in order to prevent the development of cancer or to treat it at an early stage. An effective system for the follow-up and treatment of women who test positive is perhaps the most important component of a successful cervical cancer prevention programme. At the very least, all women whose results are positive or abnormal must be counselled on appropriate follow-up and treatment options. Follow-up should be consistent with national protocols and/or based on WHO recommendations.

4. DIAGNOSIS AND STAGING WORK-UP

4.1. PATHOLOGY

A biopsy is mandatory to establish the diagnosis of cervical cancer. All lesions must be confirmed by histopathological examination. Punch biopsies from the edge of the gross tumour are recommended. Over 90% of cervical cancers are squamous cell carcinoma, followed by about 10% of adenocarcinomas and nearly 1% clear cell (mesonephric) carcinoma. Verrucous carcinoma is a well differentiated variant of squamous cell carcinoma. Other less frequent histopathologic specimens include adenosquamous carcinoma, glassy cell carcinoma, malignant Müllerian mixed tumours, adenoid cystic carcinoma, small cell carcinoma (one third to one half are neuroendocrine markers positive), basaloid (or adenoid-basal) carcinoma, sarcomas and lymphomas [65].

4.2. STAGING

Once a histological diagnosis of cervical cancer has been made, the next step is to formulate the most effective therapy for the individual patient. In order to properly manage a patient with cervical cancer, it is essential to understand the extent of the stage of disease at the time of diagnosis. A major purpose of staging is to determine the extent of disease, so as to provide a method of comparing clinical experience and treatment results among institutions without confusion or ambiguity. Staging systems should be validated by showing a correlation between stage of disease and patient prognosis. They also guide the clinician in both tailoring the treatment and assessing prognosis.

The classification of the International Federation of Gynecology and Obstetrics (FIGO), which is based on tumour size and the extent of the disease in the pelvis and distant organs, is recommended for the staging of invasive cervical cancer (see Annexes I and II) [66]. The extent of cancer is assessed clinically through the history and physical examination, including a careful pelvic examination, supplemented by a limited number of relatively unsophisticated investigations.

In many low resource settings, vaginal and rectal examinations are the only feasible approaches to staging. This assessment can be done under general anaesthesia, preferably together with a gynaecologist or gynaecologic oncologist if the conditions for a thorough pelvic examination are suboptimal. In addition, if an examination under anaesthesia is performed, it is recommended to carry out proctoscopy and cystoscopy in patients with advanced stages of the disease (FIGO stage IIB or greater) or when rectal and/or urinary complaints are present.

Imaging modalities that provide additional staging and prognostic information are computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET)/PET-CT [67–71]. All staging investigations and their results should be carefully documented in the patient's medical record.

We strongly recommend the use of a descriptive diagram depicting the extension of disease in the individual patient on admission. The diagram should be drawn immediately following the initial pelvic examination, and filed in the patient chart for easy reference during and after treatment (Annex IV).

4.2.1. Clinical staging

Clinical staging is based on clinical evaluation, including bimanual vaginal and rectal examinations, imaging studies, and specific procedures. The pelvic examination, preferably under general anaesthesia, must be performed in all cases [66].

FIGO provides a list of additional examinations allowed: endocervical curettage, hysteroscopy, cystoscopy, proctoscopy or colonoscopy, intravenous urography (IVU) and chest X ray. Suspected bladder or rectal involvement should be confirmed by biopsy and histological evidence of tumour involvement. For staging purposes, biopsy or conization is regarded as part of the clinical examination and diagnosis [66, 72, 73]. Other diagnostic procedures such as ultrasound (US), CT scans, MRI, PET/PET-CT scans, barium enema X rays and laparoscopy may be used, but results cannot alter the initial clinical stage [72, 74].

Although FIGO recommends using IVU, this has been largely replaced by the abdominal–pelvic CT scan with contrast. The FIGO staging system does not take into account the radiological findings from CT, MRI or

PET/PET-CT. However, the findings from these imaging studies should be recorded using the tumour, node, metastasis (TNM) classification and taken into account for treatment decisions.

4.2.2. Post-surgical pathologic staging

The histopathological findings after a radical surgical procedure do not change the initial FIGO clinical staging and should be documented using the TNM system (see Annexes I and II). Adequate and detailed information should be obtained from the responsible pathologist regarding potential histopathological risk factors that would impact decisions in terms of adjuvant therapy. In order to identify histopathological risk factors, the following information should be included in the histopathological report after hysterectomy:

(a) Tumour size.
(b) Histological type.
(c) Grade of differentiation.
(d) Depth of stromal invasion — total thickness of cervical stroma.
(e) Presence of lymphovascular space involvement.
(f) Status of the margins.
(g) Parametrial and/or vaginal involvement.
(h) Presence of associated precancerous lesions.
(i) Presence of lymph node involvement:
    — Number of lymph nodes contained in the surgical specimen;
    — Number of positive lymph nodes;
    — Location of nodal regions sampled and positive nodes;
    — Size of involved lymph nodes;
    — Presence of extracapsular extension.

If an unsuspected invasive carcinoma is found after hysterectomy, it should be reported separately. Since there was no evidence of disease prior to surgery, it should not be clinically staged. In this case, a complete histopathological report with the information indicated above should be submitted by the pathologist as well.

4.3. DIAGNOSTIC WORKUP

(1) Recommended baseline workup:
    (a) Complete medical history.
    (b) Physical examination, including bimanual vaginal and rectal examinations.
    (c) Tumour diagram in three dimensions with measurements.
    (d) Diagnostic procedure: punch biopsies (edge of gross tumour, four quadrants in preinvasive lesions). All lesions must be confirmed by histopathological examination.
    (e) Cystoscopy, proctosigmoidoscopy: recommended in patients with clinical stage IIB or greater disease, presence of vaginal wall infiltration, and when there are rectal or bladder complaints.
(2) Laboratory studies:
    (a) Complete blood count test.
    (b) Blood chemistry, including creatinine level; creatinine clearance or glomerular filtration rate from the creatinine in serum (see Annex III). Liver function tests should be obtained and monitored with the renal function tests in those patients who may be receiving extended field radiotherapy.
    (c) Urine analysis.
    (d) Pregnancy test in patients of childbearing age.
    (e) Optional: HIV testing and, if positive, CD4 lymphocytes count.

(3) Imaging studies:
  (a) Standard:
    (i) Chest X ray, anteroposterior (AP) and lateral.
    (ii) IVU or US of the kidneys (not necessary if CT or MRI is performed).
    (iii) CT of the abdomen and pelvis with and without intravenous and oral contrasts.
  (b) Optional:
    (i) MRI of the pelvis with and without gadolinium.
    (ii) ^{18}F-fluorodeoxiglucose (FDG) PET scan or PET/CT scan.

5. MANAGEMENT OF PREMALIGNANT LESIONS

5.1. THE BETHESDA SYSTEM

Most laboratories use the 'Bethesda system' to describe Pap test results [75]. With this system, the results are reported as:

— *Normal (negative)*: no signs of cancer or precancer.
— *Atypical squamous cells of undetermined significance (ASC–US)*: changes in the cervical cells have been found. The changes are almost always a sign of an HPV infection but may indicate that precancer is present. ASC–US is the most common abnormal Pap test result.
— *Squamous intraepithelial lesion (SIL)*: abnormal changes are seen in the cells that may be a sign of precancer. SIL can be low grade (LSIL) or high grade (HSIL). These grades are related to the grades of dysplasia and CIN. LSIL almost always indicates that an HPV infection is present, but it may also indicate mild precancer changes. LSIL is very common and usually goes away on its own without treatment. HSIL indicates more serious changes. Carcinoma in situ is a severe form of HSIL. It is most likely to progress to cancer.
— *Atypical squamous cells, cannot exclude HSIL (ASC–H)*: changes in the cervical cells have been found. These changes are not clearly HSIL but could be. Further testing is needed.
— *Atypical glandular cells (AGCs)*: cell changes are seen that suggest precancer of the upper part of the cervix or uterus.
— *Cancer*: abnormal cells may have spread deeper into the cervix or to other tissues.

If a Pap test shows abnormal cells or cervical dysplasia, further testing or monitoring will be recommended:

— Follow-up Pap tests may be recommended for mild cases;
— Colposcopy directed biopsy can confirm the condition;
— Cone biopsy may be done after colposcopy.

5.2. CERVICAL INTRAEPITHELIAL NEOPLASIA

CIN is the potentially premalignant transformation and abnormal growth (dysplasia) of squamous cells on the surface of the cervix. CIN is not cancer and is usually curable. Most cases of CIN remain stable or are eliminated by the host's immune system without intervention. However, a small percentage of cases progress to cervical cancer, usually squamous cell carcinoma, if left untreated [4, 11]. A major cause of CIN is persistent infection of the cervix with the sexually transmitted HPV, especially the high risk HPV types 16 or 18 [5].

The earliest microscopic change corresponding to CIN is dysplasia of the epithelial or surface lining of the cervix, which is essentially undetectable by the patient. Cellular changes associated with HPV infection, such as koilocytes, are also commonly seen in CIN. CIN is usually discovered by a screening test, the Pap test. Pap test results may be reported using the Bethesda system.

CIN-1 lesions are more likely to resolve spontaneously, but they should be treated if it is likely that the patient will not return for follow-up and in other special circumstances. Precancerous lesions graded CIN-2 and CIN-3 require treatment. Treatment for higher grade CIN involves removal or destruction of the neoplastic cervical cells by cryocautery, electrocautery, laser cautery, loop electrosurgical excision procedure (LEEP) or cervical conization. Therapeutic vaccines are also in development. The lifetime recurrence rate of CIN is about 20%, but it is not clear what proportion of these cases are new infections rather than recurrences of the original infection.

Table 3 summarizes CIN grades and characteristics. Depending on several factors such as the type of HPV and the location of the infection, CIN can start in any of the three stages, and can either progress or regress.

TABLE 3. GRADES OF CERVICAL INTRAEPITHELIAL NEOPLASIA

CIN grade	Definition
CIN-1	The least risky type represents only mild dysplasia or abnormal pattern cell growth and is considered a low grade squamous intraepithelial lesion confined to the basal one third of the epithelium.
CIN-2	These are considered high grade squamous intraepithelial lesions. CIN-2 represents moderate dysplasia and is confined to the basal two thirds of the epithelium.
CIN-3	In this lesion, severe dysplasia spans greater than two thirds of the entire epithelium and may involve the full thickness. This lesion may also be referred to as 'carcinoma in situ'.

5.3. TREATMENT

5.3.1. Cryotherapy

Cryotherapy eliminates precancerous lesions on the cervix by freezing. It is a relatively simple procedure that takes about 15 minutes and is performed as an outpatient procedure [18, 76]. It involves applying a highly cooled metal disc (cryoprobe) to the cervix, and freezing its surface using carbon dioxide (CO_2) or nitrous oxide (N_2O) gas. The cryoprobe is applied to the cervix twice, for three minutes each time, with a five minute thaw in between (double freeze technique).

Cryotherapy can be performed at all levels of the health care system by adequately trained and certified providers. Cryotherapy is highly effective for the treatment of small and superficial lesions, but for larger and deeper lesions the cure rate is below 80% [77]. Because the cervical area frozen has very few nerve endings, cryosurgery is generally associated with mild cramping and/or pain. Therefore, it can be performed without anaesthesia. One important disadvantage of cryotherapy is the absence of histopathological specimen for further evaluation of the extent of the disease and margins status.

5.3.2. Loop electrosurgical excision procedure

LEEP is the removal of abnormal areas from the cervix using a thin heated wire. It requires an electrosurgical unit that produces a constant low voltage and transmits it to the wire loop device, which is used to remove the abnormal tissue. The loop is made of very fine stainless steel or tungsten wire and is available in different sizes and shapes. The loop cuts and coagulates at the same time. LEEP aims to remove both the lesion and the entire transformation zone. The removed tissues should be sent for histopathological examination, allowing the extent of the lesion to be assessed. Thus LEEP serves a dual purpose: it treats the lesion and at the same time produces a specimen for pathological examination. The procedure can be performed under local anaesthesia on an outpatient basis. It is successful in eradicating precancer in more than 90% of cases. Treatment failure (persistent lesions at 6 or 12 months of follow-up) is seen in less than 10% of patients [50].

While LEEP is a relatively simple surgical procedure, it should be performed only by a well trained provider with demonstrated competence in the procedure itself, as well as in recognizing and managing intra-operative and post-operative complications such as haemorrhage. LEEP is best performed in facilities where backup is available

for management of potential complications. In most low income countries, this will limit LEEP to second level (district hospital) facilities.

5.3.3. Cold knife conization

Cold knife conization is the removal of a cone shaped volume of tissue from the cervix, including portions of the outer (ectocervix) and inner (endocervix). Conization is recommended for the treatment of dysplasia when outpatient treatment is not feasible or accessible, and to rule out invasive cancer. It is a more extensive operation, involving removal of a large area of the cervix with a scalpel, and is usually done under general or regional (spinal/epidural) anaesthesia. It takes about half an hour. The patient may be discharged from the hospital the same day or the following day. Because of possible side effects, cold knife conization should be reserved for cases that cannot be resolved with cryotherapy or LEEP excision. The extent of the conization will depend on the size of the lesion and the likelihood of finding invasive cancer. The woman's desire to reproduce must be considered, as conization may result in cervical stenosis or incompetence in some women. The cone specimen is sent to pathology for histological diagnosis and to ensure complete removal of the abnormal tissue.

Cold knife conization should be performed only by providers with surgical skills who have access to a well equipped surgical facility. Providers are usually gynaecologists or surgeons who are trained to perform the procedure, and who can recognize and manage potential complications.

5.3.4. Simple hysterectomy

Hysterectomy should not be used to treat precancerous conditions, unless there are other compelling reasons to remove the whole uterus. A desire for surgical sterilization is not an acceptable reason.

6. TREATMENT OF INVASIVE CANCER

Therapeutic approaches must be carefully tailored in order to obtain the best outcome for each patient. This guidance is intended to provide an orientation as to the best evidence based treatment strategies for both early and advanced stages of cervical cancer. However, an overall assessment of the patient, and differences in the availability and quality of surgery, radiation oncology and medical oncology services, may affect the treatment selection. Furthermore, a patient's co-morbidities, as well as social and educational factors, may impact treatment decisions and ultimate outcome. As an example, in HIV positive women, the CD4 count may influence the choice of treatment because of the potential increased toxicity [77, 78].

Radiotherapy departments in LMI countries have available teletherapy machines and often only manual or 2-D treatment planning systems. Other centres may have 3-D treatment planning systems. This guidance provides technical orientation in the treatment of cervical cancer patients for both environments.

Patients with cervical cancer may be referred to the radiation oncology department with any of the following indications:

(a) Biopsy proven cervical cancer with an intact uterus;
(b) Consideration of post-operative irradiation: the patient underwent adequate surgical procedure for cervical cancer;
(c) Consideration of post-operative irradiation: the patient underwent a hysterectomy for other reasons and a cancer was incidentally found;
(d) Consideration of post-operative irradiation after surgery: the patient underwent an inadequate oncological surgical procedure for a known invasive cervical cancer (i.e. simple hysterectomy, no lymph node dissection, no vaginal cuff resection);
(e) Palliative care in patients with metastatic disease.

6.1. DEFINITIVE (CURATIVE) TREATMENT FOR INVASIVE CANCER

To facilitate the decision making process, patients may be classified into two groups based on the FIGO staging system (Table 4).

TABLE 4. EARLY AND ADVANCED STAGE CERVICAL CANCER

Group	FIGO stage
Early stage	IA – IB1 – IIA1
Advanced stage	IB2 – IIA2 – IIB – IIIA – IIIB – IVA

6.1.1. Management strategy for early stage cervical cancer

6.1.1.1. Stage IA

6.1.1.1.1. Stage IA1 with clear margins following a cone biopsy (<1% risk of lymph node involvement)

— If fertility is desired: observation;
— If fertility is not desired: class I total abdominal hysterectomy (TAH) with or without bilateral salpingo-oophorectomy (BSO).

Patients that have medical contraindications to surgery can be treated with intracavitary BT alone at the following doses [72, 74, 79, 80]:

— High dose rate (HDR) tandem and colpostats/ring: 5–6 fractions of 7 Gy/fraction to point A (Annex X) [81];
— Low dose rate (LDR) tandem and colpostats: 55–60 Gy to point A in 1 or 2 fractions.

6.1.1.1.2. Stage IA2 with clear margins following a cone biopsy (2–12% risk of lymph node involvement)

— If fertility is desired: simple or radical trachelectomy and pelvic lymph node dissection (PLND);
— If fertility is not desired or the patient is not a candidate for trachelectomy: class II modified radical hysterectomy, and PLND ± adjuvant radiotherapy.

Patients who have contraindications to surgery can be treated with intracavitary BT alone or in combination with external beam radiotherapy (EBRT) [73, 79, 80]. Whole pelvis EBRT at 45 Gy is recommended in patients with a high risk of pathological features: tumour greater than 2 cm measured microscopically in the conization specimen and/or presence of lymphatic/vascular space invasion (LVSI).

6.1.1.1.3. Stages IA1–IA2 with margins involved with cancer or with CIN-3

— Repeat the cone biopsy.

6.1.1.2. Stages IB1and IIA1

6.1.1.2.1. Medically fit for surgery

— Class II, modified radical hysterectomy, and PLND +/– ‘tailored adjuvant radiotherapy’;
— Definitive radiotherapy.

6.1.1.2.2. Medically unfit for surgery

— Definitive radiotherapy.

These stages have a relatively good prognosis. They can be treated with either primary radiotherapy or surgery, with comparable results [82]. In small volume disease with tumour diameters of up to 4 cm and no suspected or clinical evidence of pelvic nodal disease, radiation alone provides excellent tumour control and high cure rates [72, 73, 83, 84] *(grade of recommendation A)*.

Treatment selection will depend upon physician judgement and patient factors such as age, overall medical condition, performance status (see Annex V), patient preferences and priorities *(grade of recommendation A)*.

Radiotherapy is preferable for patients with a poor surgical risk and if a gynaecologic oncology surgeon with appropriate expertise is not available.

If surgery is chosen, radical hysterectomy (Class II or III) and pelvic lymphadenectomy is the standard choice (see Annex VI). Adjuvant radiotherapy is indicated in intermediate and high risk patients (Table 5). In younger patients (premenopausal status), the ovaries can be preserved. If post-operative radiotherapy is considered at the time of surgery, the ovaries should be transposed outside the pelvis. Ovarian transposition can be performed through a laparotomy or laparoscopic procedure. If ovarian transposition is performed, the position of the ovaries outside the pelvis should be marked with radio-opaque clips for clear localization during radiotherapy treatment planning.

6.1.2. Management strategy for advanced stage cervical cancer

6.1.2.1. Stages IB2 and IIA2

Mainstay treatments for these stages are:

— Concomitant chemo-radiotherapy as in more advances stages (see Section 6.1.2.2.).

— In selected patients: class III radical hysterectomy and PLND. Most patients will require post-operative radiotherapy (or chemo-radiotherapy), mainly those with positive lymph nodes, parametrial involvement or positive tumour margins [85–88]. Based on the combination of risk factors, patients can be attributed to low, intermediate and high risk groups (Table 5). Radiotherapy in these situations can improve pelvic disease control, but without clear impact on survival [89].

The combination of both treatments (radiotherapy and surgery) can lead to higher morbidity rates and, if at all possible, should be avoided [82] *(grade of recommendation A)*. However, surgery and adjuvant radiotherapy (or chemo-radiotherapy) should be considered when BT is not available.

Neoadjuvant chemotherapy prior to surgery is considered investigational and should only be offered as part of a clinical trial [90]. Several randomized trials and one meta-analysis demonstrated that neoadjuvant chemotherapy followed by surgery can be advantageous [90–94]. However, in a recent Gynecological Oncology Group (GOG) study, closed prematurely due to lack of accrual, neoadjuvant chemotherapy was not associated with improvement in overall survival, operability rate, difference in terms of surgical pathological risk factors at the time of the radical hysterectomy or need for adjuvant therapy [95]. In addition, there was increased haematological, gastrointestinal and neurological toxicity associated with neoadjuvant chemotherapy.

6.1.2.2. Stages IIB–IVA

These patients are not candidates for surgery. Standard treatment is EBRT plus BT with or without concomitant chemotherapy [72, 73, 94, 96] (*grade of recommendation A*).

TABLE 5. RISK GROUPS FOR CERVICAL CANCER AFTER RADICAL HYSTERECTOMY

Risk group	Risk factors	Treatment recommendations
Low	Superficial stromal invasion (<1/3) T <4 cm Negative margins Negative lymph nodes LVSI (–)	No adjuvant therapy Observation
Intermediate	Negative lymph nodes LVSI(+) and one of the following: (1) Deep third stromal invasion, any tumour size (2) Middle third stromal invasion , T <4 cm (3) Superficial third stromal invasion, T ≥4 cm LVSI(–) and one of the following: (1) Middle or deep third stromal invasion (2) T ≥4 cm	EBRT 45–50.4 Gy alone *Grade of recommendation A* Consider intracavitary BT boost in patients with LVSI (+), vaginal extent or close margins (≤1 cm) *Grade of recommendation C*
High	Positive lymph nodes Positive parametrial involvement Positive margins	EBRT 45–50.4 Gy + weekly cisplatin 40 mg/m^2 (max. 70 mg/wk) or cisplatin 70 mg/m^2 and 5-Fluorouracil 1000 mg/m^2 × 4 days 2 cycles during radiotherapy (days 1 and 22), followed by 2 cycles after completion of radiotherapy (days 43 and 64) *Grade of recommendation A* Consider a BT boost to the vaginal vault in case of positive margins and/or positive parametrial involvement HDR: 5–6 Gy × 3 fractions at 5 mm from applicator surface LDR: 20–25 Gy at 5 mm from applicator surface *Grade of recommendation C*

Five randomized phase III trials in patients with disease limited to the pelvis, without retroperitoneal lymph node involvement, demonstrated a 30–50% decrease in the risk of death, a decrease in the risk of local recurrence by up to 50% and a 10–12% improvement in overall survival when adding cisplatin based chemotherapy to radiotherapy [88, 97–100] (*grade of recommendation A*). Those trials involved several clinical situations, including post-operative irradiation, various chemotherapy regimens and different disease stages. Results of these five trials led to a National Institutes of Health alert in 1999: "Strong consideration should be given to the incorporation of concurrent cisplatin based chemotherapy with radiation therapy in women who require radiation therapy for treatment of cervical cancer" [96]. However, the NCI-Canada trial in which radiotherapy alone was compared with the same radiotherapy plus cisplatin based chemotherapy did not show a survival benefit for the combined approach [101] (*grade of recommendation A*).

The most recent meta-analysis [102] has shown:

— A 6% improvement in five year survival with chemo-radiotherapy.
— A better survival for the trials in which additional chemotherapy was administered after chemo-radiotherapy.
— Significant survival benefit for both the group of trials using platinum based and those using non–platinum based regimens.
— Reduced local and distant recurrence and improved disease free survival with chemo-radiotherapy.
— Suggestion of a difference in the size of the survival benefit with tumour stage, but not across other patient subgroups. Larger benefit in patients with stages IB–IIB.
— Acute toxicity increased with chemo-radiotherapy, but data were too sparse for an analysis of late toxicity.

It was shown in all these trials that with the use of chemo-radiotherapy, the incidence and severity of acute haematologic and gastrointestinal complications are significantly increased and patients are more likely to require hospitalization or emergency room visits during treatment. Therefore:

— Optimal multidisciplinary cooperation is of paramount importance.
— Patients have to be seen weekly during chemo-radiotherapy, with close monitoring of haematological parameters and renal function.
— Frequently observed toxicities include nausea, vomiting, anorexia and diarrhea, in addition to weight loss and fatigue.
— Most patients experience granulocytopenia and anaemia, and the levels of serum magnesium and potassium should also be closely monitored.

Although chemo-radiotherapy increases acute haematologic toxicity and gastrointestinal dysfunction when compared with radiotherapy alone, there is not a clear significant correlation in the incidence of late adverse effects [103]. Symptomatic gastrointestinal and urinary tract late adverse effects of chemo-radiotherapy have been reported in 12–16% of cases [72].

It is very important to recognize that these randomized trials were conducted in a controlled research setting in high income countries, in selected groups of patients. Given the fact that adding chemotherapy to pelvic radiation increases the toxicity, it is a concern that in LMI countries, differences in nutrition, performance status, anaemia, renal function and perhaps more advanced lesions could lead to a poorer tolerance of these more aggressive regimens. Physicians must weigh the possible benefits against significant disadvantages, which include doubtful compliance, inability to treat febrile neutropenia or other possible complications, treatment interruptions that may result in delays in the administration of the radiation, and incomplete courses of therapy that could compromise cure rates [104]. In these situations, treatment with definitive doses of radiotherapy alone (external beam and BT) is a legitimate option.

Currently available data do not allow conclusions to be drawn regarding which drugs or regimens are optimal in the treatment of cervical cancer. Until further data become available, it is reasonable to suggest that weekly cisplatin should be the regimen of choice, concurrently with radiotherapy. The most commonly used cisplatin dose is 40 mg/m^2 weekly for five cycles during EBRT. This is based upon the current GOG standard. Weekly clinical checks should include a complete blood count test, urea and creatinine concentrations in serum, and calculated creatinine clearance (see Annex III).

Carboplatin has not been thoroughly evaluated in randomized trials in patients with cervical cancer. The overall response rate is somewhat lower than that with cisplatin. On the basis of available data, it is not possible to assess the relative efficacy of concurrent carboplatin and cisplatin. The routine use of carboplatin as an alternative to cisplatin cannot be justified on the basis of the available studies [105, 106].

Other chemotherapy regimens have been explored in locally advanced cervical cancer, including gemcitabine plus cisplatin chemo-radiotherapy followed by chemotherapy [107]. Although an improvement in overall survival was reported compared with radiation in combination with weekly cisplatin, the gemcitabine–cisplatin was associated with very significant acute toxicity (86% grade ≥3). This study is relevant because it was performed in LMI countries; however, the overall results are not improved compared with previously published phase III trials [88, 97, 98, 100, 108].

Unfortunately, a great proportion of the patients diagnosed with cervical cancer in LMI countries present with very advanced disease at diagnosis. Individualized management of these patients is critical, taking into account not only the stage of the disease but also general and social conditions that may preclude a more aggressive approach:

— In the absence of metastatic disease, every patient should be given the opportunity of a treatment as aggressive as can be potentially tolerated to improve her chances for cure.
— An assessment of the patient's general condition, toxicity and tumour response should be performed after approximately 40 Gy to the pelvis with EBRT. A decision must be made on whether to proceed with potentially curative therapy in which EBRT is completed to a definitive dose, followed by BT, or continue with palliative EBRT alone [88].
— In patients with massive lesions or who are in poor general condition, a short course of palliative EBRT scheme is a reasonable choice (see Section 10).

6.1.2.3. Stage IVB

6.1.2.3.1. Para-aortic nodes involvement

It is important to distinguish between patients with microscopic positive para-aortic nodes at the time of the lymph node dissection, without gross disease by imaging, and those patients who present with gross para-aortic nodes at diagnosis. Patients with positive para-aortic nodes should undergo a complete workup to rule out the presence of extra-abdominal or distant metastatic disease.

Definitive radiotherapy with or without chemotherapy with curative intent should be considered for patients with microscopic para-aortic lymph node involvement, unless medical contraindications are present. Three year survival has been reported in up to 40% of patients with positive para-aortic nodes when using cisplatin based chemo-radiotherapy and extended fields radiation (pelvis + para-aortic). However, this approach is associated with grade 3 or greater toxicity of over 30% [109].

Patients with gross para-aortic lymph nodes by imaging have an overall worse prognosis. Most significant prognostic factors include the size of lymph node metastasis, extent of the disease in the pelvis and the patient's performance status. Cure rates range from 10 to 30% when using extended fields radiotherapy with chemotherapy [110, 111].

If there is bulky pelvic disease (such as parametrial disease to the pelvic side wall), given the lower rates of pelvic control in this situation, it makes sense to treat the pelvis first and determine response before subjecting the patient to radical irradiation of the para-aortic region.

6.1.2.3.2. Distant metastasis

In these cases, cure is not possible and treatment is always palliative (see Section 10):

— Supportive and specific palliative care alone should be considered.
— Various chemotherapy agents have been used in phase I–II studies [72, 112, 113], but progression free survival (PFS) is usually only 3–5 months, and if the patient has received concurrent cisplatin during her previous radiation, responses are infrequent.
— Radiotherapy may be useful in the palliation of specific symptoms [72, 73, 114] *(grade of recommendation B)*.

6.2. OVERALL RADIOTHERAPY TREATMENT TIME

Overall treatment time is a critical factor for the outcomes of cervical cancer treated with radiotherapy. The overall treatment time is the period from the initiation of the first dose of irradiation to the day of the last radiotherapy delivery (EBRT and/or BT).

Several studies have described lower pelvic tumour control and survival rates in invasive carcinoma of the uterine cervix when the overall time in a course of irradiation is prolonged. Prolongation of the overall treatment time results in an increased failure rate of ~1% per day beyond the planned treatment time for all stages [104, 115, 116]. The non-randomized nature of these studies prohibits concluding a causative relationship with certainty, but these findings are likely the result of accelerated repopulation of tumour clonogens during treatment breaks.

The overall treatment time appears to be one of the most powerful predictors of outcome and should be a key driver in the design of the treatment plan. Unfortunately, survey data suggest that this goal is often not met in clinical practice [117, 118].

The overall treatment time, including EBRT and BT, should be no more than eight weeks [98, 118]. In patients treated with radiotherapy, overall treatment time should be as short as possible, and any interruptions or delays should be avoided. There is no justification for a planned interruption between the EBRT and the BT components of the treatment. Timely integration of external beam and intracavitary irradiation in patients with cervical carcinoma is an important factor in improving local control and survival. Delays and/or interruptions in treatment are often preventable, and radiation oncologists should take steps to avoid unnecessary protraction of treatment and to encourage patient compliance.

6.3. ANAEMIA

Anaemia is a frequent clinical feature of patients presenting with cervical cancer due to several factors:

(a) Tumour and patient related factors:
- — Prolonged vaginal bleeding;
- — Poor nutritional condition;
- — Delayed diagnosis;
- — Advanced disease;
- — Renal failure secondary to chronic obstructive nephropathy.

(b) Treatment related factors:
- — Bone marrow toxicity related to radiotherapy to the pelvis and/or para-aortic nodes;
- — Concurrent chemotherapy;
- — Lack of supportive care during therapy (iron supplementation, transfusions).

In the presence of anaemia the effectiveness and outcomes of radiotherapy are reduced due to the relative radioresistance of hypoxic tumour cells. A low haemoglobin level during radiotherapy is reflected in lower local control and survival rates [119–121].

An association between anaemia, poor tumour oxygenation and angiogenesis is likely. It is important to effectively treat symptomatic anaemia in this group of patients. However, there is not enough evidence to currently recommend the routine use of agents that directly stimulate erythropoiesis [121].

To date, no randomized data support therapeutic transfusion, and the minimum acceptable haemoglobin is unclear. Most studies take a haemoglobin value of 12 g/dL as the optimal value. It can be stated that patients should ideally be transfused once the haemoglobin level gets below that value, and that they must be transfused once the level is below 10 g/dL *(GPP)*.

The role of erythropoietin for anaemia correction appears to be limited, after a phase III trial closed prematurely due to concerns about an elevated risk of thromboembolic events of up to 19% in the group of patients receiving erythropoietin. Although analysis was quite limited due to low accrual prior to study closure, there was no suggestion of benefit with regard to PFS or overall survival (OS) in the experimental arm. In fact,

a detrimental effect was noted in the PFS and OS in the arm receiving erythropoietin compared with the standard arm [94].

7. RADIOTHERAPY TECHNIQUES

7.1. TELETHERAPY

EBRT must be planned to treat the 'clinical target volume' (CTV), which includes:

(1) The primary tumour with local extensions ('gross tumour volume' (GTV));
(2) The entire cervix and uterus;
(3) The upper vagina or at least 3–4 cm inferior to the most inferior extent of the tumour;
(4) The parametrial and utero-sacral ligaments;
(5) The lymph node chains including the obturator, external and internal iliac, common iliac, and pre-sacral nodal regions.

The prescribed dose must encompass the 'planned target volume' (PTV), which comprises the CTV plus a safety margin of 7–10 mm to account for uncertainties in daily set-up.

7.1.1. Two-dimensional treatment technique

The volume to be treated is defined on the basis of bony anatomy and clinical judgement. The limitation of 2-D treatment planning and delivery is related to the evidence supported by measurements from CT and MRI studies which have demonstrated that the routine use of standard boundaries, based on bony landmarks, may result in a geographic miss of some nodal regions [122]. However, it is equally true that most radiotherapy centres in LMI countries continue to use plain radiographs, a fluoroscopic simulator and bony landmarks in radiotherapy planning of pelvic tumours.

7.1.1.1. Conventional simulation

The use of a conventional simulator is recommended. When this equipment is not available, all field limits must be checked with radiographs.

Conventional simulation requires knowledge of the tumour position with respect to the visible landmarks on the diagnostic quality simulator radiographs. Since these radiographs provide limited soft tissue contrast, the user is restricted to setting field limits with respect to either bony landmarks evident on the radiographs or anatomical structures visible with the aid of contrast agents such as barium.

For simple computerized 2-D treatment planning, the patient's shape is represented by a single transverse skin contour through the central axis of the beams. This contour may be acquired using lead wire or plaster cast at the time of simulation.

Note: For patients undergoing post-operative radiation or extended field radiotherapy, where whole pelvis irradiation to doses exceeding small bowel tolerance are indicated, oral barium sulphate (about 500 mL) may be given orally 30–60 min prior to the simulation to make the small bowel visible on the radiographs. Loops of small bowel that lie within the anteroposterior and posteroanterior (AP-PA) fields can usually be avoided with the lateral fields by using customized shielding blocks (Figs 1 and 2). The steps to follow when using 2-D simulation are listed in Table 6.

A combination of two parallel opposed AP-PA fields is used in patients with an AP thickness of less than 20 cm when using high energy photons (≥6 MV).

TABLE 6. STEPS OF THE CONVENTIONAL SIMULATION PROCEDURE FOR A TYPICAL PATIENT

Step	Procedure
1	Determination of patient treatment position
2	Determination of beam geometry
3	Determination of field boundaries and isocentre
4	Acquisition of patient's contour
5	Acquisition of set-up radiographs
6	Marking of patient's skin

Note: Usually, a four field 'box' technique is recommended for whole pelvis EBRT (Table 7; Figs 1 and 2). A four field 'box' technique should be especially carefully considered in patients with an AP thickness of ≥20 cm or when using ^{60}Co teletherapy.

TABLE 7. TYPICAL PELVIC FIELD BORDERS FOR TREATMENT OF CARCINOMA OF THE CERVIX

Field name	Border	Bony landmarks
AP-PA fields	Superior	L4-L5 or L5-S1 inter-vertebral space
	Inferior	Lower border of the obturator foramen. In the case of vaginal extension, there should be a distal margin of 3–4 cm from the most caudal extent of the vaginal involvement
	Lateral	2.0 cm lateral to the pelvic brim to adequately cover the external iliac and obturator nodes
Lateral fields	Superior	L4-L5 or L5-S1 inter-vertebral space
	Inferior	Lower border of the obturator foramen. In the case of vaginal extension, there should be a distal margin of 3–4 cm from the most caudal extent of the vaginal involvement
	Anterior	Anterior face (cortex) of the pubic symphysis
	Posterior	Include all the sacral hollow with margin (1–1.5 cm)

It is important to make sure that the blocks do not shield any potential disease extension. This is critical when attempting to spare the rectum. The posterior blocks placed in the lateral field should extend down to the top of S3, adequately covering disease in the presacral space (presacral nodes and the utero-sacral ligaments) for patients with bulky and/or stage III lesions [123]. Studies based on MRI have demonstrated that when these blocks are large, they may shield gross disease. Therefore, it is recommended to draw the posterior edge of the lateral fields, if possible, based on information from axial imaging.

Custom individualized blocks can be placed in the AP-PA fields to cover part of the iliac bone without shielding the common iliac and/or external iliac chains of lymph nodes.

In the case of bulky disease or extension to the distal vagina, requiring inclusion of the inguinal nodes in the CTV, it is preferable to use AP-PA fields to avoid underdosing areas of gross or microscopic involvement.

Once one or more radiotherapy plans are produced; it is the responsibility of the radiation oncologist to select the plan most suitable for the individual patient. Based on his or her knowledge from the clinical evaluation, biological characteristics of the disease, imaging studies and laboratory tests, the radiation oncologist is in a position to design the planning target or to select the most appropriate plan for the individual patient. A 2-D treatment planning system will by definition produce an isodose distribution on a plane. Therefore, no 'true volumes' can be defined or calculated.

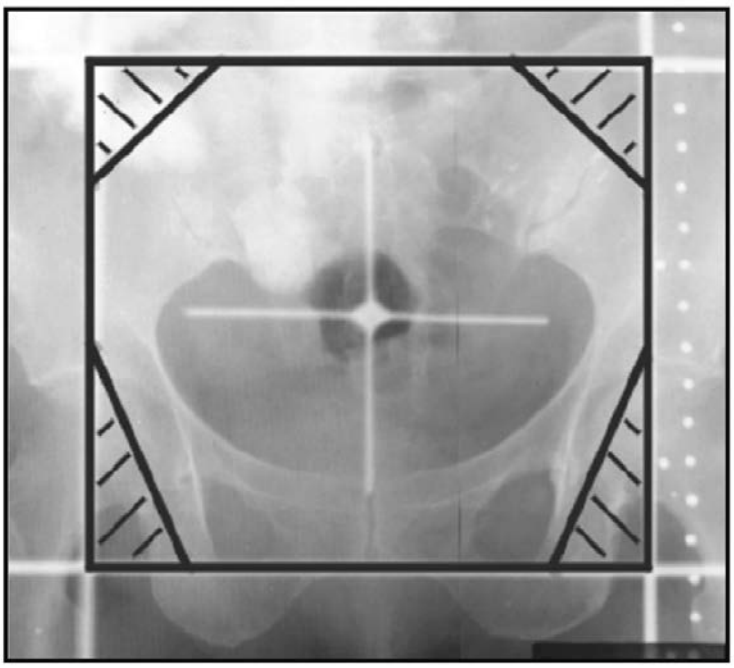

FIG. 1. Anterior simulation radiograph showing the borders of the AP-PA fields and four corner blocks.

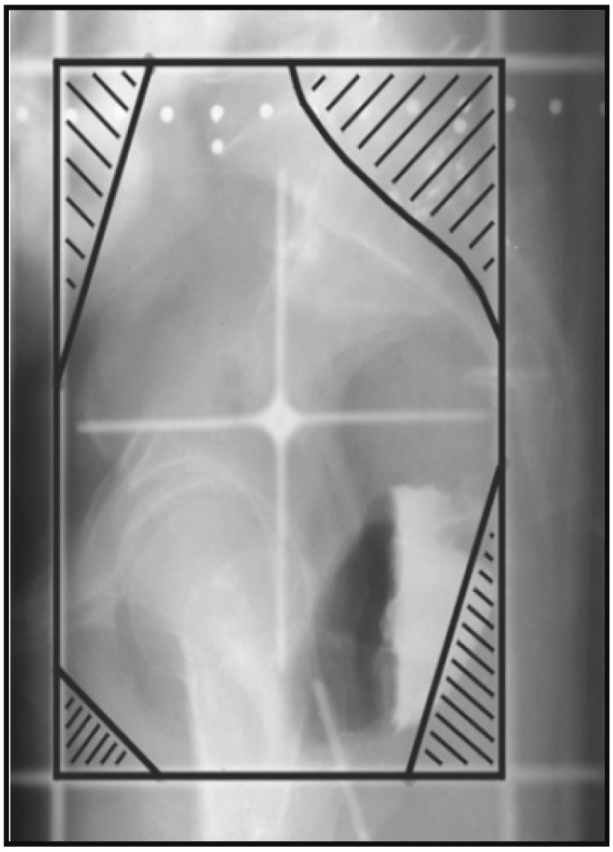

FIG. 2. Left lateral simulation radiograph showing the borders of the lateral fields and four blocks: the anterior-inferior block shields the pre-pubic tissues, the anterior-superior block shields the small bowel, the posterior-superior block shields part of the sacrum and retro-sacral tissues (may be drawn with a straight edge) and the posterior-inferior block shields the anal canal.

When evaluating a 2-D treatment plan, the radiation oncologist should be able to answer the following questions:

(1) Is the GVT encompassed by the treated area?
(2) Is the entire CTV encompassed by the treated area?
(3) Is the PTV encompassed by at least the 95% isodose curve?
(4) Are there significant hot spots inside the target area? If yes, what percentage of the prescribed dose? Is this value acceptable?
(5) Are there significant cold spots inside the target area? If yes, what percentage of the prescribed dose? Is this value acceptable?
(6) Are there hot regions outside the target area? If yes, what percentage of the prescribed dose? Is this value acceptable?
(7) What is the dose received by sensitive normal structures ('organs at risk' (OARs)) such as the rectum, bladder, sigmoid colon and small bowel? Are these doses within the tolerance of these organs?

The selected plan has to be signed by the person who produced it and by the radiation oncologist. The signature of the person producing the plan indicates acceptance of responsibility for the plan according to given parameters of patient and beam data. The signature of the radiation oncologist indicates acceptance of responsibility for the selection of the optimal plan for the individual patient in terms of effectiveness and safety.

7.1.2. Three-dimensional conformal radiotherapy treatment technique

Three-dimensional conformal radiotherapy (3-D CRT) based on CT imaging allows the delivery of radiation to the tumour target volume while limiting the dose to normal surrounding structures, thus potentially contributing to minimizing the treatment related toxicity. Recent advances in imaging technology and radiation treatment planning have made possible the development of 3-D CRT.

The use of CT planning has become standard in developed countries. Many centres are increasingly incorporating MRI and PET/PET-CT data into radiotherapy planning.

The patient data requirements for modern 3-D treatment planning systems are more elaborate than those for 2-D treatment planning. Additional information regarding 3-D CRT simulation is available in Ref. [124].

7.1.2.1. CT based simulation

Transverse CT scans contain all the information required for complex treatment planning and form the basis of CT simulation in modern radiotherapy treatment. Increased soft tissue visibility in combination with axial anatomical information available from a CT scanner or CT simulator provides the ability to localize more precisely the target volumes and critical structures.

At the time of the CT simulation, the preferred position is supine, but if the patient is obese, the prone position with the use of a belly board should be considered. In this case, daily reproducibility has to be taken into consideration. An appropriate immobilization system to ensure the patient's positioning and reproducibility is highly recommended.

Either before or during simulation, a radio-opaque marker can be placed in the cervix (metallic seed or clip) to permit identification of the location of the cervix during the planning process. When significant vaginal infiltration is present, the inferior extension of the tumour should be marked before the simulation by placing a metal clip or seed at this site. It is recommended to use contrast media marking the vagina (vaginal marker) for fluoroscopic simulation as well as for CT procedures.

Contrast material may be used to delineate the rectum during fluoroscopic simulation but is not needed if CT simulation is performed.

For patients undergoing post-operative radiation or extended field radiotherapy, where whole pelvis irradiation to doses exceeding small bowel tolerance may be used, Gastrografin or water (about 500 mL) may be given orally 45–60 min prior to the CT simulation to better visualize the loops of small bowel and better spare them from the 3-D designed radiation fields.

Once the CT scan with the patient in treatment position is completed, the radiation oncologist, in conjunction with the CT simulator therapist, should proceed with the CT virtual simulation and field design (Table 8; Figs 3 and 4). The design and delivery of 3-D CRT requires a sequence of procedures, all of which must be in place in order to improve safety, accuracy and reproducibility.

7.2. ENERGY

The minimum recommended equipment is a telecobalt (^{60}Co) machine, isocentric, with at least 80 cm source–axis distance (SAD). Higher energy photons generated by linear accelerators are preferred when available, especially for patients with an AP pelvic diameter larger than 20 cm. The source–skin distance technique or the SAD technique are both acceptable and depend on the machine and patient AP separation.

TABLE 8. CT BASED VIRTUAL SIMULATION AND 3-D PLANNING

Step	Procedure
1	Determination of patient treatment position with pilot/scout films (topogram)
2	Determination and marking of reference isocentre
3	Acquisition of CT data and transfer to virtual simulation workstation
4	Localization and contouring of target volumes and critical normal structures (GTV, CTV, PTV and OARs)
5	Transfer of patient's data and contours to treatment planning system (TPS)
6	Isocentre localization in relation to reference points
7	Determination of beam geometry; beam's eye view
8	Generation of digital reconstructed radiographs; determination of field boundaries and shielding
9	Completion of 3-D treatment plan: isodose distribution, dose–volume histograms (DVHs)
10	Plan review and approval by a medical physicist, plan approval by a radiation oncologist
11	Transfer of patient, beam and planning data to the treatment machine

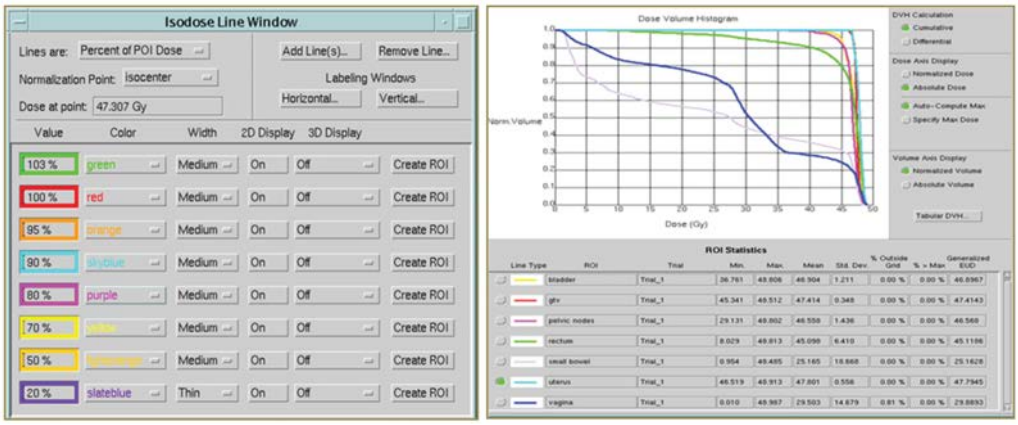

FIG. 3. 3-D CRT. Left: screen of treatment planning system showing the various dose levels requested by the planner, in different colours. Right: dose–volume histogram (DVH) corresponding to the images in Fig. 4. In this particular plan, the gross tumour volume (red) receives a mean dose of 47.4 Gy, the rectum (green) receives a mean dose of 45 Gy, the urinary bladder (yellow) a mean of 46.9 Gy, and the delineated small bowel (light purple) a mean of 25 Gy. Minimal and maximal doses for these critical organs can also be read. (Image courtesy of D. Petereit.)

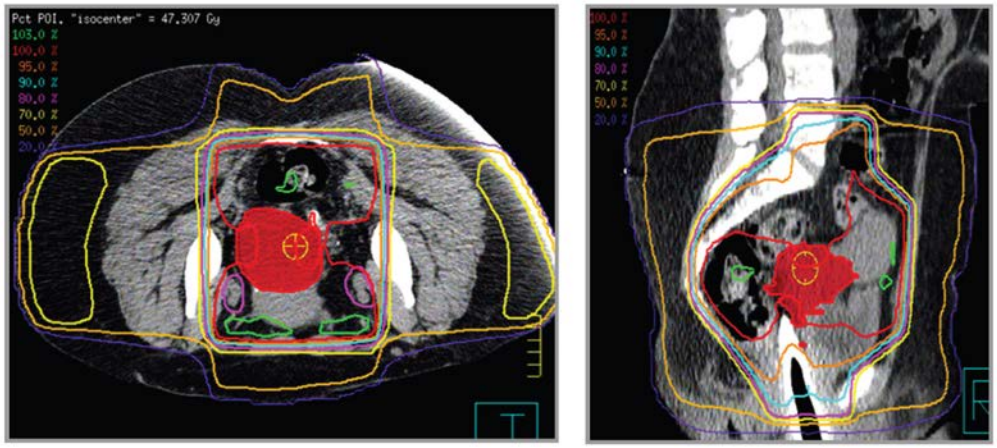

FIG. 4. 3-D CRT isodose distribution on the axial and sagittal planes; the gross tumour volume (GTV) is shown in solid red. The GTV is partially covered by the 100% isodose curve (red line), but fully covered by the 95% isodose curve (orange line). Isodoses of 70% can be seen on the lateral pelvic fat (yellow lines). In addition, small 'hot spots' of 103% can be seen inside the small pelvis (green lines). (Image courtesy of D. Petereit.)

7.3. DOSE AND DOSE PRESCRIPTION

When treating the whole pelvis, the recommended total dose is 45 Gy in 25 fractions of 1.8 Gy or 46 Gy in 23 fractions of 2.0 Gy. The dose should be prescribed at the International Commission on Radiation Units and Measurements (ICRU) reference point according to ICRU Report 50 [125] or at the isodose that encompasses the target structures [89] (Fig. 4).

Brachytherapy is usually administered towards the end of EBRT. When indicated, EBRT parametrial boost is followed using a standard 4 cm × 10 cm (Fig. 5) or customized midline shielding block, based on the point A isodose distribution (100% isodose) with an AP-PA technique (see Section 7.5 for details).

In some circumstances the EBRT fields should cover the whole vagina. In such cases the probability of a brisk radiation reaction in the vulva, perineal skin and anus should be discussed with the patient. As there is no evidence supporting elective radiation to the inguinal nodes, this strategy is discouraged, unless there is extensive involvement of the lower one third of the vagina. Doses of 45 Gy in 25 daily fractions with an AP-PA technique are frequently used. In this case it is important to obtain an optimized dose distribution by using a combination of photon energies, photons and electrons and/or differential weighting of the AP and PA fields to decrease the dose to the rectum and ensuring that the dose to the small bowel is within tolerance. This will be followed by a BT plan tailored to the anatomical extent of the tumour and aimed at delivering tumouricidal doses.

7.4. PRESCRIBING AND REPORTING PHOTON BEAM THERAPY

ICRU Report 50 establishes the recommendations for prescribing, recording and reporting photon beam therapy [125]:

— If 3-D treatment planning and delivery are available, the dose should be prescribed at the isodose that adequately encompasses the PTV (at least 98% of the PTV should receive the prescribed dose).
— Dose must be reported to the reference point (RP) (100% of the prescribed dose):
  • ICRU RP is usually at the isocentre;
  • It could be a point in the centre of the PTV.

— When the patient is treated with two AP-PA opposed equally weighted photon beams, the RP is midway between the beam entrances on the beam axis and is generally the centre of the PTV. When the four field box technique is used, with four photon beams that converge on one point, the RP is in the centre of the PTV on the intersection of the beam axes.
— Whenever possible, dose to planning organ at risk volume should be reported.
— Maximum and minimum dose in the PTV must be reported.

7.5. PARAMETRIAL BOOST

Boosting the lateral parametria is common practice at centres that treat significant numbers of cervical cancer patients presenting with stages IIB and IIIB. This strategy is employed because of the limited dose contribution from intracavitary BT to the lateral parametria and pelvic side walls. However, the incremental benefit of EBRT parametrial boosts is unclear, and there is little evidence in the literature to support its routine use [126].

Generally the parametrial boost is initiated after 45–50 Gy has been delivered to the entire pelvis and after performing the first BT implant. The radiation oncologist chooses the dose to the involved parametrium based on the bulk of parametrial disease at presentation, as well as the contribution from intracavitary BT to the external beam, in order to deliver a minimum dose to the mid-parametrium, or ipsilateral point B dose, of 60–63 Gy, provided that the pelvic side wall dose is not higher than 60 Gy when using LDR intracavitary BT or 55 Gy when using HDR intracavitary BT. The maximum parametrial boost dose is 5.4–9.0 Gy in 3–5 fractions of 1.8 Gy per fraction given AP-PA daily to the midplane if unilateral or bilateral parametrial boost is used. The prescription point should be at the centre of the unblocked portion of the field.

The overall treatment time for whole pelvis EBRT, intracavitary BT and parametrial boost should not exceed eight weeks. EBRT parametrial boost is performed unilaterally or bilaterally. When carrying out a bilateral parametrial boost, a rectangular 4 cm × 10 cm midline block with a half value layer (HVL) of 5 is used in the AP-PA fields. The superior border of the parametrial boost field should be at the bottom of the sacroiliac joints in order to protect the critical neighbouring structures (Fig. 5). Occasionally, a unilateral parametrial boost is required, based on the initial extent of the disease. However, there is evidence that a customized midline block based on the BT isodose lines (point A, 100% isodose line) is a more accurate way to boost the parametria [127].

Alternatively, interstitial image guided BT can be used when parametrial disease is still present after the whole pelvis radiotherapy, to deliver doses sufficient to achieve local control [128–130].

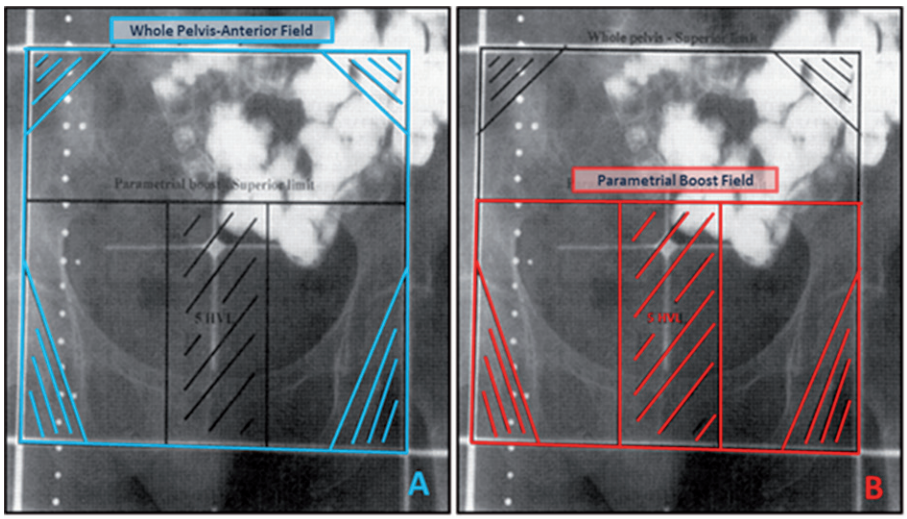

FIG. 5. Anterior simulation radiograph of the pelvis showing the borders of the AP field (A). Corner blocks are also depicted. Barium contrast can be seen in the small bowel. Parametrial boost field (B): following the initial phase of the external beam treatment (45 Gy) the upper border of the field is lowered to the level of the bottom of the sacroiliac joints, and a midline block is added, thus avoiding overdosing the bladder, the rectum and the small bowel.

7.6. PARA-AORTIC IRRADIATION

7.6.1. Prophylactic

The incidences of pelvic lymph node involvement for patients with FIGO stages IB, IIB and IIIB cervical cancer are approximately 15, 30 and 50% respectively. The incidence of para-aortic lymph node metastasis also increases with tumour stage; about 5, 20 and 30% of patients with FIGO stage IB, IIB and IIIB disease, respectively, have para-aortic lymph node metastasis at diagnosis. For each stage, the risk of lymph node involvement is correlated with the tumour size.

Patients with documented para-aortic lymph node metastasis have a 20–50% five year survival rate, depending on the extent of the pelvic disease [89]. According to this data, patients presenting with clinical stage IIB or IIIB in the pelvis can be expected to harbour subclinical or clinical metastatic disease in the lymph nodes of the para-aortic groups in 20–30% of cases.

The prophylactic irradiation of the para-aortic region has been a matter of controversy for some time. A Radiation Therapy Oncology Group (RTOG) study by Rotman et al. in 1995 [131] demonstrated a benefit in survival rate (but not in PFS) for the prophylactic irradiation of the para-aortic region in patients with bulky IB–IIA with or without positive pelvic nodes, or patients with IIB and negative nodes assessed either surgically or by lymphangiogram (Fig. 6). A European Organization for Research and Treatment of Cancer (EORTC) trial [132] randomized patients with Stage IIB and III and with pelvic lymph nodes to receive or not receive extended field irradiation. The disease free survival was not significantly different at four years between the two treatment arms, although the relapse rate in the para-aortic region was higher for patients not receiving irradiation. Overall survival rates were not reported.

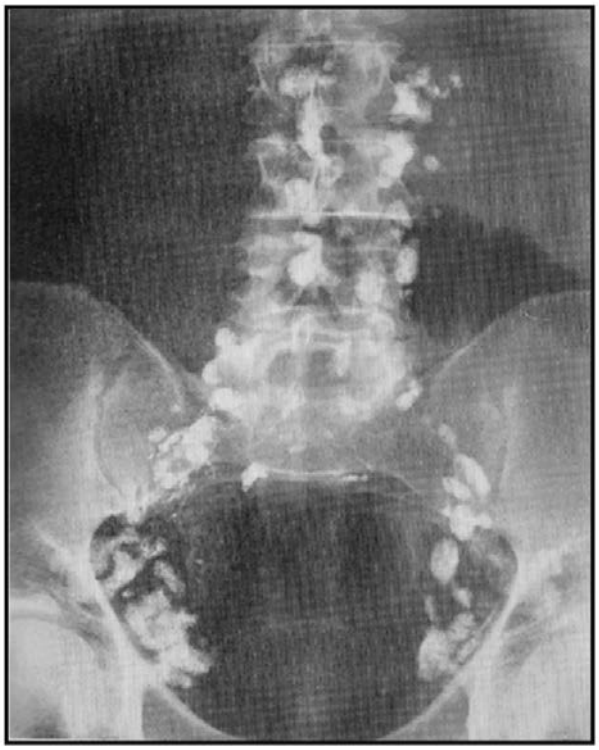

FIG. 6. Abdominal–pelvic lymphangiogram.

In the current era of concomitant chemo-radiotherapy, the prophylactic irradiation of the para-aortic nodal region is not delivered routinely. Although the role of prophylactic para-aortic nodal irradiation remains to be fully defined, the results of RTOG 90-01 clearly indicate that concurrent chemotherapy with pelvic irradiation leads to significant outcome benefits over extended field radiation without chemotherapy [98, 108].

Although the efficacy of such an approach has not been proven, some centres deliver prophylactic para-aortic irradiation to 45 Gy with concomitant chemotherapy (up to the level of L1-L2 vertebral interspace) to patients with the highest risk of metastatic para-aortic disease, namely those with common iliac lymphadenopathies or with extensive pelvic lymphadenopathies by radiologic imaging who do not undergo surgical staging *(GPP)*.

7.6.2. Therapeutic

Pelvic and para-aortic irradiation can be administered one of two ways:

(1) Treating the patient supine and using a four field technique to encompass the entire pelvic and para-aortic lymph nodes in one continuous field (Fig. 7).
(2) A four field pelvic 'box' and a separate AP-PA or four field para-aortic field. In the second case, a 'gap calculation' between the pelvic and para-aortic portals must be performed to avoid overlap and excessive dose to the small intestines.

It is considered preferable to treat the retroperitoneal nodes together, rather than dividing them into two separate fields, if possible. By simulating and treating the patient supine, the kidneys typically remain posterior, which reduces the radiation induced renal toxicity.

The upper margin of the field is usually at the T12-L1 inter-vertebral space (Fig. 7). The width of the para-aortic portals should be 9–10 cm or alternatively can be determined by CT scan. An effort should be made to shield two thirds of both kidneys' parenchyma and to keep the spinal cord dose below 45 Gy.

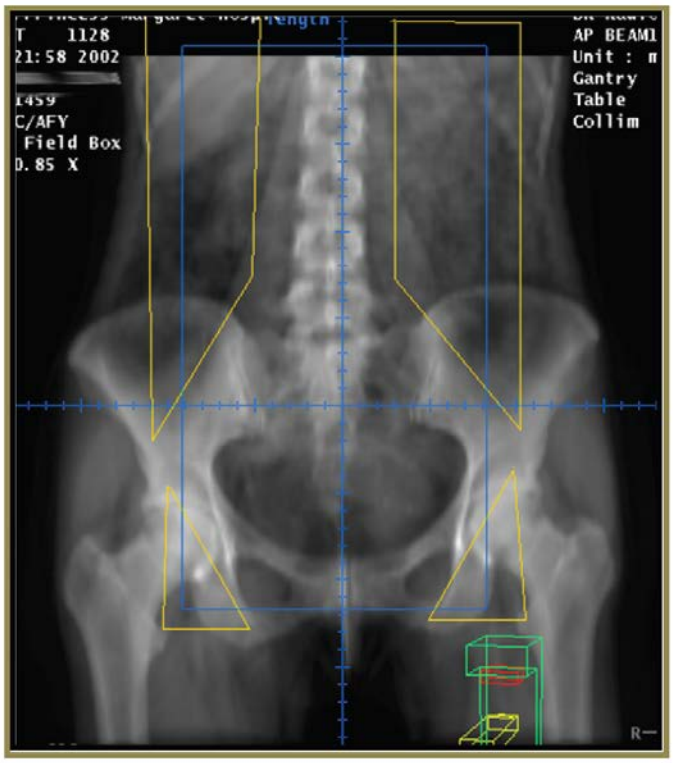

FIG. 7. Digitally reconstructed radiograph of a continuous pelvic and para-aortic field.

If para-aortic node metastases are present, patients are treated with 45 Gy to the para-aortic area plus a 5–10 Gy boost to enlarged lymph nodes through reduced lateral fields or a 3-D conformal technique. If available, intensity modulated radiotherapy (IMRT) may allow dose escalation to boost the areas of gross nodal disease while sparing the normal surrounding areas to a larger degree compared with 3-D CRT.

7.7. MILESTONES FOR 3-D CONFORMAL RADIOTHERAPY

A conformal radiotherapy programme should be built on a firm foundation of expertise in conventional radiotherapy and should not be embarked on until certain basic milestones have been met. The self-assessment questionnaire given in appendix A of IAEA-TECDOC-1588, 'Transition from 2-D Radiotherapy to 3-D Conformal and Intensity Modulated Radiotherapy' [124], provides a checklist of steps in the process.

The following milestones must be achieved before resources are committed to the establishment of 3-D CRT:

(1) Facilities are in place for the provision of conventional radiotherapy;
(2) Adequate diagnostic imaging facilities are in place for diagnosis and staging;
(3) Adequate imaging facilities are in place for planning CT scans;
(4) There is an intention to deliver curative radiotherapy;
(5) It has been demonstrated by audit that satisfactory set-up accuracy can be achieved.

Milestones in the process once the project has started are the following:

(1) Appointment of sufficient staff so that the existing programme of conventional therapy will not be compromised;
(2) Academic training of staff (radiation oncologist and medical physicist);
(3) Specification and purchase of necessary additional equipment;
(4) Practical training of radiation oncologist and medical physicist;
(5) Commissioning of TPS for 3-D CRT;
(6) Practical training of other staff (e.g. radiation therapy technologists (RTTs) or treatment planners);
(7) Extension of the QA programme to cover 3-D CRT;
(8) Establishment of clinical treatment protocols.

7.8. EDUCATION AND TRAINING REQUIREMENTS

There are significant differences between conventional 2-D radiotherapy and 3-D CRT. Making a transition from one to the other is a substantial undertaking. Experience gained by carrying out conventional 2-D radiotherapy is essential. However, additional skill sets are necessary to make the transition to 3-D CRT.

Detailed description of a 3-D CRT training programme is beyond the scope of this publication, but can be found in Ref. [124]. It is imperative that each member of the team involved in the planning and delivery of 3-D CRT understands his or her role well so that safe and effective use of this technique can be ensured.

There is increasing experience with IMRT in cervical cancer, although results are still preliminary. Uncertainties in the definition of the target volume when using CT based 3-D techniques have been identified. Image guided IMRT would provide potential advantages in this field [133]. Bladder filling control and accurate definition of margins for the PTV with image guided position verification have been advocated to achieve an optimal application of IMRT.

8. BRACHYTHERAPY

Brachytherapy (BT) is mandatory for the curative treatment of all invasive cervical cancers [65, 73, 134]. Depending on tumour volume, tumour extensions and the risk of lymph node involvement, BT is usually combined with EBRT. In most cases BT will be used as an intracavitary procedure, and in selected cases may be complemented by an interstitial implant.

8.1. DOSE RATE

According to International Commission on Radiation Units and Measurements Report 38 (ICRU Report 38) [135], BT treatment dose rates fall into three categories:

(1) Low dose rate (LDR): from 0.4 to 2.0 Gy/h. In routine clinical practice LDR brachytherapy (LDR-BT) is usually delivered at dose rates between 0.3 and 1 Gy/h. This is compatible with conventional manual or automatic afterloading techniques.
(2) Medium dose rate (MDR): more than 2.0 to 12.0 Gy/h. MDR brachytherapy (MDR-BT) can also be delivered by manual or automatic afterloading, although the latter is far more frequent.
(3) High dose rate (HDR): more than 12.0 Gy/h. Only automatic afterloading can be used in HDR brachytherapy (HDR-BT) because of the high source activity.

Another category is pulsed dose rate (PDR) BT, which delivers the dose in a large number of small fractions with short intervals, aiming at achieving a radiobiological effect similar to low dose rate over the same treatment time, typically a few days.

The selection of a specific dose rate depends on multiple factors and is discussed in IAEA-TECDOC-1257 and other publications [135–138]. Radiobiological models, retrospective studies, randomized trials and a meta-analysis have shown equivalent effectiveness in terms of local control and late complications between LDR-BT and HDR-BT [139–146]. Characteristics of radionuclides most commonly used for gynaecological BT are given in Table 9.

TABLE 9. CHARACTERISTICS OF ISOTOPES COMMONLY USED FOR GYNAECOLOGICAL BRACHYTHERAPY

	Radiosotope	Half-life	Application duration	Afterloading	
				Manual	Remote controlled
Low dose rate	^{137}Cs	30 a	Days	Yes	Yes
Medium dose rate	^{137}Cs	30 a	Hours	No	Yes
High dose rate	^{192}Ir ^{60}Co	74 d 5.26 a	Minutes	No	Yes

8.2. ADVANTAGES AND DISADVANTAGES OF HDR-BT VERSUS LDR-BT

The use of remote afterloading machines, whether HDR or LDR, offers several advantages: exposure to staff is reduced; source preparation time is shortened; and the need for transportation of the radioactive sources is lessened. In HDR-BT, treatment times are shorter, resulting in:

— No need for hospitalization (outpatient treatments);
— Less patient discomfort and lower risks of thromboembolism, since prolonged bed stay is eliminated;
— Possibility of treating patients who may not tolerate long periods of isolation;
— Reduced risk of applicator and packing displacement during the course of therapy;
— Possibility to cope with higher patient load in busy radiotherapy departments.

In HDR-BT the smaller tandem diameter, 3.2 mm compared with 6.4 mm for LDR, reduces the need for cervical dilatation, and potentially the need for heavy sedation or general anaesthesia. HDR-BT, when compared with manually loaded implants, allows an improved dose distribution through planning optimization. This,

however, is not limited to the HDR: treatment planning with some LDR remote afterloader machines allows for comparable dose optimization.

In centres with a high volume of cervical cancer patients, the use of HDR facilitates the integration of EBRT and BT, contributing to shorter overall treatment duration and potentially to better tumour control [104].

Potential disadvantages of HDR are the following:

— More labour intensive because of the number of procedures performed per patient;
— Inconvenience for the patients, since they have fractionated treatment with higher number of BT procedures;
— Costs associated with replacing the source every 3–4 months when using ^{192}I sources.

8.3. RECOMMENDATION FOR HDR-BT

Over the years, HDR-BT has been replacing conventional LDR treatment, as is evidenced by a reduction in the manufacturing of LDR equipment. The decision to select HDR-BT is also influenced by the versatility of the machine. Although cervical cancer is the most common tumour treated by HDR in developing countries, it is also possible to use it to treat a wide variety of other tumours such as lung, oesophagus, breast, bile duct, endometrium, nasopharynx, prostate, rectum, head and neck, and soft tissue tumours [147, 148].

Iridium-192 is the most commonly used radioisotope for HDR-BT (Fig. 8). However, a major drawback is the short half-life of 74 d, which requires a frequent source change (every 3–4 months). Recently, machines using miniaturized ^{60}Co sources with a half-life of 5.26 a have also become available, which is a major advantage, but experience with this HDR system is still limited.

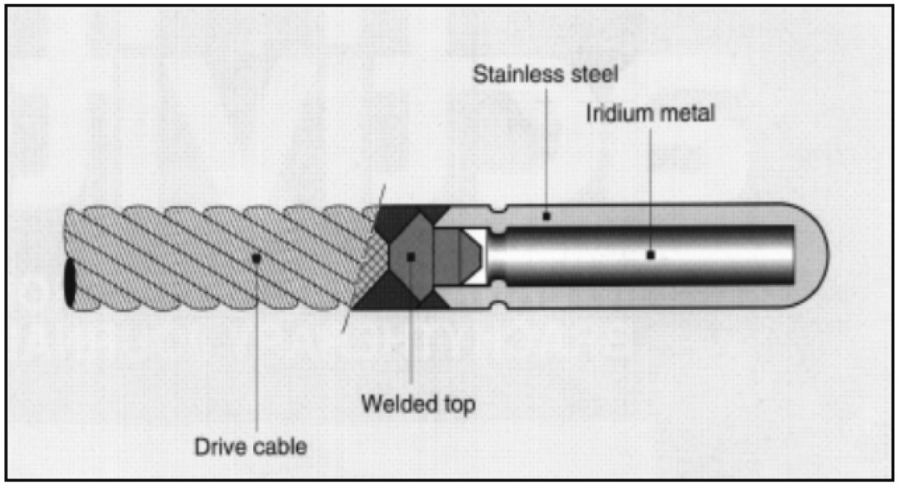

FIG. 8. Iridium-192 source for high dose rate brachytherapy; the source is welded to the end of a drive cable and encapsulated in a stainless steel capsule. (Image courtesy of Nucletron.)

The initial cost of HDR equipment is high. However, the capacity to treat more patients using HDR with little incremental cost, coupled with the versatility of the HDR machine, can offset the higher initial cost and represent an economic advantage.

8.4. APPLICATOR MODELS

Modern commercially available applicators come in different presentations (ovoid type with or without shielding, ring type) and with different names mainly representing traditional schools (‘Manchester style’,

‘Henschke style’, ‘Fletcher style’). Annex VII presents the most salient characteristics of available BT applicator models and some examples.

8.5. INTRACAVITARY BRACHYTHERAPY TECHNIQUE

8.5.1. Insertion technique

A routine HDR-BT insertion is summarized in this section [149, 150]. Insertion of LDR and MDR applicators with a tandem diameter of 6–7 mm requires cervical channel dilatation and, therefore, general or spinal anaesthesia. Light to moderate sedation with or without topical anaesthesia and/or a paracervical nerve block may be used to anesthetize patients undergoing HDR-BT because of the smaller (3.2 mm) tandem diameter [151, 152]. It has to be mentioned that the tandem diameter of CT/MRI compatible applicators for HDR-BT is larger; therefore, adequate anaesthesia should be considered. It is critical that the patient is adequately sedated and relaxed, which allows for proper applicator placement and retraction of the bladder and rectum, in order to pack these normal tissues away from the high dose region.

The patient is placed in the lithotomy position. A careful pelvic examination is required to determine the disease extent and regression compared with the initial examination, and to determine the applicator type and size. After the preparation of the vulva, perineum and vagina with iodine solution or equivalent, a Foley catheter is inserted with sterile technique and filled with 7 mL of diluted radio opaque solution. A vaginal speculum is introduced with adequate exposure of the cervix. If feasible, seed markers should be placed in both the anterior and posterior cervical lips for radiographic visualization. Additional seed markers should be placed in the most inferior extent of the disease involving the vagina.

When necessary, a sharp pointed forceps (tenaculum) may be placed on the anterior cervical lip in order to straighten out the uterine canal, which facilitates uterine sounding and minimizes the risk of uterine perforation. A uterine sound is used to measure the depth of the uterine cavity and to determine its position. Dilatation of the external cervical orifice (cervical os) is performed when required. The tandem curvature angle and length should match the uterine position as determined by sounding.

Some centres routinely use an intrauterine stent (Smit sleeve; see Annex VII), which is fixed with stitches to the cervix. The stent stays in place for the whole course of BT. It facilitates the localization of the cervical os, and prevents uterine perforations.

Pelvic ultrasound, if available, can be very useful to facilitate tandem placement and repositioning for patients with distorted anatomy. Bimanual rectal and abdominal examination should be performed regularly to clinically define the position of the uterus and to guide the insertion based on this assessment.

After inserting the intrauterine tandem, a ring or colpostats are gently placed in the vaginal fornices. Use of the ring applicator is recommended. In the case of the ring applicator, a cap with an adequate diameter is used. The cap should always be used in order to minimize the risk of vaginal necrosis, because it helps to decrease the vaginal surface dose when prescribing to point A in cervical cancer patients. For the ovoids, caps of the largest possible diameter are preferred, since this allows for a better dose distribution. The ovoids should fit snugly without compromising the packing. The tandem should bisect the ovoids on both lateral and AP views for optimal geometry (Figs 9–11).

The rectum is packed away using either a rectal retractor or radiopaque gauze (Figs 9–11), which also stabilizes the applicators. Similarly, the bladder is also packed away with radiopaque gauze using pick-up forceps.

For patients with narrow vaginal anatomy in which the introduction of vaginal ovoids or the ring device is not possible, a tandem and cylinder can be used. For patients with extensive vaginal disease in which ovoids and/or vaginal cylinders cannot be used, the best option is an interstitial implant combined with intracavitary placement of an intrauterine tandem.

Depending on the model used, the vaginal and uterine applicators may be fixed to one another. Since the tandem and ring applicator has a fixed geometry, reproducible dose distributions between applications are possible, which may obviate the need to plan subsequent insertions. Libraries (atlases) of dosimetry for standard loading of tandem and ring are available.

For the tandem and ring applicator, defined standard configurations with specific loading patterns for each applicator (dwell positions and times) have been generated and are available in the ‘library’ of the TPS [153].

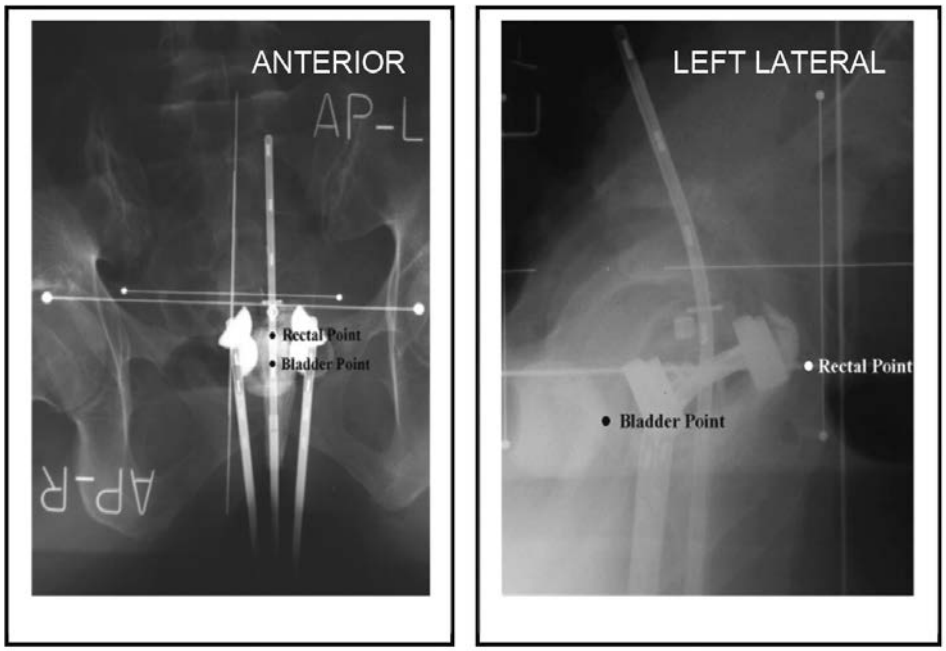

FIG. 9. Anterior and lateral localization radiographs following insertion of applicators for HDR-BT. The following elements can be identified: tandem, vaginal ovoids with their shielding, metal ring in the external os, bladder Foley balloon, posterior vaginal packing and rectal and bladder calculation points.

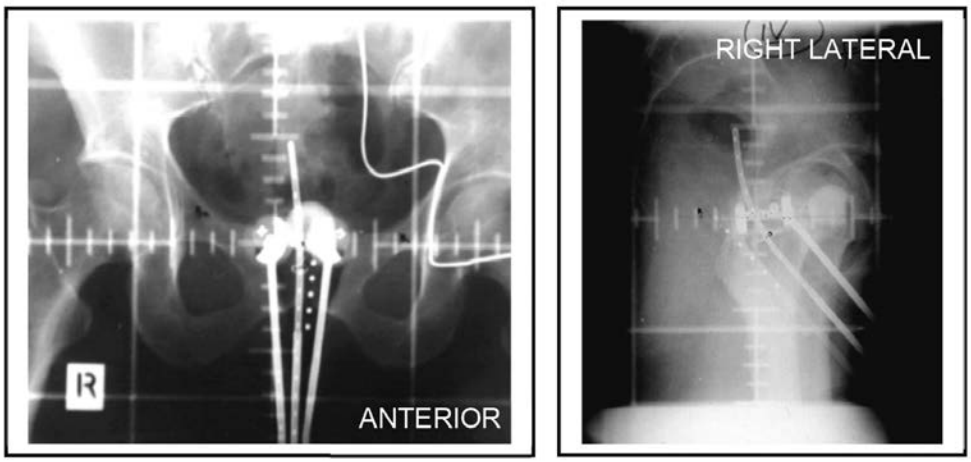

FIG. 10. Anterior and lateral radiographs following insertion of applicators for HDR-BT; the white dots indicate the position of a flat rectal retractor.

However, some intracavitary applicators (e.g. Fletcher type) are rigid but do not have a fixed geometry. These applicators require individual treatment planning for each insertion (Fig. 11).

The use of fixed applicators, e.g. tandem and ring, is recommended since it simplifies and expedites the treatment planning process and reduces the chance of error. Because multiple HDR fractions are required for treatment, applicator position reproducibility is of the utmost importance. For treatment planning using CT and/or MRI, compatible applicators are available based on the ovoid or ring type.

The 'Vienna applicator' is a tandem and ring applicator that permits the transvaginal placement of interstitial needles into the proximal parametria [128, 154]. Pötter et al. demonstrated improved dosimetry and pelvic control with this applicator for patients with bulky tumours with parametrial extension [129, 130].

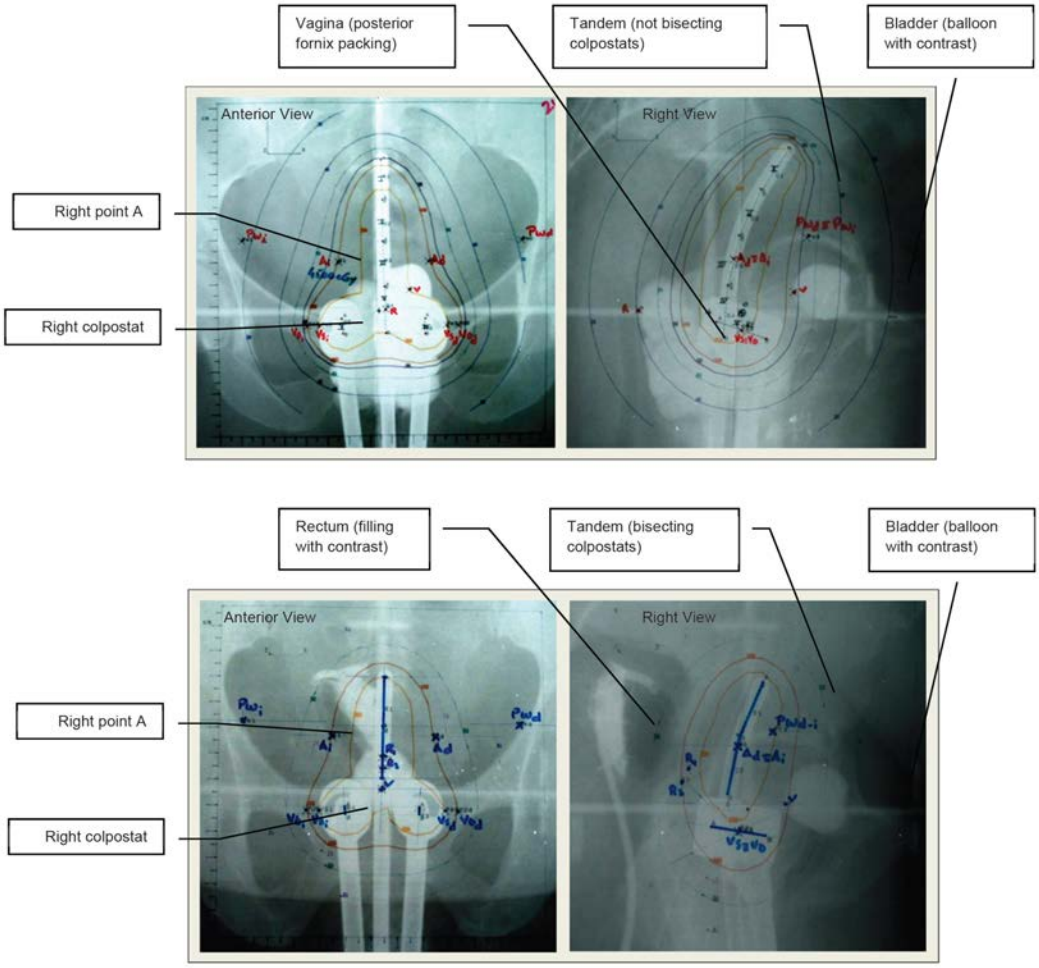

FIG. 11. Anterior and lateral radiographs following insertion of Fletcher applicators for LDR manual afterloading BT technique. (Images courtesy of S. Binia.)

8.5.2. Imaging

In order to obtain the appropriate dosimetry, imaging must be obtained for each intracavitary implant. Three levels of imaging have been defined:

— *Level 1: Conventional radiology*. X ray films are taken with either a mobile unit or a C-arm using a reconstruction box in order to produce orthogonal films for planning. High kV equipment permits adequate lateral exposure when needed.
— *Level 2: Simulator*. This allows orthogonal films to be taken in which variable isocentric angles and reconstruction techniques can be used.
— *Level 3: CT and MRI.* Axial slices from a CT scan or MRI permit not only the reconstruction of the source position, but also the reconstruction of the tumour volume, its structural changes during the treatment period and anatomic structures of interest [67].

Ideally, the applicator insertion, radiograph generation and treatment should take place in a dedicated BT suite, which avoids patient movement. However, this is not always possible. If the patient needs to be transferred, adequate vaginal packing and/or external immobilization devices should be used to minimize applicator movement [149, 150, 155]. In any case, the patient should remain supine and her movements should be minimized between the stages of imaging and treatment delivery.

8.5.3. Dose prescription

The total dose, dose schedule and time pattern for each individual patient should be clearly and precisely prescribed, recorded and signed by the radiation oncologist in the BT chart. As a minimum, the radiation oncologist should specify the dose per fraction given to point A, the number of fractions, the technique to be used and the time–dose pattern. Limiting criteria for the maximal doses or dose rates to be given to the anterior rectal mucosa and to the bladder trigone should be well defined. During the subsequent phases of imaging, treatment planning and treatment delivery, the radiation oncologist should work in close consultation with the medical physicist to obtain the best possible treatment plan.

Due to the very high dose gradient surrounding the radioactive sources (about 10% per mm), there has been difficulty expressing the dose used in intracavitary BT. There are many different methods used by various centres to prescribe and calculate the dose of a BT implant. Most prescribe an absorbed dose to point A as per the Manchester system, and others have defined different new points or variations from the originals [72, 74, 150].

Aside from all the controversies, point A is still the most commonly used prescription point for cervical cancer intracavitary BT. This is supported by extensive data correlating point A dose and tumour control and toxicity. Point A is defined as 2 cm superior to the vaginal applicator surface and 2 cm lateral to the uterine canal (defined in the AP film) (Figs 12–14).

Regardless of the system used, each centre should be consistent when reporting dose to the tumour and the normal tissues. The use of dose–volume histograms (DVHs) is encouraged. In addition, the radiobiological equivalences for different dose rates are taken into account.

Recommendations on dose and volume specification for reporting intracavitary gynaecologic BT were published in 1985 in ICRU Report 38 [135]. The recommendations given in ICRU Report 38 were developed more than 25 years ago. More recently, important changes have taken place in the field of BT such as the widespread use of HDR techniques and the development of image based treatment planning. A new ICRU report on gynaecological BT is in preparation [156].

For the organs at risk, dose constraints have to be less than 70% of the dose prescribed to point A in the case of the rectum, and less than 80% for the bladder. With adequate packing these goals are typically achieved.

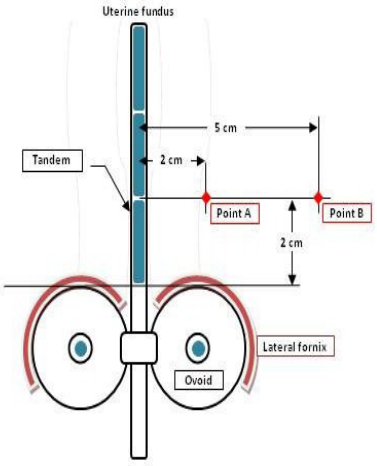

FIG. 12. Definition of point A and point B in a tandem and colpostats gynaecological BT procedure (basic theoretical representation). (Image courtesy of S. Binia.)

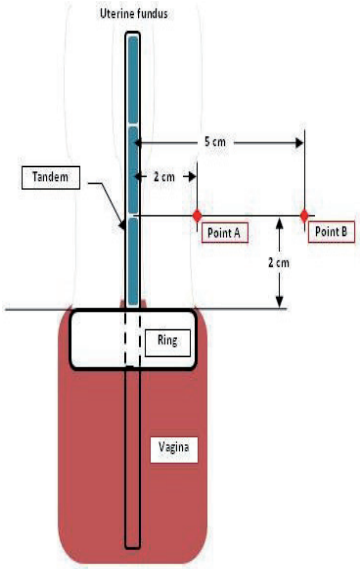

FIG. 13. Definition of point A and point B in a tandem and ring gynaecological BT procedure (basic theoretical representation). (Image courtesy of S. Binia.)

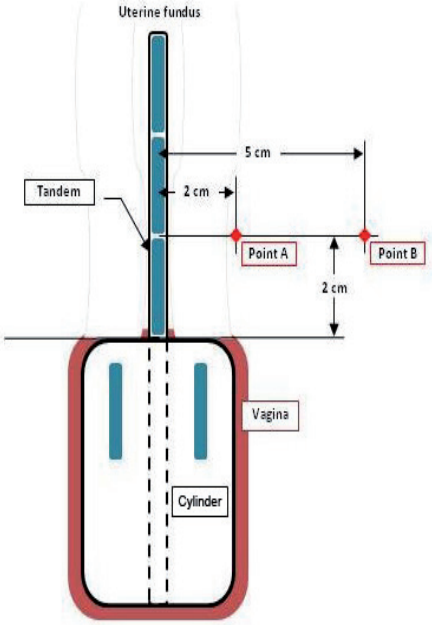

FIG. 14. Definition of point A and point B in a tandem and cylinder gynaecological BT procedure (basic theoretical representation). (Image courtesy of S. Binia.)

8.5.4. Reporting

In centres performing HDR-BT with 2-D planning (planning based on a pair of orthogonal radiographs), recording and reporting of BT applications is done following a combination of criteria described in the Manchester system and from ICRU Report 38 (Figs 15–17), similar to those using LDR-BT. Manchester point A continues to be commonly used for dose prescription along with reporting the doses at ICRU rectum and bladder points (Figs 9–15).

The ICRU rectal reference point (ICRU RP) is determined on a lateral radiograph. An anteroposterior line is drawn from the lower end of the intrauterine source position or from the middle of the intravaginal source positions. The rectal reference point is located along this anteroposterior line, 5 mm posterior to the posterior vaginal wall (Fig. 15). The literature reports a good correlation between ICRU RP and rectal complication rates [157]. Maximal dose to rectal mucosa may be located 1–2 cm cranially or caudally to the ICRU RP. Good correlation exists between the ICRU RP and calculated maximal dose to rectal mucosa [158, 159]. However, a number of studies have demonstrated that the ICRU 38 reference points for bladder and rectum underestimate the maximum organ dose compared with CT based dose assessment [160–162].

Bladder dose is reported at the ICRU bladder point (ICRU BP). A Foley catheter with the balloon filled with 7 mL of diluted radiopaque fluid is used, pulling the catheter downward to bring the balloon against the bladder neck. The ICRU BP is defined on the lateral radiograph: an anteroposterior line is drawn through the centre of the balloon where this line intersects the posterior balloon surface. In the AP radiograph the ICRU BP corresponds to the centre of the Foley balloon (Fig. 15).

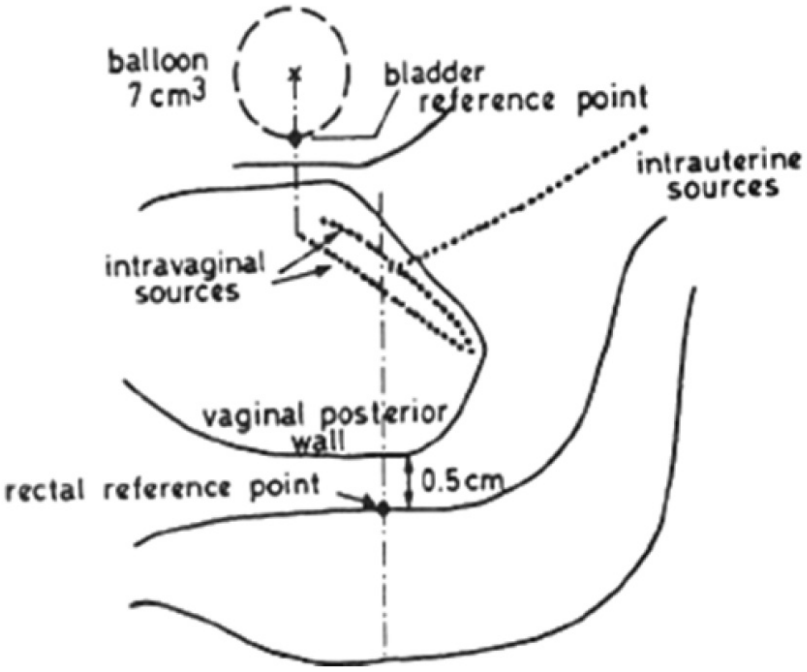

FIG. 15. Definitions for rectal and bladder reference points from ICRU Report 38 [135].

The actual maximum bladder dose, in most cases, is significantly higher than the ICRU BP and is usually located more superiorly. Hence, a second bladder point (defined by Gerbaulet) usually yields a more realistic maximal bladder dose [163]. This point is located 1.5 cm superior to the ICRU BP as defined on the lateral radiograph.

The ICRU BP was found to be reproducible but does not correlate well with bladder complications. Maximum reported dose is located approximately 2–3 cm more cranially and laterally at the level of the ovoids [158, 159].

Figures 16 and 17 display other points described in ICRU Report 38. However, they are not commonly used in the clinic, given the lack of data regarding reliability, reproducibility and clinical relevance.

8.5.5. Time dose pattern

The dose contribution to point A from BT must be reduced when switching from LDR to HDR because of the dose rate effect [136–138]. For example, using the linear quadratic model (LQ model), 40 Gy LDR is radiobiologically equivalent to 5 fractions of 6 Gy when using HDR. Early studies have demonstrated increased

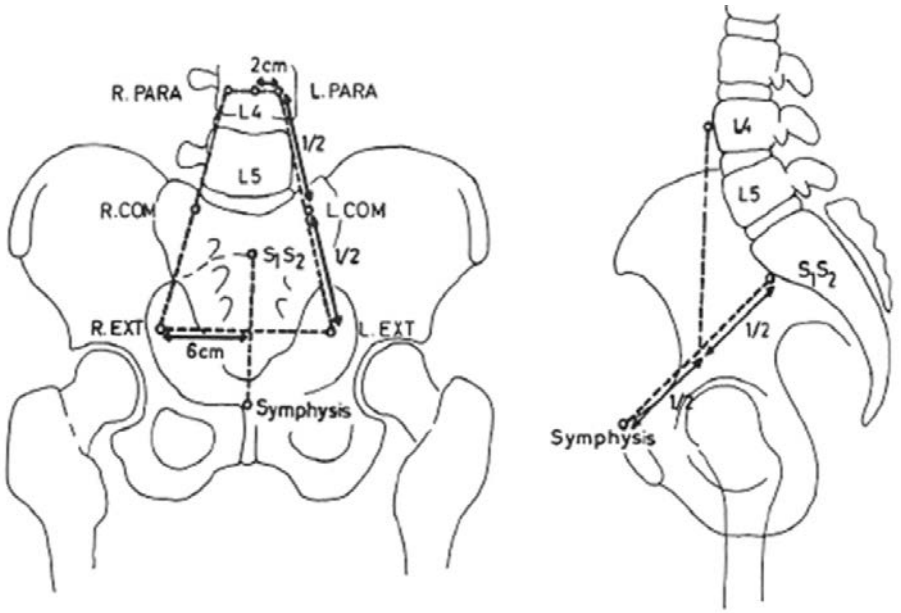

FIG. 16. Determination of the anatomical location of the pelvic and low para-aortic lymph node groups (lymphatic trapezoid). On the left is an anterior view and on the right is a left lateral view. R.EXT — right external iliac; L.EXT — left external iliac; R.COM — right common iliac; L.COM — left common iliac; R.PARA — right para-aortic; L.PARA — left para-aortic (ICRU Report 38 [135]).

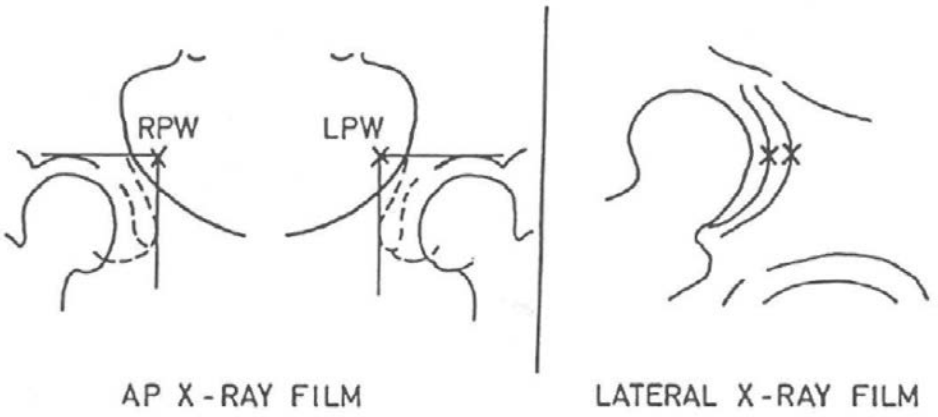

FIG. 17. Determination of the right (RPW) and the left (LPW) pelvic wall reference points in the AP and lateral radiographs (ICRU Report 38 [135]).

late complications when the dose rate effect is not taken into consideration [157, 164, 165]. Commonly used fractionation schedules are detailed in Annex XI.

A dose correction is usually recommended when the dose rate exceeds 1 Gy/h. This is particularly important for centres working with LDR/MDR afterloading equipment loaded with ^{137}Cs sources. The slow decay of caesium implies that gynaecological treatments are delivered at dose rates slowly declining with time. It is therefore very important to check the treatment protocols from time to time in order to adapt to this variability.

8.5.6. Vaginal cylinders

In situations in which there is narrow vaginal anatomy, it may not be possible to insert even the smallest colpostat. In addition, for patients with stage IIIA tumours, the disease may not be adequately covered with colpostats. In both cases, a vaginal cylinder should be used rather than colpostats, along with the intrauterine tandem.

Rectal and vaginal mucosal tolerance must be respected in order to minimize the risk of a recto-vaginal and/or vesico-vaginal fistula. Macroscopic residual tumour after initial EBRT is treated to 80–90 Gy EQD_2, while the vagina that has been involved at diagnosis but that has no signs of macroscopic disease at the time of BT is treated to 60–70 Gy EQD_2. These doses are prescribed to the vaginal surface and additional vaginal dose points should be calculated at 5 mm depth from the cylinder surface.

8.5.7. Interstitial implants

Interstitial BT may be required in the treatment of more advanced primary cervical carcinomas, with extensive parametrial and/or vaginal involvement, typically in combination with EBRT and/or intracavitary BT (see Annex VII).

Performing an interstitial BT implant requires:

— Careful definition of the 'target volume' (i.e. the gross tumour volume, based on clinical, radiological and operative findings);
— In general, these are temporary implants using ^{192}Ir;
— Definition of the geometry of the implant (e.g. single or double plane or volume implant), source distribution, dose rate and total dose, based upon tumour size, location, local extent and proximity of normal structures [166];
— Determination of the number and strength of the radioactive sources and their intended distribution within the target volume, making use of available guidelines such as nomograms, tables and computer assisted optimization techniques;
— Specification of an approximate dose rate to the target volume, which requires careful localization of the sources and computer calculation of the 3-D radiation dose distribution;
— Dose prescription based upon the treatment volume, tumour sensitivity, dose rate, prior treatments and tolerance of normal surrounding tissues is required [166].

Interstitial techniques can be divided into pure interstitial and combined intracavitary–interstitial, as in the case of the Vienna applicator [128–130, 154]. Blunt interstitial needles are placed into the parametria through holes in the ring, which serves as a template for guidance. Dosimetry of an implant for the Vienna applicator is based on intracavitary dose distribution, with dose contribution from the interstitial needles limited to about 10%.

The pure interstitial approach implies the use of template systems that are designed to assist in pre-planning and to guide and secure the position of the needles in the target volume. All rely on pelvic examination to help guide the location and depth of needle placement. The most commonly used template systems are:

— Syed–Neblett device (SNIT) (Alpha Omega Services, Bellflower, CA) [167];
— Modified Syed–Neblett [168];
— MUPIT (Martinez universal perineal interstitial template) [169].

Some of these templates have incorporated a central cylinder which allows for the placement of intracavitary radioactive sources. Usually, all interstitial techniques require special training.

9. SPECIAL CLINICAL SITUATIONS

9.1. CARCINOMA OF THE CERVICAL STUMP

In patients who have undergone a supra-cervical (sub-total) hysterectomy, the risk of developing cervical cancer is the same as that for the rest of the population. Staging and diagnostic procedures are the same as in the case of those with an intact uterus. The prognosis is the same, stage for stage; therefore, definitive therapy should

be offered [170, 171]. Surgery should be considered. Surgical challenges include altered anatomy and possible adhesions.

Radiation treatment principles are similar to those for patients who have an intact uterus, but frequently the short hysterometry does not allow the insertion of a normal length uterine tandem. As a result, the tandem length will often be 2–3 cm. There are no changes in the prescription system and the ICRU BP and ICRU RP doses should be followed. In addition, the dose to the sigmoid and small bowel should be closely monitored, since in the absence of the uterine body, these organs will lie very close to the radioactive sources. If there are limitations to performing an intracavitary implant due to the length of the remaining cervix, extracervical involvement, or rectal or bladder dose constraints, consideration should be given to performing an interstitial implant.

Considerations regarding combined modality therapy are the same as for cervical cancer with an intact uterus, based on the stage of the disease as previously discussed.

9.2. CERVICAL CANCER IN PREGNANCY

Approximately one in one thousand pregnancies is associated with cervical cancer. The goal of treatment is curative, and timing depends upon the gestational period and stage of disease (Table 10). Although treatment is highly individualized based on tumour size, FIGO stage, and the age and desires of the patient regarding her pregnancy, general treatment principles still apply and are discussed below. A multidisciplinary approach is essential [172–174].

Note: The prognosis of patients with invasive cervical cancer associated with pregnancy is similar to that of non-pregnant patients. There is no significant difference in the five year survival rate whether the patient delivers by caesarean section or normal vaginal delivery [172–174].

In the first trimester, either surgery or radiotherapy is used, depending on the stage of the disease. An evacuation of the uterus may be recommended up front. If therapeutic abortion is not done, definitive radiotherapy begins with external beam radiation. Frequent ultrasounds or monitoring of the beta-HCG are performed to check for foetal viability, as an interruption of the pregnancy will occur. In addition, if a dilation and curettage was not performed up front, it is recommended that it be done at the time of the BT to ensure complete evacuation of the placenta. After evacuation of the uterus, treatment continues.

Management in the second trimester is similar to approaches described above, but depends on other factors. In general, the second trimester is divided into the early half and the late half: management in the early half is similar to that described for the first trimester, whereas management in the second half is similar to that for the third trimester. Decisions are modified by the aggressiveness and biology of the cancer. Patients with smaller tumours and negative lymph nodes could potentially be treated more conservatively, provided that the patient is aware of the possibility of tumour progression during the pregnancy that may compromise or decrease her chances of cure.

In the third trimester, definitive treatment is usually delayed until the foetus is mature. Then, a classical caesarean section is performed followed by definitive treatment. For early stages of disease, treatment is often a radical hysterectomy and a pelvic lymphadenectomy, if feasible. If surgical treatment is not feasible, radiotherapy is used but is delayed until involution of the uterus, which typically occurs at one month. When radical surgery is performed, adjuvant radiotherapy may be required if high risk pathologic features are present.

A multidisciplinary team approach is essential in making decisions, with every effort being made to maximize patient understanding and implications of treatment.

9.3. CERVICAL CANCER IN THE HIV SERO-POSITIVE AND AIDS PATIENT

Cervical cancer is more likely to develop in the HIV positive patient due to the synergistic interaction of HIV and HPV related proteins [175]. In particular, there is a higher incidence of carcinoma in situ and early invasive lesions. Lesions tend to be multifocal in the ano-genital area. Invasive cancer of the cervix has a slightly higher incidence (odds ratio 1.6) [175]. In general, cervical cancer is diagnosed at an earlier age in the HIV positive patient [78]. Antiretroviral therapy reduces acquired immunodeficiency syndrome (AIDS) related causes of death by 75%. The medical management of HIV positive and AIDS patients diagnosed with cervical cancer should follow the general guidelines listed below:

TABLE 10. CERVICAL CANCER MANAGEMENT DURING PREGNANCY [8]

Gestational age	Stage		
	IA1–IA2	IB–IIA	IIB–III
Less than 12 weeks	Immediate hysterectomy as in non-pregnant women	Radical hysterectomy with foetus in situ, or Pelvic radiotherapy with spontaneous abortion at 20 Gy, or Evacuation of foetus followed by radiotherapy	Pelvic radiotherapy with spontaneous abortion, or Evacuation of foetus followed by radiotherapy
12–24 weeks	Immediate hysterectomy as in non-pregnant women	Radical hysterectomy with foetus in situ, or Pelvic radiotherapy with hysterectomy at 2 weeks followed by RT/BT	Pelvic radiotherapy with hysterectomy at 2 weeks followed by RT/BT
24–32 weeks	Delay management until 32nd week; at 32 weeks amniocentesis and steroids for lung maturity, if needed; then as more than 32 weeks	Delay management until 32nd week; at 32 weeks amniocentesis and steroids for lung maturity if needed; then as for more than 2 weeks	Delay management until 32nd week; at 32 weeks amniocentesis and steroids for lung maturity if needed; then as for more than 32 weeks
More than 32 weeks	Classic caesarean section plus hysterectomy	Classic caesarean section plus radical hysterectomy or classic caesarean section followed by definitive radiotherapy after involution of uterus (1 month)	Classic caesarean section followed by definitive radiotherapy after involution of uterus (1 month)

— All women should be offered the same cervical cancer screening options, irrespective of their HIV status.
— All women should be offered curative treatment for cervical cancer according to the stage of disease and their general medical condition, irrespective of their HIV status.
— Tumour stage, performance status, immune status and the presence of co-morbidities associated with immunosuppression should be carefully assessed.
— The indication for chemotherapy is tailored to the performance status and immune status of the patient. No chemotherapy is recommended if the CD4 count is below 200 cells/mm^3.
— Myelosuppression due to antiretroviral therapy may be added to that caused by cancer therapy and must be carefully monitored.
— During treatment, patients require close monitoring in the same manner as in the HIV negative setting. Special care is given to the immune status, myelosuppression and the development of mucositis [78]. HIV positive patients are particularly at risk of developing increased acute and possibly long term toxicity from radiation and, especially, from concurrent radiation and chemotherapy. Therefore, they should be closely monitored. In addition, consideration should be given to possible dose reductions in terms of dose/fraction as well as dose of chemotherapy agents.
— Close follow-up is necessary for cancer recurrence or the appearance of a new HIV related malignancy. Carcinoma in situ of the peri-anal area needs to be diagnosed early and treated aggressively.

9.4. RECURRENT DISEASE

It is important to ascertain the exact extent of disease and the disease free interval, as well as the age, general condition and symptoms of the patient before deciding on management. It is necessary to determine whether the intent of treatment is curative or palliative. The general principle is that a modality that has not been used at presentation is often employed. However, each recurrence needs to be evaluated individually with appropriate treatment instituted.

There are three possible scenarios:

(1) If the patient has distant metastasis, with or without a local-regional recurrence, palliative treatment is offered, as necessary. Cisplatin is the most active drug in patients not previously exposed to it [113].
(2) For loco-regional recurrence after radical surgery:
    — The therapeutic options are either radical irradiation or pelvic exenteration. Patients with a central recurrence have a better prognosis than those with a pelvic side wall recurrence (48% ten year survival rate if the recurrence is less than 3 cm).
    — Techniques and doses of irradiation should be similar to those used for the intact cervix, although the absence of the uterus will limit the possibility of delivering high central doses with intracavitary BT. In addition, the post-operative changes, surgical adhesions and larger volume of small bowel in the pelvis often preclude the delivery of high doses of radiation with BT even when using interstitial techniques.
    — Even though BT potentially offers the higher likelihood of local tumour control for patients with small volume central recurrence, when this is not possible, the central disease could be boosted with 3-D CRT (or IMRT) to deliver a total dose of 65–70 Gy with a shrinking field technique after a whole pelvic dose of 45 Gy. This is often delivered in combination with chemotherapy (generally weekly cisplatinum).
    — In the light of the published randomized trials that have shown an overall survival advantage for cisplatin based chemotherapy given concurrently with radiotherapy in women with FIGO stages IB2–IVA, consideration should be given to incorporating concurrent cisplatin based chemotherapy to radiotherapy in patients with a locoregional recurrence following prior radical surgery *(grade of recommendation B)*.
(3) For loco-regional recurrence following definitive radiotherapy:
    — If the recurrence is central and limited, surgery consisting of a pelvic exenteration is a potentially curative option in highly selected cases [176]. An experienced surgical team is required.
    — For patients who were previously treated with primary radiation and who experience a small central recurrence in the cervix, re-treatment with BT alone is an option for those who are not candidates for a pelvic exenteration.

— In cases involving the pelvic sidewall, cure is rarely possible. Treatment options must be highly individualized and could involve limited re-irradiation and/or chemotherapy. The intent of treatment is usually palliative.

10. PALLIATIVE THERAPY

10.1. RADIOTHERAPY

Palliative care aims to improve the quality of life of patients and their families facing problems associated with life threatening illness such as advanced cancer. Palliative care includes not only end of life care but also the management of all distressing symptoms such as pain, depression, anxiety, sleeping dysfunctions and fatigue. This can be provided by practitioners at hospitals and care centres, the community and family members.

The needs of cervical cancer patients with incurable disease should be addressed by using existing palliative care services or establishing new ones. Providers at all levels need to be trained and to have the resources necessary to manage the most common physical and psychosocial problems, with special attention to pain control. A comprehensive cervical cancer control programme should ensure that opioid, non-opioid and adjuvant analgesics, particularly morphine for oral administration, are available.

Patients with grossly recurrent and metastatic cervical cancer often have significant symptoms unresponsive to further systemic therapy. Symptoms may be due to recurrent disease in the pelvis, causing pain and/or bleeding. Distant recurrence in the brain, chest, groin and other areas may require palliation as well. The selection of treatment modality and doses of radiation in the palliative setting depend primarily on the extent of the disease in the pelvis, prior radiotherapy, the patient's performance status and the estimated length of survival. Patients with poor performance status and/or extensive distant disease should be treated using shorter regimens. If vaginal bleeding is the main concern, BT, using endocavitary and/or interstitial techniques, when feasible, often offers good symptom control with relatively low morbidity. For patients who have received prior radiation, intracavitary doses in the range of 35–40 Gy tumour dose may suffice to palliate symptoms. For those patients who may not be candidates for BT, a short course of EBRT using high dose fractionation schedules has been used. Hypofractionated pelvic irradiation usually controls bleeding and frequently provides prompt relief of pelvic pain. A variety of fractionation schemes can be used. Protracted fractionation is rarely indicated for palliation of patients with extrapelvic metastasis because the median life expectancy for these patients is short. Regimes with a few large fractions often result in adequate palliation [73, 114, 134].

Some of the common regimens used are:

— 30 Gy in ten fractions (3 Gy each);
— 20 Gy in five fractions (4 Gy each);
— 3.7 Gy bid × 2 d, repeated every 3–4 weeks, for 2–3 cycles [177, 178];
— 8–10 Gy repeated once (maximum of two) with one month interval.

10.2. SURGERY

The role of surgery in the palliative setting in cervical cancer involves primarily:

(a) Debulking large masses in an attempt to improve patient symptoms and quality of life;
(b) Attempts to relieve intestinal obstruction generally related to a mechanical obstruction from recurrent masses.

Careful preoperative evaluation is indicated before any surgical intervention, including assessment of the patient's performance and nutritional status, and history of prior radiation. Imaging studies may help to delineate the number and location of obstructions as well as the extent of intra-abdominal disease, in order to guide the surgical decision making process. Patients with recurrent disease and a short life expectancy are unlikely to benefit

from exploration. It is important to exercise good judgement and expertise to maximize the outcome for those patients with short life expectancy in order to improve their quality of life.

11. FOLLOW-UP

After completing treatment for invasive cervical cancer, patients require regular clinical follow-up not only to detect potential recurrent disease but also to evaluate potential complications derived from therapy.

11.1. SURVEILLANCE

As recurrences are most common during the first two years following treatment, patients should be seen once every three months during the first two years, then every six months for two years and yearly thereafter. General history and physical examination are recommended, in addition to a careful pelvic examination with evaluation of the external genitalia, vagina and cervix, and bimanual examination including rectal examination.

The role of an annual Pap test is currently the subject of some controversy. It has been indicated that a regular (every three months) follow-up Pap test is not warranted, given the low probability of detecting cervical cancer recurrences in the absence of symptoms.

Routine screening with radiology is not advisable, but appropriate investigation of symptoms that appear related to cancer or treatment complications is useful. For example, new development of back pain, generally with sciatic distribution and ipsilateral leg swelling, is very concerning in a retroperitoneal nodal recurrence. Therefore, further evaluation of the abdomen and pelvis with a CT scan should be considered.

Other investigations are administered as clinically indicated such as cystoscopy, rectosigmoidoscopy, chest X ray, plain bone radiographs, CT scan and colposcopically directed biopsies. Performance of these investigations will also depend upon resource availability.

It is important to educate patients regarding symptoms suggestive of recurrence, so that they bring these to the attention of their physician. Additional tests can be recommended depending upon the symptoms and findings of a physical examination. Follow-up may be done at a lower care level, but the radiation oncologist and other specialists must be informed of any significant event.

11.2. FOLLOW-UP OF ACUTE AND LONG TERM TOXICITY

Common sub-acute (up to six months after treatment) and late complications (more than six months after completing treatment) are related to the damage of surrounding normal organs: vagina, bladder, rectum, sigmoid colon and small bowel. Late bowel and bladder complications (such as bleeding, urinary dysfunction and/or bowel obstruction) are the most common late complications in up to 5–15% of treated patients. In addition, there is a potential risk of developing a recto-vaginal or vesicovaginal fistula that may require additional surgery for correction, including urinary diversion and/or colostomy.

Vaginal complications include narrowing and shortening of the vagina, resulting in dyspareunia and/or post-coital bleeding. Patients should be advised to use a vaginal dilator or to resume intercourse in order to avoid complications.

Registration and reporting of acute and late morbidity should be done following an internationally recognized and validated toxicity score such as the CTCAE version 4 (see Annex VIII).

12. SUMMARY OF RECOMMENDATIONS

(1) A biopsy is mandatory to establish the diagnosis of cervical cancer. All lesions must be confirmed by histopathological examination. Punch biopsies from the edge of the gross tumour are recommended.
(2) All patients should be offered the same treatment options irrespective of their HIV status.
(3) Radical surgery for the treatment of cervical cancer should be performed only by surgeons with a focused training in gynaecological cancer surgery.
(4) Accuracy and reproducibility of the patient's position is essential to the successful delivery of pelvic radiotherapy. This becomes even more important if 3-D CRT or IMRT is used.
(5) At a minimum, the use of a conventional simulator is recommended for treatment planning.
(6) The four field 'box' technique is recommended over the AP-PA technique. The AP-PA technique can be used only in patients with an AP separation diameter of 20 cm or less.
(7) All fields must be treated daily.
(8) Photon energies of 1.25 MV or higher are recommended for treating the pelvis.
(9) In patients with advanced (extracervical) disease, the location of the posterior border of the lateral fields should be carefully determined. When CT/MRI imaging is available, this border should be set according to the posterior extent of disease in the cardinal and uterosacral ligaments with a margin. When cross-sectional imaging is not available, the posterior border of the lateral fields should include the whole sacral hollow, and blocks in the posterior-superior and posterior-inferior angles may be considered.
(10) Block shielding in the AP-PA and in the lateral field should be designed very carefully so as not to block macroscopic disease or high risk volumes.
(11) All treatment interruptions are detrimental. There should not be any planned treatment interruptions apart from two day weekends. There should not be any planned break after completion of EBRT and prior to initiation of BT.
(12) The entire treatment course including the external irradiation and the BT components should be completed in not more than eight weeks. HDR-BT can be overlapped with EBRT to keep the total treatment duration less than eight weeks. *Do not treat with HDR and EBRT the same da*y.
(13) BT (either LDR or HDR) is a mandatory component of the curative treatment of cervical cancer. It is not acceptable to replace BT with an additional EBRT boost or 'adjuvant' chemotherapy after completion of the radiation.
(14) HDR-BT is a legitimate, convenient and cost effective modality of treatment for centres treating a large number of cervical cancer patients.
(15) The total number of HDR fractions can be safely reduced to no fewer than 2–3, thus representing convenience for the patients and the sparing of resources for the treatment centre, provided that safety and adequate tolerance are carefully evaluated for each particular patient.
(16) The tandem and ring type of applicator allows a reproducible geometry which in turn is reflected in reproducibility of the dose distribution throughout subsequent applications. Given this advantage, treatment planning can be carried out in the first fraction only.
(17) Proper applicator placement must be achieved to obtain improved local control, survival and lower morbidity.
(18) Interstitial BT should be considered for patients with disease that cannot be optimally encompassed by intracavitary BT alone.
(19) The rectal total dose and dose rate should be kept low to minimize the risk of rectal complications. When using 2–3 fractions, this can be achieved by closely monitoring the dose at the rectal point, using adequate packing, rectal retraction and dose optimization.
(20) Post-operative irradiation is indicated for patients deemed to be at intermediate or high risk of a pelvic recurrence. Patients who belong to the high risk category should be treated with a combination of chemo-radiotherapy, while patients in the intermediate risk category can be treated with post-operative pelvic irradiation only.
(21) Recently, HDR-BT systems using a miniaturized ^{60}Co source have become available. Cobalt-60 based HDR-BT systems require source replacement every five years, thus representing significant convenience and sparing of resources.

(22) Most patients with loco-regionally advanced cervical cancer (stage IB2 or greater, or positive pelvic lymph nodes) that is confined to the pelvis are candidates for chemo-radiotherapy. However, the benefits of adding concurrent chemotherapy to radiotherapy should always be weighed against the risk of serious acute toxicities, particularly in patients who are frail or immunocompromised, or have comorbidities.

(23) It is important to effectively treat anaemia (haemoglobin <10 g/dL) in this group of patients using packed red blood cells. There is not enough evidence to recommend the routine use of agents that directly stimulate erythropoiesis.

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Annex I

INTERNATIONAL FEDERATION OF GYNECOLOGY AND OBSTETRICS (FIGO) STAGING SYSTEM

The International Federation of Gynecology and Obstetrics (FIGO) staging system is presented below [I–1].

Stage I: The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded)

IA: Invasive carcinoma which can be diagnosed only by microscopy, with deepest invasion ≤5.0 mm and largest extension ≤7.0 mm

IA1: Measured stromal invasion of ≤3.0 mm in depth and extension of ≤7.0 mm

IA2: Measured stromal invasion of >3.0 mm and not >5.0 mm with an extension of not >7.0 mm

IB: Clinically visible lesions limited to the cervix uteri or pre-clinical cancers greater than stage IA[1]

IB1: Clinically visible lesion ≤4.0 cm in greatest dimension

IB2: Clinically visible lesion >4.0 cm in greatest dimension

Stage II: Cervical carcinoma invades beyond the uterus, but not to the pelvic wall or to the lower third of the vagina

IIA: Without parametrial invasion

IIA1: Clinically visible lesion ≤4.0 cm in greatest dimension

IIA2: Clinically visible lesion >4.0 cm in greatest dimension

IIB: With obvious parametrial invasion

Stage III: The tumour extends to the pelvic wall and/or involves lower third of the vagina and/or causes hydronephrosis or non-functioning kidney[2]

IIIA: Tumour involves lower third of the vagina, with no extension to the pelvic wall

IIIB: Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney

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[1] All macroscopically visible lesions — even with superficial invasion — are allotted to stage IB carcinomas. Invasion is limited to a measured stromal invasion with a maximal depth of 5.0 mm and a horizontal extension of not greater than 7.0 mm. Depth of invasion should not be greater than 5.0 mm taken from the base of the epithelium of the original tissue-superficial or glandular. The depth of invasion should always be reported in mm, even in those cases with 'early (minimal) stromal invasion' (~1 mm). The involvement of vascular/lymphatic spaces should not change the stage allotment.

[2] On rectal examination, there is no cancer-free space between the tumour and the pelvic wall. All cases with hydronephrosis or non-functioning kidney are included, unless they are known to be due to another cause.

Stage IV: The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous oedema, as such, does not permit a case to be allotted to Stage IV

IVA: Spread of the growth to adjacent organs

IVB: Spread to distant organs

REFERENCE TO ANNEX I

[I–1] FIGO COMMITTEE ON GYNAECOLOGIC ONCOLOGY, Revised FIGO staging for carcinoma of the vulva, cervix and endometrium, Int. J. Gynaecol. Obstet. **105** 2 (2009) 103.

Annex II

CORRELATION BETWEEN THE TUMOUR, NODE, METASTASIS (AJCC) AND FIGO STAGING SYSTEMS

TABLE II–1. STAGING OF CARCINOMA OF THE UTERINE CERVIX [II–1]

TNM parameter	AJCC	FIGO	Description
Primary tumour (T)	TX	—	Primary tumour cannot be assessed
	T0	—	No evidence of primary tumour
	T_{is} [a]	0	Carcinoma in situ
	T1	I	Cervical carcinoma confined to uterus (extension to corpus should be disregarded)
	T1a[b]	IA	Invasive carcinoma, diagnosed only by microscopy. Stromal invasion with a maximum depth of 5 mm measured from the base of the epithelium and horizontal spread of 7 mm or less. Vascular space involvement, venous or lymphatic, does not affect classification
	T1a1	IA1	Measured stromal invasion 3 mm or less and 7 mm or less in horizontal spread
	T1a2	IA2	Measured stromal invasion more than 3 mm and not more than 5 mm with a horizontal spread of 7 mm or less
	T1b	IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a2/IA2
	T1b1	IB1	Clinically visible lesion 4 cm or less in greatest dimension
	T1b2	IB2	Clinically visible lesion more than 4 cm in greatest dimension
	T2	II	Cervical carcinoma invades beyond uterus but not to pelvic wall or to the lower third of vagina
	T2a	IIA	Tumour without parametrial invasion
	T2a1	IIA1	Clinically visible lesion 4 cm or less in greatest dimension
	T2a2	IIA2	Clinically visible lesion more than 4 cm in greatest dimension
	T2b	IIB	Tumour with parametrial invasion
	T3	III	Cervical carcinoma extends to the pelvic wall and/or involves lower third of vagina or causes hydronephrosis or nonfunctioning kidney
	T3a	IIIA	Tumour involves lower third of the vagina, no extension to pelvic wall
	T3b	IIIB	Tumour extends to pelvic wall or causes hydronephrosis or nonfunctioning kidney
	T4	IVA	Tumour invades mucosa of bladder or rectum and/or extends beyond true pelvis

TABLE II–1. STAGING OF CARCINOMA OF THE UTERINE CERVIX [II–1] (cont.)

TNM parameter	AJCC	FIGO	Description
Regional lymph nodes (N)[c]	NX	—	Regional lymph nodes cannot be assessed
	N0	—	No regional lymph node metastasis
	N1	IIIB	Regional lymph node metastasis
Distant metastasis (M)	M0	—	No distant metastasis
	M1	IVB	Distant metastasis

Note: AJCC — American Joint Committee on Cancer; FIGO — International Federation of Gynecology and Obstetrics; TNM — tumour, node, metastasis.

[a] FIGO no longer includes Stage 0 (T_{is}).

[b] All macroscopically visible lesions — even with superficial invasion — are T1b/IB.

[c] Regional lymph nodes include paracervical, parametrial, hypogastric (obturator), common, internal and external iliac, presacral and sacral.

TABLE II–2. AMERICAN JOINT COMMITTEE ON CANCER (AJCC) STAGE GROUPING FOR CARCINOMA OF THE UTERINE CERVIX [II–1]

Stage	Primary tumour	Regional lymph nodes	Distant metastases
0[a]	T_{is}	N0	M0
I	T1	N0	M0
IA	T1a	N0	M0
IA1	T1a1	N0	M0
IA2	T1a2	N0	M0
IB	T1b	N0	M0
IB1	T1b1	N0	M0
IB2	T1b2	N0	M0
IIA	T2a	N0	M0
IIA1	T2a1	N0	M0
IIA2	T2A2	N0	M0
IIB	T2b	N0	M0
IIIA	T3a	N0	M0
IIIB	T1	N1	M0
	T2	N1	M0
	T3a	N1	M0
	T3b	Any N	M0
IVA	T4	Any N	M0
IVB	Any T	Any N	M1

[a] FIGO no longer includes Stage 0 (T_{is}).

REFERENCE TO ANNEX II

[II–1] EDGE, S.B., et al., AJCC Cancer Staging Handbook, Springer, New York (2010).

Annex III

CREATININE CLEARANCE CALCULATION

Creatinine clearance (eC_{Cr}) can be calculated using the Cockcroft equation [III–1]:

$$eC_{cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times (0.85 \text{ if Female})}{72 \times \text{Serum Creatinine (in mg/dL)}}$$

REFERENCE TO ANNEX III

[III–1] COCKCROFT, D.W., et al., Prediction of creatinine clearance from serum creatinine, Nephron. **16** 1 (1976) 31.

Annex IV

TUMOUR DIAGRAM

Tumour diagrams are drawing templates that are used to document the extent of disease based on clinical examination. Manual drawing of tumour extent should follow gynaecological examination.

Figure IV–1 shows a tumour diagram, which allows graphical documentation of cervical carcinoma and involved lymph nodes [IV–1].

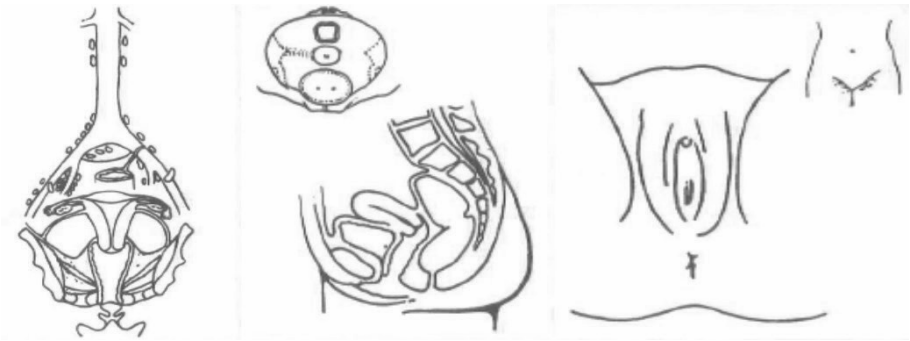

FIG. IV–1. Tumour diagram [IV–1].

Figure IV–2 shows a tumour diagram with the possibility of 3-D documentation of tumour spread. Colour coding can be used for clear documentation of infiltration of the cervix, parametria, vagina, bladder and rectum. Growth pattern (infiltrative or exophytic) can be depicted using different patterns of drawing. Tumour dimensions and the length of vaginal extension can also be documented. This template was developed for the purpose of the EMBRACE study (an international study on MRI guided brachytherapy in locally advanced cervical cancer) and was tested in the dummy run for this study. Currently it is used not only for the purposes of the study but also for the clinical routine in more than 20 institutions worldwide [IV–2, IV–3].

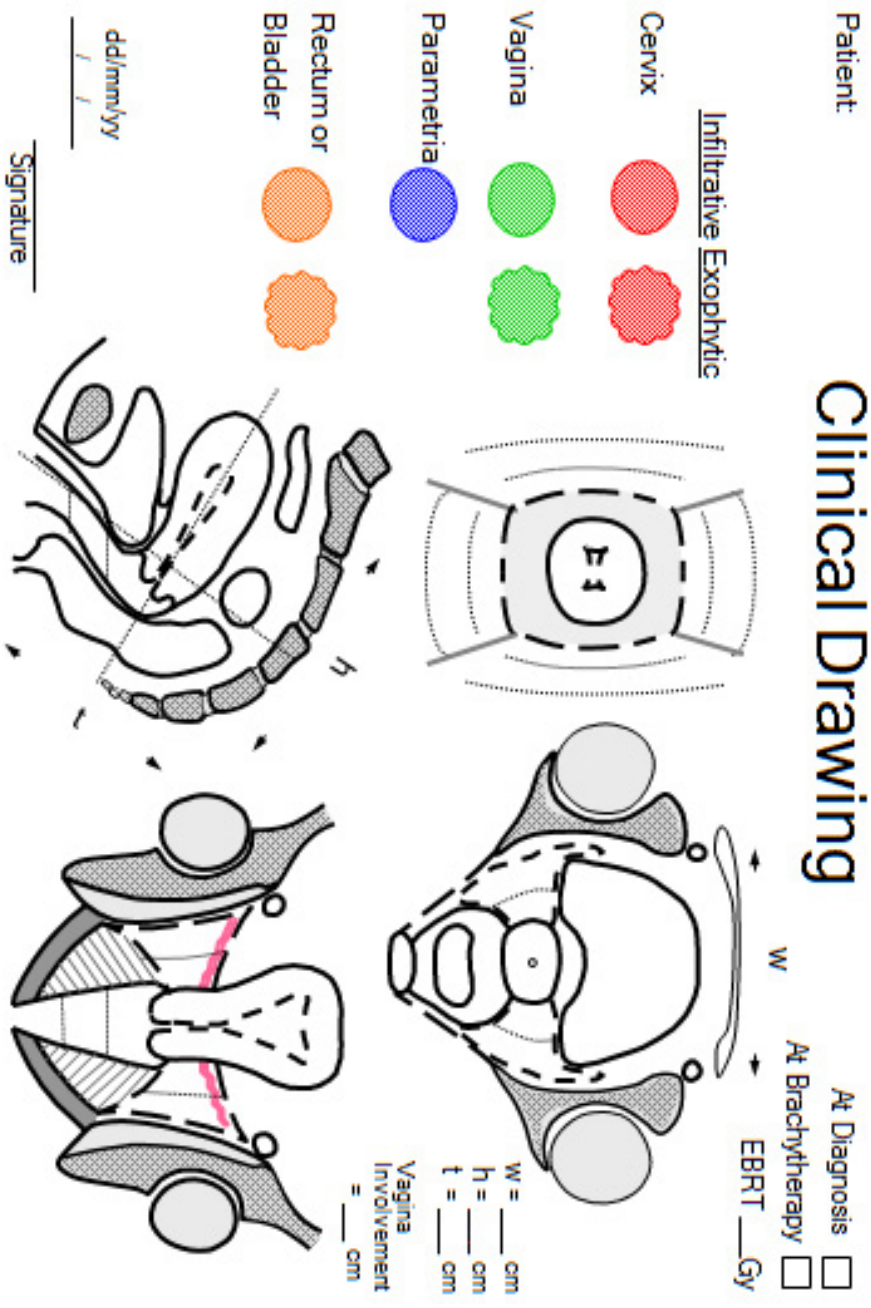

FIG. IV–2. Advanced tumour diagram [IV–2].

REFERENCES TO ANNEX IV

[IV–1] GREENE, F.L., et al., AJCC Cancer Staging Handbook, Springer, New York (2002).

[IV–2] SHENFIELD, C.B., et al., A Template for Clinical Drawings in Cancer of the Cervix (2009), https://www.embracestudy.dk/AboutAppendix.aspx

[IV–3] FIDAROVA, E., et al., Dummy run as a QA tool in the EMBRACE Study, Radiother. Oncol. **91** (2009) S28.

Annex V

PERFORMANCE STATUS SCALES

Eastern Cooperative Oncology Group (ECOG) Score [V–1]

The ECOG score (published by Oken et al. in 1982), also called the World Health Organization (WHO) or Zubrod score (after C. Gordon Zubrod), runs from 0 to 5, with 0 denoting perfect health and 5 death [V–1]:

0 — Asymptomatic
1 — Symptomatic but completely ambulant
2 — Symptomatic, <50% in bed during the day
3 — Symptomatic, >50% in bed, but not bedbound
4 — Bedbound
5 — Death

Karnofsky Performance Scale [V–2]

100 Normal, no complaints, no evidence of disease
90 Able to carry on normal activity: minor symptoms of disease
80 Normal activity with effort: some symptoms of disease
70 Cares for self: unable to carry on normal activity or active work
60 Requires occasional assistance but is able to care for needs
50 Requires considerable assistance and frequent medical care
40 Disabled: requires special care and assistance
30 Severely disabled: hospitalization is indicated, death not imminent
20 Very sick, hospitalization necessary: active treatment necessary
10 Moribund, fatal processes progressing rapidly

REFERENCES TO ANNEX V

[V–1] OKEN, M.M., et al., Toxicity and response criteria of the Eastern Cooperative Oncology Group, Am. J. Clin. Oncol. **5** 6 (1982) 649.
[V–2] KARNOFSKY, D.A., BURCHENAL, J.H., The Clinical Evaluation of Chemotherapeutic Agents in Cancer: Evaluation of Chemotherapeutic Agents (MacLEOD, C.D., Ed), Columbia Univ. Press (1949).

Annex VI

SURGERY: DEFINITION OF COMMON GYNAECOLOGICAL OPERATIONS USED FOR TREATMENT OF CERVICAL CANCER

Table VI–1 summarizes surgical procedures that are commonly used for the treatment of cervical cancer [VI–1, VI–2].

TABLE VI–1. COMMON GYNAECOLOGICAL OPERATIONS FOR CERVICAL CANCER

Operation	Technique
Conization	Removal of a cone shaped volume of tissue from the cervix, including portions of the outer (ectocervix) and inner (endocervix) mucosa
Simple trachelectomy	Caudal part of the uterine cervix and upper vagina are removed, but parametria are preserved
Radical trachelectomy	Caudal part of the uterine cervix, parametria and upper vagina are removed. In most cases this is followed by a bilateral pelvic lymphadenectomy and suture of the proximal vagina to the remaining part of the cervix. The uterine body, fallopian tubes and ovaries remain in place
Vaginal hysterectomy	The whole uterus (including the cervix) is removed through the vagina
Radical hysterectomy	The whole uterus (including the cervix) is removed together with parametria and upper vagina
Total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO)	The whole uterus (including the cervix) is removed together with both ovaries and fallopian tubes
Pelvic exenteration	Removal of the uterus, upper part of the vagina or the whole vagina, both ovaries and fallopian tubes, together with the urinary bladder and urethra (anterior exenteration), or rectum (posterior exenteration), or both (total exenteration). Anterior exenteration requires urinary diversion, posterior exenteration-diverting stoma. Types of surgical resection and reconstruction are highly case dependent

Table VI–2 describes types of radical hysterectomy [VI–2, VI–3].

TABLE VI–2. TYPES OF RADICAL HYSTERECTOMY

	Extrafascial type I/type A	Modified radical type II/type B	Radical type III/type C2
Cervical fascia	Completely removed	Completely removed	Completely removed
Vaginal cuff removal	Small rim removed	Proximal 2 cm removed[a]	Proximal 2 cm removed[a]
Bladder	Partially mobilized	Partially mobilized	Mobilized
Rectum	Not mobilized	Rectovaginal septum partially mobilized	Mobilized
Ureters	Not mobilized	Unroofed in ureteral tunnel	Completely dissected to bladder entry

TABLE VI–2. TYPES OF RADICAL HYSTERECTOMY (cont.)

	Extrafascial type I/type A	Modified radical type II/type B	Radical type III/type C2
Lateral parametrium	Resected at the level of cervix	Resected at the level of ureters	Resected at pelvic sidewall
Dorsal parametrium	Resected at the level of cervix	Partially resected	Resected at pelvic insertion
Uterus	Removed	Removed	Removed
Cervix	Completely removed	Completely removed	Completely removed

[a] Length of resected vagina depends on the presence of precancerous changes or cancer invasion.

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Annex VII

BRACHYTHERAPY APPLICATOR MODELS

The most commonly used brachytherapy applicators are listed and described in Table VII–1 and shown in Fig. VII–1.

TABLE VII–1. BRACHYTHERAPY APPLICATOR MODELS [VII–1]

Applicator model	Characteristics
Manchester	Includes one intrauterine tube and two ovoid shaped vaginal colpostats. In modern high dose rate (HDR) models, a clamp fixes the position of the ovoids relative to the intrauterine tube
Fletcher suit	Includes an intrauterine tube and two cylindrical colpostats. The vaginal sources lie in the fornices perpendicular to the axis of the vagina. The intrauterine tube comes in various angulations and the vaginal colpostats in various sizes
Henshcke	The vaginal colpostats are hemispherical in shape and the vaginal sources lie approximately parallel to the axis of the intrauterine tube
Ring and tandem	Carries two radioactive lines: one in the rigid intrauterine tandem and one in a ring shaped part that is placed against the cervix. The intrauterine tube comes in different lengths and angles, and the ring is available in different diameters
Moulage	This method developed at the Institut Gustave Roussy (France) consists of the construction of an individualized mould (‘moulage’) made of liquid plaster and acrylic to maximize individual anatomical adaptation. The afterloading catheters are placed in the mould according to the individual tumour topography
CT/MRI compatible models	All the above applicator models are available in CT/MRI compatible versions. These are made of plastic and carbon-fibre, thus making them compatible with CT and MRI scans. CT and MRI scans performed on the patient with the applicator in place allows 3-D treatment planning based on images and volume delineation
Syed–Neblett template	Two plastic plates joined by screws that tighten to fix in place up to 38 stainless steel needles. Six additional needles can be placed around the central cylinder. This applicator can be used for interstitial only or for combined interstitial and intracavitary techniques
MUPIT	‘Martinez universal perineal interstitial template’. This is an interstitial template that uses needles to various depths and angulations. Treatment can be adapted to various tumour volumes in the pelvis using HDR and optimization. It has been adapted for use with HDR remote afterloading units and modern image based treatment planning
Vienna applicator	Modification of the ring and tandem model in which needles can be inserted laterally through holes in the ring carrier. This applicator is CT/MRI compatible using zirconium needles, and may be useful to cover proximal parametrial extension of tumour
Vaginal cylinders	Designed to treat the mucosa of the vaginal wall at the vaginal cuff or to various lengths. Cylinders are commercially available in different diameters and lengths

FIG. VII–1. Brachytherapy applicator models. (Images courtesy of Nucletron.)

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Annex VIII

ADVERSE EVENTS

The incidence and severity of acute haematologic and gastrointestinal complications are significantly increased when chemotherapy is administered concurrently with radiotherapy. Major late complications of pelvic radiotherapy are associated with smoking, race and obesity, among other factors [VIII–1].

The National Cancer Institute Common Terminology Criteria for Adverse Events version 4 (CTCAE v4.0) is used for adverse event reporting [VIII–2]. It comprises grades 1 through 5 with unique clinical descriptions of severity for each adverse event based on the general guidelines (Table VIII–1). Grade refers to the severity of the adverse event.

TABLE VIII–1. GRADING FOR ADVERSE EVENTS IN CTCAE V4.0

Grade	Description
0	No adverse event (absent) or within normal limits
1	Mild adverse event (minor; no specific medical intervention; asymptomatic laboratory findings only, radiographic findings only; marginal clinical relevance)
2	Moderate adverse event (minimal intervention; local intervention; non-invasive intervention (packing, cautery))
3	Severe and undesirable adverse event (significant symptoms requiring hospitalization or invasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation)
4	Life-threatening or disabling adverse event (complicated by acute, life-threatening metabolic or cardiovascular complications such as circulatory failure, haemorrhage, sepsis; life-threatening physiologic consequences; need for intensive care or emergent invasive procedure; emergent interventional radiological procedure, therapeutic endoscopy or operation)
5	Death related to adverse event

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Annex IX

THE BASIC RADIOTHERAPY CLINIC

The key to describing the operation of a radiation oncology clinic is the need to consider its essential components: facility layout, equipment, human resources and procedures. It is obvious that in order to start operations, a facility must be equipped with at least the basic equipment. No radiotherapy centre should be operated without qualified personnel: radiation oncologists, medical physicists, radiotherapy technologists and other medical and technical staff as required.

The term 'basic' implies that the clinic has the essential equipment and adequate staffing required for treating most tumours, with the intention of achieving local control of the disease to the extent possible. The clinic should conduct a cancer registry and have procedures for the follow-up of treated patients.

Table IX–1 lists the requirements for buildings, equipment and staffing that ought to be satisfied by a basic cancer therapy centre treating approximately 500 new cancer patients per year with teletherapy (about 50% of them with curative intent) and about 200 patients per year with brachytherapy (BT). The work is organized in two shifts. Staffing needs should be adjusted according to the number of patients treated. The staff's training requires that senior professionals or specialized trainers be available at the clinic.

The basic radiotherapy unit is equipped with a ^{60}Co unit or a single-energy linear accelerator, without a multileaf collimator (MLC), portal imaging or networking. With the increasing complexity of radiotherapy treatments, the number of trained staff will need to increase.

TABLE IX–1. ESSENTIAL EQUIPMENT AND STAFFING FOR A BASIC RADIOTHERAPY CLINIC [IX–1]

Buildings	A megavoltage bunker (space for an additional one is desirable) An X ray bunker for an orthovoltage unit A simulator room A dosimetry planning/physicists room A high dose rate (HDR) bunker[a] A mould room Ample clinical space (for consulting, examination, changing and waiting rooms)
External beam therapy	A single-photon energy teletherapy unit An orthovoltage unit Beam measurement and QA/RP[b] equipment A simulator, preferably a CT simulator A computerized treatment planning system (TPS) Film processing equipment Patient immobilization devices and mould room materials and accessories
Brachytherapy	A BT afterloader (HDR is preferable) An X ray C-arm A computerized TPS for BT A full range of applicators Quality assurance physics equipment

TABLE IX–1. ESSENTIAL EQUIPMENT AND STAFFING FOR A BASIC RADIOTHERAPY CLINIC [IX–1] (cont.)

Personnel	4–5 radiation oncologists 3–4 medical physics staff[c] 7 radiation therapy technologists[d] 1–3 radiation oncology nurses[c] 1 maintenance technician/engineer

[a] A low dose rate brachytherapy (LDR-BT) unit can treat only approximately 80–100 patients per year. Centres with a larger number of cervical cancer cases per year require HDR-BT.

[b] QA/RP — quality assurance and radiation protection.

[c] An increase of 50% is required if staff are also responsible for administration of chemotherapy. In this case, a chemotherapy suite must be available.

[d] This includes at least one, and preferably two, senior clinically qualified radiotherapy medical physicists. Other physics staff must be clinically qualified radiotherapy medical physicists, resident physicists or dosimetrists.

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Annex X

QUALITY ASSURANCE

Quality assurance (QA) in radiotherapy consists of a series of procedures that ensure the consistent and safe fulfilment of the dose prescription to the target volume with minimal dose to the normal tissues and minimal exposure to personnel and the public. It involves both clinical and physics aspects. In turn, a quality system can be defined as the organizational structure, responsibilities, procedures, processes and resources for implementing QA [X–1].

Radiotherapy is a multidisciplinary specialty, involving complex equipment and procedures. Many separate but interlinked stages and processes are necessary to progress from the initial clinical decision to undertake treatment through to the treatment delivery itself and subsequent follow-up. It is universally recognized that QA is vital at all levels of the overall radiotherapy process to ensure the achievement of a safe and effective treatment. Historically, QA has been carried out in many areas of radiotherapy, particularly in the more readily defined physical and technical aspects of equipment, dosimetry and treatment delivery. However, more recently, there has been growing acceptance that QA should be wider in scope, to embrace all aspects in a unified comprehensive manner. Coupled with the increased complexity of radiotherapy techniques and associated quality control and with the increasing demands on quality of treatment, this has led to the recognition that a systematic approach is both necessary and desirable. In turn, this has given rise to recommendations for more formalized quality systems or processes. Some of these recommendations have arisen following radiotherapy accidents, where the implementation of a quality system is seen as reducing the probability or the consequences of accidents and errors. However, while the adoption of a QA system will indeed fulfil this role, the more fundamental reason for following this approach is to help provide good quality treatment.

The general aim of developing a quality system in a radiotherapy department is to provide a formal written scheme to ensure that all important aspects of QA in the department are defined, documented, understood and put into practice.

The main areas of a QA programme include clinical policies, treatment planning and delivery, a quality control programme for machine and equipment performance, maintenance programmes, investigative and reporting procedures for incidents and accidental medical exposures, and a system of quality audits. Larger countries with many radiotherapy centres can develop and implement their own national audit systems. Smaller countries or individual centres in other countries can rely on regional networks or on audits conducted by the IAEA following the QUATRO (Quality Assurance Team for Radiation Oncology) methodology. The IAEA publication ‘Comprehensive Audits of Radiotherapy Practices: A Tool for Quality Improvement’ describes this methodology in detail [X–2].

The establishment of such a comprehensive QA programme should be in accordance with the Basic Safety Standards (BSS) [X–3].

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Annex XI

RELEVANT RADIOBIOLOGY

An extensive radiobiological review is not within the scope of this publication. However, there are some important points to consider:

Hypoxia

Many authors have emphasized the importance of the relationship between tumour oxygenation and its radiosensitivity. In practical terms, the level of haemoglobin during treatment should be maintained above 10 g/dL [XI–1, XI–2]. Patients should undergo a weekly cell blood count test and the following treatment should be considered for anaemic patients:

— Iron supplement therapy for iron-deficiency anaemia;
— Packed red blood cells transfusion when Hb level is lower than 10 g/dL.

Total duration of the treatment

It is important to restrict the total duration of the treatment to less than eight weeks to avoid accelerated repopulation of the tumour. The loss of tumour control probability has been reported as 0.6–1% per day of treatment prolongation [XI–3–XI–6].

BT dose rate

When changing practice from low dose rate brachytherapy (LDR-BT) to high does rate brachytherapy (HDR-BT), the total dose needs to be decreased while the number of fractions should be increased in order to maintain local control and minimize complications [XI–7–XI–9].

Biologically effective dose calculations

Traditionally, when calculating the biologically effective dose (BED) for a fractionation schedule, a α:β ratio of 10 Gy is used for tumours, a α:β ratio of 3 Gy for the normal tissues and 1.5 h for the half-life (T½) of normal tissue repair [XI–7–XI–9]. An important yet often forgotten element in theoretical calculations of isoeffects is the reference LDR used in the model, i.e. 0.5 Gy/h for ^{226}Ra.

These are generic values for many tissues where the injury is mediated by direct damage to the late-reacting tissues.

In addition to the total dose (D), dose per fraction (d) and fraction number (n), the BED is also another critical radiobiologic parameter. It is calculated applying the linear quadratic (LQ) equation:

$$BED = D \cdot RE$$

where $D = n \cdot d$ and RE means relative effectiveness.

For external beam radiation therapy (EBRT):

$$RE = 1 + \frac{d}{\alpha/\beta}, \text{ then } BED = n \cdot d \cdot \left(1 + \frac{d}{\alpha/\beta}\right)$$

For tumours: α/β = 10 Gy
For late effects: α/β = 3 Gy

For BT:

The LQ formula for the BED of any irradiation that lasts more than about 10 min is not simple.
The well known BED formula is:

$$BED = n \cdot d \cdot \left(1 + \frac{d}{\alpha/\beta}\right),$$

but instead:

$$BED = n \cdot d \cdot \left(1 + \frac{g \cdot d}{\alpha/\beta}\right),$$

where g is the dose rate factor, being 1.0 for a very short irradiation, decreasing towards zero for duration of many days; g becomes as small as 1–3% for duration of a week.

$$g = \frac{2}{\mu \cdot t \cdot \left\{1 - \frac{1}{\mu \cdot t \cdot [1 - e^{-(\mu \cdot t)}]}\right\}},$$

where the repair constant

$$\mu = \frac{0.693}{\bar{T}^{1/2}}$$

and t is the duration of the BT fraction.

This formula allows for the simultaneous build-up and repair of radiation damage during continuous constant irradiation, assuming mono-exponential repair at a chosen T½.

The formula for g contains only the repair half-time and the duration of irradiation, always in the form of their ratio, which is the dose-rate factor with major influence (0.693/T½). Both dose per fraction and the tissue specific ratio α/β also have major influences on the resulting equivalence or non-equivalence of any schedules. All three factors have to be defined each time.

$$RE = 1 + \frac{g \cdot d}{\alpha/\beta}$$

$$g = \frac{2}{\mu \cdot t \cdot \left\{1 - \frac{1}{\mu \cdot t \cdot [1 - e^{-(\mu \cdot t)}]}\right\}},$$

$$\mu = \frac{0.693}{T^{1/2}} \quad \text{which unit is } h^{-1}$$

t = duration of a fraction in hours

For tumour: α/β = 10 Gy; T½ = 1.5 h
For late effects: α/β = 3 Gy; T½ = 1.5 h

When applying LDR-BT *g* tends to 0, while with HDR-BT *g* tends to 1.

Radiobiological normalization

To enable intercomparison of combined external beam therapy and BT with different dose rate and fractionation schedules, physical doses are normalized to doses equivalent to 2 Gy per fraction (EQD_2, previously LQED). Since 2 Gy is a commonly used dose per fraction, values of equivalent to 2 Gy dose (EQD_2) are easy to interpret by radiation oncologists:

$$EQD_2 = \frac{BED}{1 + \frac{2}{(\alpha/\beta)}}$$

It is easier to compare schedules when BEDs are expressed as equivalent doses (LQED or EQD_2). Each component of the total BED, the BED for BT and the BED for teletherapy, is divided by the relative effectiveness (RE) of a 2 Gy per fraction application and then summed. The result is a dose in Gy, as if the treatment had been delivered using 2 Gy applications:

$$EQD_2 \text{ for tumour} = \left(\frac{BED_{10} \text{ for ICBT}}{1.2}\right) + \left(\frac{BED_{10} \text{ for EBRT}}{1.2}\right)$$

$$EQD_2 \text{ for late effects} = \left(\frac{BED_3 \text{ for ICBT}}{1.67}\right) + \left(\frac{BED_3 \text{ for EBRT}}{1.67}\right)$$

Table XI–1 shows the dose recommendations for combining LDR-BT or HDR-BT with EBRT for different stages of cervical cancer. These values are not physical doses but doses normalized to 2 Gy per faction.

TABLE XI–1. DOSE RECOMMENDATIONS FOR COMBINING BT WITH EBRT

Stage	Treatment	Tumour EQD_2, Gy	Rectum EQD_2, Gy	$Bladder_A$ EQD_2, Gy	$Bladder_B$ EQD_2, Gy
IA	BT alone	75	<70	<75	90–95
Early (≤4 cm) IB1, IIA, IIB (proximal)	EBRT + BT	80–85	<70	<75	<100
Advanced (>4 cm)	EBRT + BT	85–90	70–75	75–80	<100

Note: $Bladder_A$ — ICRU bladder point [XI–10]; $Bladder_B$ — 1.5 cm superior to the ICRU bladder point as defined on the lateral radiograph.

Table XI–2 presents commonly used BT schedules (different doses per fraction and number of fractions). It should be noted that in case of image guided BT, the dose constraint of 70–75 Gy EQD_2 to the most exposed 2 cc of the rectum should be respected [XI–11].

TABLE XI–2. COMMONLY USED BRACHYTHERAPY SCHEDULES[a]

Dose rate	Number of fractions	Dose per fraction, Gy	Total tumour dose EQD_2, Gy	Total rectum dose EQD_2[b], Gy
HDR	2	9	74.5	69.4
HDR	3	8	82	74.9
HDR	4	7	85.7	77
LDR	1	35	81.3	67.9

Note: HDR — high dose rate; LDR — low dose rate.
[a] Total EBRT dose is 46 Gy in 23 fractions.
[b] Assuming 70% of the dose at point A.

Timing of HDR-BT

Intracavitary HDR-BT application can be given concomitantly with EBRT every week in early stage disease (tumour size ≤4 cm).

EBRT and BT should not be administered on the same day. When a patient is treated with chemo-radiation, cisplatinum should not be given on the day of BT.

For advanced stage disease or when the tumour size is greater than 4 cm, HDR-BT is given towards the end of EBRT or after completion of EBRT when shrinkage of the tumour occurs.

The entire treatment should be completed within 7–8 weeks. Hence, if required, it may be necessary to modify the schedule and perform two insertions per week.

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ACRONYMS AND ABBREVIATIONS

2-D	two-dimensional
3-D	three-dimensional
3-D CRT	three-dimensional conformal radiotherapy
AGCs	atypical glandular cells
AIDS	acquired immunodeficiency syndrome
AJCC	American Joint Committee on Cancer
AP	anteroposterior
ARV	antiretroviral
ASC–H	atypical squamous cells, cannot exclude HSIL
ASC–US	atypical squamous cells of undetermined significance
BED	biologically effective dose
BSO	bilateral salpingo-oophorectomy
BT	brachytherapy
CIN	cervical intraepithelial neoplasia
CT	computed tomography
CTV	clinical target volume
DNA	deoxyribonucleic acid
DVH	dose–volume histogram
EBRT	external beam radiatotherapy
EORTC	European Organization for Research and Treatment of Cancer
EU	European Union
FDA	Food and Drug Administration (United States of America)
FIGO	International Federation of Gynecology and Obstetrics
GAVI	Global Alliance for Vaccines Initiative
GOG	Gynaecological Oncology Group
GPP	good practice point
GTV	gross tumour volume
Gy	gray
HDR	high dose rate
HIV	human immunodeficiency virus
HPV	human papilloma virus
HSIL	high grade squamous intraepithelial lesion
HVL	half value layer
ICRU	International Commission on Radiation Units and Measurements
ICRU BP	ICRU bladder point
ICRU RP	ICRU rectal reference point
IMRT	intensity modulated radiotherapy
IVU	intravenous urography
LBC	liquid based cytology
LCO	Laboratory of Cellular Oncology
LDR	low dose rate
LEEP	loop electrosurgical excision procedure
LMI countries	low and middle income countries
LQ model	linear quadratic model
LSIL	low grade squamous intraepithelial lesion
LVSI	lymphatic/vascular space invasion
MDR	medium dose rate
MRI	magnetic resonance imaging
MUPIT	Martinez universal perineal interstitial template
NCI	National Cancer Institute (United States of America)
OAR	organ at risk

PA	posteroanterior
Pap test	Papanicolaou test
PET	positron emission tomography
PFS	progression free survival
PLND	pelvic lymph node dissection
PTV	planned target volume
QA	quality assurance
RTOG	Radiation Therapy Oncology Group
SAD	source–axis distance
SIL	squamous intraepithelial lesion
SNIT	Syed–Neblett device
STD	sexually transmitted disease
TAH	total abdominal hysterectomy
TNM	tumour, node, metastasis
TPS	treatment planning system
UN	United Nations
US	ultrasound
VIA	visual inspection with acetic acid
VILI	visual inspection with Lugol's iodine
WHO	World Health Organization

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