Cervix Carcinoma
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1 Introduction

Cervical cancer has a low incidence in Western Europe and North America but still a high incidence in developing countries (91). The human papilloma virus (HPV 16/18/31/33) plays an important role in the genesis of cervix cancer and is observed in 90% of all women with cervix cancer (6,68,99). In recent decades, an increase of rapidly growing tumors was noticed in young women (40).

Symptoms are dependent on the stage of disease with no symptoms in early disease and various symptoms such as vaginal discharge and bleeding in advanced disease according to the individual tumour extension (91).

The most important prognostic factors are tumour size, tumour extension, and nodal involvement (3, 21,39,41,88).

Brachytherapy plays an essential role in the treatment of all invasive cancer of the cervix. In radical treatment, brachytherapy is usually combined with external beam treatment, but it can also be combined with surgery pre- and/or postoperatively. More recently, radiotherapy has been combined with simultaneous platinum based chemotherapy in advanced cervical cancer (from IB2 to IVA) (46, 112). Brachytherapy is mainly applied as an intracavitary procedure, in selected cases complemented by interstitial implants. Radical brachytherapy for cervix cancer is always based on the use of intrauterine and intravaginal sources. However, there are several different approaches involving:

- a wide range of applicators (individually moulded applicators; different sized standard applicators with ovoids or with a ring) (chapter 7);
- different loading patterns based on different sources (iridium-192 wire; cesium-137 and iridium-192 using stepping source technology) (chapter 8);
- different dose prescribing and reporting systems related to historical traditions (mg.h, dose to point A, standard and individualised 60 Gy volume adaptation, sectional image assisted dose and volume prescription) (chapter 8);
- different dose rates used (LDR, MDR, PDR, HDR) (chapter 9)
- different schedules of dose (rate) and fractionation (chapter 9).

Fig 14.1: Historical techniques of cervical cancer brachytherapy (Paris)

A. Classical Paris method: X-ray control with radium application, three intrauterine tubes and one vaginal colpostat.
B. First moulded applicator with radium tubes at the beginning of the sixties;
C. Delouche applicator: different length and size adapted to anatomy and tumour volume
2 Anatomical Topography

The uterus is located in the central part of the pelvis between the bladder and rectum. It is divided into the corpus and cervix and is connected to the pelvis by the parametria and by the sacro-uterine ligaments to the sacrum. Only the posterior part of the cervix is covered by peritoneum (pouch of Douglas). All these structures are directly accessible per vaginam and per rectum through the pouch of Douglas.

The typical position of the uterus is anteversion and anteflexion, but it may also be straight or retroflexed. The cervix has a central orifice (the external os) with an anterior and a posterior lip, and an internal orifice (isthmus) with the endocervical canal between the two. The diameter of the cervix varies between 2 and 5 cm, with a width of 2.5 - 5 cm and a thickness of 2 - 4 cm. The length varies between 2 and 5 cm (as the length of the endocervical canal). The length of the uterine cavity varies somewhere between 4 and 10 cm.

The main regional lymph nodes are parametrial and then iliac, presacral and para-aortic; involvement of the para-aortic node is considered as distant metastasis.

The whole uterus including the cervix and the vaginal wall are densely vascularized and their tolerance to radiation is very high. In contrast, critical organs which are directly adjacent to the cervix like the rectum and bladder are more radiosensitive. In some cases, the very radiosensitive small or large bowel (sigmoid) may be in direct contact to the uterine wall as well. The vagina must also be considered as an organ at risk.

3 Pathology

Squamous cell carcinomas represent 80 - 90% of all cervical cancer. Adenocarcinoma is the second most frequent histological subtype and usually originates from the endocervix (5). It usually occurs in young women. The prognosis of cervical adenocarcinoma compared with squamous cervical carcinoma is controversial. Rare forms like mesonephroid adenocarcinoma, adenosquamous carcinoma and undifferentiated carcinoma, or glassy cell tumors are generally considered to have a worse prognosis. If there is concomitant endometrial invasion, the survival rate is significantly lower.

Different macroscopic forms are described: exophytic, ulcerative, infiltrating, which most often present in combination.

There are different patterns of local spread (FIGO staging) (33) (see Appendix).

4 Work Up

Gynecological examination remains the essential part of tumour assessment. It is carried out jointly by the gynecological surgeon and the radiation oncologist, under general anesthesia if necessary.

The pelvic examination starts with the inspection of the external genitalia, the uterine portio and the vaginal walls. If possible, the uterine cavity is probed with a semiflexible hysteroscope to measure the length of the uterine cavity. Next, bimanual abdominovaginal and abdominorectal examination is performed (right hand right pelvis, left hand left pelvis). The pelvic examination is completed by a bidigital rectovaginal examination (bimanual).
Directly after the examination the findings are recorded by the examining physician on a specific form: height, width and length of the cervix and the tumor and its extension. This documentation includes a drawing of the pathologic anatomy in the frontal, sagittal and transverse planes. An individually made imprint provides precise, reliable and reproducible information about normal anatomy and tumour topography at the portio and in the vagina (see chapter 7.5) (13).

In all cases a biopsy, or preferably punch biopsies, are systematically performed for histology. In order to assess location and the dimension of the uterus (cervix, corpus) and tumour (including tumour volume) precisely, sectional imaging is recommended.

Transabdominal, transvaginal or preferably transrectal sonography and CT scan, help to check precisely the location and the dimension of the uterus and partly the gross tumour extension (32, 113,114,117).

For orientation in the sagittal, coronal and transverse planes and for gross tumour delineation, MRI represents the method of choice (44,55,56,76,117).

Sectional imaging methods, in particular CT and MRI, may also be used for assessing the topography of bladder, rectum, sigmoid, and intestine (31,113,114). Again, there is some advantage for MRI, as the discrimination of soft tissue structures is more accurate (44). CT scan or MRI are able to detect regional and/or distant lymph node metastases; in case of suspected lymph node involvement US/CT assisted fine needle biopsies can be taken. Recognizing the general difficulties in the assessment of lymphatic spread, laparoscopic approaches are being increasingly used to obtain better information about lymph node involvement and to better tailor the radiotherapy treatment strategy (21,43).
Fig 14.2 (continued): Bilateral Stage III B cervix cancer:
B. MRI (T2 weighted) shows an extensive tumour (high signal intensity; normal uterus: low signal intensity), expanding the uterus in the side to side and in anterior - posterior direction with infiltration of the major part of the uterine body; bilateral parametrial extension right more than left; infiltration along both sacro-uterine ligaments with extension into the perirectal space. Width 8.2 cm, thickness 6.8 cm, height 9.8 cm, as measured from coronal and sagittal MRI; volume of GTV (w x t x h x 0.52) 284 cm³. Transverse CT shows a large soft tissue mass extending bilaterally into the parametria: no discrimination between uterine and tumour tissue possible (for endocavitary combined with interstitial brachytherapy of this patient compare chapter on interstitial gynaecological brachytherapy Fig 17.8).

Further diagnostic studies depend on the tumour extent: rectoscopy and cystoscopy to identify organ infiltration, intravenous pyelography to detect ureteral obstruction, chest radiography to identify lung metastases; barium enema to check large bowel disease, scintigraphy to detect bone metastases.

Laboratory studies are performed including blood count (hemoglobin level), urinanalysis, general chemistry (including creatinine) (109).

Based on all these findings - including general medical status - the different possibilities for treatment will be decided upon by the gynaecological surgeon and the radiation oncologist.

In the context of definitive radiotherapy, limited disease is usually defined as disease primarily accessible by brachytherapy, whereas extended disease means that tumour extension and tumour volume will only allow brachytherapy after tumour shrinkage by external beam therapy.
5 Indications

Indications for brachytherapy will be divided according to stage, schematically separated between limited disease and locally extensive disease.

| Brachytherapy combined or not with external beam radiotherapy and/or with surgery plays a crucial role in invasive cervical cancer treatment (stage I-IVA) as it permits the delivery of a very high radiation dose to the central pelvis, while sparing bladder, rectum and small bowel. Uterovaginal brachytherapy should therefore always be considered as a major curative or palliative treatment option. |

5.1 Limited Disease

Limited disease in invasive cancer of the cervix is stage IA/B1 and stage IIA/B (with a tumour size of less than 4cm) /, tumour extension limited to the upper third of the vagina and/or to the internal third of the parametrium and accessible by brachytherapy. There is no standard treatment and different treatment protocols may be applied: surgery alone; radiotherapeutic and surgical combinations; radiation therapy alone: brachytherapy alone, brachytherapy with additional external beam irradiation.

5.1.1 Surgery alone

Classical surgery is the transabdominal approach according to Wertheim-Meigs: en bloc tumour resection including total hysterectomy, partial colpectomy, bilateral oophorectomy, and systematic pelvic lymphadenectomy, starting usually with paraaortic lymph node assessment (10,11,20,77).

More recently, a vaginal surgical approach according to the classical technique of Schauta has been reported assisted by laparoscopic pelvic lymphadenectomy (21,43,67).

5.1.2 Radiotherapeutic and surgical combinations

Brachytherapy in the setting of these radiotherapeutic and surgical combinations aims at sterilisation of microscopic disease, at performance of surgery in tissues sterilised from tumour, at reduction of extensive surgery allowing an increase in local control with a decrease in surgical morbidity (compared to radical surgery alone).

Surgery in this setting aims to remove eventual residual macroscopic and microscopic disease in the tumour region, to increase locoregional control, to assess lymph node status by the performance of lymphadenectomy and so aid selection of indications for external beam irradiation, and to decrease morbidity from brachytherapy (compared to the combination of external irradiation and brachytherapy).

To obtain optimal results, brachytherapy and surgery must be individually adapted for each case and treatment combination (39,42).

5.1.2.1 Uterovaginal brachytherapy followed by surgery +/- postoperative external irradiation

A uterovaginal brachytherapy is performed, followed six weeks later by surgery which consists of total hysterectomy with adapted resection of the parametria, partial limited colpectomy, and bilateral oophorectomy, and pelvic lymphadenectomy. After surgery external beam irradiation with concomitant chemotherapy is given if there are positive pelvic nodes.
5.1.2.2 Surgery followed by vaginal brachytherapy

In women under 40 years with a small tumour (equal or less than 2 cm), surgery can be performed first to preserve ovarian function: after transposition of the ovaries, total hysterectomy and pelvic lymphadenectomy are performed with frozen sections. If pelvic nodes are positive, para-aortic lymphadenectomy is performed. Vaginal brachytherapy may be indicated if there is a high risk of vaginal recurrence because of close surgical margins. In case of positive margins or tumour emboli, or positive pelvic nodes, concomitant chemoradiation followed by vaginal brachytherapy is given (40,51,77).

5.1.2.3 External irradiation plus brachytherapy followed by surgery

If there is a barrel-shaped cervix, which is initially inaccessible to brachytherapy, pelvic external beam irradiation combined with concomitant chemotherapy (if tumor size exceeds 4 cm) precedes brachytherapy allowing a shrinking of the tumour volume which then can be appropriately irradiated by pre-operative brachytherapy.

5.1.3 Definitive Radiotherapy

Dependent on tumour volume, tumour extension, and the risk of lymph node involvement, brachytherapy may be used alone or in combination with external beam radiotherapy. In stage IA tumours, brachytherapy alone is indicated, if surgery is not a treatment option, since the risk of lymph node involvement is very low (<1%).

In IB1 tumours with little risk of microscopic parametrial and lymph node invasion, the dose of external beam radiotherapy is kept low (true pelvis, 30 - 40 Gy).

5.2 Locally extended disease

Locally extended disease includes stage IB2, IIA/B when the tumoral size exceeds 4cm or when the extension is beyond the upper third of the vagina and/or beyond the inner third of the parametria, stage IIIA, stage IIIB, stage IVA, and stage IVB (with paraaortic lymph node involvement). A combination of external beam radiotherapy with concomitant chemotherapy and brachytherapy (intracavitary +/- interstitial brachytherapy) is the treatment of choice. In certain specific situations surgery is performed.

5.2.1 Definitive radiotherapy with concomitant chemotherapy

The individual strategy is dependent on tumour volume, tumour extension, and the risk of lymph node involvement.

Several randomized trials with more than 3000 patients included have shown a benefit of a concomitant radiochemotherapy regimen in terms of overall survival, disease-free survival and local control as well as metastases (46,112). The absolute benefit in progression-free and overall survival was 16% and 12% respectively. The standard treatment in locally advanced tumors i.e. tumors exceeding 4cm, is external beam radiotherapy combined with concomitant Platinum based chemotherapy and according to tumour shrinkage during external beam radiotherapy, endocavitary brachytherapy +/- interstitial brachytherapy. The role of concomitant chemotherapy during brachytherapy has not been clearly demonstrated. For patients with Stage III and IVA, the real benefit of this concomitant radio-chemotherapy approach has not been clearly defined.

5.2.2 Combination of surgery with postoperative radiotherapy

In extended disease, surgery first is rarely indicated. If it has been done, the following recommendations are given:
* Postoperative brachytherapy alone in case of high risk of vaginal recurrence alone (rare), e.g. with close margins at the vaginal vault.

* Postoperative brachytherapy with external beam therapy if there is a high risk of vaginal and/or pelvic recurrence, which represents the most frequent case in this situation. There has been a randomized trial which also showed a benefit of a concomitant radiochemotherapy regimen in this postoperative situation (46).

6 Target Volume

The GTV includes the primary tumor volume and its extent is based on clinical examination and sectional imaging. The overall CTV for treatment always remains the same, but the dose to the respective target depends on the treatment strategy chosen, in particular if radical radiotherapy alone is used or a combination of radiotherapy and surgery. So, the CTV for brachytherapy depends on the treatment strategy.

In the intact cervix in stage I A and IB1, the CTV for brachytherapy is at least the entire cervix for any stage and treatment protocol. In addition, usually some part of the corpus uteri (at least half), the upper part of the vagina (one third/fourth) and the medial part of the parametria (one third) are included, depending on the individual tumour extent. Without precisely assessing the GTV and defining the PTV, standard protocols are usually applied (based on the historical experience of a "school") related to a certain amount of radiation (mg.h, (35,36) TRAK) or related to a certain dose to a fixed point (e.g. point A, (59,61,62)).

If individual assessment of the GTV and thus definition of the CTV is performed, individual and precise volume adaptation of the treatment protocol becomes possible.

The target volume is identified and selected by the clinician based on clinical examination and sectional imaging. The treated volume is based on dose calculation for the selected application technique with a selected loading pattern which includes standardised or individualised treatment planning (with radiographs and/or sectional images (CT/MRI) (9,32,44)).

The treated volume should always include the CTV. The treated volume becomes comparable by relating it to a fixed dose, e.g. to 60 Gy, which is then called the 60 Gy reference volume (ICRU 38). These volumes may be quite small in preoperative intracavitary brachytherapy, as surgery contributes to local control (mean 129 cm$^3$ in the IGR series (39)); they must be sufficient to cover any microscopic spread in early disease treated by intracavitary brachytherapy alone (123-185 cm$^3$ in a recent Manchester series (60)); they are more extensive when combining intracavitary brachytherapy and external beam therapy as definitive treatment for advanced limited and for extended disease (250 - 450 cm$^3$ in the IGR (52), "group des neuf"/Dijon (4,53), and Vienna series (96)); they are small in postoperative vaginal brachytherapy +/- external beam therapy.

In conclusion, the PTV depends on treatment strategy: pre-operative brachytherapy, combination of external beam radiotherapy and brachytherapy, post-operative brachytherapy.

6.1 Preoperative Brachytherapy: radio-surgical approach

The PTV includes at least the whole cervix plus safety margins through the site where the surgeon will operate: in the parametrium between the internal and middle third; in the vagina between the upper and middle third. The PTV includes the two lower thirds of the uterus. If there is bulky endocervical growth, the PTV is enlarged at this level to achieve a higher dose in the endocervix.

In the determination of this preoperative CTV/PTV the doses and irradiated volumes of critical organs must be taken into consideration.
Fig 14.3: Stage IIB Cervix Cancer 41x 61 mm (pretreatment MRI (A)) and 4 cm by clinical examination (Combined radiosurgical approach, IGR). GTV after EBT (45 Gy) plus cis-Platinum was only 2.5 cm, as assessed by clinical examination (B). CTV was 69 cm³. Intracavitary brachytherapy dose was 15 Gy and the overall treated volume (60 Gy) was 242 cm³. In the pathologic specimen from colpohysterectomy, performed 6 weeks later, no tumour cells were found.

6.2 Definitive Radiotherapy: combination of external beam radiotherapy and brachytherapy

The PTV of brachytherapy in principle must encompass the extent of primary tumour plus safety margins. The treated volume is limited by the maximal tolerance of critical organs. Thus, in extended disease, the whole primary tumour extent at diagnosis may not be completely covered by the treated volume but most of it at least.

In definitive radiotherapy the target is usually related to the GTV at diagnosis and/or at the time of brachytherapy. If a precise assessment of target and treated volume is aimed at, the GTV at the time of brachytherapy must be used. Target definition may vary depending on gross tumour volume, topography and the treatment strategy chosen.

* For stage IA, IB1, the target is the entire cervix with a safety margin into the corpus (half of the corpus), upper third of the vagina and internal third of the parametria.
* For stage IB2, brachytherapy is preceded by external beam therapy, which leads to significant tumour shrinkage.
* For tumours extending into the proximal part of the parametria (proximal stage IIb) the parametria are to be included in the CTV as far as possible taking into account the dose to critical organs.
* For tumours extending into the vagina (stage IIA/IIIA), the respective part of the vagina e.g. the upper half or the whole vagina, including safety margins of about 2 - 3 cm, has to be included in the CTV for brachytherapy, depending on the individual pattern of spread.
* For tumours extending far into the parametria (distal IIB/IIIB), there is no clear agreement on the determination of the CTV for brachytherapy. Endocavitary brachytherapy alone can only cover the tumour extension which is directly adjacent to the cervix. As brachytherapy usually follows external beam therapy – because of tumour extension not accessible to brachytherapy at the start of treatment -, the GTV at the time of brachytherapy after tumour shrinkage may be used to define the CTV in these cases, taking into consideration the extension of the GTV at diagnosis. As much as
Fig 14.4: GTV at diagnosis in definitive radiotherapy of limited disease (stage IIB with proximal parametrial extension): Drawing (1) and MRI study (2) (T2-weighted). The tumour extends into the left parametrium in the dorsal direction. Dimensions of the GTV (white arrows) are 4 cm in width and 4 cm in thickness. By MRI the height is 3.5 cm. The volume as calculated by $w \times t \times h \times 0.52$ (ellipsoid formula) is $29 \text{ cm}^3$, which corresponds to the volume measured by volumetry (76). The dorsolateral extension into the left parametrium is maximal 3 cm from the uterine canal (compare Fig 14.14A for endocavitary brachytherapy of this patient).
Fig 14.5: GTV at diagnosis (A,B) and after 45 Gy EBT at the time of brachytherapy (C) in extended disease (stage IIBd with distal parametrial extension): Drawing (A) based on clinical examination; MRI study (B,C) (T2-weighted). The tumour (white arrows) expands the uterine cervix, infiltrates the left parametrium (open white arrows) and the uterine body (white arrows). Dimensions of the GTV at diagnosis and after EBT are 5/4 cm width, 4/3 cm thickness, and 5.5/5 cm height, respectively. The corresponding volume was 57 cm³ at diagnosis and 31 cm³ at the time of brachytherapy. With regard to the intrauterine canal, the extension is 3 cm into the left lateral parametrium and 2 cm into the left posterior direction (compare Fig 14.14B).

Possible of the GTV at diagnosis should be included into the treated volume considering the tolerance of normal tissue. With distal parametrial tumour extension which cannot be included in the treated volume, endocavitary brachytherapy must be combined with a boost given by external beam therapy and/or interstitial brachytherapy.
6.3 Postoperative Brachytherapy

If there is no residual disease, the CTV is the vaginal cuff with 5 mm depth into the vaginal wall; if there is residual disease the CTV encompasses residual macroscopic and/or microscopic disease plus a safety margin of 2 - 3 centimeters.

7 Techniques

This chapter and the following describe intracavitary preoperative brachytherapy and definitive brachytherapy in the intact cervix. Interstitial parametrial brachytherapy and postoperative vaginal brachytherapy are described in detail elsewhere (chapter on interstitial gynaecologic brachytherapy, (17) and endometrial cancer (15)).

7.1 General introduction

7.1.1 Intracavitary techniques based on modern afterloading devices

All classical techniques used radium-226 which was introduced with the applicator. All modern techniques developed in the 1950’s and 1960’s are based on afterloading devices ($^{60}$Co, $^{137}$Cs, $^{192}$Ir), where the application and the irradiation are separated from each other. All these devices use intruterine and intravaginal sources. However, several different approaches have been developed over past decades with a significant range of applicators: mainly different sized standard applicators with ovoids or with a ring and individualised moulded applicators. Many of these applicator systems (rigid, fixed or semifixed, metallic or plastic) - except the individualised moulded applicators - are nowadays commercially available for LDR/MDR/HDR/PDR brachytherapy, usually in combination with afterloading devices. These applicators imitate in principle the basic classical and modern application techniques as described below: Paris (intrauterine catheter plus corks/ovoids), Manchester (intrauterine catheter plus ovoids), Stockholm (intrauterine catheter plus plate).

The 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”, “Fletcher-style” etc.). They are applicable for the different radioactive sources nowadays in use, which are most frequently Cesium-137 and Iridium-192. The individualised moulded applicators represent the most individualized approach, but it is also possible to use adaptations of standard rigid applicators to fit in most clinical situations: different lengths, angles and curvatures of the intrauterine catheter; different shapes and sizes of ovoids or rings; rectal shielding in the ovoids; rectal retractors; fixed or non fixed geometry. The majority of them are used with individualised vaginal packing.

For different forms of treatment planning, CT- and/or MRI compatible applicators are available (based on the ovoid or ring type). There are few publications about the advantages and disadvantages of the different applicators. To assess the different application techniques, multiple variables have to be taken into consideration: above all, the potential of adjusting to different anatomical and pathological situations; size and form of the vaginal sources with or without integrated shielding; spacing between the vaginal sources; length, curvature, and angle of the intrauterine catheters; fixed or nonfixed geometry between ovoids/ring and intrauterine catheter; variability of loading (ring/ovoids and intrauterine catheter); capability for sparing rectum and bladder; potential for treating extended vaginal and parametrial tumour extension.
Usually, out of the large variety of applicators available, a particular applicator set - including variations of the vaginal and intrauterine source carriers - is selected for use in each institution allowing for some individualization of treatment based on anatomy and pathology.

7.1.2 General description of an uterovaginal implant

The application is performed under spinal or general anesthesia. The patient is positioned in the dorsal lithotomy position. The radiation oncologist starts with a thorough gynaecologic examination, assessing the present tumour situation, the topography of the uterus, and the organs at risk. This is repeated if there is more than one fraction of brachytherapy.

A bladder catheter is inserted for calculation of the dose to the bladder neck and to report it according to the ICRU definition of the bladder point (63). The balloon of the bladder catheter is inflated with radiopaque solution (7 cm³) and is pulled towards the base of the bladder until it is placed at the bladder neck.

Vaginal specula (um) are (is) introduced and a cervical forceps is put on the front and/or the posterior lip of the cervix, whenever possible. A semi-flexible hysterometer is inserted into the cervical os to measure precisely the length of the uterine cavity and to document its curvature. If the tumor has destroyed the cervical os, careful attention is needed to try to identify it. If this is impossible, the position of the instrument in relation to the cervical os may be checked by transabdominal ultrasound or endosonography.

Perforation must be avoided whenever possible. The most common occasion for perforation is a significant tumour mass destroying the portio (no cervical os), the most common site is the posterior part of the cervix/tumour in the anteflected and anteverted uterus. In any case perforation must be detected, as this is crucial to decide whether to proceed or interrupt treatment and about additional measures (e.g. antibiotics). The suggestion is often clinical but not always, as there are significant numbers of clinically undetected perforations (62). The best way to prove perforation is by sectional imaging with the applicator in place (US, CT, MRI).

After the determination of the intrauterine dimensions with the intrauterine probe, a dilatation is performed up to the width necessary for the application (e.g. Hegar 6). If the diameter of the intrauterine device is small (e.g. 3 mm), there is no need for significant dilatation. After this procedure a final decision on the type of applicator is made depending on tumour diameter and topography as well as physics related considerations: length and curvature of the intrauterine catheter; type of vaginal source carriers (ovoids, ring). When using the mould technique this decision is taken at the time the mould is made on the basis of the vaginal impression. Metallic markers are inserted, if possible inside the two cervical lips to identify the cervix later on the radiographs in relation to the applicator.

The intrauterine catheter is inserted through the cervical os into the uterine cavity. A flange on the intrauterine catheter may be used to indicate the length of the uterine cavity which is pushed against the cervix and prevents perforation at the uterine fundus. The vaginal applicator(s) is/are then introduced gently (ovoids, ring, mould...). The ring is pressed against the cervix. The ovoids are pushed into the fornices. The axis of the vaginal part of the applicator is usually perpendicular to the axis of the intrauterine part. If the anatomy is very narrow, an intrauterine catheter may be used alone extending into the vagina, usually in combination with a vaginal cylinder. Depending on the applicator used, the vaginal part may be fixed to the intrauterine catheter. In the ovoid and ring technique, the whole applicator is usually pressed by packing against the fornices/cervix. Depending on the applicator, the packing (and/or e.g. a plastic rectal retractor) is individually introduced to allow for more distance between the posterior and anterior part of the applicator and the rectum and bladder, respectively. For the mould applicator, which is adapted to the tumour topography and
anatomy of the patient, packing and shielding are not necessary: after a time period of 24 hours the mould does not move significantly during brachytherapy, and it pushes away the bladder and rectum significantly.

At the end of the application a flexible tube with radiopaque markers may be inserted into the rectum and positioned near the anterior rectal wall in order to calculate the dose at specific points inside the rectum. Such a tube may also be used for introducing some contrast medium into the rectum. This is in addition to the ICRU rectum reference point at the anterior rectum wall which needs to be calculated and reported.

Two radiographs (anterior-posterior and lateral) are taken with a reference box (isocentric reference frame) after the position is changed from lithotomy to supine with the thighs together (position of brachytherapy) directly after the end of the application (HDR) or later (LDR/PDR/MDR brachytherapy). The position of the applicator (including the packing if used), the bladder balloon, and the rectal probe are checked. The radiographs for treatment planning may be taken later to allow some adaptation of the applicator to the individual patient situation, which usually takes about 24 hours. After this time period, a constant position of the applicator can be assumed.

7.2 “Manchester” based techniques (59,61,62,116).

The classical Manchester technique was based on using one intrauterine tube with a choice of two standard lengths (4 cm and 6 cm) and one non standard length (3.5 cm) (each tube has a rubber flange at its cervical end to hold the tube in the correct position) and two vaginal ovoids ellipsoid in shape, two small (2 cm), two medium (2.5 cm), or large (3 cm) in diameter held apart in the vagina by a washer or a spacer (Fig 6.22). The geometry in vivo was not fixed though in a perfect insertion the ovoid sources are at right angles to the uterine tube.

![Modern Manchester applicator set (A)](https://example.com/figure14.6a)

The different angles and lengths of the intrauterine tubes are demonstrated as well as the shape and size of the different ovoids (B,C). There is a clamp to fix the position of the ovoids and the intrauterine tube to each other (Nucletron ®).
The modern Manchester applicators physically mimic the classical technique. The intrauterine tubes have the same fixed lengths and fixed cervical flange and are angled at 40 degrees to the line on the vaginal component of the tube. The vaginal ovoids have kept their ellipsoid shape (large, medium, small, half) with the small ovoids extended posteriorly by 5 mm to build packing into them. These three afterloading tubes are held together and their relative positions fixed by a clamp ensuring an ideal physical arrangement. The whole system is held in place in the individual patient by vaginal gauze packing. When the vagina is too narrow for this arrangement a vaginal cylinder is fitted to the vaginal part of the uterine tube (61).

Nowadays uterine tubes with different lengths graduated in centimetres are commercially available allowing for adaptation according to the individual anatomy (with a fixed uterine flange) and angled at varying degrees to the line of the vaginal component (0°,15°,30°,45°) (Fig 14.6).

7.3 "Fletcher" based techniques (22,35,54).

![Fig 14.7: Fletcher based Technique](image)

Fig 14.7A-C: Classical Fletcher applicator set (A) which is available for a Cesium source and – with a smaller tube diameter - for an Iridium source. The different angles and the different lengths of the intrauterine tubes are demonstrated as well as the shape and size of the different colpostats (diameter 20,25,30 mm) (B, C). Shielding is integrated into the anterior and posterior part of each colpostat. There is a clamp to fix the position of the ovoids and the intrauterine tube to each other (Nucletron ®).

D: CT/MRI compatible Fletcher-like applicator set for Iridium, which is also available for Cesium. The colpostat dimensions are identical to the metallic version. The outer diameters are slightly larger. No shielding is integrated. The whole system is fixed with a screw (Nucletron ®).
In the early 1950s, Fletcher developed a system for radium that combined a rigid metallic intrauterine tandem with cylindrical colpostats; the latter are positioned against the cervix, perpendicular to the axis of the vagina (35). Subsequently, this system was modified by Delclos and Suit for manual afterloading and then for remote afterloading (Fletcher-Suit-Delclos applicator (22)). Later, a European version was proposed by Horiot (54) to be adapted to the use of cesium sources and different afterloading machines.

The intrauterine tandem is available in a variety of curvatures. The length can be adjusted by positioning an adjustable flange. The cylindrical colpostats are 2 cm in diameter but can be enlarged by the addition of caps to 2.5 or 3.0 cm diameter (Fig 14.7). Tungsten shielding is integrated into the anterior and posterior part of the standard colpostats to reduce the dose to bladder and rectum. The tandem and colpostats are selected to conform to the tumor volume and topography and the individual patient’s anatomy. The position of the applicator is maintained by vaginal packing which is also used to reduce the dose to the bladder and rectum.

Because the Fletcher-Suit-Delclos applicator allows independent positioning of the uterine tandem and ovoids, source positions can be readily adapted to different anatomical and pathological situations (4,35,54).

7.4 “Stockholm” based techniques (8,115)

The classical “Stockholm method” was based on a flexible intrauterine tube and a flat box (plate) in the vagina pushed by an individual packing device against the cervix. The tube and the box were implanted independently of each other. Therefore no fixed geometry was present.

The rigid uterine tandem with a ring applicator was developed during the 1960ies as an afterloading device (115), first for Cesium-137 sources, and then also for Iridium-192.

Fig 14.8: Stockholm based Technique

Fig 14.8A: Classical metallic ring applicator set (A) which is available for an Iridium and a Cesium source. The different lengths and angles of the intrauterine tube are demonstrated (B). The ring is available in different diameters (26, 30, 34 mm diameter source-source position) and the intrauterine tube in different lengths (20, 40, 60, 80 mm) (B). Acrylic caps cover the ring tube to reduce the dose to the vaginal mucosa. The ring and the intrauterine tube are fixed to each other with a screw. A rectal retractor is also shown which can be additionally used (Nucletron ®).
C: CT/MRI compatible carbon ring applicator set for Iridium, which is also available for Cesium. The ring and tube dimensions are comparable to the metallic version. The outer diameters are slightly larger. Therefore no cap is necessary. The whole system is fixed with a screw (Nucletron ®).

The length and the curvature of the intrauterine tandem is chosen dependent on the size and the bending of the uterine cavity. The diameter of the ring which is perpendicular to the axis of the intrauterine tube is also chosen according to the individual anatomical situation. The ring is covered by a cap for reduction of the dose to the vaginal mucosa. The ring is fixed to the intrauterine tandem. The angle between the ring and the tandem is always 90 degrees. The angle between the ring and the axis of the vagina is selected according to the angle between the axis of the vagina and the uterus. The applicator is fixed against the cervix by an individual packing device (8).

7.5 **Institut Gustave- Roussy technique** (37,38)

The classical “Paris method” was based on two “corks” (ovoids) situated in each lateral fornix perpendicular to the intrauterine tube connected by a transverse metal spring and, independent of this, a hollow gum elastic tube in the uterine cavity (see Fig 6.21 in chapter on reporting). Later, a vaginal cork was sometimes added to ensure a more uniform dose distribution in the cervix.

The Manchester and Fletcher based techniques (see above) are in regard to their application techniques related to the original “Paris method”.

The other techniques developed in Paris (Créteil (95)), Saint-Cloud (23)) have much further advanced and individualised the application techniques by introducing the mould technique systematically.

This method developed at the IGR has four basic aims: personalized tailored irradiation, perfect knowledge of dose distribution, total radioprotection, and good tolerance by the patient. To realise these four aims, four means are used: mould applicator (specific for this technique), miniaturized radioactive sources, computerized dosimetry, remote afterloading machine:

*moulded applicator (moulage)*

In order to construct this personalized applicator perfectly adapted to each case (anatomy, tumour volume, vaginal extensions…) four steps are necessary:

Taking a cervico-vaginal impression: lithotomy position, introduction of speculum; placement of strips of gauze into each lateral fornix; injection inside the vagina of liquid paste which is, extracted from
the vagina after it has solidified by the help of the strips of gauze. There is no need for any kind of anaesthesia. This cervico-vaginal impression allows the visualisation of tumour topography to later guide the positioning of the catheter for the radioactive sources.

Acrylic mould fabrication: submersion of the cervico-vaginal impression into liquid plaster; splitting the dry plaster into two parts; varnishing the internal surface of the two halves; spreading the surface with liquid, synthetic, autopolymerized resin distributed in a thin layer; removal of the rough hollow applicator after drying.

Fig 14.9: IGR Technique: Individual mould applicator

A: Cervico-vaginal impression showing clearly the exocervical tumour volume with an extension to the right lateral vaginal wall (stage IIA).

B: Introduction into liquid plaster.

C: The definitive applicator  D: Applicator insertion
E: Placement of the dummy sources.

F, G: AP and lateral radiographs with the mould delineated and certain reference points for dose calculation: A: cervix; B: Bladder ICRU point; C: Rectal points (in the rectal probe); D: Pelvic wall points.

Drawing and positioning of the vaginal catheters: taking into account the anatomy of the patient, the tumour topography and the target volume, the position of the two vaginal catheters is drawn. The two catheters must be parallel to the anterior superior surface of the mould (parallel to the surface of the cervix), lateralised to the left and right part of the cervical lip, parallel to each other, and separated by a distance equal to the mean length of the two vaginal sources. The depth of the vaginal catheters in the mould is decided according to the projected source length, from 3 up to 6 mm in a short and long source, respectively. The lengths of the vaginal catheters and their space are determined according to the dimensions of the tumour. This length can be modified and adapted for the loading with the radioactive source dependent on the situation shown on the radiograph.

The two vaginal catheters are introduced and fixed on the internal surface of the moulded applicator.

Final preparation of the mould applicator: Different modifications of the mould are necessary: one hole for the cervical os, an indication for the external meatus of the urethra, and several perforations to fix the mould to the vaginal wall and to allow circulation of the liquid antiseptics for daily vaginal irrigation with liquid antiseptics, which is done through a tube inserted into the mould. These perforations eliminate the risk of displacement of the device, the vaginal mucosa herniates through each perforation.

No vaginal packing is necessary, as the packing is integrated into this moulded applicator, keeping the catheters in place at the same position and keeping the same topography throughout the whole period of brachytherapy (104).

With this system the patient can move out of the bed without risk of displacement of the material and the complications of prolonged bed rest such as thrombosis can be prevented and better tolerance is obtained.
8 **Dose Calculation and Treatment Planning**

8.1 **General introduction**

Because of the very high dose gradient around the sources used in brachytherapy (about 10% per mm), there were many difficulties in past decades in expressing the dose in intracavitary brachytherapy. Historically, the classical methods of Paris and Stockholm used mg.h to prescribe the dose in a radium implant. With the Manchester system fixed distances related to anatomy and applicator, respectively were used: reference points: A and B. Later on, considering that these different parameters were insufficient to express the dose, the volume concept was developed.

Around the world different schools, according to their own experience, tried to express the dose in intracavitary brachytherapy to adapt the dose distribution to the different clinical situations and to be able to compare their experience with each other.

The first basis of a “common language” was established at the end of the seventies by the GEC (15). Based on this, some years later recommendations on dose and volume specification for reporting intracavitary therapy in gynecology were published by the ICRU (63).

Dose calculation and treatment planning in intracavitary brachytherapy is performed according to different levels. However, independent of the level of dosimetry which is applied, the aim is to achieve the optimal therapeutic effect possible: from mg.h to TRAK; from standard dose distributions (atlas/computer library) and standard dose specification at points to individualisation; from dose adaptation at points to adaptation in volumes; from 2 D to 3 D dose calculation; from radiography based treatment planning to sectional imaging based 3D treatment planning with individual assessment of target volume and critical organs.

All over the world, a large amount of intracavitary gynaecological brachytherapy is performed based on standard application techniques and standard dosimetry programs. Standard dosimetry for a given standard geometry includes a defined loading pattern of the vaginal and the intrauterine sources and their relation to each other. This is usually derived from a classical method with a long tradition of defined loading patterns for radium. This loading pattern leads to a pear-shaped distribution when viewed from anterioposterior and a banana-shaped distribution when viewed laterally (Fig 14.10 - 14).

The aim of this differential loading has always been to achieve a significant dose in the pear/banana-shaped target, whereas the critical organs nearby (anterior/posterior) have to be spared as much as possible.

Therefore, the minimum requirements for dose calculation - independent of the method applied - are the calculation of the dose at one reference point (e.g. at point A, see Fig 14.16) or for more than one reference point (Fig 14.15C,D) and for certain points at critical organs like the ICRU rectum and bladder point (Fig 14.15B). In addition, the height, width and thickness of the brachytherapy volume is indicated which is characterised by the isodose going through point A (Fig 14.16) and related to the dimensions of the GTV and PTV, respectively (height, width and thickness). The lateral dimensions of the pear-shaped dose distribution can be adapted to the lateral dimensions of the GTV and the PTV, respectively. In order to meet these minimum requirements for dosimetry a treatment planning approach based on projection images (radiographs) is necessary, correlating the radiography based data from the applicator and from reference points to isodose distributions for the given geometry of sources. For this approach, there are precalculated isodose distributions available either in a hard copy atlas or in a “library” of a computerized treatment planning system, which are usually based on the experience of one of the traditional schools.
As a basic standard for treatment planning nowadays, two projection images (radiographs) are taken at the end of the application with a reference frame which allows individual dose calculations for different reference points in a three dimensional radiography based approach with an appropriate computer assisted treatment planning system (81). This approach allows a more detailed assessment of dose distribution based on reference points for the rectum, the bladder and also at points further away (e.g. at the recommended ICRU reference points) (compare Fig 14.11-13). Estimate of GTV and PTV from clinical examination, radiographs and sectional images can also be correlated with dose distribution. Specific care must be taken to visualise the critical organs on radiographs with radiopaque markers or devices, including the posterior vaginal wall. Reference points are accurately drawn onto the radiographs in order to specify the dose at certain points in relation to the sources, (to the GTV and to the PTV if possible) and to patient anatomy, including critical organs. The points well recognized so far are those recommended by the ICRU for critical organs (see chapter below) and Manchester point A and B. By digital transfer, the reference points considered and the sources are entered into the computerized treatment planning system.

If a standard applicator with a standard geometry of sources has been used, a standard program with a specific loading pattern is available which has been generated for the “library” of the computer. The dose and volume adaptation is based on or starts from such standard program. Often, point A is a reference point already available in these standard programs. If an applicator is used without a fixed geometry, the dose distribution has to be calculated for the individual applicator geometry by entering specific dose points along the applicator into the Treatment Planning System and can then be adapted.

Dose to critical organs must be limited in accordance with clinical experience: e.g. less than a certain percentage of the dose in point A to the ICRU rectum reference point (or to the in vivo measurements in the rectum in the Manchester experience (59,61)) and less than a certain percentage to the ICRU bladder reference point. These limitations can also be expressed as absolute dose values, e.g. 65 - 80 Gy in extensive disease at a given reference point. As the position of the rectum in relation to the applicator and to the GTV is radiographically known, modification of the dose volume relationships is often possible by adapting the respective source configuration. This can be extended to more than one point for a given critical organ to arrive at a more representative estimate of the dose. For fractionated brachytherapy, such limitations apply for each brachytherapy fraction. However, the total overall dose for the critical organ must be taken into account, depending on the treatment schedule applied, including external beam therapy if given. If different dose rates are used as in LDR/MDR brachytherapy or different large doses per fraction as inHDR brachytherapy a weighting factor for the biological effect is needed to check that tolerance limits are not exceeded.

The treated volume, which represents the volume encompassed by the prescribed dose, is adapted as closely as possible to the PTV, which in principle is not possible exactly in radiography based dosimetry. Therefore, for large tumours, this isodose is extended as far as possible (e.g. beyond point A) in order to cover as much of the PTV as possible. In small tumours and in a small cervix, this isodose may be reduced and may be even placed within the isodose going through point A. Nevertheless, the entire cervix with some safety margin is included in every case. This dose volume adaptation is usually only in the range of a few millimeters, but is quickly significant in terms of doses (about 10% change per mm) and volumes (3D effect) (Fig 14.16). Such treated volumes may vary by a factor of 2-3, e.g. going from 50 to 150 cm³ for a prescribed dose of 85 Gy or from 150 to 450 cm³ for the 60 Gy reference volume. For the dimensions and volume of the treated volume (prescribed isodose) a correlation is made with the respective dimensions of the tumour and the target: e.g. a macroscopic tumour with 4 cm width, 3 cm thickness, and 4 cm height (25 cm³) is being treated with a certain dose (e.g. 85 Gy) with a pear-shaped volume measuring 6 cm in width, 4.5 cm in thickness and 6 cm in length (~80 cm³). Even at a basic level as many as possible of the suggested parameters should be calculated, as they are crucial to achieve the therapeutic goal.
These are in particular the height, width and thickness of the target and the respective dimensions of the pear-shaped dose distribution of the treated volume. As a minimum (if the height is not accessible), the maximum width and thickness of the target and the maximum width and thickness of the pear-shaped dose distribution must be calculated, as well as at the level of point A (width and thickness). The treated volume may be different from or identical to the reference volume which is introduced for treatment comparison (see 14.16 and chapter 6.8 on ICRU recommendations).

For recording and reporting, the dimensions and the volume should be given for the treated volume (ICRU 38), for the 60 Gy reference volume (ICRU 38), and also for the isodose going through point A (width and thickness also at the level of point A); the dose rate should be given at point A and for the 60 Gy encompassing isodose (see in detail chapter 6.8 on reporting). If other dose rates than classical LDR are used (50 cGy/hour), an isoeffective dose can be indicated e.g. for the “point A dose” and for the “point A volume” and for the “60 Gy reference volume” based on weighting factors from biological modelling of clinical experience (see chapter 6.8 on reporting and chapter 4 on radiobiology).

Recently, a full 3D treatment planning approach has been introduced based on CT and MRI, respectively (9,32,44,113,114). After the sectional images have been directly entered into the treatment planning computer via a network, a delineation of GTV/PTV and critical organs is performed and dose volume relations are assessed.

Dose distributions are displayed as DVH for the GTV/PTV and for organs at risk. Dose adaptation is then additionally based on these parameters, not only looking at dose points (radiography), but also at dose volume relations, for the rectum and bladder (CT and MRI) and for the GTV and PTV (MRI). Limitations are being set up for dose volume relations for the rectum, where a certain dose is limited to a certain rectal tissue volume e.g. of 2 cm³/5 cm³.

For the PTV at the time of brachytherapy (as seen on MRI with the applicator in place) the prescribed dose can be precisely adapted so that the PTV is enclosed by the prescribed isodose (as much as possible). If this is not possible to a sufficient degree (e.g. because of extensive lateral parametrial or posterior pararectal extension) additional interstitial brachytherapy or an external radiotherapy boost may be considered.

8.2 Modern Manchester method: Standard dose rate to point A in standard implants (small, medium, large) (59, 61,62,116).

Various defined standard programs are available for the different possible arrangements of applicators allowing for a standard dose rate to point A – the cardinal feature of the Manchester system. The loading patterns for the Cesium pellets (maximum strength 40 mCi) mimic the loading patterns of the classical radium Manchester system: 20 mg, 15+10 mg, 15+10+10 mg radium-equivalent content in short, medium and long intrauterine tubes, respectively; 22.5 mg, 20 mg, 17.5 mg for large, medium and small ovoids, respectively, on each side.

This was achieved by using linear patterns of active and inactive pellets each 2.5 mm diameter in the Selectron system, and replacing 5 mg of Radium with one active pellet. The dose rate at point A is kept constant no matter which applicator is used but has been changed from 53 cGy per hour in the classical system to 140 to 180 cGy per hour to point A in the modern system depending on the decay of the sources.
Fig 14.10 A1,2: Standard dose distributions showing 100%, 50% and 200% isodose lines with a standard Manchester applicator for ovoids with 20 mm (A1) and 30 mm (A2) in diameter. The position of the active pellets is indicated. Transverse planes are given at the plane of the ovoids (at 10 mm from the top of the ovoids) and at point A. The dimensions of the volume of the isodose going through point A are shown. The reference volume of the isodose going through point A is 267/312 cm$^3$ (HWT) for small and large ovoids, respectively, which corresponds roughly (divided by 2) to a computer calculated volume of 133/156 cm$^3$ (modified from isodose curves as provided by Wilkinson (116), with permission).

In brachytherapy alone this isodose corresponds to a physical total dose of 65 Gy which is isoeffective to 75 Gy in classical dose rate (59,61,62). For combined treatment in advanced disease this nowadays corresponds to a physical dose of 40 Gy EBT and 32.5 Gy (isoeffective to 37.5 with 50 cGy/hour (57, 62)), which is a total isoeffective dose of 77.5 Gy.

To aid understanding, the dimensions of the 60 Gy volume (60 Gy – 40 Gy EBT = 20 Gy) are also given, although these have never been used in the Manchester method. This becomes possible, as the 50% isodose which is indicated corresponds an isoeffective dose of ~ 19 Gy (37.5/2). The HWT volume for the small ovoids is then 11.6 cm in height x 8.7 cm in width x 7.2 cm in thickness, - 727 cm$^3$, which corresponds roughly (divided by 2) to a computer calculated volume of 363 cm$^3$. The HWT volume for the large ovoids is then 12.4 cm in height x 10.1 cm in width x 7.4 cm in thickness, which is 927 cm$^3$. This corresponds roughly (divided by 2) to a computer calculated volume of 463 cm$^3$. 
A correction factor for the reduction of total dose was introduced (see below). An adaptation of the standard dose distribution is performed, if the maximum dose measured by a rectal probe (5 points) is greater than two thirds of the dose to point A. The AP “pear” and lateral “banana” shaped volume defined by the isodose going through point A (reference dose) is dependent on the length of the intrauterine tube and the size of the ovoids employed. In practice this varies between 101 and 155 cm³. The corresponding 60 Gy isodose volumes for the definitive treatment of small volume disease by brachytherapy alone vary between 120 and 185 cm³ (60).

There is no adaptation of the standard source arrangements to the individual tumour volume and the only differences between the treatments is dictated by the external beam dose and its distribution.
8.3 Classical and modified Fletcher method

8.3.1 Standard loading patterns (mg.h) in standard implants (small, medium, large) (Classical Fletcher method) (22,35).

Standard loadings limit the linear intensity of radium or cesium in the intrauterine tandem and the dose rate at the lateral surface of the vagina. The amount of radiation is expressed as a product of activity and treatment time in mg.h (radium-equivalent) and is limited by anatomical considerations and by the volume of disease and selected treatment schedule. Variations in the loadings selected for the tandem and the colpostats are also based on anatomical and pathological considerations.

X-rays are taken in the operating room to verify the position of the applicator is appropriate and orthogonal films are used to calculate the dose to various pelvic points and structures. Doses are calculated to points representing the paracervical areas, regional nodes ("Fletcher trapezoid"), vaginal mucosa, bladder, rectum, and other structures.

With this system, the length of the intrauterine tandem (determined by the length of the uterine canal), the size of the vaginal ovoids (determined by the capacity of the vaginal vault), and the position of the system in the pelvis significantly influence the dose distribution. To maximize the depth dose (to the endocervix and parametrial tissues), the whole length of the intrauterine canal is usually loaded and the largest colpostats that can be used without inferior displacement of the applicator are fitted in the vagina. The classical loading pattern for a 6.5-7.5 cm intrauterine canal is 15 + 10 + 10 mg radium-equivalent for small residual disease and 15 + 15 + 10 mg for bulkier endocervical lesions; small (2 cm diameter) ovoids are usually loaded with 10-15 mg while medium ovoids are loaded with 15 - 20 mg and large ovoids with 20 - 25 mg. If there is irregular anatomy (narrow vault, short uterine canal), the loadings are adapted. The loading pattern also may be adapted to the individual pathology (e.g., lesions involving mainly one cervical lip, invasion of one fornix, parametrial shortening, growth along the vaginal wall, or massive central disease expanding the cervix and/or isthmus).

Dose distributions are given for a plane perpendicular to the sources (paracoronal) passing through the center of the colpostats and the proximal and distal intrauterine source.

If the dose at the rectum is related to a reference dose in point A, which is regarded as inadequate for this system, the rectal dose is usually below the reference dose due to the typical colpostat position (perpendicular to the vaginal axis) and to the shielding inside the colpostats (posterior and anterior). Although this system does not depend upon an evaluation of the dose to paracentral reference points, correlative studies have demonstrated that the standard loadings, source positions, and applicator geometry recommended in the Fletcher-Suit-Delclos system usually results in a dose rate of approximately 45 - 55 cGy/hr at Point A.

8.3.2 Modified Fletcher method (Dijon): Individual volume adaptation (60 Gy reference volume) based on standard implants (small, medium, large) (4,22,54).

In principle dosimetry follows the guidelines of the classical Fletcher system as outlined above. The dose is nowadays prescribed in terms of TRAK which depends on the tumor volume and its location. An integral part of this system is to adapt the volume to take account of dose volume relationships of organs at risk (rectum, bladder) as well as of the target. A volume adaptation (modification of the TRAK) is therefore performed for each individual patient.
Figure 14.11: Modified Fletcher method

Fig 14.11.A: Typical Dose distribution showing the 60 Gy volume (60 Gy EBT – 40 Gy BT = 20 Gy) with a standard Fletcher applicator with cylindrical colpostats (20 mm diameter) in a patient with a tumour 5 cm in width at diagnosis and 3.5 cm wide at the time of brachytherapy. Transverse planes are given at the plane of the colpostats and at point A. TRAK was 6.6 cGy at 1 meter. The dimensions of the 60 Gy reference volume are drawn. The HWT product is 560 cm³, which corresponds roughly (divided by 2) to a computer calculated volume of 280 cm³.

To aid understanding the isodose line is given going through point A, although this has never been used in the modified Fletcher system. The dose in point A corresponds to 42 Gy in 72 hours. The product of these dimensions is 252 cm³, which corresponds roughly (divided by 2) to a computer calculated volume of 126 cm³. As 40 Gy were given by EBT the total dose given to this volume is 82 Gy (modified from isodose curves as provided by Barillot, with permission).

Knowledge of the dose distribution in a particular patient is based upon the anatomic, tumoural, and implant parameters as identified on the two orthogonal films taken at the end of the implant. Computerized dosimetry based on these radiographs gives the dose to different points and volumes for cervix, bladder, rectum, nodes, pelvic walls. These parameters are recorded and reported according to ICRU 38 recommendations. The dimensions and the amount of the 60 Gy reference volume are reported as height, width, and thickness, with small letters (h, w, t), if brachytherapy is to be reported (independent of treatment schedule with or without EBT) and with capital letters (H, W, T), if a combination treatment with external beam radiotherapy is to be reported. The reference volume in cm³ is reported simply as the product of these three dimensions, which means an overestimate of this pear-shape volume by a factor of about 2.

Dose and dose rate to critical organs are decided on the basis of risk of complications. This risk is estimated from the calculated HWT volume and the reference dose to critical organs. These
parameters are correlated (according to the experience of the “groupe des neuf”) with a defined probability of late side effects, in particular for the rectum and the bladder (4,9,30,98). The duration of the brachytherapy treatment can be varied as well as the loading pattern of the implant. As two implantations are performed, the first implant is usually done according to the classical guidelines outlined above, whereas the major individual adaptation is done at the time of the second implant when all individual parameters are available from the dosimetry of the first implant.

Typical dimensions and volumes for the 60 Gy brachytherapy volume are height 7 cm, width 6 cm, thickness 5 cm, product 210 cm³ (corresponding to a computer calculated volume of ~100 cm³). For a combination treatment, in which 40 Gy of external beam therapy are given with open fields the 60 Gy reference volume is the 20 Gy brachytherapy volume (60 - 40=20 Gy) and the dimensions are Height 10 cm, Width 9 cm, Thickness 8 cm, and the product 720 cm³ (4,19,53) (corresponding to a computer calculated volume of ~360 cm³). During the last decade, the dimensions of these reference volumes have been reduced.

Typical doses for rectum and bladder are strongly dependent on the reference volume and the individual topography and for the ICRU reference points range between 60 and 80 Gy and 70 and 90 Gy, respectively (4,19,30,98).

Fig. 14.11.B1,2: Anterior-posterior and lateral localisation films indicating the position of the applicator (small diameter), the bladder balloon, the rectal probe and various reference points (pelvic wall point, point A) including ICRU rectum and bladder points.

8.4 Institut Gustave-Roussy method: Individual 60 Gy volume adaptation based on individual moulds (16,37,38,42).

The positioning of the sources is dictated by the anatomy of the patient and the topography of the tumour. Individually selected lengths are used for the sources case by case (from 16 - 88 mm, with steps of 8 mm).

The uterine sources are usually 48, 56, 64, and 72 mm in length (rare or occasionally 40, 80, 88 mm). They must “cover” at least the two lower thirds of the uterus: the upper limit corresponds to the junction of the upper and middle thirds of the uterus; the lower limit is projected in the plane of the
vaginal sources. For adenocarcinoma with major endocervical growth, the length is further extended into the uterine cavity.

The vaginal sources most often used are 24, 32, and 40 mm (and occasionally 16 and 48 mm). They are parallel to each other and to the surface of the cervix in front of the right and the left anatomical limits of the cervical lip. The distance between the two sources is equal (+/- 1cm) to the average length of them both. Depending on the tumour extent, the individual length of each source is adapted, resulting e.g. in a length of the right source of 32 mm and the left source of 40 mm if tumour extends to the left parametrium or to the left vagina. If there is vaginal extension, the length of the sources is chosen according to the topography.

This positioning and length of the sources is decided provisionally at the time of the manufacture of the individual mould. Position and length can be modified when checking films are taken, taking account of the width, thickness and height of the PTV. The decision of treatment duration depends on the applicator geometry, the patient anatomy, the tumour topography and the dose to critical organs at ICRU points. The reference dose should encompass the PTV which is the CTV with an additional margin of 0.5 cm to 1 cm. A dose of 60 Gy is given to this reference isodose. For the 60 Gy encompassing isodose for brachytherapy alone, the classical variation in width is between 53 and 65 mm, in thickness between 20 and 57 mm and in height between 56 and 102 mm. (39).

Several additional dose points are calculated: tumour related (silver seeds), in the rectal tube, in the bladder (AlG point), at the sigmoid, at the right and left pelvic wall, at the lymphatic trapezoid of Fletcher (six points).

The TRAK is recorded for the whole treatment.

The 60 Gy reference volume for limited disease (Ib, IIbp) averages 129 cm³ for preoperative treatment (computer calculated, range from 36 - 487 cm³), with preoperative brachytherapy alone. The mean dimensions are height 8.7 cm (3.3 - 12), width 6.1 cm (2.5 - 9.5), thickness 5.2 cm (2.1-8.9) (39).

In combination treatments for extensive disease (IIbd/III) the 60 Gy reference volume averages 340 cm³ (139 - 689 cm³) for a 15 Gy brachytherapy volume (60 minus 45 Gy external beam therapy in distal stage IIB) and 544 cm³ (273 - 782 cm³) for a 10 Gy brachytherapy reference volume (60 minus 50 Gy external beam radiotherapy in stage III). Mean dimensions of the reference volume for stage III combination treatment were mean height 10.3 cm (2.5 - 15.5), for the mean width 6.9 cm (2.1-12.8), and for the mean thickness 6.6 cm (1.9 - 11.9) (52).

The dose at the ICRU rectum point averaged 40 Gy (8.5 - 97 Gy) for limited disease and about 60-75 Gy (38 - 102 Gy) for extensive disease after combination treatment. For the bladder ICRU point the dose is about 32 Gy (7.2 - 80 Gy) for limited disease and about 65 - 75 Gy (31 - 92 Gy) for extensive disease. Dose to the pelvic wall is 14 Gy (0.2 - 33 Gy) from brachytherapy alone in limited disease and 56 Gy (34 - 62 Gy) in extensive disease from combination treatment. Dose to the external iliac and paraaortic nodes is 12 Gy (1.2 - 48 Gy) and 5 Gy (0.2 - 21 Gy), respectively in limited disease and is 56 Gy (35 - 74 Gy) and 52 Gy in extensive disease (39,52). The bladder point defined by Alain Gerbaulet (AlG point: 1.5 cm cranial to the ICRU point as defined on the lateral radiograph) usually gives higher values and is more representative of the maximum bladder dose. These data are confirmed by information provided by MRI (9).
Fig 14.12: IGR method

Fig 14.12.A: Patient with locally advanced disease with a mould applicator. Dose distribution showing different isodose lines. Representation of the Surface of the large pear (60 Gy Reference Volume) and one Coronal Plane. Doses for different reference points including point A are given. 60 Gy Reference Volume is 400 cm$^3$. Anterior-posterior and lateral radiographs showing the applicator in place and ICRU-reference points in bladder (balloon) and rectum, at the pelvic wall and in the lymphatic trapezoid for dose calculation and treatment planning (compare Fig 14.3).

Maximum dose for the rectum is 20 Gy, other dose points indicate a dose of 10-12 Gy.
Dose for the sigmoid point is 13.9 Gy
Dose at the Bladder ICRU point is 26 Gy, at point AIG dose is 31.9 Gy
Pelvic Wall Point Doses are right 9.7 Gy and left 7.4 Gy
Dose at Point A is 37.4 Gy and at Point B 9.2 Gy.
Dose from external beam therapy was 45 Gy, dose from intracavitary brachytherapy 15 Gy specified at the 60 Gy Reference Volume.
Fig 14.12: IGR method (continued 1)

Fig 14.12.B: Clinical examples: Limited stage IIB proximal disease treated with external irradiation 20 Gy, brachytherapy 40 Gy and surgery.

At the time of brachytherapy with the applicator in place, Anterior-Posterior (A) and lateral (B) radiographs are taken. GTV is delineated.

40 Gy reference isodose (60 Gy reference volume): frontal plane (C), sagittal plane (D).

The black arrows indicate where the dimensions of the 60 Gy reference volume are measured: Width, Height and Thickness, Shape and surface of the 60 Gy reference volume (E).
Fig 14.12: IGR method (continued 2)

Fig 14.12.B: Clinical examples: 2). Locally extended stage III disease treated with external irradiation 45 Gy, and brachytherapy 15 Gy.

At the time of brachytherapy lateral with the applicator in place Anterior-Posterior (A) and (B) radiographs are taken. GTV is delineated.

15 Gy reference isodose (60 Gy reference volume): frontal plane (C), sagittal plane (D).

The black arrows indicate where the dimensions of the 60 Gy reference volume are measured: Width, Height and Thickness Shape and Surface of the 60 Gy reference volume (E)
Nowadays, systematic MRI performed during brachytherapy, immediately after the insertion, just before source loading, allows an accurate definition of GTV and CTV and appropriate modification of treatment.

8.5 Vienna method: Individualised dose and volume adaptation (80 - 90Gy) (assisted by radiography, MRI, and standard loading programs) based on standard ring applicators (small, medium, large)

The Vienna method utilises a HDR iridium-192 stepping source. After implantation of the applicator, AP and lateral projection images are obtained.

Reference points are drawn on these images to calculate the dose at certain points in relation to the applicator and the GTV, and PTV using the treatment planning system. These reference points are the ICRU 38 points and Manchester point A.

Fig 14.13: Vienna Method

For the ring applicator, defined standard configurations with specific loading patterns for each applicator (dwell positions and times) have been generated and are thus available in the “library” of the treatment planning system. These standard dose distributions are used for starting dose calculations (Fig 13B-D). Point A is the reference point in these standard programs where the dose is prescribed.

Limitations are set for the dose to the critical organs: less than 70% of the dose at point A to the ICRU rectum reference point (5 Gy per fraction) and less than 80%, if possible, to the ICRU bladder reference point. As the position of the rectum is radiographically known relative to the applicator and the GTV, an adaptation is often possible by adapting dwell times and/or dwell positions in one posterior part of the ring. These limitations apply for each brachytherapy fraction. In the treatment schedule for small tumours, the upper limit for brachytherapy dose is nominally 24 - 30 Gy (6x4 - 5 Gy), and in large tumours 16 - 20 Gy (4x4 - 5 Gy). Applying the linear quadratic model (alpha beta value 3) and taking into account the respective treatment schedule from external beam therapy (four field box technique: 25 x 1 Gy for limited disease with shielding the brachytherapy volume in the ap/pa direction and 25 x 2 Gy for extended disease), the total physical dose is 49 - 55 Gy and 61 -
70 Gy for the rectum, corresponding to a total isoeffective dose for tolerance limits for small tumours of 56 - 68 Gy and for large tumours of 70 - 80 Gy. Analogous tolerance limits, although less strict, apply for the bladder. Doses at the vagina vary significantly (from 8 - 30 Gy per fraction), and also depend on the shielding of the ring (cap).

Fig 14.13: Vienna Method (continued 1)
B-D: Standard dose distributions showing 100%, 50%, 75% 150% and 200% isodose lines with a ring applicator of 26 (small: B), 30 (medium:C), and 34 mm (large:D) diameter (source to source distance) of the same intrauterine length. Transverse planes are given at the plane of the vaginal sources (ring) and at point A. The dimensions of the 60 and 85 Gy reference volume are shown in width, thickness and height. The 60/85 Gy isodose lines correspond within the standard radiochemotherapy dose schedule (45 Gy EBT plus 4 fractions of brachytherapy with 7 Gy per fraction) to the 3.4 (~50%) and 7 Gy (~100%)-isodose. The 100% isodose also corresponds to the volume of the isodose (computer calculated) going through point A (mean 101 cm³). For TRAK values compare text. The mean standard 60 Gy volume (computer calculated) is 274 cm³ (from 247 to 306).

Fig 14.13B: Standard dose distribution with a small size ring applicator (see above)
Fig 14.13: Vienna Method (continued 2)

Fig 14.13C: Standard dose distribution with a medium size ring applicator (see above)

Fig 14.13D: Standard dose distribution with a large size ring applicator (see above)
The treated volume is adapted to the GTV/PTV as far as possible using information from clinical examination and MRI. In any case, the entire cervix with some safety margin is included in the PTV. Adaptation leads to differences in the range of only a few millimeters. However, this difference is significant in terms of volumes. The larger treated volumes are about 90 to 155 cm³, the smaller volumes 46 - 90 cm³. A minimum dose per fraction of 7 Gy is prescribed to this volume (with isoeffective total doses from 73 - 90 Gy, see below). The dose is recorded at point A and varies from 6 - 8 Gy per fraction depending on the volume. The dose at other reference points averages about 8/4 Gy (PWP), 7/4 Gy at the external iliac and 5/3 Gy at the common iliac points for 6 and 3 fractions, respectively. The mean dimensions of the “point A volumes” (reference isodose for the brachytherapy volume going through point A) are about 7 - 10 cm in height, ~6.2 cm in width, and ~4 cm in thickness. For the 60 Gy reference volume, these dimensions average about 8.5 cm in height.

Fig 14.13: Vienna Method (continued 3)

Fig 14.13E: Typical individual adaptation of the standard dose distribution for a large bilateral tumour in a favourable anatomical situation with a large individual vaginal packing. Increase of the dwell times in the intrauterine tube results in bilateral enlargement of the treated volume by ~2 mm each side at the level of point A and an appropriate adaptation for the PTV of brachytherapy. The encompassing isodose is 7 Gy per fraction. The dose at point A becomes 8 Gy per fraction. The overall total dose of brachytherapy for this PTV was nominally 28 Gy (4x7 Gy) and at point A 32 Gy (4x8) which is isoeffective to 40 and 48 Gy, respectively. The total dose of EBT (45 Gy) and BT (40 Gy) at the PTV encompassing isodose was 85 Gy and in point A right and left 93 Gy. Dimensions of the 60 Gy reference volume and the treated volume (85 Gy) (and the point A volume (93 Gy)) are indicated. The volumes were 350 cm³ and 120 cm³ (and 101 cm³), respectively. TRAK was 2.3 cGy at 1 meter. Dose to rectum and bladder (2 cm³) were mean 3.3 Gy and 5 Gy per fraction, resulting in an overall total isoeffective dose of 68 Gy and 90 Gy; dose at the respective ICRU points were mean 3 Gy per fraction for the rectum and 4 Gy for the bladder.
7.1 cm in width, and 5.4 cm in thickness for limited disease and 9.7, 8.6, and 7.1 cm, respectively for extended disease (96). The computer calculated volumes average 87 cm$^3$ (from 46 - 155 cm$^3$) for the reference isodose going through point A corresponding to a total isoeffective dose for the reference isodose at point A from 73 - 83 for limited and from 80 - 90 Gy for extended disease. The 60 Gy reference volumes average 176 and 316 cm$^3$, respectively, in limited and extended disease assuming an isodose of 4.7 Gy and 3.1 Gy to be isoeffective (50 Gy EBT + BT (96)).

**Fig 14.13: Vienna Method (continued 4)**

Fig 14.13F: Typical individual adaptation of the standard dose distribution for a large tumour extending into the lateral and posterior parometrium on the left. Increase of the dwell times in the ring on the left and reduction by one ring position on the right (compare figs. 5,14 (same patient)). Asymmetrical enlargement of the treated volume (100\%: 89 Gy) in the posterior left lateral direction according to individual tumour spread without overall significant enlargement of the treated volume (108 cm$^3$). The bilateral dimensions of the 89 and 60 Gy volume are indicated, which differ by 8 mm and 9 mm, respectively, in the lateral direction. The dose to point A is 7.3 Gy on the right side and 8.6 Gy on the left. The 60 Gy reference volume is 316 cm$^3$. (For dose to the critical organs compare Fig 14.14)

Sectional image based treatment planning for dose calculation has been systematically used since one decade. If the axis of the uterine tandem is chosen as the reference axis, the following relationships hold (see fig. 5.2 (imaging chapter)): (para) sagittal MRI planes parallel to the axis of the uterine tandem correspond roughly to the lateral radiograph (if the axis of the uterine tandem is not laterally deviated), (para)coronal MRI planes parallel to the axis of the uterine tandem correspond roughly to the anteriorposterior radiograph (if the axis of the uterine tandem is parallel to the craniocaudal body axis), (para)transverse planes (MRI/CT) parallel to the axis of the vaginal sources (ring) have no corresponding projection images. If sectional images cannot be introduced digitally into the computerized treatment planning system, the main issue is to confirm on the images
with the applicator in place the appropriate position of the applicator in the uterine cavity, to estimate gross tumour volume and its relation to the implant and to critical organs. Since 1997, it has been possible to enter sectional images directly into the treatment planning system. Delineation of GTV and PTV and critical organs is performed and dose volume relations are assessed. Dose distribution (e.g. 7 Gy volume) is displayed as a DVH for the GTV/PTV and for organs at risk. Dose adaptation is additionally based on these parameters, not only looking at dose points (radiography) but also at dose volume relations, for the rectum and the bladder (CT and MRI) and for the GTV/PTV (MRI). Limits have been defined for dose volume relations for the rectum, where a mean dose per fraction of 5 Gy (total dose 20 Gy) is limited to a rectal tissue volume of 2 cm³. In the recent Vienna experience, grade III/IV complications were seen after ~7 Gy per fraction (isoeffective total dose >85-90 Gy) if the rectal tissue volume was more than 2-4 cm³ (31). For the PTV as delineated on MRI with the applicator in place the prescribed dose of 7 Gy is adapted so that as much as possible of the PTV is enclosed. In the majority of cases, >80% of the PTV receives the prescribed dose. If a major part of the PTV is not covered by the prescribed dose (e.g. extensive lateral and/or posterior-lateral pararectal extension) additional interstitial brachytherapy is considered.

![Fig 14.14: Typical MRI based treatment planning based on ring applicator and stepping source technology (Vienna method)](image)

![Fig 14.14.A: MRI study with the applicator in place (patient of Fig 14.4). PTV of brachytherapy is delineated in the transverse plane 5 mm above the level of the top of the ring (pointed line). The prescribed dose based on the standard plan does not encompass a major part of the PTV in the posterior lateral direction (A1). Increase of the dwell times in the ring on the left side and one additional position in the posterior part leads to an almost complete coverage of the PTV at the limits of rectal tolerance with the 100% isodose (85 Gy) "touching" the rectal wall, but not going beyond the limitations in terms of dose volume relations (A2) (44), as the rectal wall volume included in the 100% isodose is below 1 cm³.](image)

In principle, dose calculation and treatment planning are performed as outlined above for each single fraction of HDR brachytherapy, which is extremely challenging in terms of resources. For practical reasons in our experience we use the following procedure: substantial differences in the implant, in the GTV and in the topography are checked for each subsequent application (2nd - 6th). If the subsequent application is almost identical to the preceding one, sectional imaging with the applicator in place is not repeated. Individual dosimetry is then based only on the radiographs (with all reference points), and starts with the treatment plan which was selected the time before. Adaptations are performed, if necessary. In our early experience (93 - 97), CT with the applicator in place was carried out in 389 (181 patients) out of 694 applications (189 patients). Whereas at the
beginning of sectional image based treatment planning about one third of treatment plans were individually adjusted, nowadays based on MRI this is about 80 - 90%.

Fig 14.14: Typical MRI based treatment planning based on ring applicator and stepping source technology (Vienna method) (continued 1)

Fig 14.14.B: MRI study with the applicator in place for a patient with stage IIB disease with distal parametrial extension treated in 3/99 (patient from Fig 14.5) and favourable anatomy. According to individual tumour topography, the dwell times and positions were adapted in the left lateral and posterior part of the ring. At the same time the dwell times and positions on the right side of the ring could be reduced to spare the rectum (rectal probe inside). No adjustment was made for bladder sparing. The PTV of brachytherapy including cervix and adjacent proximal part of the uterine body
Fig. 14.14 (continued): was contoured (35 cm$^3$) as well as the rectum (57 cm$^3$) and bladder (261 cm$^3$). The dose distribution is shown on transverse planes at the level of the vaginal sources, 1 and 2 cm above and at the midparasagittal and midparacoronal planes. Isodose lines indicate 89 Gy, 75 Gy, and 60 Gy. These doses are calculated based on the alpha-beta model (10 Gy) and the recommendations of ICRU 38: EBT was 49 Gy at the ICRU point, BT 4 x 7 Gy for the isodose encompassing the PTV (no chemotherapy). Maximum reference isodose width was 6 cm (89 Gy) and 9 cm (60 Gy), which was 3.4 cm (89 Gy) and 5 cm, (60 Gy) on the left at the level of the ring and 2.5 cm (89 Gy) and 4.6 cm (60 Gy) on the left at point A, respectively. Maximum reference isodose thickness was 4.5 cm and 6.8 cm, maximum height 7.9 and 10.0 cm. The reference volume (mean) for 85 Gy was 91 cm$^3$ (104, 108, 90, 63 per fraction (adaptation for tumour shrinkage)), 316 cm$^3$ for 60 Gy. The isoeffective dose to point A on the right side was 89 Gy, on the left 95 Gy. TRAK was 1.77 cGy at 1 meter.

Fig 14.14: Typical MRI based treatment planning based on ring applicator and stepping source technology (Vienna method) (continued 2)

Fig 14.14.C: DVH evaluation revealed that 85%/96%/100% of the PTV was encompassed by the 89 Gy- 75 Gy- 60 Gy-isodose (C1). For the rectum the doses for the 2 cm$^3$ and 5 cm$^3$ volumes were 4.1 Gy and 3.5 Gy, respectively, which corresponds to 59% and 50% of the prescribed dose (C2). For the bladder the doses for the 2 cm$^3$ and 5 cm$^3$ volumes were 5.9 Gy and 5.2 Gy, respectively, corresponding to 84% and 74% of the prescribed dose (C2). The total dose to the rectum was 49 Gy (EBT) plus a nominal 16.4 Gy (4 x 4.1)/14 Gy (4 x 3.5) to the 2/5 cm$^3$ volume, which corresponded to the mean dose per fraction for the whole treatment (little variation). The total biologically weighted dose was 71 Gy and 68 Gy. For the bladder this was 4 x 5.9/5.2 Gy in the 2/5 cm$^3$ volume, the total biologically weighted dose was 90 Gy and 82 Gy, respectively. The doses at the ICRU rectum and bladder reference points averaged 5 Gy (3.6-6.4) and 4.7 Gy (3.5-6.5), for the total dose of brachytherapy 20.1 and 18.7 Gy, respectively.

The patient (44 years) was treated 3/99, overall treatment time was 38 days. She was in continuous complete remission at three years. Grade 1 side effects were noticed in the vagina, grade 0 in the rectum and bladder (Lent-Soma Score).
8.6. Common language in intracavitary brachytherapy: ICRU 38 recommendations

The existence of many different methods and traditions for prescribing, recording and reporting intracavitary brachytherapy applications (as reviewed in the preceding chapters) implies the need to agree on common language and terminology to facilitate communication between centres and to make possible reliable and relevant comparison of methods and clinical results.

8.6.1 The ICRU 38 recommendations (63).

The ICRU recommendations have been described and discussed in detail in chapter 2 on Physics and 6 on Reporting. They are applicable to all types of intracavitary brachytherapy applications; they are not be repeated here. Only some aspects which are specific to cervix brachytherapy are discussed. These recommendations address the following:

- description of the technique used,
- total reference air kerma (TRAK),
- description of the reference volume,
- absorbed dose at reference points,
- time dose pattern.

Total reference air kerma (TRAK):

The TRAK is a well defined physical quantity which can be easily calculated for any brachytherapy application. The TRAK is an important quantity and all biological effects are directly related to the TRAK. However, this relation is not unique: it depends on the time-dose pattern and geometrical conditions.

In order to correlate with the biological effects, the TRAK has first to be weighted by a factor related to the time-dose pattern. The numerical value of this factor depends on the biological system and effect, and on dose level and dose rate. It thus varies with the distance from the sources.

In addition, the absorbed dose and the biological effects on the tissues located at a certain distance from the sources can be predicted from the TRAK (provided that a weighting for the time factor has been applied). In contrast, the dose distribution and the effects on the tissues located close to the sources depend on the source arrangement and can thus not be predicted from the TRAK alone. A direct relation between the TRAK and the dose distribution close to the sources is valid only for a given source arrangement (within a given „system”).

60 Gy reference volume and its dimensions (see also Fig 14.16):

In intracavitary applications, the dose gradient is very steep as a function of the distances to the sources, especially in the vicinity of the sources. For reporting and comparison purposes, it is therefore difficult to define a reference point (as in external beam therapy) where the dose can be considered as representative of the dose distribution in a target or organ volume. An alternative approach to compare different intracavitary applications is to agree on a dose level and to report the dimensions of the tissue volume enclosed in that isodose surface.

For reporting and comparison purposes, ICRU 38 defines the Reference Volume as the volume encompassed by the 60 Gy isodose surface. It is independent from the individual target volume and the treated volume as selected by the clinician for a specific treatment. It recommends to report the three orthogonal dimensions of the 60 Gy volume: height h, width w, and thickness t. The three dimensions of the 60 Gy volume, and not only their product should be reported. Due to its pear shape, the product of the three dimensions is about twice the computer calculated 60 Gy volume.
In case of standard applications the dimensions and the volume are known from precalculated dose distributions, in case of individualised geometry, the dimensions and the volume are to be calculated case by case.

For reporting brachytherapy alone (with or without external beam therapy) the dimensions of the 60 Gy Reference Volume have to be indicated encompassed by the 60 Gy isodose by brachytherapy only (h,w,t). For reporting brachytherapy combined with external beam therapy, the dose for external beam therapy has to be subtracted from 60 Gy and the reference volume for the resulting isodose has to be indicated: e.g if 45 Gy are given with open field external beam therapy, this is 15 Gy, and the reference volume encompassed by the 15 Gy isodose of brachytherapy is to be reported. In addition, the dimensions are to be recorded as Height, Width, and Thickness (H,W,T).

![Diagram of plane a and plane b](image)

Fig 14.15: ICRU 38 Recommendations:
A: Dimensions of the Reference Volume AP and lateral (compare for details also Fig 6.27)

The dose level should be selected in such a way that the Reference Volume should not be too different from the Treated Volume (i.e. the volume receiving the dose considered as appropriate to achieve the goal of the treatment). If the selected dose level is too low, the Reference Volume becomes spherical; if the selected dose level is too high, the Reference Volume is closely surrounding the individual sources. In both cases, it contains little useful information.

The concept of Referenve volume has been introduced by the ICRU for comparisom purposes only. Specification of the 60 Gy Reference Volume does not imply that the ICRU recommeds 60 Gy as prescription dose. However, without an agreement on a dose level it is hardly possible to compare, in a relevant way, applications performed in different centres using different techniques.

If this 60 Gy volume is also used for prescription then - from a practical point of view- it looks easier to start with the determination of the isodose enclosing 60 Gy taking into account the clinical situation and other information and particular in which area, in which points, in which volume this dose of 60 Gy must be prescribed. Afterwards, the different data will be reported according to the ICRU recommendations.

Absorbed dose at reference points

ICRU 38 defines several reference points for reporting:
Related to rectum and bladder two reference points are defined which are located relatively close to the sources: the "ICRU-bladder reference point" and the "ICRU-rectum reference point" (Fig 14.15B). They are reproducible and reliable, but they do not necessarily represent the maximum dose to these organs at risk. Therefore, in addition reporting of more points indicating different doses to the organ at risk is encouraged, also mean and maximum doses.
Related to bony structures and lymph node topography, two sets of reference points relatively far from the sources are defined: the pelvic wall reference points (Fig 14.15C) and the points in the lymphatic trapezoid (Fig 14.15D). They indicate the dose to the lateral margins of the small pelvis and to the different lymph node regions: external iliac, common iliac, low paraaortic.

**Time dose pattern**

The total duration of the brachytherapy application and the dose rate are to be reported. If several sessions are performed, the duration of each session and the interval(s) have also to be indicated. When brachytherapy is combined with external beam irradiation all the data concerning time dose pattern are also reported: dose per fraction, total dose, treatment time of external beam irradiation and overall treatment time.

**8.6.2 Recent and future developments for recommendations for a common language in endocavitary brachytherapy**

The recommendations given in the ICRU report 38 (63) were developed 15 - 20 years ago. More recently, important changes have taken place in the field of brachytherapy: dramatic progress in imaging, more powerful and accurate 3D treatment planning, and the development of high dose rate (HDR) and pulsed dose rate (PDR) stepping source brachytherapy.
Therefore, changes may be helpful to increase the usefulness of the ICRU 38 recommendations for the future.

Furthermore, as shown in a recent GEC ESTRO-survey on the use of these ICRU 38 recommendations (97), major parameters, in particular TRAK and 60 Gy reference volume have been poorly reported in clinical practice and in published work, and hardly ever from centres using HDR brachytherapy. Furthermore, there has been no common language for reporting time dose pattern between the traditions based on LDR, MDR, and HDR brachytherapy.

Therefore, a more comprehensive approach must be developed taking into account the different dose rates applied and the different imaging methods which are being increasingly used.

The concept of „Reference Volume“ was introduced by the ICRU on the background of LDR brachytherapy. The dose level selected to define the reference volume may need to be adapted to take into account the development of HDR and PDR.

When modifying the time-dose pattern, weighting factors have to be evaluated (based on established biological models) and applied to the quantity “absorbed dose” to obtain another quantity, the “Biologically Weighted Dose”, that has to be correlated with the biological/clinical effects.

It must be kept in mind, when modifying the time-dose pattern, that the weighting factor is not a unique/single value, but varies significantly with dose, dose rate, tissue or effect. Therefore, the tissue/effect for which the weighting factor is evaluated (and the numerical value of this weighting factor) should always be reported in addition to the (physical) absorbed dose.

In order to allow integrating the traditional methods of reporting based on point concepts and more recent methods based on volume concepts, different “levels for reporting” are identified in brachytherapy, in the same way as proposed for external beam therapy in ICRU Report 50 (see chapter 6).

At level 1 - 2, doses at accurately defined „point A“ and ICRU recommended reference points can be reported, while for the same applications, level 2-3 includes reporting the dimensions of volumes encompassed by different isodose surfaces (including isodose through point A, 60-Gy Reference Volume, Treated Volume, Organ Volumes). In any case, reporting at level 2 shall always include all information that should be reported at level 1.

Reporting on points and volumes will allow for a common language which makes either practice understandable to everyone. As an example for such proposal, the direct correlation between the “60 Gy volume”, the “85 Gy volume” and the “dose to point A” is illustrated for a given source geometry (Fig 14.16).

The volume concept stays closely connected to the reporting of doses at specific points, such as a well defined “point A“ (level 1). The different levels for reporting will have to be clearly defined and will become integrated. Dose to points and volumes in the target and in critical organs will become determinable in a valid, reliable and reproducible way, if in addition to traditional practice, the potential of modern imaging and computer technology is adequately taken into account (for more detail see chapter 6 on reporting, in particular 6.8).
Fig 14.16: Definitive cervix cancer brachytherapy (IB, IIB proximal). Reporting doses and volumes for five different clinical situations (tumour sizes) and treatment schedules. For cases (a), (b) and (c) brachytherapy is combined with external beam therapy. For cases (d) and (e), brachytherapy alone is applied (d) preop. BT ("IGR"); (e) BT alone ("Manchester"). The same brachytherapy technique is assumed for all cases. For cases (a), (b) and (c), the Treated Volume is defined by the 85 Gy isodose. For cases (d) and (e) the Treated Volume is defined by the 60 and 75 Gy isodoses, respectively.

For the five clinical cases, the GTVs are shown together with the 60-75-85-95 Gy isodose curves. On the lower part of the figure, the different isodoses are presented at a larger scale to illustrate the differences in the volume dimensions. (for details see legends of figure 6.28)
9 Dose, Dose Rate, Fractionation

9.1 General Introduction

Different schools developed different empirically based standard protocols. Based on these, various methods and systems have been used for expressing the treatment time, the amount of radiation, the radiation dose and the treated volume in gynaecological brachytherapy: milligram-hours (historical Paris method, classical Stockholm and Fletcher system); doses to reference points (Manchester system, ICRU recommendations). When target assessment became more accurate, volume and dose adaptation became possible: individual volume adaptation (Chassagne, IGR), individual dose adaptation (Perez (91)), 3D image based individual dose and volume adaptation (Vienna method). In these systems brachytherapy was adapted to different CTVs in different ways: adapting the amount of mg.h (Fletcher (35) Horiot (53,54)), adapting the brachytherapy dose at a reference point (91), adapting the brachytherapy volume for a given dose (Chassagne, Gerbaulet, IGR), adapting the brachytherapy volume and dose in the PTV/GTV (Vienna method). In the classical Manchester system the dose to the reference point stays by definition the same, independent of the CTV (59,61,62). However, in Manchester derived systems (Perez; Vienna method) the dose to point A is adapted according to tumour extension.

9.2 Manchester method (LDR (140-180 cGy/hour)) (59,61,62)

9.2.1 Definitive Brachytherapy in limited disease

Using radium in the classical Manchester system in patients with small volume stage I and IIA disease, a dose of 75 Gy was given to point A in two insertions of equal length 7 to 10 days apart. At 53 cGy per hour this resulted in treatment times of 140 hours (2 x 70 hours). No additional external beam therapy was given. TRAK for the radium treatment lay in the range of 5.7 to 6.7 cGy at 1 meter. With the caesium system described above the total dose has been reduced to 6500 cGy at Point A at the dose rate of 140 - 180 cGy per hour. Typical treatment times per insertion are around 20 hours [116]. TRAK is dependent on the length of the intrauterine tube and the size of the ovoids and varies from 4.73 to 5.52 cGy for short tubes and from 5.52 to 6.3 cGy at 1 meter. The change in total dose was necessary as the results of randomised trials at the time of the introduction of the new caesium system clearly showed that with a dose rate change of this type a reduction of total dose of between 10 and 17% must be made to ensure optimum results. (57,62)

When dose rates and doses to the bladder ICRU reference point were calculated in 20 patients, they were averaged 56% (range 17% to 90%) of the dose to Point A. (58). The dose to the rectum was kept below two thirds of the dose to Point A in all cases by careful vaginal packing.

For medium volume disease, external beam therapy with a parametrial wedge delivered 32.5 Gy to Point B (15 Gy to Point A) in 16 fractions in 21 days. This was complimented by 60 Gy to point A (radium) and 55 Gy using the modern cesium system.

9.2.2 Definitive Radiotherapy including LDR Brachytherapy in extended disease

For stage IIb and III disease and for patients with enlarged lymph nodes, a four field box conformal technique is used extending from below the disease in the vagina to the top of the fifth lumbar vertebra (or above any paraaortic nodes). Typically 40 Gy in 4 weeks in 20 fractions (with 8 - 20 MV) is complimented by 30 to 32.5 Gy brachytherapy (Caesium) to point A in one insertion (previously 37.5 Gy radium). Manchester has discontinued the parametrial wedge treatment.

For very bulky central disease in patients with no enlarged lymph nodes or in patients where there is concern about whether a good quality intracavitary treatment will be possible, a smaller simple four
field box technique (10 - 12 cm length) is sometimes used applying 45 Gy by external therapy to treat the pelvis homogeneously and, in this situation 20 - 22.5 Gy is prescribed at point A in one insertion (62) (previously 2500cGy Radium).

TRAK for the two brachytherapy schedules is 2.07 to 3.15 cGy for 32.5 Gy at point A and 1.44 to 2.07 cGy for 20-22.5 Gy at point A depending on the applicators used.

9.3 Modified Fletcher method (LDR) (54)

9.3.1 Definitive LDR brachytherapy +/- EBT in limited disease

Amount of brachytherapy, external beam therapy, dose and fractionation are related to the tumour volume, the disease extension and the nodal status. According to Horiot (53,54) the indications are:

* tumour size less than 1cm: two applications of brachytherapy: TRAK 7.2 cGy at 1 meter, 80 to 100 Gy to upper vagina.
* tumour size 1-3cm +/- proximal extension: external radiotherapy (20 - 40 Gy) plus intracavitary brachytherapy: TRAK 4-4.5 cGy at 1 meter; 30-60 Gy to upper vagina.
* tumour size 3-6cm +/- proximal extension: external radiotherapy 40 Gy plus intracavitary brachytherapy: TRAK 4-4.5 cGy at 1 meter; 40-60 Gy to upper vagina.

The dose rate (0.8 - 1 Gy/h) at the surface of the applicator is kept constant by modifying the activity of the source as a function of colpostat size. (54)

In Dijon three time periods of treatment strategies can be defined. The first period between 1970 and 1978 with 289 patients, the second period between 1979 and 1984 with 199 patients and the third period between 1985 and 1994 with 154 patients (3,4).

The mean HTW volumes for patients treated in the first period were 606 cm$^3$ for stage Ib, 711 cm$^3$ for stage IIa and 850 cm$^3$ for IIb. The mean HWT volumes for patients treated in the second period were 612 cm$^3$ for stage Ib, 630 cm$^3$ for stage IIa and 773 cm$^3$ for IIb. For patients treated in the third period mean HTW volumes were 498 cm$^3$ for stage Ib, 472 cm$^3$ for stage IIa, 511 cm$^3$ for IIb (3,4, 53).

Pourquier et.al. (98) reported maximum bladder doses from intracavitary brachytherapy and cumulative bladder doses from both the intracavitary and external beam treatment for all 624 patients (stage I to IV, treated between 1970 - 1994): For an EBT dose of 20 Gy, the bladder doses were on average 24 Gy and 44 Gy, for EBT of 30 Gy the doses were on average 30.5 Gy and 60.5 Gy, for EBT of 40 Gy the doses were on average 24.8 to 30.6 Gy and 65.8 to 71.1 Gy and for EBT of 50 Gy the doses were on average 24.3 to 32.3 Gy and 74.3 to 82.5 Gy.

Crook et.al. (19) reported data from 348 patients with stage Ia to IIIb treated between 1975 and 1983. For hwt volumes between about 100 cm$^3$ and 200 cm$^3$ the cumulative rectal doses (from both the intracavitary and external beam treatment) were between between 60 Gy and 90 Gy. They reported a correlation between the mean rectal dose from intracavitary brachytherapy alone and mean HWT volumes. For HWT volumes between about 500 cm$^3$ and 800 cm$^3$ the cumulative rectal doses were between about 60 Gy and 80 Gy.

Barillot et.al. (4) reported for 624 patients (stage I to IV, treated between 1970 - 1994) new decision rules for rectal and bladder dose based on correlation curves. Only one G3/G4 rectal complication was demonstrated within the area delimited by HWT values below about 750 cm$^3$ and reference rectal dose rate below about 50 cGy/h. Keeping dosimetric parameters within this safe zone may avoid the occurrence of severe rectal complications. Although a correlation has been found between
bladder complications, bladder dose and bladder dose rate, the decision rules are not so clear due to the small number of severe complications observed. However, the safe zone can be defined by reference bladder dose below about 70 Gy and bladder dose rate below about 50 cGy/h.

9.3.2 Definitive LDR brachytherapy + EBT in extended disease:

According to Horiot (4,53,54) the indications are:

* tumour size 3-6cm with or without proximal tumour extension: external radiotherapy 40 Gy + endocavitary brachytherapy: TRAK 4 - 4.5 cGy at 1 meter; 40 - 60 Gy to upper vagina.
* tumour size >6cm +/- distal parametria +/- inferior vagina: external radiotherapy 40 - 50Gy + endocavitary +/- interstitial brachytherapy: TRAK 3.5-4.5 cGy at 1 meter; 50 - 70 Gy to upper vagina.

If there are positive nodes the total dose delivered must be between 55 to 65/70Gy (65/70 Gy to a very limited volume). (In the classical Fletcher method, doses in mg.h radium (TRAK) have been correlated with doses to point A: if the anatomy is favourable, doses to point A are reported to be in the range of 85 - 95 Gy (73)).

The mean HTW volumes for patients treated in the first period were 1061 cm$^3$ for stage IIIa and 990 cm$^3$ for stage IIIb. The mean HTW volumes for patients treated in the second period were 705 cm$^3$ for stage IIIa and 775 cm$^3$ for stage IIIb. The mean HTW volumes for patients treated in the third period were 474 cm$^3$ for stage IIIa and 528 cm$^3$ for stage IIIb (4,54).

Dose and dose rate to critical organs are decided based on the risk of complications. This risk is estimated from the calculated HTW volume and the reference dose to critical organs. These parameters are correlated (according to the experience of the “group de neuf”) with a given probability of late side effects, in particular for the rectum and the bladder. The duration of application can be adapted as well as the radioactive length and/or the activity.

The dose rate (0.8 - 1 Gy/h) at the surface of the applicator is kept constant by modifying the activity of the source as a function of colpostat size (4,54).

For dose(rate) to the rectum and bladder see the studies presented above (9.3.1)

9.4 IGR-method (LDR) (37,38).

9.4.1 Preoperative radiotherapy in limited disease

For limited stage IB and proximal IIA/B disease preoperative brachytherapy is adapted to tumour stage:

Tumour size less than 4 cm (IB1/IIB): brachytherapy in one session, or in two sessions if the geometry of the implant is not perfectly adapted to the anatomy and/or to the topography of the tumour. The reference isodose is by definition 60 Gy and must encompass the target volume (upper third of the vagina, internal third of the the parametrium, upper third of the uterus). The maximum dose to the bladder and rectum is less than 50 Gy taking into consideration the volume of bladder and rectum irradiated. Dose rate is from 0.3 to 0.6 Gy per hour at the level of the reference isodose.

Tumour size more than 4 cm (IB2/IIB): external irradiation 20 Gy plus brachytherapy. The reference isodose for brachytherapy is 40 Gy (60 Gy minus 20 Gy (dose of external irradiation)). For bladder and rectum the mean dose delivered by brachytherapy is 30 Gy. Dose rate is 0.3 to 0.6 Gy per hour at the level of the reference isodose. From 1999, in this clinical situation, treatment starts with concomitant chemoradiation up to 45 Gy followed by brachytherapy : the reference isodose is 15 Gy.
For limited disease with known risk factors, postoperative external beam therapy is given: pelvic irradiation with central shielding adapted to the previous radiation therapy according to the dose delivered to the nodes by brachytherapy or external irradiation + brachytherapy performed 6 weeks before surgery (ranging from 30 - 40 Gy).

In a series of 441 patients treated at IGR with preoperative brachytherapy, the mean TRAK was 4.6 cGy at 1 meter (ranging from 1.4 to 9.1), the mean dose rate 0.55 Gy per hour, the mean dose to the bladder 32 Gy (7.2 - 80), to the rectum 40 Gy (8.5 - 97), to the iliac external nodes 12 Gy (1.2 - 48), to the paraaortic nodes (0.2 - 21 Gy), to the pelvic wall 14 Gy (0.2 - 33) (39).

9.4.2 Definitive Brachytherapy and EBT in extended disease

Tumour size less than 4 cm: external irradiation 45 Gy plus brachytherapy in one session with the reference isodose of 15 Gy (total dose 60 Gy). Irradiation must be radical, so the total dose to bladder and rectum is higher than in preoperative brachytherapy: bladder 65 - 70 Gy, rectum 60 - 65 Gy.

Tumour size more than 4 cm: external irradiation with concomitant cisplatin based chemotherapy 45 Gy plus brachytherapy (one or two sessions) intracavitary +\- interstitial with a reference isodose of 15 Gy. Total dose to bladder is 70 - 75 Gy, to rectum 65 - 75 Gy.

In these situations with a high dose delivered to the critical organs, the organ volume irradiated to a high dose must carefully be taken into account.

The dose rate is the same as in limited disease: 0.3-0.6 Gy per hour.

The TRAK is about 2 cGy at 1 meter.

If there is nodal involvement with extended disease an external irradiation boost is applied adapted to the positive nodes with 5 - 15 Gy to an appropriate small volume.

9.5 Vienna method (HDR/PDR)

9.5.1 Definitive HDR Brachytherapy and EBT in limited disease (Vienna) (96)

Intracavitary brachytherapy is given in 5 - 6 fractions of HDR-brachytherapy of 7 Gy in 5 - 15 minutes as the prescribed dose to the “PTV” at weekly intervals (to point A or close to point A). External beam therapy is given simultaneously four days a week with a linac with a four field box technique in 1.8 - 2 Gy fractions up to a total dose of 40 - 50 Gy at the ICRU-point (45 Gy with concomitant cisplatin chemotherapy). Central shielding outlined according to the 7 Gy isodose of the brachytherapy volume is inserted in a.p./p.a. portals from the beginning. The overall treatment time is 6 weeks.

TRAK averages 2.8 cGy at 1 meter for 6 fractions in small tumours. The physical total dose at point A is 60-67 Gy in small tumours (5 - 6 fractions). The corresponding biologically weighted dose for conventional fractionated radiotherapy (analogous to LDR brachytherapy) calculated using the linear quadratic model (alpha beta value of 10) is 73 - 83 Gy. Dose per fraction at the pelvic side wall, and at the internal and common iliac lymph nodes are 1.35, 1.2, and 0.85 Gy, respectively (ICRU points) (range of medium dose rate). The treated volume by brachytherapy and EBT (isoeffective dose of 73 - 83 Gy) is 87 cm³; the 60 Gy reference volume (taking the 4.7 Gy isodose as isoeffective (based on 25 Gy EBT dose)) is 180 cm³. The mean dose per fraction at the ICRU rectum reference point is 4 - 5 Gy, adding up to 24 - 30 Gy in 6 fractions and together with the dose from EBT (25x1Gy) to 49 - 55 Gy. The corresponding isoeffective dose (alpha beta value of 3, see above) is 56 - 68 Gy. Bladder
doses are similar, but somewhat higher. Doses at the vagina vary significantly, also dependent on the shielding of the ring, with doses from 8 - 20 Gy per fraction.

9.5.2 Definitive PDR Brachytherapy and EBT in limited disease (Leuven, Vienna)

In the Leuven experience the total dose of brachytherapy is the same as for LDR brachytherapy, if a dose per pulse is applied at a dose rate between 50 and 80 cGy per hour. A maximum dose to the PTV is given respecting a maximum dose of 65 - 70 Gy to the rectum and of 70 - 75 Gy to the bladder.

In the Vienna experience, a dose per pulse is applied with a dose rate between 50 and 100 cGy per hour. The total dose at point A is 50 - 60 Gy given in two fractions about two weeks apart. The TRAK is 3.4 - 4 cGy at 1 meter. In addition, 25 Gy from external beam therapy is added applying the same technique for shielding as for combination treatment with HDR brachytherapy.

9.5.3 Definitive HDR Brachytherapy and EBT in extended disease (Vienna) (96)

For patients with extended disease brachytherapy starts at the latest during the last week of external beam therapy. External beam therapy is given with a four field box technique in 1.8 - 2 Gy fractions up to a total dose of 45 - 50 Gy at the ICRU-point (45 Gy with concomitant cis-platin chemotherapy). Four (3 - 5) single fractions of HDR brachytherapy with 7 Gy are applied over 10 - 20 minutes twice weekly 4 times (3 - 5), partly concomitant with EBT covering the GTV/PTV as much as possible. The overall treatment time is 6 - 7 weeks.

TRAK averages 1.4 - 1.9 cGy at 1 meter for 3 - 4 fractions in large tumours. The physical total dose at point A is 73 - 78 Gy in large tumours (4 fractions). The corresponding isoeffective dose (see above) is 80 - 90 Gy, respectively. The doses per fraction at the pelvic side wall, at the internal and common iliac lymph nodes are 1.4, 1.2, and 0.9 Gy, respectively (ICRU points) (at medium dose rate). The treated volume from brachytherapy and EBT (isoeffective dose of 80-90 Gy) has been 87 cm³ (it is nowadays slightly larger ~ 110 cm³), the 60 Gy reference volume (taking the 3.1/3.4 Gy isodose as isoeffective depending on the total dose of EBT: 50/45 Gy) is 316/290 cm³. The mean dose per fraction at the ICRU rectum reference point is 4 - 5 Gy, adding up to 12 - 20 Gy in 4 fractions and together with the dose from EBT (25x2Gy) to a nominal dose of 62-70 Gy. The corresponding isoeffective dose (alpha beta value of 3) is 70 - 80 Gy. Bladder doses are in principle similar, but somewhat higher. Doses at the vagina vary significantly, with doses from 10-30 Gy per fraction.

9.5.4 Definitive PDR Brachytherapy and EBT in extended disease (Leuven, Vienna)

In the Leuven experience, treatment starts with 50 Gy external beam therapy (45 Gy with simultaneous cis-Platin chemotherapy) without any shielding of the brachytherapy volume. The total dose of brachytherapy is similar to LDR brachytherapy (50 - 80 cGy per hour). A maximum dose to the PTV is given respecting a maximum dose of 65 - 70 Gy to the rectum and of 70 - 75 Gy to the bladder.

In the Vienna experience treatment starts with 50 Gy external beam therapy (45 Gy with simultaneous cis-Platin chemotherapy) without any shielding of the brachytherapy volume. A pulse dose is applied with a dose rate between 50 and 100 cGy per hour. The total dose in point A is 30 Gy given in one fraction. The TRAK is 2 cGy at 1 meter. The maximum biologically weighted dose to the rectum is 70 - 80 Gy and to the bladder 75 - 90 Gy.
10 Monitoring during Brachytherapy

10.1 LDR, MDR, PDR brachytherapy

Monitoring during the implant has two goals: to check the quality of the irradiation and to assure good patient tolerance.

The position of the applicator inside the patient must be checked daily for every standard applicator. With a mould applicator a radiograph must be taken the day after the implant; these films are the basis for the computerised dosimetry, because after the second day, the applicator and consequently the radioactive sources keep their definitive position until the end of the irradiation.

MDR and PDR brachytherapy is systematically accomplished with a remote afterloading machine; nowadays, LDR brachytherapy is also performed in >90% of cases with an afterloading device. The aim of a remote afterloading machine is total radioprotection for the personnel and the patient’s family. The patient tolerates the treatment better physically and psychologically and dose distribution can be optimised (possibilities of partial disconnection, change of source length during the application).

Medical monitoring is comparable to that of the different LDR brachytherapy procedures. Several days are necessary, usually from one day and a half to six days. Usually, patients are treated with heparin to prevent thromboembolic disorders (less than 1% in modern LDR brachytherapy experience). Antibiotics are not prescribed routinely (“prophylactially”), but only if there is an urinary or other infection. Symptomatic treatment for pain is given, if necessary.

If the brachytherapy lasts longer than one or two days, rectal discharge must be avoided. A specific diet for food therefore must be followed the days before application, excluding for example vegetables, fruits, and fresh bread.

10.2 HDR Brachytherapy

Mild forms of acute bladder reactions occur regularly as side effects immediately after HDR brachytherapy and usually disappear spontaneously within 1 or 2 days. No specific treatment is necessary.

11 Results

11.1 Local control and survival

Results of treatment for cervix carcinoma are often difficult to compare because of differences in the classification used and, above all, because of the different treatment schedules and methods of brachytherapy (techniques, doses, volumes, dose rates) (34). For clarity, the main results are presented essentially in table form, according to stage distribution and to the main therapeutic approaches as previously presented. Other patient and treatment related factors, which are also of major importance, such as tumour volume (3,88), and overall treatment time (29,45), are not dealt with in the following presentation of results.

For limited disease (stage IB, IIA) radiotherapy or surgery may be used with similar effects on outcomes (27). However, adverse side effects in the urinary tract are more pronounced after surgery (69).
Classification

In invasive carcinoma of the cervix, a distinction is made taking into account the treatment regimen between limited disease and extended disease.

Limited disease includes FIGO stages IB, IIA and IIB, when involvement of the vagina is limited to the upper third (proximal IIA) and/or when involvement of the parametria is limited to their internal third (proximal IIB). These limits determine the limits in terms of surgical indications. With regard to large volume stage IB (IB₂: > 4.0 cm), some authors now consider IB₂ locally advanced disease.

Locally advanced disease consists of stages IIIA-IIIB, IVA and also IIA-IIB when tumour involvement of the vagina extends beyond the upper third (distal IIA) and/or when tumour involvement of the parametria extends beyond the internal third (distal IIB). A major problem is that most studies do not refer to this classification. Stage II is then defined regardless of tumour extension.

11.1.1 Limited disease

11.1.1.1 Surgery (+/- postoperative radiotherapy)

<table>
<thead>
<tr>
<th>Authors</th>
<th>N° pts</th>
<th>Stage</th>
<th>5-yr survival (%)</th>
<th>Postop RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Averette (1)</td>
<td>726</td>
<td>IB, IIA</td>
<td>88</td>
<td>No</td>
</tr>
<tr>
<td>Bianchi (7)</td>
<td>97</td>
<td>IB</td>
<td>96 (83 in N+)</td>
<td>N+ only</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>IIA</td>
<td>93 (76 in N+)</td>
<td></td>
</tr>
<tr>
<td>Brunswig (10)</td>
<td>200</td>
<td>I</td>
<td>79</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>284</td>
<td>II</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>Burghardt (11)</td>
<td>122</td>
<td>IB</td>
<td>82</td>
<td>T size</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>IIA</td>
<td>50</td>
<td>N+</td>
</tr>
<tr>
<td></td>
<td>195</td>
<td>IIB</td>
<td>77</td>
<td>±</td>
</tr>
<tr>
<td>Dargent (20)</td>
<td>103</td>
<td>IB</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td></td>
<td>42</td>
<td>IIA</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td></td>
<td>55</td>
<td>IIB prox.</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>Kristensen (68)</td>
<td>162</td>
<td>IB</td>
<td>87</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>73</td>
<td>IIA</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td></td>
<td>57</td>
<td>IIB</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>Masterson (75)</td>
<td>120</td>
<td>IB</td>
<td>87</td>
<td>No</td>
</tr>
</tbody>
</table>

Table 1: Results of surgery (+/- postoperative radiotherapy)

The 5-yr survival rate according to stage varies from 79 to 84% for stage I and from 54 to 77% for stage II. These results are comparable to the results of the last annual report: 90% and 67% for stage I and II respectively (34).

11.1.1.2 Combined radiotherapy and surgery

The retrospective largest series presented here systematically included brachytherapy (LDR) followed by surgery and completed by external beam radiotherapy, performed before brachytherapy in IB₂ cases or after surgery in case of positive nodes.
### Table 2: Results of preoperative radiotherapy and surgery

<table>
<thead>
<tr>
<th>Authors</th>
<th>N° pts</th>
<th>Stage</th>
<th>5-yr survival (%)</th>
<th>Local control (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bachaud (2)</td>
<td>115</td>
<td>IB, II</td>
<td>82</td>
<td>87</td>
</tr>
<tr>
<td>Calais (12)</td>
<td>70</td>
<td>IB</td>
<td>92</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>IIA-B prox.</td>
<td>78 (10 yr OS)</td>
<td>93</td>
</tr>
<tr>
<td>Durand (24)</td>
<td>228</td>
<td>I</td>
<td>81 OS</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>84</td>
<td>II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fletcher (36)</td>
<td>983</td>
<td>IB, IIA</td>
<td>60 (?)</td>
<td></td>
</tr>
<tr>
<td>Gerbaulet (39)</td>
<td>288</td>
<td>IB</td>
<td>88 DFS</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td>103</td>
<td>IIA-B prox.</td>
<td>83 DFS</td>
<td>89</td>
</tr>
<tr>
<td>Grigsby (47)</td>
<td>118</td>
<td>IB</td>
<td>81 DFS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>82</td>
<td>II</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>Lasry (70)</td>
<td>415</td>
<td>T1 331</td>
<td>82 OS 10y</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T2 84</td>
<td>59</td>
<td>85</td>
</tr>
<tr>
<td>Muirhead (79)</td>
<td>1576</td>
<td>IB, IIA</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>Pernot (92)</td>
<td>205</td>
<td>IB</td>
<td>78 DFS</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>101</td>
<td>II</td>
<td>60</td>
<td>70</td>
</tr>
</tbody>
</table>

For the French school (24,41,78), the advantage of combining brachytherapy and surgery is to select patients who need complementary EBRT and to decrease the morbidity induced by brachytherapy and by surgery, each treatment being completed by the other. Nevertheless, this combined treatment must be reserved for stages IB and proximal II, as distal stage II is considered as locally advanced disease and is treated by definitive radiotherapy (92).

For these series, 5-year survival ranges from 81 to 92% for stage IB and from 78 to 85% for proximal stage II. If the tumour size exceeds 4 cm, patients are treated with a combination of external irradiation and concomitant chemotherapy, followed by brachytherapy. In these cases the role of complementary surgery is still questionable, as no available data have shown a benefit from surgery in this situation.

#### 11.1.1.3 Definitive radiotherapy

A larger number of results have been published for all stages of uterine-cervix cancer, including limited disease, some of which are reported here. The treatment consists of a combination of external beam radiotherapy and brachytherapy. The selection is mainly based on the treatment methods described in detail before: Manchester, Fletcher, Dijon, IGR, Vienna.
### Table 14.3: Results of definitive radiotherapy in limited disease

<table>
<thead>
<tr>
<th>Authors</th>
<th>N° pts</th>
<th>Stage</th>
<th>5-yr survival (%)</th>
<th>Local control (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manchester 80-88 LDR Hunter 1993</td>
<td>294</td>
<td>I/IIA IB IIB</td>
<td>90-94 (DFS)</td>
<td>71 (OS)</td>
</tr>
<tr>
<td>Horiot (93) (62)</td>
<td>45</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Horiot (93) (62)</td>
<td>70</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perez (87) LDR</td>
<td>384</td>
<td>IB 128 IIA 353</td>
<td>85</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>1993</td>
<td>IIB</td>
<td>70</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>1993 (62)</td>
<td>IB</td>
<td>72</td>
<td>77</td>
</tr>
<tr>
<td>Fletcher (35) LDR</td>
<td>494</td>
<td>IB IIA-MDAH IIB-MDAH</td>
<td>84</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>207</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>French cooperative group LDR</td>
<td>229</td>
<td>I MDAH IIA-MDAH IIB-MDAH</td>
<td>89 (89)</td>
<td>93 (95)</td>
</tr>
<tr>
<td>Horiot (53)</td>
<td>315</td>
<td></td>
<td>81 (85)</td>
<td>83 (88)</td>
</tr>
<tr>
<td>Kim (66) LDR</td>
<td>314</td>
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<td>76 (76)</td>
<td>80 (78)</td>
</tr>
<tr>
<td>Lowrey (74) LDR</td>
<td>169</td>
<td>IB IIA</td>
<td>82</td>
<td>89</td>
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<tr>
<td></td>
<td>83</td>
<td></td>
<td>78</td>
<td>91</td>
</tr>
<tr>
<td>Pernot (92) LDR</td>
<td>130</td>
<td>IB IIA</td>
<td>81</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td>64</td>
<td></td>
<td>74</td>
<td>84</td>
</tr>
<tr>
<td>Pernot (92) LDR</td>
<td>173</td>
<td>IIA-B prox.</td>
<td>74</td>
<td>79</td>
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<tr>
<td>Coia (18) HDR</td>
<td>203</td>
<td>IB</td>
<td>80</td>
<td>90</td>
</tr>
<tr>
<td>Joslin (64, 65) HDR</td>
<td>95</td>
<td>I II</td>
<td>94</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>170</td>
<td></td>
<td>62</td>
<td>74</td>
</tr>
<tr>
<td>Peterieit (93) HDR</td>
<td>59</td>
<td>IB II</td>
<td>86</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>64</td>
<td></td>
<td>65</td>
<td>80</td>
</tr>
<tr>
<td>Vienna HDR</td>
<td>42</td>
<td>IB/IIB</td>
<td>85 (DSS)</td>
<td>97</td>
</tr>
<tr>
<td>Pötter (96)</td>
<td>124</td>
<td></td>
<td>69 (DSS)</td>
<td>82</td>
</tr>
</tbody>
</table>

In conclusion, mean 5-year survival for stage IB is 85%, with a mean local control of 90%, for stage IIA 78 and 83 respectively, while for stage IIB the outcome varies considerably - probably due to patient selection – from 50% to 76% for survival and 60% to 87% for local control.

#### 11.1.2 Locally extended disease

The main treatment is definitive radiotherapy, combining external beam irradiation and brachytherapy, more recently associated with concomitant chemotherapy. Chemotherapy is also indicated in limited disease with high-risk factors (IB2, positive nodes).

In conclusion, the mean 5-year survival for distal stage IIB varies from 65 - 70%, with local control rates of about 77%, for stage IIIB from 34 - 52%, with local control from 44 - 66%, and for stage IVA from 0 - 20%, with local control from 18 - 48%.
Table 14.4: Results of definitive radiotherapy in extended disease

<table>
<thead>
<tr>
<th>Authors</th>
<th>N° pts</th>
<th>Stage</th>
<th>5-yr survival (%)</th>
<th>5-y Local control (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manchester 1993</td>
<td>50</td>
<td>III</td>
<td>34 OS</td>
<td></td>
</tr>
<tr>
<td>LDR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hunter 2001 (62)</td>
<td>293</td>
<td>III</td>
<td>52 DFS</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>IV</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>Perez (86)</td>
<td>73</td>
<td>a*</td>
<td>44 OS</td>
<td>67</td>
</tr>
<tr>
<td>LDR</td>
<td>25</td>
<td>b*</td>
<td>60 OS</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>93</td>
<td></td>
<td>36 DSS</td>
<td>78</td>
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<tr>
<td>Houston MDAH (26, 28)</td>
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<td>IIIA</td>
<td>61 OS (62)</td>
<td>68 (63)</td>
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<td>216</td>
<td>MDAH</td>
<td>39 OS (50)</td>
<td>45 (57)</td>
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<td></td>
<td>32</td>
<td>IV</td>
<td>20 OS</td>
<td>18</td>
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<td>French cooperative group LDR (53)</td>
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<td>Distal II</td>
<td>65 OS</td>
<td>78</td>
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<td></td>
<td>416</td>
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<td>42 OS</td>
<td>66</td>
</tr>
<tr>
<td>Paris IGR (42)</td>
<td>60</td>
<td>Distal II</td>
<td>70 OS</td>
<td>77</td>
</tr>
<tr>
<td>LDR</td>
<td>107</td>
<td>IIIB</td>
<td>42 OS</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pernot (92)</td>
<td>106</td>
<td>III</td>
<td>38 OS</td>
<td>56</td>
</tr>
<tr>
<td>LDR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joslin (64, 65)</td>
<td>50</td>
<td>IIIB</td>
<td>33 OS</td>
<td>44</td>
</tr>
<tr>
<td>HDR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peteriet HDR (93)</td>
<td>78</td>
<td>IIIB</td>
<td>48 DSS</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>IVA</td>
<td>19 DSS</td>
<td>48</td>
</tr>
</tbody>
</table>

*In the analysis by Eifel et al. (26) patients were grouped according to the total dose applied in terms of radium mg.h (>\(\leq\) 6000) or dose to point A: a: \(>\leq\) 85 Gy (mean 89); b: < 85 Gy.

The increasing use of HDR brachytherapy has been controversial for decades (compare 25). Few results, which can be taken as comparable to LDR and which may be representative, have been listed in tables 4 and 5 (64,65,93,96,105; for a retrospective comparative overview see 82; for a comparison of dose and fractionation see 94 and 108). The results of a few prospective comparative trials between LDR and HDR brachytherapy are presented here (Table 6). These trials did not always meet the current criteria for a prospective controlled comparative evaluation of different treatments. Therefore, the results shown in the table must be interpreted with much caution.
Table 14.5: Results of trials comparing low dose-rate and high dose-rate in cervix cancer brachytherapy

<table>
<thead>
<tr>
<th>Authors</th>
<th>Patients (n)</th>
<th>Stage</th>
<th>5-yr survival (%)</th>
<th>Local control (%)</th>
</tr>
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<tr>
<td></td>
<td>HDR</td>
<td>LDR</td>
<td>HDR</td>
<td>LDR</td>
</tr>
<tr>
<td>Gupta (48)</td>
<td>102</td>
<td>120</td>
<td>I-III</td>
<td></td>
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<tr>
<td>Patel (83)</td>
<td>35</td>
<td>39</td>
<td>I</td>
<td>78</td>
</tr>
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<td></td>
<td>90</td>
<td>93</td>
<td>II</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>111</td>
<td>114</td>
<td>III</td>
<td>43</td>
</tr>
<tr>
<td>Rotte (102)</td>
<td>42</td>
<td>28</td>
<td>I</td>
<td>83</td>
</tr>
<tr>
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<td>59</td>
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<td>75</td>
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<td></td>
<td>11</td>
<td>88</td>
<td>III</td>
<td>37</td>
</tr>
<tr>
<td>Shigematsu (106)</td>
<td>143</td>
<td>106</td>
<td>IIIB-III</td>
<td>60</td>
</tr>
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<td>Teshima (111)</td>
<td>32</td>
<td>28</td>
<td>I</td>
<td>66-89</td>
</tr>
<tr>
<td></td>
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<td>II</td>
<td>61-78</td>
</tr>
<tr>
<td></td>
<td>147</td>
<td>82</td>
<td>III</td>
<td>47-45</td>
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</tbody>
</table>

11.1.3 Concomitant radio-chemotherapy.

In patients considered at high risk of recurrence including pelvic failures and distant metastases i.e. patients with a tumour size greater than 4 cm or with unfavourable prognostic factors after initial surgery, nine randomized controlled trials have been published in the last years assessing the role of concomitant chemoradiotherapy (46). Six of them showed a statistically significant benefit with radiochemotherapy. A systematic review of these trials and meta-analysis demonstrated a potential absolute survival benefit of 12% with concomitant radiochemotherapy, with a highly significant reduction of distant metastases as well as local recurrences for both platinum and non-platinum groups (46). In the trials however, it must be pointed out that 68% of enrolled patients had Stage I and II disease and that patients with para-aortic node involvement were excluded. It is therefore difficult to extrapolate these results to patients with locally advanced disease, Stage III and IV (46, 112).

There has been some controversy as well, because the reported results in the randomized arms with radiation alone, without chemotherapy, were rather poor, as compared to the largest series published in the literature. Potential explanations were a low total dose of irradiation and an overall treatment time exceeding 52 days in most trials. It has even been stated that the potential loss of local control due to an increased overall treatment time was equal to the benefit of concomitant radiochemotherapy (45,85).

In the trials, the use of concomitant chemotherapy during brachytherapy was not systematically included so that the value of this combined treatment cannot be clearly stated.

Acute toxicity was not systematically reported in detail in all trials. From the meta-analysis, however, it was concluded that acute toxicity was significantly increased in all trials (haematological and gastrointestinal toxicity). Late toxicity was recorded only in few trials (three of them) without there being any long-term follow-up. Long-term toxicity was defined as beginning 42 to 90 days after completion of radiation. No evidence of differences between the treatment groups was observed (46) but longer follow-up is obviously necessary.
11.2 Adverse side effects

The diversity and severity of early and late complications in patients with gynecological tumors have led to the development of different scoring systems. The two systems which have been the most widely used are the Franco-Italian glossary and the RTOG-EORTC Lent-Soma scale (72,84,103). The Franco-Italian glossary scored the complications in four grades of increasing severity in 14 different organs or normal tissues and took into account different treatments (14). The aim of this glossary was to standardize complication assessment and allow comparisons between different therapeutic strategies. This glossary is specific for gynaecological tumors. It has been shown to be very useful in evaluating treatment protocols. Prospective evaluation of complications appeared to be the best approach as it made it possible not only to grade them at a particular point in time, but also to record their duration and their possible re-occurrence.

With this information about the evaluation of mostly late complications, their occurrence has been modified by adapting brachytherapy techniques (19). These data have been recently updated and have confirmed the reliability of the glossary with good correlation of morbidity with survival over time (4). In this series, the glossary had limited usefulness in the grade 3 complication group which appeared to comprise an inhomogeneous cohort of patients. The scoring 3 did not take into account the assessment of the complication by the patient with potential long-term detriment, and a division into three subgroups was therefore proposed.

The RTOG-EORTC Lent-Soma scale was designed in 1995 with the aim of encompassing all complications regardless of tumor site. This scale combines acute and late morbidity, for objective and subjective symptoms. It is not specific for pelvic malignancies and is restricted to post radiation changes. It is still under evaluation in prospective studies and clinical trials.

The main complications following treatment of cervical cancer involve the bowel and urinary tract. The overall actuarial 5-year severe complication-rate ranges between 8 and 10%. Late sequelae mainly occur during the first 3 to 5 years following treatment, with a decrease later on. Digestive complications usually occur earlier than urinary complications (30 months vs 48 months). There is a continuous risk of all types of complications as demonstrated in the Eifel series (73) of 1784 patients with an estimated rate of 0.34% per year after treatment: rectal complications increased by 1% during the first 2 years with a decrease to 0.06% per year after, while bladder complications increased by 0.7% during the first 3 years, later stabilising at 0.25% per year.

Factors responsible for radiotherapy-induced toxicity are divided into two categories: some are directly linked to the radio-brachytherapeutic techniques and doses, others are independent of irradiation, and include surgery, concomitant chemotherapy, diabetes, HTA…We will focus in this chapter on the factors directly related to irradiation.

11.2.1 Total dose

Perez (87) showed that the most significant factor affecting the appearance of complications was the total dose of irradiation to the pelvic organs by both whole pelvic irradiation and intracavitary insertions. The incidence of complications significantly increased when the dose exceeded 80 Gy. A more recent analysis with a larger number of patients (up to 1456) confirmed the role of the total dose (89). For the bladder, a dose below 80 Gy correlated with less than 3% of morbidity while this rate reached 5% with higher doses. In the rectosigmoid, the incidence of morbidity significantly increased when the total dose exceeded 75 Gy: 4% with doses below 75 Gy and 9% with higher doses. The dose to the latero-pelvic wall was also a significant factor influencing small intestinal complications: the complication rate was less than 1% with a total dose of 50 Gy or less, 2% with 50 to 60 Gy, and 5% with higher doses. The influence of total dose was also demonstrated by other authors. As an example, Sinistretero (107) reported a mean total dose of 55.7 Gy for patients without
complications, 61.8 Gy for patients with grade 1 complications, 63 Gy for grade 2 complications and 74 Gy for grade 3 complications.

### 11.2.2 Volume

In the combined external irradiation and brachytherapy approach, the complications closely correlated to the volume. Esche (30) et al. demonstrated a significant increase in the volume included within the 60 Gy isodose when the external irradiation dose exceeded 30 Gy. In the same Dijon experience, Crook (19) et al. were able to draw scattergrams according to the severity of complications scored in three different types as a function of the 60 Gy reference volume and reference doses to critical organs. Barillot (4) recently updated these data with 642 patients treated with radiotherapy alone for intact uterine cervix carcinomas between 1970 and 1994. The analysis was divided into 3 periods: 1970-1978 (use of standard prescriptions), 1979-1984 (implementation of individual adjustments), 1985-1994 (systematic individual adjustments). Comparison of the 3 time-periods showed a significant reduction of the external radiation dose (dose above 40 Gy in 47% of patients before 1979 vs 36% after 1984), in the use of a parametrial boost (55% vs 39%), of the use of vaginal cylinder (28% vs 11.5%) and in the HWT volume (842 cm³ vs 503 cm³ on average). The total sequelae/complication rate for all toxicity grades, all stages, all organs was 51%. The five-year actuarial rate by grade of toxicity was: G1 42%, G2 23.5%, G3 10%, G4 3%. There were no G4 toxicity in the third period. The rate of G3 complications dropped from 16% to 6% over time: from 5% during the first period to 0% during the third period in stage I, from 8% to 6% in stage II and from 23% to 12% in stages III. With this approach of customized treatment planning, the authors were able to eradicate lethal complications and significantly decrease G3 toxicity in all stages while maintaining high cure rates in early stages. The authors however recommended a cautious reduction of the dose in stage III.

### 11.2.3 Influence of the brachytherapy technique

Perez (89) compared the incidence of complications in 298 patients treated either with mini vaginal colpostats with or without shields or with the standard Fletcher-Suit applicator. In this series, grade 3 - 4 complications occurred in 7.6% of the patients treated with the standard applicator while the complication rate reached 26.9% in patients treated with the minicolpostats and 36.6% with the minicolpostats with shields. The use of vaginal cylinders has also been reported as predictive factor of complications. In the Dijon series reported by Barillot (4), it was the most powerful factor for predictive complications. The effect of using vaginal cylinder applicators was carefully studied by Tan et al (110) at the Clatterbridge center. A single line source brachytherapy technique has been developed to boost the tumor after whole pelvis external beam radiotherapy for radical treatment of stage Ib to IV cervix carcinomas. With this technique, when vaginal cylinders of limited length were used, a very low rate of severe toxicity was observed (G3 urinary tract 0.6%, G3 bowel 1.4%). This experience suggested that vaginal cylinders may reflect a selection of worse cases not suitable for a standard technique.

### 11.2.4 Influence of dose-rate

The role of dose-rate in relation to complications outcome has been widely debated. Two randomized trials (83,106) and one large retrospective study (82) have compared high dose-rate to low dose-rate treatment in cervix cancer. For Shigematsu (106), with similar 5-year survival rates, a higher rectal complication rate was observed in the high dose-rate arm (with a schedule of 3 fractions of 10 Gy to point A). Conversely, a significantly higher rate of recto-sigmoid complications was noticed in the low dose-rate group (one or two brachytherapy sessions up to 35 Gy to 37.5 Gy to point A in the Patel trial (83). In the retrospective analysis from Orton (82), moderate and severe complications were significantly higher in the low dose-rate group with radium applications 77 hours. In the former analysis however, the comparison was performed between historical series of patients.
treated with radium without any sophisticated dosimetry and more recent patients treated with high
dose-rate using more advanced technology. Haie et al. (50) conducted a randomised trial comparing
two pre-operative brachytherapy low dose rates in cervical carcinoma. The statistical analysis
carried out by the prevalence method, showed that the higher dose rate (0.73 Gy/h) was associated
with 45% of complications at 2 years versus 30% for the lowest dose rate (0.38 Gy/h). The severe
complications were also increased (13% versus 7%). Two other authors: Newman (80) and
Rodrigus (100) reported increased morbidity following the introduction of remote afterloading, with
increased dose rate, for cancer of the cervix. Rodrigus et al decided to reduce the brachytherapy
dose per application from 25 Gy to 20 Gy in order to prevent the risk of complications with increasing
dose rate (0.54 Gy/h versus 1.07 Gy/h). These authors observed an increase in late gastro-intestinal
sequelae of 12% and in late rectal complications of 7% with an increase of dose rate above 0.5 Gy/h
for rectal and bladder complications. A significant increase in complications was also seen in the
Manchester trials when comparing the classical dose rate of Radium (0.53 Gy/h) with dose rates of
Cesium (1.4 - 1.8 Gy/hour). The rate of complications at 5 years was the same with a total dose of
60 Gy of Cesium as with 75 Gy of Radium, (dose ratio of 1.25), whereas for the same total dose
applied with Cesium (75 Gy), there was an increase in complications at 5 years from 15% to 56%
compared to the same dose given with Radium (62). Leborgne et al (71) also showed a marked
dose-rate effect at 1.6 Gy/h to point A. The highest complication rates were observed with a
schedule of two fractions of 24 Gy or three fractions of 15.3 Gy. With these schedules the grade 2
and 3 rectal or bladder complications were 83% and 30% respectively.

11.2.5 Other factors

* Previous pelvic or abdominal surgery has been shown to have an impact on colonic or small
intestinal late injuries. The risk appeared to be proportional to the number of previous laparotomies
irrespective of time or purpose.

* Extended fields to the para-aortic area have been shown from 3 randomised studies comparing
pelvic to pelvic plus para-aortic radiotherapy to have an impact on the incidence of gastro-intestinal
complications (17,49,101). For Chatani et al (17), the overall complication rate was 30% in the para-
aortic arm, with 7% of enteritis ileus and less than 10% in the pelvic arm. Rotman (101) reported a
6% lethal complication rate in the para-aortic arm compared with 1% in the pelvic arm.

* Concomitant radiochemotherapy is also a factor increasing the complication rate.

12 References

alone or in combination with surgery in stage Ib, Ila and “proximal” IIb carcinoma of the cervix.
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Customized Treatment Planning in Cervix Carcinomas: Baseline Results to Compare New


80. Newman G. Increased morbidity following the introduction of remote afterloading, with increased dose rate, for cancer of the cervix. *Radiother Oncol* 1996; **39**: 97-103.


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