15
Endometrial Cancer
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1 Introduction

The frequency of occurrence of endometrial cancer has been rising in recent decades. Its incidence in Western countries is high (25 cases/100000 women), whereas it is low in Eastern countries (2 cases/100000 women). It has become the fourth most common cancer in females, after breast, lung, and bowel cancer (22,74,81).

The majority of these cancers are seen in menopausal women, with a median age of 60 years. Only 25% occur in premenopausal women. The risk of development of endometrial cancer is significantly increased in women with obesity, diabetes mellitus, hypertension, and nulliparity, late menopause, unopposed estrogen, and if there is complex atypical hyperplasia (74,81).

The main symptom (90%) is vaginal discharge with bleeding in the majority (90%). Because of this characteristic symptom in the postmenopausal woman, the disease is most often diagnosed at an early stage (22).

The most important prognostic factor is the extent of disease at diagnosis, defined by nodal involvement, tumour invasion beyond the uterus, tumour grading and depth of myometrial infiltration. These different prognostic factors are often correlated to each other. Histological subtyping is also important with a worse prognosis for those histologies which do not correspond to the classical endometrioid adenocarcinoma (4,10,30,43,54,56,82).

The main treatment for endometrial cancer is surgery (33,35,37,47,53,66,77). Traditionally, surgery has been total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO) with excision of a small cuff of vagina and lymph node sampling (pelvic +/- paraaortic) in some cases, in particular those at high risk of lymphatic spread. Lymph node dissection has recently been integrated more systematically into the primary surgical strategy (47). The number of women who are regarded as medically inoperable has decreased significantly (22,27) due to developments in anesthesia and postoperative intensive care and also partly due to the possibilities offered by laparoscopic approaches (3).

Surgery has traditionally been combined with radiotherapy, to prevent vaginal recurrence (reported in up to 10 - 15% after surgery alone) and pelvic lymph node recurrence. In the past, this has often been preoperative radiotherapy, mainly as uterovaginal or vaginal brachytherapy. Increasingly, surgery is performed first and the treatment strategy is based on pathohistological findings (43). Based on the individual assessment of different risk factors for vaginal and/or pelvic lymph node failure the appropriate adjuvant radiotherapeutic treatment strategy is then chosen, either "wait and see" or brachytherapy with or without external beam therapy.

As nowadays fewer women are irradiated as part of their primary treatment (37,47,66,77), radiotherapy for recurrent disease is becoming an increasingly important issue (see also chapter on interstitial gynaecological brachytherapy (17)).

Antineoplastic drug treatment (hormonal therapy or chemotherapy) has played no role in the curative management of this disease and is limited to palliative indications.
2 Anatomical Topography

The uterine corpus is formed by a large smooth muscle with different layers, varying in thickness from 10 - 30 mm (myometrium). Its cavity is covered by cylindrical epithelium with many different functions and different thickness, the endometrium. The top, the back and the upper parts of the front wall are covered by serosa, the perimetrium (peritoneum). The uterine body which is very well vascularized has a high tolerance to radiation (22,74).

The coronal shape of the uterus and uterine cavity is similar to a pear with the fundus and the two entrances to the Fallopian tube at the top (Fig 15.2). At the bottom it opens into the endocervical canal. Its sectional shape is usually wider than it is thick with the largest dimensions at the fundus: e.g. 5 cm width x 4 cm thick (fundus) and 4 cm width and 3 cm thick (isthmus) (Fig 15.3). The length of the uterine cavity is about 4 - 10 cm. Anatomically it is closely related (within the range of mm) to the bladder (posterior wall), to the small and large bowel (more particularly to the sigmoid), and more distantly to the rectum. The intact vagina with its thin wall (thickness of a few mm) has close relationships to the rectum and to the posterior bladder wall and is more distant from the urethra.

Fig 15.1: Topography of the vagina
A: Sagittal and transverse MRI after hysterectomy with a 30 mm diameter applicator. Close topographical relationships with bladder, bowel and rectum. Thickness of vaginal wall ~ 2mm.
B: Dimensions of the vaginal wall by endorectal sonography without (B1) and with (B2) vaginal Applicator. Wall thickness varies from 4 to 2 mm.

The topography of the vaginal stump after hysterectomy is dominated by close relationships to the rectum, the posterior-caudal part of the bladder and to different degrees to parts of the bowel, which may be lying directly on the cuff (Fig 15.1A). The topographic relationships are even closer than in the preoperative situation as the uterus itself has been removed (18,20).
The cuff itself has varying dimensions, in particular in thickness, depending also on the filling status (Fig 15.1B).

3 Pathology

The majority of tumours arise from the fundus and the uterine corners (about 80%) with exophytic and endophytic growth patterns. The most common type of invasive uterine tumour is the endometrioid adenocarcinoma comprising about 75 - 80% of all cases (4,22). The major discrimination within this histological group is according to the amount of differentiation. Whereas in the well differentiated tumours, well-preserved glands are seen in more than 90% (predominantly tubular structures: grade 1), this applies for less than 50% in the poorly differentiated tumours (predominantly solid structures: grade 3) (4,74). This differentiation correlates with biological aggressiveness, the frequency of lymph node metastases and thus with prognosis (grading defined according to FIGO) (32). The various histologic mixture subtypes of endometrioid carcinoma are of minor clinical importance: secretory, papillary, ciliated cell, adenosquamous, adenocanthoma. The mucinous subtype carries the same prognosis as endometrioid carcinoma, but the prognosis is much worse in serous papillary carcinoma (< 10% of endometrial cancer) because of its myometrial invasion and early pelvic lymphatic and peritoneal spread and also in clear cell carcinoma. Another rare aggressive form is also the undifferentiated small cell carcinoma (< 1%).

Since 1988, the FIGO staging of endometrial cancer has required surgical removal of the uterus, as since then staging has been exclusively related to pathohistological examination particularly depth of myometrial invasion (<1/2 vs >1/2 of the myometrium) and tumour differentiation (grading), defining stage I A,B,C and providing relevant clinical information in stage II-IVA. Stage III allows for discrimination between local invasion (serosa, adnexae, positive peritoneal cytology IIIA), vaginal metastases (IIIB), and lymph node metastases (IIIC) (32). The old FIGO clinical staging system (31), which discriminates stage I according to the length of the uterine cavity is still in use for staging in definitive radiotherapy: clinical FIGO stage IA <8cm, IB >8 cm.

The pathogenesis of vaginal recurrence has not yet been clarified. One widespread hypothesis is that there is tumour contamination along the mucosal surface by the medical interventions. The vast majority of vaginal recurrences (90%) occur at or around the vaginal cuff.

4 Work Up

Systematic work up includes the following: history, general and gynaecological examination, one biopsy and/or systematic biopsies (corpus/cervix); fractionated curettage; chest radiograph; abdominal CT; cystoscopy and rectoscopy in advanced disease.

For postoperative radiotherapy, the pathologic tumor stage is determined based on the surgical report and on a thorough pathohistologic examination of the uterus (grading, depth of infiltration) and the vaginal stump (free margins). After lymph node sampling, there is additional information on pathologic lymph node stage. Clinical examination assesses the vaginal scar and the width and length of the vagina.

Staging for preoperative brachytherapy is done according to the results of clinical examination and fractionated curettage and is supported by modern imaging methods (e.g. US).

For definitive radiotherapy, the clinical stage is defined according to the histopathologic report from fractionated curettage (cervix/corpus), the measurement of the length of the uterine cavity, and the
findings from clinical examination, which mainly addresses position and size of the uterus and excludes parametrial infiltration. MRI (Fig 15.2) and endosonography enable a more precise assessment of tumour location and extension in the uterine cavity and through the uterine wall (depth, invasion of the cervix). Hysteroscopy is nowadays used to determine accurately the location of the tumour within the uterine cavity. Computed tomography and transabdominal sonography are of limited value as they only allow the determination of size and position of the uterus. Cystoscopy and rectoscopy are recommended to exclude infiltration of rectum and bladder in advanced disease.

For brachytherapy for recurrent disease, clinical examination, endosonography, vaginal impression and MRI (CT) of the pelvic region are needed to define appropriately the location, extension, and volume of the recurrent tumour and its relation to critical organs such as the bladder, urethra, ureter, rectum, and bowel (see Fig 16.2, 6-7; 17.8-9).

4 **Indications, Contra-indications**

Endovaginal brachytherapy prevents local recurrence in the vagina. The specific indication for brachytherapy after TAH-BSO and excision of a vaginal cuff depends on the different risk factors for
vaginal recurrence, which are in particular: stage, grade, depth of myometrial infiltration, invasion of the cervix, histology and surgical margins. The indication for (additional) external pelvic radiotherapy depends on risk factors for pelvic recurrence, which are mainly nodal involvement, grade, depth of myometrial infiltration, extrauterine spread and histology. The assessment of lymph nodes has been based on clinical judgement (cN0). The place of external pelvic radiotherapy after additional extensive lymph node sampling (39) or dissection (47) ("Wertheim"-like) has not been clarified (pN0/pN1/2) (24). The risk of recurrence is a composite of histologic grade (1,2,3), depth of infiltration (A: 1, B: 2, C: 3), vessel invasion (lymphatic, blood) (yes: 4), intrauterine spread (cervix, stage II) (5), extrauterine spread (e.g. lymph node involvement) (III A: 7, IIIB: 8, IV A: 9) and infavourable histologic subtype (4). The number in parentheses ( ) are taken from the risk score proposed by Kucera et al. (42A,43), in which the different risk factors are given a number, which are added to give a total. The risk of recurrence can be estimated as being low (score: 0-2), intermediate (score 3 - 4) or high (5 and higher). According to this risk score, patients with stage II and III disease, unfavourable histology and patients with vessel invasion are always high risk patients (score 5 and higher).

4.1 Postoperative vaginal radiotherapy

4.1.1 FIGO stage I (pT1, cN0, cM0)

Postoperative brachytherapy is performed according to the individual risk of vaginal recurrence (Table 1,2).

<table>
<thead>
<tr>
<th>FIGO Stage I (pT1)</th>
<th>Depth of infiltration</th>
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<tr>
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Table 15.1: General indications for brachytherapy (BT) and additional external beam therapy (EBT) depending on grade and depth of infiltration in FIGO stage I (32,33) in clinically node negative (cN0) patients after TAH-BSO +/- lymph node sampling (pN0).

4.1.2 FIGO stage II/III

Primary surgery is followed in every case by external beam and brachytherapy of the vaginal cuff.

4.2 Preoperative brachytherapy and postoperative external beam radiotherapy

In the past, preoperative brachytherapy of the vaginal vault was performed routinely (6,18-21,51,63, 64,77,78,80). For clinical FIGO stage II/III, there were two possibilities: vaginal or utero-vaginal brachytherapy. BT was followed postoperatively by external pelvic radiotherapy if there were poor prognostic factors (myometrial invasion, G2/3, stage II/III, unfavourable histology).
4.3 Radiotherapy alone

If surgery is medically contraindicated, brachytherapy to the whole uterus and of the upper part of the vagina is the essential part of the curative treatment (11,17,22,28,40,44,48,55,63,70,71,72,75,79). External pelvic radiotherapy is added if there are unfavourable prognostic factors in stage I (myometrial infiltration > 50%, grade 3) and always in stage II/III.

If the tumour is inoperable because of local extension (fixation in the true pelvis), external beam therapy is the main treatment with an additional brachytherapy boost.

4.4 Brachytherapy for recurrence

Brachytherapy is indicated for the treatment of recurrence (7,23,26,36,45). Depending on the site, extension, volume of recurrence, and previous treatment, endovaginal and/or interstitial brachytherapy is performed, with or without external beam therapy with curative intent, if possible (see chapters on vagina (16) and interstitial gynaecological brachytherapy (17)).

4.5 Histologic subtypes

Independent of stage, certain histologic subtypes (clear cell, seropapillary, undifferentiated) with an unfavourable prognosis are always treated postoperatively by external beam therapy combined with brachytherapy.

6 Target Volume

6.1 Postoperative vaginal brachytherapy

The target is the vaginal mucosa of the vaginal cuff (including the scar) and, for some authors, the whole length of the vaginal walls. However, about 90% of vaginal recurrences occur at the vaginal cuff, and only about 10% in the distal part, mainly in the periurethral region. Therefore, to avoid vaginal morbidity (vaginal dryness, shortening, stenosis), the mucosa of the vaginal cuff and the adjacent mucosa only are taken as the target for brachytherapy, which corresponds to the upper third of the vagina. The resulting mean target length is about 3 - 5 cm. The target width (laterolateral) and thickness (anteroposterior) refer to the respective dimensions of the vagina (~25 - 40 mm). The target depth in the vagina is chosen at a few mm below the mucosal surface (for dose prescription). The most common used prescription point is 5 mm from the applicator surface. The vaginal mucosa must be in direct contact to the applicator surface. The varying thickness of the vaginal wall (2 - 8 mm) may be taken into consideration, particularly if the wall is very thin, as this will affect the dose at the anterior rectal wall (see Fig 15.1). Special care must be taken at the vaginal cuff with its often irregular surface and shape after surgery. If there is a thicker scar or some distance between the applicator and the mucosa, target points are individually adjusted (e.g. up to 10 mm), but the close vicinity of the bowel which may lie directly on the vaginal cuff, must be kept in mind (see Fig 15.1A).

The gynecologic examination (endovaginal and endorectal) is the essential tool for adequate target definition, taking into account the information from surgical and histopathological reports (surgical margins). In specific situations, endovaginal and endorectal ultrasound may add useful information, e.g. with regard to the depth of the scar, the thickness of the vaginal wall, and the position of critical organs.
6.2 Preoperative (utero-) vaginal brachytherapy

The upper third of the vagina is taken as the target volume with 5 mm depth into the vaginal wall in stage I. In stage II, the uterine isthmus and the cervix can be included in addition.

6.3 Radiotherapy alone

The CTV for uterine brachytherapy is the macroscopic tumor and its microscopic extension into the uterine wall. If the tumor is limited to the uterine body (stage I), the whole body and the adjacent part of the cervix represents the CTV. If the tumor is adjacent to the cervix or infiltrates it (stage II), this site is also completely included. Efforts should be made to delineate the GTV in its location and dimensions (depth) (Fig 15.2) as it represents the most relevant part of the CTV ("whole uterine wall"). For practical reasons, the complete diameter of the uterine wall is usually taken as the thickness of the CTV, including the endometrium, the different layers of the myometrium, and the serosa (Fig 15.3). Depending on the pattern of spread, some parametrial tissue may be included in the target in patients with advanced stage I, or II- and in stage III-tumours.

The CTV for vaginal brachytherapy is the vaginal vault and the adjacent vaginal wall in the upper third of the vagina.

Fig 15.3: Endovaginal ultrasound for assessment of the uterine wall thickness at the fundus/uterine body (A), and at the level of the cervix (B) for treatment planning. Wall thickness varies for this patient between 10 mm (anterior wall) and 22 mm (thickness of the fundus).

For adequate definition of the CTV in uterine brachytherapy, information from fractionated curettage (uterine body/cervix), hysteroscopy, and from imaging studies should be available (MRI, sonography (CT)). Hysteroscopy allows the accurate determination of the tumour location within the uterine cavity, CT the delineation of uterine anatomy and of critical organs, endosonography and MRI (in addition) tumour location, tumour volume estimate and the delineation of its macroscopic extension into the uterine wall.

The ideal way to define CTV therefore is to perform hysteroscopy and MRI/endosonography before the application, to enable appropriate planning of the uterine brachytherapy procedure. In addition, MRI or CT should be performed with the applicators in place (Fig 15.2).
For adequate target definition in vaginal brachytherapy, gynecologic examination is usually sufficient. If there is vaginal tumor extension (IIIA), a vaginal impression and endosonography may be beneficial (e.g. to assess the depth of infiltration).

6.4 Brachytherapy for recurrence

The classical sites are at the vaginal stump and in the periurethral region, less frequently the middle third of the vagina is involved. For brachytherapy (after tumour shrinkage by external beam therapy), a combination of endovaginal and interstitial brachytherapy is performed, if necessary. The CTV is determined individually and encompasses the macroscopic tumour at the time of brachytherapy plus a safety margin for microscopic disease (a few mm). If necessary and possible, tumour extension at diagnosis is also included. The adjacent parts of the vagina should also be included in the CTV and depending on the site, the medial part of the paracolpium and parametrium, respectively. Specific care must be taken because of the proximity of adjacent healthy structures (e.g. urethra, bladder, rectum, bowel).

7 Technique

7.1 Postoperative brachytherapy

7.1.1 Applicators

**Individualized customized moulds** (6,18,19,20,21,27,63,78)

A vaginal mould applicator is made individually for each patient (see chapter 14.7.5). Such an applicator follows exactly the contours of the vaginal cuff for each patient. The width and thickness of the applicator correspond exactly to the individual anatomy. Different numbers of channels may be used to give adequate target coverage according to the anatomy of the patient: e.g. two lateral sources, when the vagina is flat; three sources (one posterior and two anterior), if the vagina is round.

![Image: Postoperative Brachytherapy: moulded individual applicator (multiple channel applicator)](image)

**Standardized applicators**

The standard vaginal brachytherapy applicators are the following:

- cylindrical applicators (various diameters (20 - 40 mm) and lengths (2.5 - 10 cm)) with a dome cylinder at the top and with one central channel or 2 - 3 channels in different configurations;
- two ovoids (different sizes) with one channel each and variable distances between the ovoids;

Example of a moulded applicator (IGR technique) with three catheters suitable for HDR or LDR brachytherapy (compare Fig 15.9). Three sources were chosen according to the size and the round shape of the vagina. In case of a smaller or flatter vagina shape, two sources only would be designed.
- ring applicator (different diameters) with different dwell positions and dwell times and a cap (compare ring applicator in cervix cancer).

By choosing an appropriate applicator, some adaptation can be achieved, using standard applicators.

Fig 15.5: Postoperative Brachytherapy: standardised one channel cylindrical applicators (Nucletron). Diameter is 25, 30, 35 mm; length of each element is 25 mm; in the middle of each element a thin radioopaque circular wire is on the surface of the cylinder; for the dome part this circular wire is at 5 mm from the flat bottom side (compare Fig 15.8B). The single elements with a central hole are forwarded over the metallic tube and are fixed with a screw against the top. A radioopaque dummy wire is shown and an intra-uterine tube which is used in case of pre-operative brachytherapy.

7.1.2 Technique of application

In LDR brachytherapy a general anesthesia is often given; the patient then has to stay in hospital. In HDR brachytherapy, the application is usually performed on an outpatient basis without the need for general anesthesia or analgesia. In some cases local anesthesia may make the procedure more comfortable to the patient (e.g. lidocaine-gel). The rectum must be cleared (by an enema). The woman must be fasted, as drugs for sedation may occasionally be indicated.

The patient is positioned in the dorsal lithotomy position. The bladder is emptied by a catheter. The application starts with a gynaecologic examination (including abdominorectal and rectovaginal bimanual investigation) in order to check the anatomy in general (vaginal length, width, elasticity), and in particular the position of the vaginal cuff (condition of the scar). In a vagina with widely varying diameters (e.g. narrowing towards the vaginal cuff), the device must be carefully adjusted, which can be best achieved by using the mould technique. A narrow vaginal introitus leads to some discomfort if a large cylindrical applicator is chosen. To identify later the position of the applicator in relation to the vaginal mucosa on the radiographs taken for treatment planning, silver clips of different size may be put in certain places, e.g. at a certain mucosal depth (transverse and sagittal markers).

A bladder catheter is first introduced, and filled with radiopaque solution (7 cm³) and finally pulled towards the bladder neck. The application itself depends on the technique chosen:
If the mould technique is used, the individually prefabricated applicator (Fig 15.4) is gently introduced into the vagina.

If a standardized applicator technique is used, the individual size of the applicator is chosen based (Fig 15.5) on the estimate of the dimensions of the vaginal cuff and the vagina.

In any technique, careful attention must be paid to maintaining close contact between the applicator surface and the vaginal mucosa, in particular at the vaginal cuff.

For a cylindrical applicator, this can usually be achieved by choosing a diameter that leads to some distention of the extensible vagina which fills the whole vagina.

For a ring applicator, this is achieved by adequate packing, and for two ovoids by fixing their position, e.g. with a screw and with packing.

The applicator (covered with gel) is introduced by gently pressing it forward and dorsally to open the vaginal introitus and then advancing towards the vaginal cuff.

The cylindrical applicator is kept in place mainly by the vaginal muscle tone. It seems to be advantageous to fix it additionally with a specific device against the body of the woman or to the table, after the woman has been turned from lithotomy position into the normal supine position. Slight pressure should be maintained against the applicator to prevent it from moving away from the vaginal cuff. During this procedure, the applicator must not be pushed dorsally against the rectal wall.

Before fixing the applicator, a flexible tube may be inserted into the rectum and positioned near the anterior rectal wall to measure the dose at different points in the rectum (in vivo-dosimetry).

To document the position of the applicator in relation to the vagina, bladder and rectum, two orthogonal radiographs (AP and lateral view) are taken immediately at the end of the application with the woman in the same position as during the brachytherapy application (supine, thighs together). The position of the applicator is checked by evaluating those radiographs. If the positioning is suboptimal, the position is changed and new radiographs are taken.

The treatment duration (minutes/hours/days) varies according to the dose and dose rate chosen. For LDR or PDR brachytherapy, special care is necessary to maintain an appropriate position of the applicator throughout the whole treatment period. After finishing treatment, the applicator is removed and after a little rest, the woman can leave the hospital.

### 7.2 Preoperative (utero-)vaginal brachytherapy

In principle the same techniques are applied as in postoperative brachytherapy. For uterovaginal brachytherapy, a tandem is added to the vaginal applicator (see chapter 14).

### 7.3 Radiotherapy alone

#### 7.3.1 Applicators

Different types of applicators are available which meet the demands for appropriate brachytherapy of endometrial cancer to varying degrees. The whole uterine wall should be included in the CTV, as at present it is hardly possible to discriminate precisely between exophytic and infiltrative growth patterns by means of imaging - without histopathologic specimens obtained by surgical removal of the uterus. As a consequence, an application technique must be chosen which allows treatment of the whole uterine wall by
brachytherapy. In small superficial and limited tumors only, a dose encompassing the endometrium and the inner part of the myometrium may be sufficient.

The following applicator devices are therefore recommended (one channel-applicator only in a small uterus):

**Individualized packing methods**

The classical Heyman packing technique (radium-226 (29)) has been modified for the needs of afterloading devices using rather small radiation sources (caesium-137 (71,72), iridium-192). Nowadays, long thin flexible tubes are available with capsules of different sizes at their top (e.g. 4/6/8 mm diameter) (28,69). By individual packing with such capsules, the application can be adapted to the individual pathologic anatomy of the uterine cavity (Fig 15.6A). Furthermore, applicators are available, in which the catheters are pressed mechanically against the uterine wall (umbrella-technique) (62) (Fig 15.6B). These arrangements will usually lead to an adequate dose distribution in the uterine corpus (compare Fig 15.10C).

If the cervix and the adjacent vagina are to be included for definitive treatment, a cervicovaginal mould applicator, two ovoids, or a ring may be added.

![Definitive Brachytherapy: Individualized packing methods](image)

**Fig 15.6: Definitive Brachytherapy: Individualized packing methods**

*Figures are not visible in the text.*

**Standardized applicators**

- Two or three channel-applicators (Y-shaped). Such standard devices consist of two rigid applicators with a curved end to reach the two uterine horns (Fig 15.6C) (69). A third applicator may be added to reach the mid-point of the uterine fundus. The applicators are fixed together after insertion. Vaginal gauze packing keeps the applicator in place. This technique leads to an appropriate dose distribution in a small or medium sized uterus with superficial tumour extension. This applies for caudocranial and laterolateral directions, whereas - depending on the thickness of the uterus - dose distribution
may be suboptimal in the anterioposterior direction. Depending on the tumor extension into the cervix, this technique may be supplemented by two ovoids or a ring applicator (compare Fig 15.10B).

**Fig 15.6: Definitive Brachytherapy (continued): Standardized applicators**

C: Standard two channel applicators ("Y"/Rotte applicator (69), Nucletron®)

D: Standard one channel applicators in different diameters and with different intrauterine tubes (40,67) (Nucletron®)

- **One channel-applicator.** This applicator consists of one curved metallic tube (varying curvature) with a flange (indicating the length of the uterine cavity), which is fixed against the cervix by a vaginal cylinder (Fig 15.6D). This applicator only gives an adequate dose distribution in a small uterus with a superficial tumour (compare Fig 15.10A).

### 7.3.2 Technique of application

To some extent, the method of application is dependent on the size of the uterus and the dimensions of the uterine cavity: the larger the uterus, the less suitable are rigid applicator devices.

For adequate target definition the individual anatomy of the uterine corpus, cervix and uterine cavity (including the thickness of the uterine wall) should be documented in relation to the position of the applicator within this pathologic anatomy. Therefore, sectional imaging (US, CT, MRI) before application and/or with the applicator in place is nowadays integrated into the application procedure.

The easiest way to perform such an application is under spinal or general anesthesia, but it may be performed using a combination of systemic analgesia and sedation.

The patient is positioned on a special gynecologic table in lithotomy position. The bladder is emptied by a catheter. The application starts with a clinical examination (including abdominorectal and rectovaginal bimanual investigation) in order to confirm the pathologic anatomy and the position and size of the uterus.

The application starts with attaching a cervical forceps to the front lip of the cervix. A uterine tube is inserted into the cervical os to measure the length of the uterine cavity precisely, to explore directly its spatial dimensions (uterine fundus), and to document its curvature. Depending on the technique of application, variable dilatation of the cervical os and canal is indicated. The amount of dilatation required increases with the number of catheters to be introduced, which depends on the individual dimensions of the uterine cavity. For example, a large uterine cavity
will usually need more than 10 catheters, which requires as wide a dilatation as possible (up to Hegar 12 - 14). The introduction of a 2 - 3 channel-applicator usually requires a dilation up to about Hegar 8. Less dilatation is necessary for a one channel applicator depending on its diameter (3-6 mm).

If at this time a pyometra is diagnosed, special care must be taken to prevent spread of infection, e.g. by perforation. In LDR brachytherapy, pyometra constitutes a temporary contraindication.

**Modified Heyman packing.**

The application starts with introducing the flexible tubes - after inserting a rigid metallic guide - with a largish capsule (diameter e.g. 8 mm) for packing the uterine fundus and horns. This is followed by introducing a decreasing number of tubes towards the cervix, the capsules of which are somewhat smaller (down to a diameter of e.g. 4 mm). The packing can be stopped after the uterine cavity has been filled, but is usually extended to the uterine cervix. The number of tubes applied varies significantly with the individual anatomy, but according to widespread experience between 5 and 18. Finally, the vagina is packed or a mould is introduced, to keep the applicators in place.

When using the umbrella technique which is usually combined with an intravaginal mould, the applicator with the closed umbrella is first introduced into the uterine cavity like a one channel applicator. When the applicator is in an appropriate position, the umbrella is opened from the distal end of the applicator mechanically.

**Two or three channel-applicators (Y-shaped)**

One of the two curved applicators is introduced and the end is gently advanced towards one corner of the uterine fundus taking into account the measured length of the uterine cavity. The second one is introduced in the same way into the opposite corner. Both applicators are finally fixed together, usually by a screw. The whole applicator is stabilized to a certain extent by a vaginal packing which is pressed against the portio.

**One channel-applicator**

The curved metallic tube is introduced into the uterine cavity as far as the measured intrauterine length. This length is defined in advance by a flange on the metallic tube so that the applicator is „fixed” in front of the cervical os. The vaginal fixation is achieved with a cylindrical applicator advanced over the metallic tube and pressed against the flange.

For bladder and rectum the same systems are used as in postoperative brachytherapy.

For documenting the position of the applicator in relation to the uterus (e.g. by hysteroscopy), the bladder and rectum, and as a basis for dose calculations, two isocentric orthogonal radiographs (AP and lateral view) are taken immediately at the end of the application with the woman in the same position as during the performance of brachytherapy (supine, thighs together). In a modified Heyman packing, specific radiographic markers must be introduced into the plastic catheters so that it becomes possible to recognize single catheters in the AP-view as well as in the lateral view (Fig 15.11). The position of the applicators is checked by evaluating these radiographs. If the position is suboptimal, it is changed and new radiographs are taken. If possible, sectional imaging is performed (US, CT, or MRI) with the applicator in place, to allow for individual sectional image-based treatment planning.

To start the brachytherapy, intrauterine catheters or the (rigid) applicator are carefully connected to the flexible tubes of the afterloading machine as in postoperative brachytherapy. Special care must
be taken when considering the computed dose calculations for the single catheters, in particular if there are different loading patterns or dwell times and source positions for the different catheters.

After finishing treatment and disconnecting the tubes, the woman is brought back into the application room, placed in the lithotomy position, and the applicator or the intrauterine tubes are removed. The cervix and the vagina are finally inspected and then the woman is kept in hospital for observation for any type of complication. In particular, abdominal pain, blood pressure, temperature, and vaginal bleeding must be monitored.

**Endocervical and endovaginal brachytherapy (supplementary to intrauterine brachytherapy)**

If radiotherapy is performed as a definitive treatment, the areas adjacent to the uterine corpus (uterine cervix, upper part of the vagina) must be treated as well, as they are at risk for recurrence and metastases, respectively. Depending on the CTV and technique of uterine brachytherapy, the CTV and technique of endocervical and/or endovaginal brachytherapy must be decided. Devices for endocervical brachytherapy may be used with special attention to the upper part of the vagina (ovoids, ring, endocervical applicator with a vaginal cylinder) or vaginal applicators as described for postoperative brachytherapy of the vaginal cuff. Depending on the technique of intrauterine application, endovaginal brachytherapy can either be performed at the same time or separately from the intrauterine treatment.

The performance of such an application is described in detail in the respective chapters.

**8 Treatment Planning and Dose Calculation**

**8.1 Preoperative and postoperative vaginal brachytherapy**

**8.1.1 General aspects**

The position of the applicator is checked with regard to coverage of the CTV and its relation to critical organs on two (orthogonal) radiographs taken at the end of the application (Fig 15.8A, 15.9A). The dose distribution is calculated to achieve a prescribed dose at a defined distance from the surface of the applicator (most often at 5 mm) (Fig 15.7 - 9). This corresponds to the treated volume, which should be calculated and recorded in all its dimensions (length (height), width, thickness) and volume (computer calculated cm³).

In the commercially available treatment planning systems, there is the possibility of designing standard programmes for dose calculation with defined standard applicators and given dose specification points („library“). Dose calculation and treatment planning is often based only on the standard treatment plans available from the “library” (in the computer) without digital entering of data from the radiographs. In difficult situations it may be advantageous to use full 3D treatment planning based on different points as outlined on the radiographs.

The reference dose for reporting is specified at 5 mm from the applicator surface in all directions. In addition, the dose at the applicator surface should be reported (Fig 15.7).

For any applicator type, the applicator dimensions and the dimensions of the reference volume (reference isodose) must be reported: reference volume length, thickness and width (Fig 15.7). The reference volume length corresponds to 90% of the reference depth dose (compare chapter 6.7 on reporting intraluminal brachytherapy). In the clinical context of intravaginal brachytherapy this is of no obvious clinical relevance, as the difference in reference volume length at 90% from that at 100% is minimal (mm). In the widespread common practice of postoperative vaginal brachytherapy, the points
for prescription (target at 5 mm mucosal depth) and for reporting (specification point 5 mm from the applicator surface) are identical (see Table 2). Therefore, usually the dimensions of the reference volume are identical to those of the treated volume, and correspond to the minimum target dose at the target depth.

Nevertheless, if the target depth is chosen differently (thin vaginal wall, thick scar at the cuff), the prescription depth and dose and the reference dose should be recorded separately (61) (Fig 15.7B,C). The dimensions of the individual treated volume should then also be calculated and documented as well as the dimensions of the reference volume.

As most of the reference/treated volume is filled with the applicator, it is important to indicate the reference/treated volume with the applicator volume subtracted. This leads to the assessment of the volume of tissue treated within a certain dose gradient (dose at 5 mm tissue depth and dose at the applicator surface). Taking a cylindrical applicator with a diameter of 30 mm and a target length of 4 cm, the dimensions of the reference/treated volume are 4 cm x 4 cm x 4 cm for the target and 3.5 cm x 3 cm x 3 cm for the applicator (50 cm$^3$ and 25 cm$^3$) and the treated tissue volume is 25 cm$^3$. This volume is treated with a dose ranging from the reference dose (100%) to the applicator surface dose (~140-160%) (Fig 15.7,8).

The 200% isodose (classical volume of overdosage) seems to be of no value for these applications, as it always lies within the applicator. The volume of the 150% isodose is more appropriate, as this represents a small volume if any in applicators of 30 mm diameter and less.

Dose and volumes are also calculated at reference points for the bladder and rectum (ICRU points), but additional points may be selected, e.g. for the bowel or urethra.

### 8.1.2 One channel cylindrical applicator

For a one channel cylindrical applicator, additional dose specification points may be chosen at the applicator surface. If there are differences in target depth (e.g. at the apex of the vaginal cuff with large scars) different prescription points may be used (e.g. at 10 mm at the apex and 5 mm along the vaginal wall) (see Fig 15.7C).

With commercially available treatment planning systems, it is possible to design standard programmes for dose calculation with defined standard applicators and given dose specification points (“library”). The resulting treated volume represents a cylinder (symmetrical about the axis) for an applicator with a defined diameter and curved shape at the top based on dwell time adaptation (Fig 15.8B). If this standard treatment plan does not fit to the individual clinical practice of prescription, the dose distribution must be individually adjusted.

As the diameter of the applicator is usually > 25 mm, there is only a little or no tissue exposed to the overdosage volume (150/200% of the prescribed dose at 5 mm).

Care must be taken not to increase the dose to the reference points in the organs at risk above tolerance doses, particularly at the anterior rectal wall (the thickness of the vaginal wall with the applicator in place is usually clearly less than 5 mm, compare Fig 15.1), but also to the bowel adjacent to the vaginal cuff, and the bladder and urethra.
Fig 15.7 Reporting Vaginal Brachytherapy

Fig 15.7A: Prescription and reporting point are identical at 5 mm from the Applicator Surface.

Fig 15.7B: Prescription and reporting point are not identical: Prescription point is at 3 mm from the Applicator Surface (depth of the vaginal wall), Reference Point remains at 5 mm from the AS.

Fig 15.7C: Prescription different at the vaginal vault (at 10 mm from the AS) and along the vaginal wall (at 5 mm from the AS). Reporting at 5 mm for the vaginal wall and at 10 mm for the vaginal vault.

Dose Reporting for a given Applicator Diameter (AD) for different prescription practice. Prescription Depth and Prescribed Dose (PD); Reference Depth (RD), Applicator Surface (AS), Reference Volume Length (RVL), Active Source Length (ASL). Reference volume width (RVW) and thickness (RVT) are not in the diagram.
If a "pear" shaped volume for a one channel cylindrical applicator is required, a specific larger form of the dome colpostat must be chosen. If the standard applicator is chosen, the "pear" shaped dose distribution leads to an increased mucosal surface dose and an increased dose to the organs at risk because of the axial symmetry of the one channel applicator.

**Figure 15.8: Postoperative Brachytherapy with a standard cylindrical cylindrical one channel applicator:**

A. Localisation X-ray film AP (1) and lateral (2) showing the applicator (with radioopaque marking) the central channel for the source and the rectal probe

B. Standard isodose distribution in the central plane (midsagittal/coronal (1) and midtransverse (2) plane) for a standard HDR application with a 30 mm diameter applicator. The hatched area indicates the applicator. The source dwell positions are marked. The reference isodose (5 Gy) is 100%. The dimensions of the reference volume (90% of the reference isodose dose at 5 mm depth) are Length 41 mm, Width and Thickness 40 mm. In case of a cylindrical applicator Width and Thickness are by definition identical. The dose at the applicator surface (Vaginal mucosa) is 160% of the reference dose except at the cylinder apex, where the surface dose is slightly higher.

### 8.1.3 Multiple channel applicators

For a multiple channel standard or individually moulded applicator (cylindrical/non cylindrical), a ring applicator or for 2 ovoids the dose is also specified at 5 mm from the mucosal surface in the central plane of the applicator, in the mould, in the ring, or in the ovoid perpendicular to the applicator axis. A
plane parallel to and through the central longitudinal axis of the applicator must also be defined, in which the dose can be specified along the whole surface including the apex of the vaginal cuff (5 mm). Further specification points may be chosen at the surface of the ring and the ovoids and for different target prescription points at the apex of the vaginal cuff (e.g. at 10 mm). Special attention must be taken, to include all vaginal wall (CTV) in the reference isodose. Additional reference points may be taken for the rectum and bladder. The standard dose distribution which results from these two or multiple channel type applicators is asymmetrical and more flat with a larger latero-lateral extension than anterior-posterior. The advantage of these multiple channel applicators is some dose sparing in the posterior and anterior direction.

Fig 15.9: IGR method: Postoperative brachytherapy with an individual mould applicator with three channels:
A: Localisation X-ray film AP view (1) and lateral view (2). The applicator surface is marked with a radioopaque wire. Radioopaque markers indicate the position of the three channels. Bladder balloon filled with contrast medium and rectal probe.
B: Typical isodose distribution in the three planes sagittal (1), frontal (2), and central for an individual mould applicator with three channels (computerized HDR dosimetry). The reference isodose is 5 Gy at 5 mm from the applicator surface. The length of the Reference Volume (5 Gy isodose line, at 5 mm depth) is 40 mm, the width 50 mm and the thickness 40 mm.
8.2 Definitive radiotherapy

The position of the applicator(s) is checked on the radiographs in relation to the uterus, bladder, bowel, and rectum, as far as possible (Fig 15.11A).

Independently of the method of application used, dose specification points must be indicated on the lateral and AP radiographs (taken in a reference frame). There is no consensus on which standard reference points should be used. One point has been proposed, which is located 2 cm caudal to the top of the (most advanced) applicator and 2 cm laterally “point My” (Myometrium) (69). Another point is 2 cm from the tip of the applicator laterally “A-line” (40,67). In an individualized approach, the dose is specified at the uterine serosa (28,55,69). For this purpose, the thickness of the uterine wall must be determined, in relation to the tubes, which is best achieved by CT or MRI with the tubes in place. Several points can then be indicated at the fundus, at the middle of the corpus and at the isthmus towards the cervix. If possible, reference points on the surface of the uterine cavity and at the macroscopic tumor margin are added. Reference points in organs at risk are indicated: for the bladder along its posterior wall (not primarily at the bladder neck); for the rectum, sigmoid, and small bowel as far as possible (if radiography is used organs should be delineated with contrast medium).

If the individual anatomy is taken into account, there are no standard programmes in the available treatment planning systems. Nevertheless, some authors have reported using pear shaped standard programs (“bottom of the pear at the fundus”) based on the “A-line” (40,67) or have specified dose at the reference point “My” (69), at the Madison point (75), or at point S (5). When adapting the Heyman packing method (developed for radium) for afterloading technology (44,71,72) and more particularly for stepping source technology (HDR-brachytherapy) a more individualized approach has been reported taking the individual anatomy into account (5,28,55,69).

A similar individualized approach has been proposed by Pernot (63) for LDR brachytherapy based on the umbrella technique (62) and systematic CT evaluation.

For an individualized dose calculation approach two radiographs must be taken and the applicators and reference points are used for a 3 D-reconstruction using the treatment planning system.

The resulting treated volume - at least in “Packing”- methods, but to some degree also in applications with a one, two or three channel-applicator - follows the outer surface of the uterus, if there is not too much variation in uterine wall thickness. This individualized treated volume can be achieved by adjusting the dwell times and the positions of a stepping source appropriately. The calculated doses at reference points in the posterior bladder wall and in parts of the small bowel may be rather high if the dose is related to the outer surface of the uterus. Dose distribution is also often suboptimal in the cervical region, as there is usually only one capsule or two in a row which leads to a treated volume with axial symmetry, which does not necessarily correspond to the individual anatomy.

The individual treated volume and its dimensions (height, width, thickness) should be calculated and documented as well as the dose at specific dose points. The treated volume should correspond to the uterine volume (CTV) as much as possible. Thus, the volume and its dimensions will vary considerably: from about 50-100 cm³ in a small uterus to about 250 cm³ in a large uterus; it may even go up to about 350 cm³ in a very large uterus (55). The corresponding total reference air kerma rates (TRAK) vary considerably, between 2.5 and 6 cGy at 1 meter for 6 fractions of 7 Gy, HDR brachytherapy. For LDR brachytherapy (50 cGy/hour) the TRAK is 6 to 7 cGy at 1 meter corresponding to the classical prescription pattern for radium with 6.000-7.000 mg.h.

A more sophisticated approach can be performed based on CT or MRI imaging with the applicators in place (55) and entering all these data directly into the planning computer.
Fig 15.10: Definitive Brachytherapy
Schematic diagram showing different sizes of uterus (small, medium, large), different tumour sizes and different application methods, which are appropriate to different degrees. The most appropriate technique is the Heyman Packing method, but it may be replaced under certain circumstances by simpler techniques. The GTV is drawn as it presents after curettage. The dimensions of the uterus and the wall are indicated at different levels: fundus, top and mid of the uterine cavity, cervix. The reference point “My” (Myometrium) is indicated and the outer surface of the uterus for dose specification. In parallel, the isodose lines (200%, 100%, 50%) are drawn with the respective distances from the sources to the outer uterine surface. The dimensions of the 60 Gy brachytherapy volume are shown which corresponds to a fractionated HDR brachytherapy schedule of 6 x 7 Gy at the 100%-isodose (alpha beta value 10).

Fig 15.10 A,B: Small uterus (width 3.6 cm, length 6.3 cm (intrauterine cavity 4.7 cm), thickness 3 cm) and a small rather superficial tumour (A) which can be treated with a one channel applicator using a stepping source, by increasing the dwell times at the fundus which results in a pear shaped isodose distribution (“inverted pear”) (B). The 60 Gy reference isodose encompasses significant parts of the myometrium, the 200% isodose major superficial parts of the uterine wall. The dimensions of the 60 Gy brachytherapy volume are 6.3 cm in length, 4.5 cm each in width and thickness; the reference volume is 64 cm³.
Fig 15.10 C,D: Medium sized uterus (width 7.2 cm, length 8.8 cm (intrauterine cavity 6.9 cm), thickness 4.2 cm) and a small rather superficial tumour which can be treated with a two channel applicator, which results in a pear shaped isodose distribution at the fundus ("inverted pear"). The 60 Gy reference isodose encompasses significant parts of the myometrium, the 200% isodose major superficial parts of the uterine wall, including the uterine cornu. The dimensions of the 60 Gy brachytherapy volume are 8.8 cm in length, 4.8 cm in width and 4 cm in thickness; the reference volume is 85 cm³.
C: Large uterus (width 8.3 cm, length 10.6 cm (intrauterine cavity 8.5 cm), thickness 6 cm) with tumour deeply infiltrating the myometrium, which can only be treated appropriately with Heymann Packing. The 60 Gy reference isodose encompasses significant parts of the myometrium, the 200% isodose major superficial parts of the uterine wall, including the uterine cornu. The dimensions of the 60 Gy brachytherapy volume are 12 cm in length, 6.7 cm in width and 5.5 cm in thickness; the reference volume is 221 cm³.
Fig 15.11: Definitive Brachytherapy: Heyman Packing in a medically inoperable woman with Norman Simon applicators (compare Fig 15.2)

Fig 15.11A: AP (1) and lateral (2) X-ray localisation films taken for treatment planning with 14 Norman Simon applicators in place with different radiographic marker wires and an isocentric localisation frame. Each applicator has been identified individually. Gauze packing in the vagina; rectal probe and Foley bladder catheter.

Fig 15.11B: MRI assisted treatment planning with 200%, 100% and 50%-isodoses in all projections (1: coronal, 2: transverse, 3: sagittal). The 100% isodose is covering most of the uterine wall and of the GTV in the upper anterior uterine wall. Maximum dimensions of the 60 Gy brachytherapy volume were in height 10 cm, in width 6 cm, and in thickness 7 cm, resulting in a volume of 210 cm³. TRAK was 6 cGy at 1 meter. Total dose and fractionation was 42 Gy in 6 fractions of 7 Gy (isoeffective to about 60 Gy). Three years after treatment the woman is well and in continuous complete remission.
9  **Dose, Dose Rate, Fractionation**

9.1  **Postoperative vaginal brachytherapy (vaginal cuff)**

For LDR brachytherapy alone the total dose calculated at 5 mm from the vaginal mucosa is 50 Gy delivered in one session (in 4 - 5 days). From a study of 239 patients performed at IGR, the following parameters were obtained comparing 50 Gy vaginal brachytherapy alone applied pre- or postoperatively (21): TRAK 3.2/2.98 cGy at 1 m; 60 Gy reference volume 103/90 cm³; length 5.5/5 cm, width 5.9/5.8, thickness 5.1/4.8 cm; dose to the bladder (ICRU point) 36/43 Gy; dose to the rectum (ICRU point at the central plane) 68/67 Gy and to the rectal catheter 40/37 Gy; pelvic wall 11.3/9.7 Gy. Applicator dimensions are 5 - 5.5 cm wide and 4 - 4.5 cm thick.

If brachytherapy is combined with external beam radiotherapy, this is performed after external beam irradiation is completed. The dose of brachytherapy depends on the dose previously given by external beam irradiation: e.g. 45 Gy EBT followed by a brachytherapy boost of 15 Gy.

In HDR brachytherapy, the total dose at 5 mm depth for vaginal brachytherapy alone is between 15 and 24 Gy applied in 3 to 4 fractions: 3 - 4 x 5-5.5 Gy, 3 - 4 x 6 Gy up to 3 x 7 Gy (27,41,42,52,57, 18-21,59,61). The applicator/vaginal surface dose is between 7 and 11 Gy per fraction. The overall total isoeffective vaginal surface dose is between 36 and 58 Gy (alpha-beta value of 10). The time interval between fractions is one week. Treatment time is 5 to 15 minutes for HDR-Ir 192-brachytherapy. The dose as measured by the rectal probe is 60 - 90% of the prescribed dose. TRAK is 1.2 cGy at 1 meter for 4 fractions of 5 Gy.

The total dose recommended for a combined treatment is somewhat lower, e.g. 3 x 5 Gy at 5 mm tissue depth (59,61), vaginal surface dose ~8 Gy per fraction (biologically weighted vaginal surface dose ~ 36 Gy) with 45 to 50 Gy EBT at the ICRU reference point. If additional external pelvic radiotherapy is given, the brachytherapy volume must be excluded after about 40 Gy to spare the rectum.

In a recent French survey of post-operative brachytherapy in 655 patients treated with HDR (total median dose 24 Gy with median 6 Gy per fraction), the total median dose to the bladder, assessed in 49 % of the patients, was 19 Gy (2 - 38). The total median dose to the rectum, assessed in 42% of the patients, was 24 Gy (7 - 28) (27).

In PDR brachytherapy the total dose in 5 mm depth is 45 Gy with 50 cGy per fraction per hour.

9.2  **Radiotherapy alone**

For LDR brachytherapy alone, a target dose of 70 - 80 Gy is proposed for the uterus (outer contour) and 45 - 55 Gy for the upper third of the vagina, which is usually delivered in two sessions one week apart. If there are risk factors for pelvic disease, pelvic radiotherapy is recommended of 30 to 45 Gy with 35 to 50 Gy given additionally by endocavitary brachytherapy to the corpus (19,20).

For HDR brachytherapy, the total dose and fractionation are similar to the HDR-experience in cancer of the cervix. The total dose of brachytherapy varies between 30 Gy (Sorbe et al. 1988), 42 Gy “point-A line” (40,41) and 50 Gy “point My” (69) in 5 to 6 fractions. Technique, dosimetry and prescription and reporting practice are not homogenous (see paragraph 15.8).

The time interval between fractions is usually one week. Treatment time varies between 5 to 30 minutes in HDR-Ir 192-brachytherapy depending on the activity of the source and the volume treated.
If brachytherapy is combined with external pelvic radiotherapy, EBT is given to a total dose of 40 to 50 Gy (EBT). With open fields of external beam therapy, to spare normal adjacent tissue, the brachytherapy volume should be excluded at least after 25 Gy of EBT, if e.g. 42 Gy is added by brachytherapy (40,41). The nominal total dose to the A-line/point My (outer surface of the uterus) will then be 67 Gy corresponding to an isoeffective dose in LDR brachytherapy of about 86 Gy (calculated based on the alpha beta model and an alpha beta value of 10). The 60 Gy brachytherapy volume corresponds to the dimensions of the 100%-isodose volume and depends significantly on the dimensions of the uterus and the technique applied. It varies from about 50 cm³ to 300 cm³ (compare Fig 15.10). TRAK averaging 2.7 cGy at 1 meter (ranging from 2.0 to 3.9). Bladder doses at the posterior wall are close to the 100%-isodose.

Brachytherapy for the vaginal vault is given with the dose and fractionation used for postoperative brachytherapy, (3-4 x 5 Gy at 5 mm depth) (40,41).

10 Monitoring

In principle, monitoring is similar to that of patients with cervix cancer brachytherapy (see chapter 14).

11 Results

Overall results are dependent on risk factors. The most important classical risk factors are stage (I vs. II vs. III vs. IV), myometrial invasion (A vs. B vs. C), grade (1 vs. 2 vs. 3), type of histology, and age (>60 years is an adverse prognostic factor). In historical published series, most often retrospective, there is often no clear correlation between risk factors, treatment strategy and outcome in terms of local (vagina, pelvis) and distant failure. Nowadays, there is international agreement to differentiate a stage I low risk group (grade 1,2; minimal invasion) from a high-risk group (grade 3; deep infiltration).

The risk of recurrence related to histologic grade, depth of infiltration, vessel invasion (lymphatic, blood), intrauterine spread (cervix, stage II), extraterine spread (e.g. lymph node involvement) and histologic subtype can be estimated as being low, intermediate or high and can be quantified using a risk score proposed by Kucera et al. (43). According to this risk score, patients with stage II and III disease, unfavourable histology, and vessel invasion are designated as high risk patients.

The overall five-year survival rate according to the FIGO Annual report (1998) (33) is 86% in stage I, 66% in stage II, 44% in stage III, and 14% in stage IV. In stage I adenocarcinoma, the disease specific survival rates vary according to the risk factors between 100% at 5 years for low risk patients and ~70% for high risk patients (42A).

11.1 Surgery

Variable rates of vaginal and pelvic failures after surgery alone have been reported. The overall recurrence rate is between 5 and 40% depending on the various prognostic factors and the type of surgery (24). Vaginal recurrence alone is reported in between 2 - 3% (66) and 15% (15). In high-risk patients with stage I, grading 3 and myometrial invasion > ½, the reported vaginal and pelvic recurrence rates are about 20 to 30 %. In low risk patients (stage I, superficial spread: any grade; myometrial invasion < ½; grade 1,2) the recurrence rate is below 5% (15,47,66). In the intermediate risk group (stage I, grade 3, myometrial invasion < ½; grade 1,2; myometrial invasion > ½), the vaginal and pelvic recurrence rates are in between, for example 14% in the Dutch trial (14).
In a large series reported by the Gynecologic Oncology Group on the relationship between surgical-pathological risk factors and outcome in 1180 patients with clinical stage I and II, vaginal and pelvic failures were 34.6% in the group of patients treated with surgery alone compared to 12.5% in the group treated with radiation therapy. Among the recurrences observed in the group without adjuvant radiation, 18.2% were located in the vagina and 31.8% in the pelvis (56).

In low risk patients (G1+2, myometrial invasion < ½) after surgery alone, only 17 out of 641 patients (2.7%) had vaginal recurrence, of whom 15 were successfully salvaged (66).

In a series of 811 FIGO stage I and 116 stage II endometrial cancers, hysterectomy was the sole treatment in 492 patients (15). Patients were divided into two groups according to risk factors: low-risk with grade 1 and 2 tumours confined to the inner third of the myometrium and high-risk with grade 3 and/or tumours expanding to the middle third or beyond. Isolated vaginal recurrences occurred in 32 patients who were treated with surgery alone: 10 in 308 low-risk patients (3.2%) and 22 in 184 high-risk patients (11.9%). In contrast with the series reported by Poulsen (66), nearly 45% of the patients with a vaginal recurrence died from cancer within one year and 77% within 5 years.

It is still not clear, whether lymph node surgery (various forms of sampling or dissection) contributes to a decrease in pelvic lymph node recurrence (39,47).

In the recently published Dutch randomised trial (14) after surgery alone (intermediate risk group: IB G2,3; IC G1,2) the actuarial 5-year probability of locoregional relapse was 13.7%, 3.4% in the pelvis and 10.2% in the vagina (vaginal vault 6.4%).

### 11.2 Adjuvant radiotherapy: vaginal brachytherapy, external beam radiotherapy

In most published reports (table 15.2), there is clear evidence that radiotherapy contributes significantly to a reduction in locoregional relapse, both vaginal and pelvic. The relapse rate is dependent on the treatment modality chosen.

In the Dutch randomised trial (14) assessing the role of postoperative external radiotherapy versus surgery alone in Stage I endometrial carcinoma (IB G2/3, IC G1/2) 715 patients were enrolled: 354 were assigned to postoperative irradiation (EBT 46 Gy alone) and 361 to no further treatment. Locoregional control was significantly improved by radiotherapy (4% versus 14%), overall survival was not significantly different (81% versus 85%).

These results compare well with the randomised trial published by Aalders et al. long ago (1) where, for patients with deep myometrial invasion, the pelvic recurrence rate was reduced from 15% to 5% by pelvic radiation. Another recent trial (Gynecologic Oncology Group nr. 99) showed 19 pelvic recurrences in 202 patients treated with surgery alone compared to 1 out of 188 for patients receiving adjuvant pelvic radiation (68).

There is no clear indication in the literature that vaginal brachytherapy, added as a boost to pelvic external beam radiotherapy, contributes to an improvement in overall pelvic or vaginal control. The overall pelvic control rates vary between 85 and 99% (1, 24, 34, 41, 42A, 68).
### Table 15.2: Results of Brachytherapy +/- EBRT in combination with surgery

<table>
<thead>
<tr>
<th>Author</th>
<th>N° pts</th>
<th>Stage</th>
<th>Brachytherapy</th>
<th>Survival %</th>
<th>Recurrence %</th>
<th>Complications %</th>
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<td>108</td>
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<td>HDR</td>
<td>2 AS</td>
<td>84 VR</td>
<td>0.9 PR</td>
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<td>91 1 PR</td>
<td>14 2 7.9</td>
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<td>HDR</td>
<td>1-2 AS</td>
<td>90 PR</td>
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<td>2 3 yr DFS</td>
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<td>2 RFS</td>
<td>88, 86, 58</td>
<td>7.2 Gr3-4</td>
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<td>2 OS</td>
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<td>1-2 DFS</td>
<td>86 VAG</td>
<td>2.7 Gr3-4</td>
</tr>
</tbody>
</table>

Legends: BT 1: preoperative brachytherapy; BT 2: postoperative brachytherapy; AS: Actuarial Survival, CSS: Cause Specific Survival, DFS: Disease Free Survival, RFS: Recurrence Free Survival, OS: overall survival; VR vaginal recurrence, PR pelvic recurrence; DM: distant metastasis

### Table 15.3: Combined surgery and radiation in endometrial carcinoma stages I-II

<table>
<thead>
<tr>
<th>Authors</th>
<th>N° pts</th>
<th>Treatment (N)</th>
<th>Type of Radiation %</th>
<th>5 yr OS %</th>
<th>Vaginal Rec. (N)</th>
<th>Complications %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gerbaulet (19)</td>
<td>325</td>
<td>A: surgery alone 12 B: surgery + radiat. 313</td>
<td>Preop. BT 69% Postop. BT 27% Postop EBRT 30%</td>
<td>A: 4/12 B: 2/313 Preop. Vag. BT: 9% (Gr III 1%) P &lt; 0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Michel (53)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
With pre- or postoperative vaginal brachytherapy +/- EBT the vaginal and pelvic relapse rate ranges for stage I from 0 to 15% (Table 15.2,3,4). Vaginal relapses are reported in 0 to 2.7%. Vaginal relapse rates below 1% are reported for low risk patients after vaginal brachytherapy alone (stage IA, G3, IB, grade 1,2), whereas for intermediate risk patients, overall relapse rates rise to about 5% with vaginal brachytherapy alone or with combined treatment. For high risk patients (IC, G3) recurrence rates up to 15% are reported, even after combination treatment (Table 15.4).

The treatment strategy is tailored to the individual risk of vaginal and pelvic relapse taking into account grade and myometrial infiltration (compare Table 15.1 for indication) and nowadays increasingly to the amount of lymph node surgery (EBT). After vaginal brachytherapy alone low risk patients (stage IA, G3, IB G1,2) have an excellent outcome in terms of pelvic control (~100%) and disease specific survival (~100%) (16,41). Patients at intermediate risk (IB, G2,3, IC, G1,2) have been treated by vaginal brachytherapy +/- external beam therapy (Table 15.4A,B) and also with external beam therapy alone (68,24,34). The outcome is also excellent with pelvic control of about 92 - 98% and DSS of about 90 - 97% (14,18,24,27,34,42,50,52,64,68) (Table 15.2,4). For patients at high risk (IC G 3), pelvic control is between 80 and 90% and DSS about 70-75% (see in detail Table 2,4).

For patients with stage II disease, pelvic control and disease specific survival is comparable to the corresponding risk groups with stage I disease after combination treatment with external beam therapy and vaginal brachytherapy (Table 15.2).

For patients with stage III disease, the outcome is significantly worse. However, pelvic control after external beam therapy to the whole pelvis and vaginal brachytherapy is reported to be about 80 to 90% particularly for patients with local extrauterine extension (infiltration of the serosa, adnexa and vaginal spread (IIIA,B)). The major site of treatment failure in these patients is related to distant failure which is separated into intraabdominal spread and hematogenous spread. The overall 5 year disease specific survival rates are reported to range widely from 30 - 70%. Outcome in patients with lymph node involvement (IIIC) is also significantly worse with 5 year disease free survival for patients with positive nodes being 55% compared to 91% when nodes are negative (20).

Whereas the results for adenoacanthoma and adenosquamous tumours compare well with the results for classical endometrioid carcinoma, histologic subtypes such as serous papillary tumours and the clear cell tumours have a significantly worse outcome with 5 year survival rates of 27 and 42%, respectively (33).
### Table 15.4: Results from Vienna series of 743 patients with stage I endometrial cancer with different treatment strategies tailored to specific risk groups: a: 1982-1992; b: 1993-1997 (41,42)

**FIGO stage 1 (pT1)** — Vienna experience 1982-1992 (431 patients):

<table>
<thead>
<tr>
<th>Grade</th>
<th>TS</th>
<th>N</th>
<th>PF</th>
<th>DF</th>
<th>DSS</th>
<th>TS</th>
<th>N</th>
<th>PF</th>
<th>DF</th>
<th>DSS</th>
<th>TS</th>
<th>N</th>
<th>PF</th>
<th>DF</th>
<th>DSS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>G1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BT</td>
<td>42</td>
<td>0</td>
<td>0</td>
<td>100%</td>
<td>EBT+BT</td>
<td>80</td>
<td>2</td>
<td>1</td>
<td>94%</td>
</tr>
<tr>
<td><strong>G2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>EBT+BT</td>
<td>84</td>
<td>2</td>
<td>2</td>
<td>92%</td>
<td>EBT+BT</td>
<td>111</td>
<td>7</td>
<td>3</td>
<td>87%</td>
</tr>
<tr>
<td><strong>G3</strong></td>
<td>BT</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>100%</td>
<td>EBT+BT</td>
<td>53</td>
<td>3</td>
<td>5</td>
<td>82%</td>
<td>EBT+BT</td>
<td>55</td>
<td>8</td>
<td>4</td>
<td>74%</td>
</tr>
</tbody>
</table>

**FIGO stage 1 (pT1)** — Vienna experience 1993-1998 (367 patients):

<table>
<thead>
<tr>
<th>Grade</th>
<th>TS</th>
<th>N</th>
<th>PF</th>
<th>DF</th>
<th>DSS</th>
<th>TS</th>
<th>N</th>
<th>PF</th>
<th>DF</th>
<th>DSS</th>
<th>TS</th>
<th>N</th>
<th>PF</th>
<th>DF</th>
<th>DSS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>G1</strong></td>
<td>no BT</td>
<td>15</td>
<td>1</td>
<td>7%</td>
<td>-</td>
<td>(86%)</td>
<td>EBT+BT</td>
<td>62</td>
<td>1</td>
<td>1</td>
<td>94%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>G2</strong></td>
<td>BT</td>
<td>118</td>
<td>1</td>
<td>1</td>
<td>97%</td>
<td>EBT+BT</td>
<td>74</td>
<td>2</td>
<td>2</td>
<td>91%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>G3</strong></td>
<td>no BT</td>
<td>2</td>
<td>1</td>
<td>50%</td>
<td>-</td>
<td>BT</td>
<td>169</td>
<td>1</td>
<td>1</td>
<td>93%</td>
<td>EBT+BT</td>
<td>44</td>
<td>4</td>
<td>4</td>
<td>76%</td>
</tr>
</tbody>
</table>

**Depth of infiltration**

TS: Treatment Strategy; N: number of patients; PF: Pelvic failure; DF: Distant Failure; DSS: Disease Specific Survival;
11.3 Definitive radiotherapy

If Radiotherapy alone has been given, the reported results based on clinical staging are somewhat inferior to those of definitive surgery based on pathological staging. The overall local control rates reported are about 75% (60 - 86%), the disease specific survival is about 65% (49 - 86% (Table 15.5)). Usually the major treatment contribution is from intracavitary brachytherapy. In some series locoregional control and the overall outcome are more favourable in stage IA disease than in IB and II (40,70,76) and are also dependent on grade (40,49,79) and histological subtype (44). In a series of 139 patients treated with individualised exclusive LDR brachytherapy in Nancy (Iridium wires with the umbrella technique), the 5-year actuarial locoregional control was 83% (63). Kupelian reported the MD Anderson experience with a local control rate of 86% in stage I and II disease using LDR brachytherapy with a tandem and/or Heymann Packing dependent on the size of the uterine cavity. In the Vienna series of HDR brachytherapy in 280 patients local control was 86% for stage IA, 69% for IB and 61% for stage II (with a one channel applicator) (40). When using a one channel applicator only, results seem to be suboptimal, particularly in large volume extensive disease (40) in contrast to the series using more individually adapted techniques (28,44,63,70).

Table 15.5: Results of definitive brachytherapy +/- EBT

<table>
<thead>
<tr>
<th>Author</th>
<th>N° pts</th>
<th>Stage</th>
<th>Treatment</th>
<th>Survival %</th>
<th>Recurr. %</th>
<th>Complic. %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Churn</td>
<td>37</td>
<td>I to II</td>
<td>B</td>
<td>DSS 68</td>
<td>-</td>
<td>Gr 2-3 8</td>
</tr>
<tr>
<td>Knocke</td>
<td>280</td>
<td>I to III</td>
<td>A-B</td>
<td>DSS 77</td>
<td>25</td>
<td>Gr 3 5</td>
</tr>
<tr>
<td>Kupelian</td>
<td>152</td>
<td>I to IV</td>
<td>A-B</td>
<td>DSS I II 86</td>
<td>III IV 49</td>
<td>I II 14 Gr 3 5</td>
</tr>
<tr>
<td>Landgren</td>
<td>124</td>
<td>I-II</td>
<td>A-B-C</td>
<td>OS 68</td>
<td>22</td>
<td>Gr 3 7</td>
</tr>
<tr>
<td>Lehoczy</td>
<td>171</td>
<td>I</td>
<td>A</td>
<td>DSS 74</td>
<td>23</td>
<td>Gr 3 0</td>
</tr>
<tr>
<td>Pernot</td>
<td>139</td>
<td>I to III</td>
<td>A-B</td>
<td>OS 55</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>Rouanet</td>
<td>119</td>
<td>I-II</td>
<td>B</td>
<td>DSS 65</td>
<td>24</td>
<td>Gr 3 8</td>
</tr>
<tr>
<td>Varia</td>
<td>73</td>
<td>I-II</td>
<td>A-B</td>
<td>OS 43</td>
<td>40</td>
<td>Gr 3 10</td>
</tr>
</tbody>
</table>

Legends: Treatment  
A: Brachytherapy alone  
B: EBRT + Brachytherapy  
C: EBRT alone  
Survival  
OS: Overall Survival  
DSS: Disease Specific Survival

Comments: This table includes more than one thousand patients treated with brachytherapy alone or EBRT + brachytherapy. The mean DSS is about 65% and the loco regional control is 75%.

These results will be further improved, if individualized brachytherapy treatment techniques (in particular modified Heyman Packing) and 3 D treatment planning based on modern imaging are systematically introduced (1 treatment failure out of 49 (28)).

11.4 Adverse side effects

11.4.1 Radiotherapy in combination with surgery

Complications include toxicity related to surgery and to radiation therapy, including brachytherapy.
Surgery

Postoperative complications consist generally of urinary complications and also include lymphocysts (20 to 30% of the cases). Digestive complications are less frequent.

Morbidity related to radical surgery has been reported to be greater in endometrial cancer than in cervix cancer, due to the general condition of the patients (35). The frequency of complications seems to decrease with newer surgical techniques: complications occurred in 25% patients treated by laparoscopy compared with 45% in patients who had a laparotomy in a retrospective comparative study (3).

Pelvic lymphadenectomy increases the risk of complications, especially in the sub-group of patients who receive complementary external irradiation. In a multivariate analysis, Corn (12) reported pelvic lymphadenectomy as an independent significant factor for complications (p=0.0049). The risk of complications with a treatment combining pelvic lymphadenectomy and irradiation has been shown to increase with age (30).

Postoperative External Beam Therapy alone

The risk of severe complications mostly gastro-intestinal after treatments combining external irradiation and surgery ranges between 5.5% (12) and 7.8% (65). In a randomized study assessing the value of postoperative irradiation, an overall rate of late complications, 25%, occurred in the radiation group, 3% of them being grade 3 or 4 (13). All patients with severe complications had symptoms from the gastro-intestinal tract. Acute toxicity was the most important factor predisposing to late complications. The radiation technique was also a predictive factor, with a significant increase in complications when a two field technique was used. In this trial, no complementary brachytherapy was given and the patients were not submitted to a routine lymphadenectomy.

Pre- and postoperative vaginal brachytherapy +/- EBT.

Acute side effects may result from vaginitis, mild cystitis and/or proctitis during or immediately following brachytherapy. These symptoms usually disappear spontaneously within a few days. In a series of 102 patients treated with HDR brachytherapy alone using three weekly fractions of 5 Gy, 19 acute mild side effects occurred without any long-term complications (2).

The main late side effects are vaginal dryness, shortening and stenosis, chronic cystitis, proctitis, sigmoiditis and enteritis (with or without ulceration and bleeding), and rarely necrosis and fistula (between bladder, vagina, rectum).

In the IGR series of 239 patients (21), which can be taken as representative for LDR brachytherapy series, brachytherapy was combined with external irradiation according to the classical risk factors. The overall crude rate of long term complications of grade II and III were 18.8% and 6.6%, respectively, scored with the Franco-Italian glossary (9). The following organs were particularly involved: vagina 17 pts. grade II, 9 pts. grade III; bladder 4 pts. grade II; rectum 3 pts. grade II; colonsigmoid 2 pts grade II, 1 grade III; small bowel 1 pt. grade II, 1 pt. grade III.

The dose per fraction appears to be a significant factor for complications. In 404 patients treated by HDR brachytherapy alone, with different doses per fraction, vaginal complications increased with the dose per fraction: 31% in the group of patients treated 6 times 4.5 Gy, 50% in the 6 x 5 Gy group, 60% in the 5 x 6 Gy group, and 79% in the 4 x 9 Gy group. The overall complication rate also increased, ranging from 11.2% in the lowest dose per fraction group to 87.5% in the highest dose per fraction group (73).

In a series of 141 patients treated with HDR brachytherapy alone, with 4 fractions of 8.5 Gy calculated at the surface of the vaginal mucosa, no grade 3, 4, or 5 complications were observed.
The incidence of grade 1 and 2 vaginal complications was 15.3%, bladder complications 5.6% and rectal complications 2.1%.

Chadha (7) using a schedule of 3 fractions of 7 Gy specified at 0.5cm from the surface of the applicator reported two complete vaginal stenoses without any severe vesical or rectal complications.

The individualization of the depth of the reference dose according to the vaginal thickness reduces the risk of late complications. In a study of 217 patients with a customized prescribed isodose depth chosen at 3, 4, or 5 mm from the applicator surface, estimated by inspection and palpation, the incidence of complications decreased when compared with a standard prescribed isodose at 5 mm from the vaginal surface (61). The reduction in the rate of reactions was particularly evident for grade 2 complications. The reduction was greatest for late bladder reactions, dropping from 10% to 1% (p=0.005) and was also significant for the vagina: 34% in the standard treatment versus 18% with the individualized treatment (p=0.005).

The length of the vagina to be treated also appears to be a matter for debate. It is generally admitted that the upper third of the vagina is a sufficient length for prophylactic treatment. In a retrospective survey including 655 patients, 24% of the patients still received treatment to the whole vagina. This treatment led to an increase in vaginal complications without any difference in terms of local control (27). The change in the mean age of this population with younger and sexually active patients, will probably lead to a better analysis of vaginal complications.

In the Vienna experience with HDR brachytherapy, the treatment strategy has evolved over the last two decades, reducing total dose and dose per fraction and the treated volume without decreasing local control (see Table 4) (41). In the old series (up to 1993) the dose per fraction was 2x10 Gy at 20 mm and later 2x7 Gy at 20 mm from the source axis corresponding to 12 Gy and 8.5 Gy at 5 mm from the applicator surface with the 25 mm applicator most frequently used. The respective applicator surface doses were 18 Gy and 13 Gy per fraction (150%). The whole vaginal length was treated in most patients. If there was additional external beam therapy the dose to the midpelvis averaged 54 Gy (bilateral large arc technique Kucera (42B)). The overall crude rate of reversible late side effects in a representative subset of 143 patients was the following: vaginal introitus necrosis n=6 (4.2%), colpitis n=62 (43%), proctitis n=12 (8.4%), cystitis n=8 (5.6%). Irreversible complications (overall 3.5%) were 2 patients with rectovaginal fistula (1.4%), 2 patients with rectal stenosis (1.4%) and 1 patient with ureteric stenosis (0.7%) (42B). The majority of these complications (~80%) were seen in patients treated by EBT + BT.

From 1993-1998 the total dose of brachytherapy was 21 Gy (3x7 Gy) at 5 mm and the cylinder was individually adapted to the individual vaginal topography with two thirds of the vagina as CTV (1993-1998). The dose from EBT was 40 Gy to the vagina and 50 Gy to the pelvis using a four field box technique. The side effects were scored prospectively with the LENT SOMA scale in 332 patients after EBT + brachytherapy. There were 91 grade 1 (slight mucosal atrophy), 61 grade 2 (moderate atrophy, adhesions, shortening), 34 grade 3 (shortening > two thirds), 5 grade 4 (ulceration and/or fistula) complications; in 218 patients after BT alone the side effects in the vagina were 99 grade 1, 12 grade 2, and 5 grade 3. For the bladder after EBT + BT there were 31 grade 1, 13 grade 2, 2 grade 3, and 1 grade 4; for the rectum 9 grade 1 and 24 grade 2; for the bowel 16 grade 1, 10 grade 2, 1 grade 3 and 1 grade 4 complications. After BT alone there were 17 grade 1 and 1 grade 2 bladder complications; for the rectum 2 grade 1 and 1 grade 2; for the bowel 3 grade 1.

From 1999 onwards, the dose was reduced to 4x5 Gy at 5 mm for brachytherapy alone, and 3x5 Gy in the combination treatment, and the treated volume was reduced to the upper third of the vagina. The late effects at the vagina were significantly reduced compared to the preceding periods: in 110 patients there were no grade 2,3,4 effects at the vagina with either BT alone or with BT + EBT observed by 2/2002, and only few grade 1 (14/4). For the bladder and the bowel no grade 2, 3 and 4
Complications from the small and large bowel (except the rectum) reported in different series are usually mainly related to the dose and volume given by external beam therapy.

11.4.2 Definitive radiotherapy

After definitive radiation therapy using LDR brachytherapy, grade 1 complications occurred in 10% of the patients, grade 2 in 4.3%, grade 3 in 3% and grade 4 in 1.4% (63). The complications were mostly located in the rectosigmoid. Among the 18 patients with severe complications, 5 were still alive with a mean follow-up of 8.8 years. The complication rate decreased significantly with the use of new techniques and computerized dosimetry. Similar experience is reported after HDR brachytherapy. The overall actuarial rate of side effects was 24% grade I, 5.7% grade II, and 5.2% grade III/IV. For the different organs, the actuarial rate of grade III/IV side effects were bladder 0.9%, rectum 0.4%, vulvovagina 0.8% and bowel 3.5% (40). With the systematic use of 3D image based treatment planning and the Heymann packing method in Vienna, the rate of side effects was significantly reduced in the last decade.

12 References


77. Thomas L, Bataillard A, Bremond A, et al. Standards, options and recommendations for the radiotherapy of patients with endometrial cancers. FNLIIC (National Federation of Cancer Campaign Centers) and CRLCC (Regional Cancer Campaign Centers). *Cancer Radiother* 2001; **5**: 163-92.


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