The GEC ESTRO Handbook of Brachytherapy

SECOND EDITION

PART II: CLINICAL PRACTICE

17
Endometrial Cancer

Peter Hoskin, Taran Paulsen Hellebust, Remi Nout, Ina Jürgenliemk-Schulz, Christine Haie Meder, Erik Van Limbergen, Richard Poetter

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1. SUMMARY

Endometrial cancer presents in most women at an early stage confined to the uterus and initial treatment is by hysterectomy. Post-operative treatment is indicated for intermediate and high risk patients defined by age, stage, grade and the presence or absence of lymphovascular space invasion.

Vaginal vault brachytherapy is indicated in intermediate risk patients having one of the following risk factors: grade = 2 or 3, myometrial invasion >50%, lymphovascular space invasion or cervical stromal invasion. The PORTEC 2 trial confirmed that it is as effective as external beam pelvic radiotherapy in this group of patients and associated with less toxicity. Vaginal relapse is reduced to only 2-3%. Mucosal atrophy occurred in 36% of patients in PORTEC 2 as the main toxicity; grade 3 GI toxicity was <1%.

Intrauterine brachytherapy is indicated for patients with endometrial cancer who are unfit for surgery either alone (stage I or II) or with external beam therapy (stage III). Accurate staging is now possible with MR scanning. Specific applicators are required, either Heymans or Norman Simon capsules, or the Rotte Y applicator to ensure good coverage of the IR-CTV which includes the entire wall of the uterus and vaginal cuff to which a minimum dose of 60Gy should be delivered. With MR imaging a HR-CTV incorporating the GTV can be defined which receives a higher dose. Outcome in this group of patients is predominantly defined by their comorbidities rather than the endometrial cancer. Toxicity is mainly vaginal dryness and shortening with occasional grade≥3 urinary and bowel toxicities in <5%.

2. INTRODUCTION

The incidence of endometrial cancer has been rising in recent decades and it has become the fourth most common cancer in females, after breast, lung, and bowel cancer [22,74,81] in western countries where the incidence is high (15-25 cases/100000 women in Europe) compared to other parts of the world for example Eastern countries (2 cases/100000 women) [1] However despite the rise in incidence, mortality rates show a decrease in Europe and hence an increased prevalence of women who have experienced endometrial cancer [2][3].

The majority of these cancers are seen in postmenopausal women, with a median age of 65 years. Only 10% occur in premenopausal women. The aetiology of endometrial cancer is mainly related to exposure to excess of unopposed oestrogens. This explains the majority of the risk factors for endometrial cancer development: obesity, diabetes mellitus, hypertension, and null parity, late menopause and if there is complex atypical hyperplasia. An increased incidence is recognised in women with breast cancer who take long term tamoxifen in whom the risk is estimated to be 2 in 1000 per year; the benefit of tamoxifen in breast cancer however considerably outweighs this risk [4]. It is estimated that less than 5% of the endometrial cancers are attributable to potential hereditary genetic factors. These are most often younger patients with Lynch syndrome, who have a 60-70% lifetime risk of developing endometrial carcinoma.

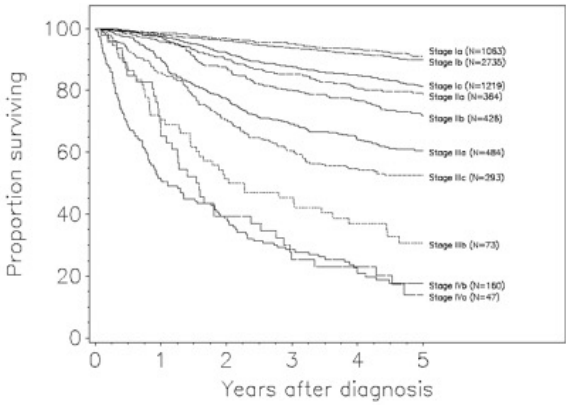
The main symptom (90%) is vaginal discharge and bleeding. Because this characteristic symptom arises in the postmenopausal woman, the disease is usually diagnosed at an early stage; over 70% of tumours are confined to the uterine corpus (stage I) at presentation. [5].

Staging is based on clinical extent and surgical pathology. The 2009 FIGO staging is shown in table 15.1.

Table 15.1: TNM Classification for Endometrial Cancer

PRIMARY TUMOR (T)

TNM	FIGO	Surgical-pathologic findings
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis*		Carcinoma in situ (preinvasive carcinoma)
T1	I	Tumor confined to corpus uteri
T1a	IA	Tumor limited to endometrium or invades less than one half of the myometrium
T1b	IB	Tumor invades one half or more of the myometrium
T2	II	Tumor invades stromal connective tissue of the cervix
T3a	IIIA	Tumor involves serosa and/or adnexa
T3b	IIIB	Vaginal involvement or parametrial involvement
	IIIC	Metastases to pelvic and/or para-aortic lymph nodes
	IV	Tumor invades bladder mucosa and/or bowel mucosa, and/or distant metastases
T4	IVA	Tumor invades bladder mucosa and/or bowel mucosa



Stage	Patients (n)	Mean age (yr)	Overall survival (%) at 1 year	2 years	3 years	4 years	5 years	Hazards ratio[a] (95% CI)
Ia	1063	59.7	98.5	96.8	95.0	93.2	91.1	Reference
Ib	2735	62.7	98.2	96.1	93.7	91.7	89.7	1.1 (0.9–1.4)
Ic	1219	65.8	97.6	92.3	87.7	84.7	81.3	1.8 (1.4–2.3)
IIa	364	63.8	95.8	90.3	85.1	80.5	78.7	2.6 (1.9–3.5)
IIb	426	63.4	97.4	87.5	80.1	76.4	71.4	3.2 (2.4–4.2)
IIIa	484	63.1	89.9	77.3	69.2	64.3	60.4	5.6 (4.3–7.3)
IIIb	73	68.9	70.6	51.7	45.5	36.9	30.2	11.2 (7.8–16.0)
IIIc	293	60.8	85.7	70.7	60.4	54.6	52.1	9.2 (7.0–12.2)
IVa	47	64.8	65.6	39.4	25.9	23.4	14.6	18.1 (12.3–26.7)
IVb	160	65.5	51.1	38.6	28.4	21.8	17.0	20.3 (15.3–26.9)

[a]Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for age, stage and country.

Fig. 7. Carcinoma of the corpus uteri: patients treated in 1996–98. Survival by FIGO surgical stage, $n = 6864$.

Figure 15.1: Survival from endometrial cancer by stage: FIGO results

The most important prognostic factors are tumour type and grade, the extent of the disease at diagnosis (depth of myometrial infiltration, nodal involvement and tumour invasion beyond the uterus), presence of lymphovascular invasion and increasing age at presentation. Histological subtyping is important with a worse prognosis for those histologies that do not correspond to the most common (80%) classical endometrioid adenocarcinoma, in particular clear cell and serous cancers. The 5-year survival rate for endometrioid adenocarcinoma is 80-85%, compared to 50-60% for serous and clear cell cancers.

Stage is the other important prognostic factor; the impact on survival according to the 23rd FIGO annual report [6], using the 1988 classification is shown in figure 15.1. Because most women present with FIGO stage I and the endometrioid subtype the overall prognosis is good.

The main treatment for endometrial cancer is surgery. Traditionally, surgery has been total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO) with excision of a small cuff of vagina. Lymph node sampling (pelvic +/- para-aortic) is performed with increasing incidence, in particular in patients at high risk of lymphatic spread. At a minimum the nodal regions are inspected and only suspicious nodes are removed. There is no evidence that staging lymphadenectomy improves local control or survival [7] and it is usually performed only in high risk tumours, in particular those with high grade adenocarcinoma, clear cell or papillary serous histology. Sentinel node biopsy has a 90% predictive power in uterine cancer and can be used to predict those patients who may benefit from lymphadenectomy [8].) The number of women who are regarded as medically inoperable has decreased due to developments in anaesthesia and postoperative intensive care and also due to the possibilities offered by laparoscopic and transvaginal approaches. Laparoscopic total hysterectomy is associated with less pain, a decreased length of hospital stay, faster resumption of daily activities and improved quality of life compared to TAH-BSO [9][10][11].

Surgery has traditionally been combined with radiotherapy, to prevent vaginal recurrence, which is reported in up to 10 - 15% after surgery alone, and pelvic lymph node recurrence. In the past, this was often preoperative radiotherapy, mainly as utero-ovaginal or vaginal brachytherapy but after recognition that most patients present with low risk features, the usual approach today is for primary surgery with the adjuvant treatment strategy based on histopathological findings as discussed below.

Despite early diagnosis, surgery and adjuvant treatment, vaginal recurrences are still regularly observed. Radiotherapy for recurrent disease is therefore an important issue (see also chapter on interstitial gynaecological brachytherapy).

In high risk histological subtypes disseminated intraperitoneal and distant site metastases are the common pattern of relapse. Adjuvant chemotherapy based on platinum drugs and taxanes is under investigation both alone and in chemoradiation schedules as in the PORTEC-3[12] and GOG258 [13] trials.

3. ANATOMY

The uterine corpus is formed by a large smooth muscle with different layers, varying in thickness from 10 - 30 mm (myometrium). Its cavity is lined by the endometrium formed by

cylindrical epithelium with many different functions and different thicknesses. The top, the back and the upper parts of the front wall are covered by serosa. The uterine body which is very well vascularized has a high tolerance to radiation.

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. 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). The length of the uterine cavity varies from about 4 - 10 cm. Anatomically it is closely related to the bladder (posterior wall), to the small and large bowel, in particular 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.

The topography of the vaginal vault 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. The topographic relationships are even closer than in the preoperative situation as the uterus itself has been removed.

The vault itself has varying shape and dimensions, in particular in thickness.

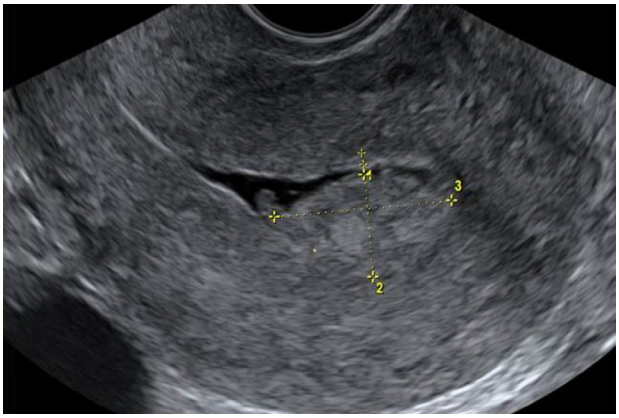
4. PATHOLOGY

The majority of tumours arise from the fundus and the uterine cornua (about 80%) with exophytic and endophytic growth patterns. The most common type of invasive uterine tumour (comprising 75 - 80% of all cases) shows a strong resemblance to normal endometrial glands and is endometrioid adenocarcinoma [14][15]. These tumours are usually found in a background of endometrial hyperplasia, hence an oestrogen rich environment. The degree of differentiation correlates with biological aggressiveness, the frequency of lymph node and distant metastases and thus with prognosis. The various histologic subtypes of endometrioid carcinoma are of minor clinical importance and include secretory, papillary, ciliated cell, adenosquamous, adenoacanthoma. The mucinous subtype carries the same prognosis as endometrioid carcinoma, but the prognosis is much worse in serous carcinoma (< 10% of endometrial cancer) because of its early pelvic lymphatic, peritoneal and distant spread and also in clear cell carcinoma. In contrary to the endometrioid type, serous and clear cell types are more often found in the background of an atrophic endometrium. Another rare aggressive form is the undifferentiated small cell carcinoma (< 1%), which is often widely disseminated but may be chemosensitive. In contrary to the previous epithelial tumours, the mesenchymal and mixed tumours such as leiomyosarcoma, stromal cell sarcoma and carcinosarcoma (formerly mixed Müllerian tumour), are rare tumours and are clinically regarded as a separate entity.

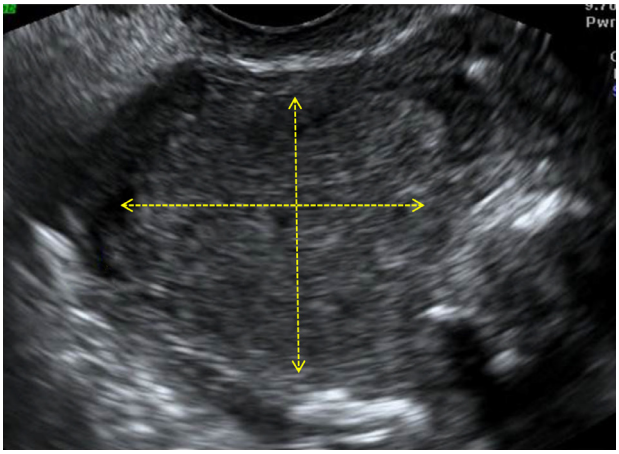
Considerable interobserver variability exists among pathologists both in typing and grading of endometrial cancer, underscoring its complexity and inherent heterogeneity. Some serous tumours show a strong resemblance to papillary endometrioid tumours,

Figure 15.2: Transvaginal ultrasound showing primary uterine carcinoma

a. Stage IA



b. Stage IB



both having a different clinical behaviour. Epigenetic characterisation of endometrial cancer may help to better characterize endometrial malignancies. Recent work from the cancer genome atlas research network included both endometrioid and serous cancers and identified four distinct groups predictive of progression free survival[16]. As expected the group containing the serous tumours had the lowest progression free survival. However patient selection and treatment was not controlled for and clear cell cancers were not included; clearly further studies in this area are needed.

Current understanding of risk groups in endometrial cancer divides patients into three groups based on the following adverse factors:

- Grade 2 or 3
- Myometrial invasion greater than 50%
- Cervical stromal invasion (Stage 2)
- Lymphovascular space invasion (LVSI):

LOW RISK: none of the above

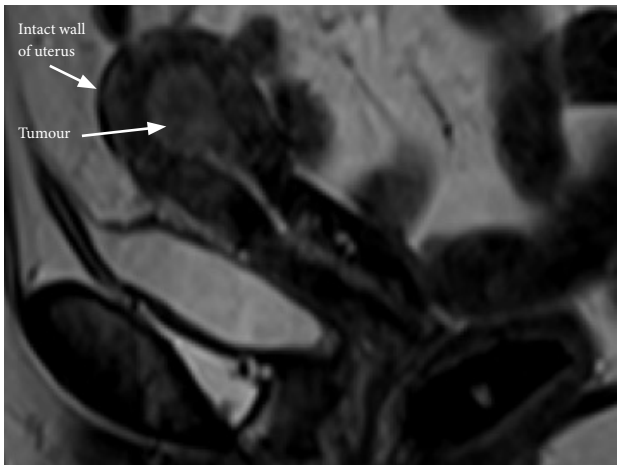
INTERMEDIATE RISK: 1 of the above factors

HIGH RISK: 2 or more of the above factors

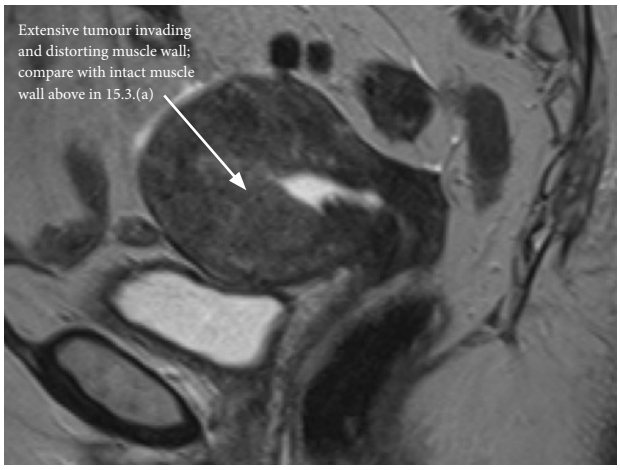
Intermediate risk has been divided into 'high intermediate' and 'low intermediate'. High intermediate risk is based on the pres-

Figure 15.3: Diagnostic MRI scan to show localized uterine cancer (a) not invading the myometrium and (b) invading >50% of myometrium: Stage IB

a. Non-muscle invasive endometrial cancer (IA)



b. Stage IB showing extensive invasion of uterine wall



ence of 2 of the following: age >60yrs, Grade 3, >50% myometrial invasion or LVSI.

An alternative classification divides endometrial cancers into Type I and Type II. Type I is characterised by women who are obese, have hyperlipidaemia, signs of hyperoestrogenisation, anovulatory uterine bleeding, late onset of menopause and infertility with hyperplasia of the ovaries and endometrium. These features are associated with grade 1 or 2 cancers, superficial invasion and high progesterone sensitivity with a relatively favourable outcome having a 78% 5 year survival compared to only 59% in those cases without these features [17].

A more sophisticated analysis from which a nomogram to individualise risk based on age, grade, myometrial invasion and LVSI has been constructed for locoregional relapse, disease free and overall survival. [17].

5. WORK UP

In approximately 5-10% of patients presenting with postmenopausal vaginal bleeding, endometrial cancer is the underlying cause. Systematic work-up includes the following: history, general and gynaecological examination and transvaginal ultrasound which provides information on endometrial thickness and tumour extent as shown in figure 15.2 followed by pipelle sampling, EUA for systematic biopsies of both endometrium and cervix with hysteroscopy or fractional curettage. Ultrasound may also be useful both in screening high risk patients such as those on prolonged tamoxifen and in evaluating premenopausal women. Cystoscopy and rectoscopy are indicated in advanced disease.

For the majority of stage I low grade patients a chest radiograph and transvaginal ultrasound combined with gynaecological examination are sufficient to assess the disease extent prior to surgery. For patients with more advanced stage disease and high grade histology, CT of the chest and abdomen is used to screen for involved lymph nodes and rule out distant metastasis, while pelvic MRI is recommended for evaluating the local tumor extent. MRI will correctly predict the surgical stage in 70-80% of cases [19] as shown in figure 15.3.

6. INDICATIONS FOR BRACHYTHERAPY

Surgery consisting of hysterectomy and bilateral oophorectomy is the most important treatment for the majority of endometrial cancer patients. More than half of the patients will not require any further adjuvant treatment and have an excellent 95% recurrence free survival. The most frequent indication for brachytherapy is that of postoperative treatment, where the aim is to prevent local vaginal recurrence. Less frequent indications for brachytherapy are the primary treatment in patients that are no surgical candidates and the treatment of recurrent vaginal disease.

6.1 Postoperative radiotherapy

With the advent of risk based adjuvant radiotherapy, it was already recognised that patients with grade 1 and 2 endometrioid type tumours without invasion in the myometrium had a very low risk of disease recurrence with surgery alone. The role of post-operative radiotherapy for stage I intermediate risk endometrial cancer has been subject to a number of multicentre randomised trials in recent years focussing in all but one case principally on the use of external beam irradiation.

The PORTEC 1 study [20] randomised 714 stage I intermediate risk patients with at least one risk feature on histology,>50% myometrial invasion, grade 2 or grade 3 (excluding >50% invasion AND grade 3) to receive either post-operative external beam treatment delivering 46Gy in 23 fractions or no adjuvant postoperative radiotherapy. Mature results have confirmed a 9% reduction in pelvic relapse (5% with postoperative radiotherapy versus 14% without at 5-years) in this patient population but no reduction in distant metastasis or in endometrial cancer deaths. The GOG-99 study [21] included 392 surgically staged patients and was similar in design but included lymphovascular invasion

as a risk feature for entry in addition to myometrial invasion and histological grade. The results of this study confirmed the conclusions of PORTEC 1. Both studies then identified a subgroup of patients that showed the largest reduction of pelvic recurrence, referred to as the 'high-intermediate' risk group. In PORTEC-1 age >60, grade 3, and deep (>50%) myometrial invasion were independent risk factors for pelvic recurrence and patients with two of these three risk factors showed the largest reduction in pelvic recurrence (20% without versus 5% with radiotherapy at 5-years), while remaining patients had a prognosis similar to low risk patients. GOG99 confirmed the adverse effects of age, tumour grade and depth of myometrial invasion, but did include lymph vascular space invasion as a risk factor. In both studies the majority (75%) of the pelvic recurrences in the no additional treatment arms were vaginal recurrences of whom most were salvaged successfully with combined external beam radiotherapy and brachytherapy. As a result of these trials external beam radiotherapy was abandoned in patients that did not fulfil the risk group criteria low-intermediate risk who have a prognosis similar to low-risk patients.

A third and the largest study was the MRC ASTEC study [22] which in its radiotherapy arm randomised 905 patients with at least one of the following risk factors defined by stage I with >50% myometrial invasion, grade 3, clear cell or papillary serous histology or pathologically positive pelvic lymph nodes to receive either external beam radiotherapy, 48.6Gy in 27 fractions, or no further treatment. In this study brachytherapy was permissive in both arms and approximately 50% of patients in the no additional treatment arm and in the radiotherapy arm received vaginal brachytherapy, explaining the relative low rate of isolated vaginal or pelvic relapse (6.1% at 5 years) in the no additional treatment arm (versus 3.2% with external beam radiotherapy). Again no difference in recurrence free or overall survival was seen between the two groups.

In summary these large randomised trials found that postoperative radiotherapy reduced the risk of pelvic recurrence threefold, that did not translate in a reduction in distant metastases or endometrial cancer related death, but did come at the cost of increased toxicity. This was predominantly mild to moderate gastro-intestinal toxicity (25%); however, severe grade 3-4 toxicity was reported in 3-8% after radiotherapy.

Both the finding that the majority of pelvic recurrences in patients that did not receive postoperative radiotherapy were located in the vagina and the increased toxicity with external beam radiotherapy formed the rationale for the PORTEC-2 trial [23]. In this trial 427 high-intermediate risk patients were selected based on the combination of risk factors from the PORTEC-1 trial and randomised to receive 46Gy in 23 fractions external beam or vaginal brachytherapy delivering 21Gy in 3 fractions HDR or 30Gy single dose LDR at 5mm depth. These doses are equivalent to an EQD2 of 29.75Gy ($\alpha\beta10$) and 42Gy ($\alpha\beta3$). Updated results with a median follow-up of 89 months show that the risk of vaginal recurrence after external beam radiotherapy was 1.9% at 5 years and 2.4% at 8 years, compared to 2.4% and 2.9% after vaginal brachytherapy, excluding a clinically relevant difference in vaginal recurrence rate between both treatments. Although the rate of regional nodal recurrences was higher after vaginal brachytherapy 4.7% compared to 0.9% at 5-years, there was no difference in isolated nodal recurrences (0.5% vs 1.5%) with the majority of patients having simultaneous nodal and distant relapse. There was no difference in rate of distant metastasis (7.2% versus 9.3% at 5 years) or overall survival (83.9% in both arms at 5 years) between both arms. On the other hand there was significantly less gastrointestinal toxicity with vaginal brachytherapy and patient reported outcomes found that patients treated with external beam radiotherapy had significantly higher rates of diarrhoea, faecal leakage, need to remain close to the toilet and limitations in their daily activities due to bowel problems. These results indicate that vaginal brachytherapy is very effective in preventing vaginal recurrence, but with a more favourable toxicity and patient reported outcomes profile compared to external beam radiotherapy.

The findings of PORTEC-2 have been confirmed in a Swedish trial [24] using again a different combination of risk factors for patient selection. In this trial 527 medium risk patients were randomised between vaginal brachytherapy (HDR 6x3Gy or 3x5.9Gy; LDR 20Gy) or external beam radiotherapy combined with the same vaginal brachytherapy. The external beam dose was 46Gy in 1.8-2Gy fractions. The HDR brachytherapy doses at 5 mm equate to an EQD2$\alpha/\beta10$ of 19.5Gy or 23.4Gy and EQD2$\alpha/\beta3$ of 36Gy or 31.5Gy respectively. The locoregional relapse rate in the combined arm was 1.7% compared to 5% in the brachytherapy alone arm with no difference on survival and significantly more toxicity in the combined arm.

In conclusion, vaginal brachytherapy alone is the treatment of choice in 'high-intermediate' risk patients. Both the definitions of PORTEC and GOG are being used for patient selection and the majority of patients will be included in both definitions, irrespective of surgical staging.

Patients with endometrioid type stage IA grade 3 but with lymphovascular space invasion, stage IB grade 3, stage II/III/IV, and patients with clear cell or serous histologies have a higher risk for nodal involvement and distant metastasis and are therefore considerd high risk patients. These patients should receive external beam radiotherapy to cover subclinical nodal disease. The role of chemotherapy in this group with high risk of distant metatstases is under investigation. The low rates of vaginal recurrence after postoperative external beam radiotherapy alone leave little room for improvement by an additional vaginal vault brachytherapy boost. Routine use of an additional vaginal vault brachytherapy boost is therefore not recommended. The clearest indication for a boost with vaginal vault brachytherapy is in the very rare event of a close or positive vaginal margin. Traditionally however, a brachytherapy boost has mainly been considered in patients with a high risk of vaginal recurrence such as in the case of cervical stromal involvement (stage II), especially in those with clinical overt cervical involvement [11]. Prospective evidence of a benefit in local control is lacking, while there is an additional risk of treatment related morbidity. These recommendations are in keeping with the ESMO-ESGO-ESTRO Consensus Guidelines [25].

6.2 Radiotherapy alone with the uterus in situ

For medically inoperable stage I/II and advanced disease stage III/IV primary radiotherapy can achieve good results (results section). MRI is recommended to assess the local tumour extent, depth of myometrial invasion, cervical extension, infiltration of the parametria and involvement of regional lymph nodes.

If surgery is medically contraindicated, in stage I patients brachytherapy to the whole uterus and the upper third of the vagina is indicated. MRI is a valuable investigation for treatment planning to evaluate the extent and position of the tumour, depth of myometrial invasion and cervical extension.

External pelvic radiotherapy is added if there are unfavourable prognostic factors in particular myometrial infiltration >50% and grade 3, or stage II and higher stages. This will be similar to the treatment of advanced cervical cancer. Adaptation of the GEC ESTRO guidelines using 3D conformal brachytherapy after 45-50Gy external beam is recommended.

6.3 Brachytherapy for recurrence

Brachytherapy is indicated for the treatment of local recurrence. Depending on the site, extension, volume of recurrence, and previous treatment, endovaginal and/or interstitial brachytherapy is performed, with or without external beam therapy. 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. Another hypothesis is that lymphatic drainage towards the vagina may play a role. Two thirds of vaginal recurrences occur at or around the vaginal cuff whilst the next most common site is the suburethral region [26]

High salvage rates are reported with this approach when radical doses are delivered and this should be the aim unless there are distant metastases or other serious co-morbidites (see chapters on vagina and interstitial gynaecological brachytherapy).

7. TARGET VOLUME

7.1 Postoperative vaginal brachytherapy

The rationale for post-operative vaginal vault brachytherapy is that the majority of vaginal recurrences occur at the vaginal cuff. The next most common site is the periurethral region but this accounts for only 10% of the total recurrences. The target volume for postoperative brachytherapy has therefore been limited to the vaginal wall of the upper third of the vagina. The resulting typical target length is 3 - 4 cm and the thickness may vary according to the thickness of the vaginal wall. Special care must be taken that the applicator has direct contact at the vaginal cuff with its often irregular surface and shape after surgery. Careful choice of an adequate applicator using a cylinder, ovoids, or individual mould applicators is crucial for target coverage. Verification with MR or CT to confirm close apposition should be considered.

7.2 Radiotherapy with the uterus in situ

The CTV is best defined taking into account all available information which will include description of the hysteroscopy findings, CT and MR imaging.

Wherever possible target definition should be based on MRI or, if not available, CT planning images with the intrauterine applicators in situ. If the tumour is limited to the uterine body (stage I), or invading the cervix (stage II) the whole body and the cervix with upper third vagina makes up the CTV. Efforts should be made to delineate the GTV in its location and dimensions (depth) as it represents the most relevant part of the CTV. Depending on the pattern of spread, parametrial or paravaginal tissue may also be included in the target where there is advanced stage III disease.

Whilst 100% coverage of the CTV should be the aim this is often not achievable. One study [27] reports that treatment outcome was excellent even though only 68% of the CTV could be covered with the prescribed dose of 60 Gy to the D90 EQD2. A high risk CTV (HR-CTV) and an intermediate CTV (IR-CTV) for endometrial cancer may be appropriate allowing lower doses to the regions of the uterus not directly involved with tumour [28][29] similar to the concept developed for cervical cancer [30]. The HR-CTV has been defined based on the GTV plus adjacent muscular wall extended up to serosa in the regions with infiltration into the outer half. The IR-CTV encompassed the entire uterus.

7.3 Brachytherapy for recurrence

Retreatment for recurrence even after previous radiotherapy is possible using brachytherapy. The CTV is determined individually based on examination under anaesthetic, vaginal ultrasound and MRI and encompasses the macroscopic tumour at the time of brachytherapy plus a safety margin for microscopic disease. Tumour extension at diagnosis and adjacent parts of the vagina should be also 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) which should be defined as organs at risk on planning MR or CT scans with the applicator in situ.

For further details see chapter on interstitial vaginal brachytherapy.

8. TECHNIQUE AND TREATMENT PLANNING

8.1 Postoperative vaginal brachytherapy

8.1.1 Applicators

Standard applicators:

The standard vaginal brachytherapy applicators, shown in figure 15.4, include the following:

- cylindrical applicators with one central channel
- multichannel applicator; or several channels in different configurations [31];
- two ovoids (different sizes) with one channel each. Variable distances between the ovoids and use of the same or different sizes in one patient can be used to ensure good cover at the vault [32].

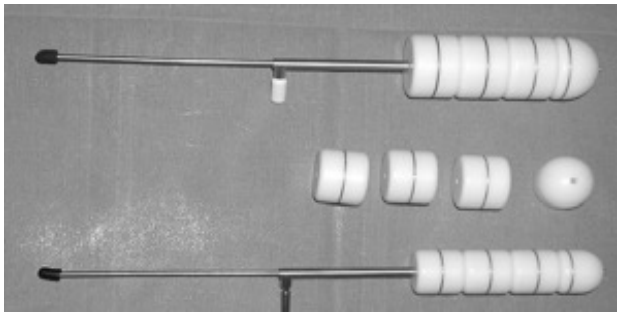
Individualized customized moulds:

A vaginal mould applicator is made individually for each patient (see Fig 15.4c). 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

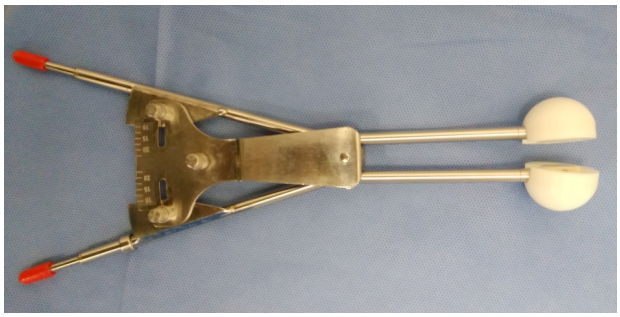
Figure 15.2: Transvaginal ultrasound showing primary uterine carcinoma

a. Cylindrical 'vaginal stump' applicators; note varying diameters from 2.3 to 3.5cm

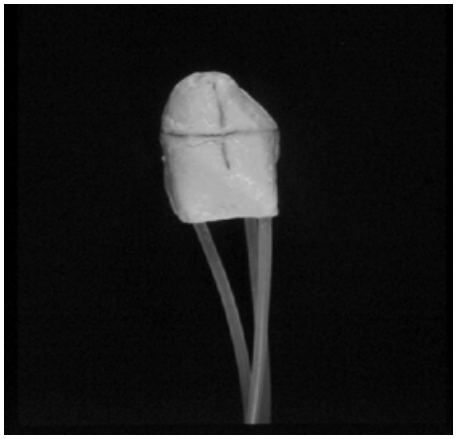
b. Multisection stump applicators which can be modified to fit the vaginal length



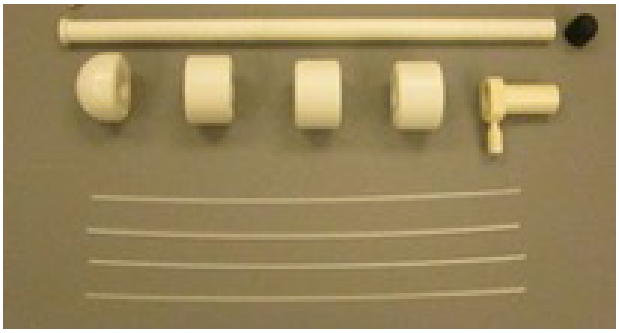
d. Ovoids for use with high dose rate afterloader; these will be held in position by an external clamp fixed to the couch.

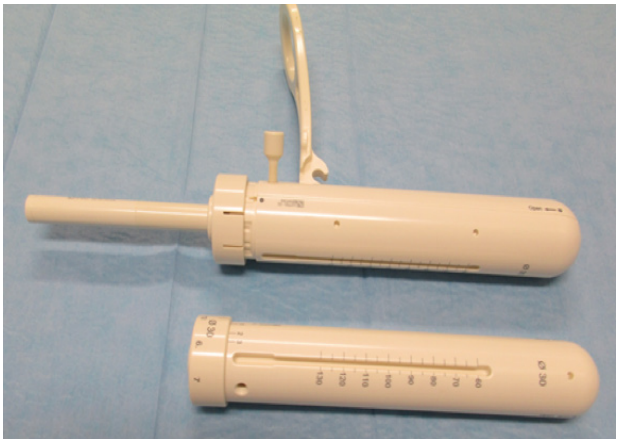


e Mould with three source guide tubes used for PDR delivery



c. Multichannel vaginal applicators, of particular use for eccentric recurrent tumour





two anterior), if the vagina is round. An individual selection can also be made based on a pre-fabricated library of moulds [33].

Applicator choice depends on postoperative anatomy: dome shaped cavities can be treated by all standards (see above) as well as customized applicators. Vaginal scars, dividing the vaginal cuff in 2 symmetrical or asymmetrical fornices are contraindications for cylinders, but should be treated by 2 symmetrical or asymmetrical ovoids or customized moulds. When a fornix is too small to contain an ovoid a customized mould technique is indicated

8.1.2 Technique for applicator insertion
Brachytherapy is preferably started 4-6 weeks after surgery. Care must be taken that the surgical scar at the vaginal vault has healed sufficiently, which usually takes at least 3 weeks. In HDR brachytherapy, the application is usually performed on an outpatient basis, whereas in case of PDR or LDR the patient needs to be hospitalized. Usually there is no need for general anaesthesia or analgesia. Use of lubricants is essential, in some cases local anaesthesia or mild sedation may make the procedure more comfortable. A urinary catheter and medication to prevent defecation such as loperamide might be needed for PDR but not for HDR when the treatment process is very short. CT-based treatment planning has shown that bladder filling might increase dose to the rectum, however by emptying the bladder small bowel loops can move into the vicinity of the anterior surface of the vagina. Therefore, a moderately filled bladder (~100cc) is most appropriate and for HDR can be achieved by asking the patient not to void within the hour prior to brachytherapy.

The patient is positioned in the lithotomy position. The application starts with a gynaecologic examination (including abdominal and rectovaginal bimanual investigation) in order to check the anatomy in general (vaginal length, width, elasticity, filling state of rectum), and in particular the position of the vaginal cuff (condition, healing of the scar) and the local postoperative anatomy (shape of the vault dome and fornices).

With 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.

In some patients with widely varying vaginal diameters, usually narrowing towards the vaginal cuff individual mould applicators are most appropriate. If a standardized applicator technique is used, the individual size of the applicator is chosen based on an estimate of the dimensions of the vaginal cuff and the vagina.

The cylindrical applicator is kept in place mainly by the vaginal muscle tone, but naturally tends to slide out. In HDR brachytherapy the applicator will be fixed in position using a clamp attached to the treatment couch. In LDR/PDR brachytherapy where the applicator will remain in situ for some hours or days it will require additional fixation. A bandage or corset can be employed or the applicator can be fixed by suturing to the labia (under general anaesthetic). A slight pressure should be maintained against the applicator to prevent it from moving away from the vaginal cuff. The applicator must not be pushed dorsally against the rectal wall, rather aiming for a neutral position to evenly spread peripheral dose between anterior rectal wall and posterior bladder wall.

All LDR/PDR applicators sutured or non-sutured can also be contained by an Elastoplast Brachy Slip as explained in the anal canal chapter.

A typical HDR treatment lasts 10-15 minutes. For LDR or PDR brachytherapy the treatment duration (hours or days) varies according to the dose and dose rate chosen and special care is necessary to maintain an appropriate position of the applicator throughout the whole treatment period. After finishing treatment, the applicator is usually removed and the woman can leave the hospital.

8.2 Brchytherapy with the uterus in situ

8.2.1 Applicators
Different types of applicators are available which allows treatment of the whole uterine wall by brachytherapy.

Individualized packing methods
The classical Heyman packing technique using radium-226 has been modified for the needs of afterloading devices (Norman Simon capsules) using small afterloading iridium or cobalt sources comprising long thin flexible tubes with capsules of different sizes at their top (e.g. 4/6/8 mm diameter) as shown in figure 15.5. By individual packing with such capsules, the application can be adapted to the individual pathologic anatomy of the uterine cavity as shown in figure 15.5.

Standardized applicators
Two or three channel-applicators (Y-shaped) ("Rotte applicator" in various sizes for length and width) consist of two rigid applicators with a curved end to reach the two uterine horns shown in figure 15.6. A third applicator may be added to reach the midpoint of the uterine fundus. The applicators are fixed together after insertion. Vaginal gauze packing keeps the applicator in place which for PDR may be augmented by additional fixation (e.g. by elastoplast brachytherapy slip (see anal canal chapter). This technique leads to an appropriate dose distribution in a small or medium sized uterus with superficial tumour extension. This applies for caudocranial and lateral directions, whereas - depending on the thickness of the uterus - dose distribution may be suboptimal in the anterioposterior direction.

One channel-applicator. A uterine tandem with a vaginal cylinder can be used but is only suitable for a small uterus with a superficial tumour.

A single channel applicator has been recommended for patients with a maximum uterine width of 5 cm or less [34]. For patients with a maximum uterine width greater than 5 cm a two-channel Y-shaped was shown to have a better coverage of the CTV. The dosimetric impact of one-, two- and three-channel applicators has been investigated in three patients with CT-based treatment planning [35]. The width of the uterus varied from 4.5 to 5.5 cm and the three-channel applicator provided greater latitude in dose and uterus coverage compared to the one- and two-channel applicators. However it has been shown that even a large uterus could be covered by the prescription isodose without violating the OAR constraints as often happens when using Norman Simon modified Heyman packing [27].

Figure 15.5: Norman Simon capsules (top right) and CT planning images of capsules in situ with CTV and isodoses

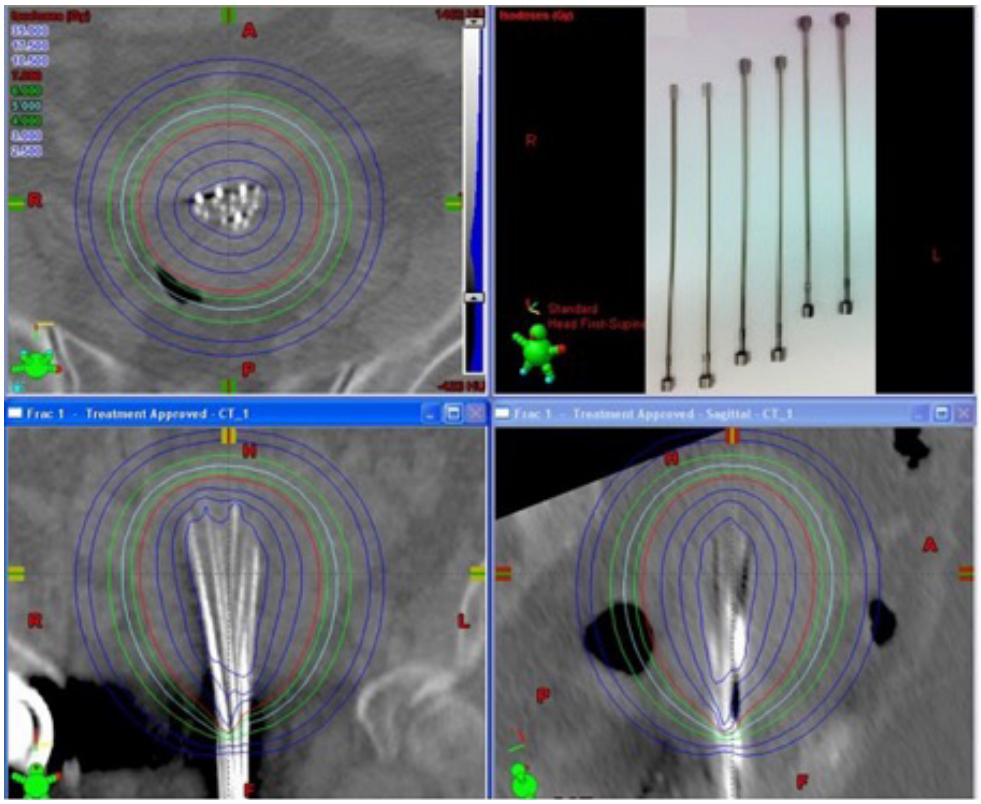
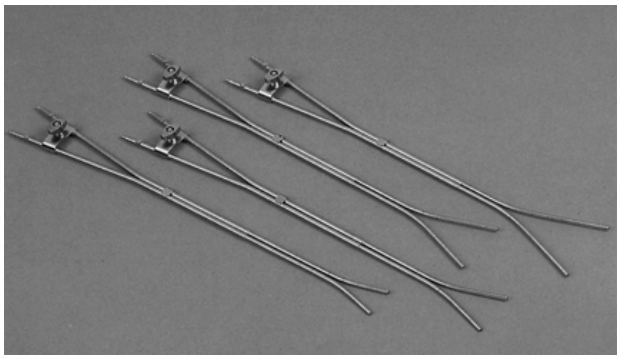


Figure 15.6: Rotte Y applicators



8.2.2 Technique of application

The easiest way to perform such an application is under spinal or general anaesthesia, but it may be performed using a combination of systemic and local analgesia with or without sedation.

The patient is positioned in the dorsal lithotomy position and a bladder catheter inserted. The procedure starts with a clinical examination including abdominal and rectovaginal bimanual investigation in order to confirm the pathologic anatomy and the position and size of the uterus.

Transabdominal ultrasound at this time is also very valuable to confirm the relation between the tube and the uterine cavity. Depending on the technique of application, variable dilatation of the cervical os and canal is indicated increasing with the number of catheters to be introduced. The number of catheters depends on the individual dimensions of the uterine cavity.

Norman Simon capsule packing.

A large uterine cavity being treated with Norman-Simon capsules (modified Heyman's capsules) will usually need more than 10 catheters, which requires as wide a dilatation as possible (up to Hegar 10 - 12). The packing is complete after the uterine cavity has been filled, but is usually extended to the uterine cervix. A capsule in the cervical canal will prevent this closing down during treatment and make removal easier. This is of particular importance in PDR treatment with a longer time period of many hours or days, as the internal cervical os may become narrow again and prevent extraction of the tubes with the capsules. The number of tubes applied varies significantly with the individual anatomy, but between 5 and 18 is typical. Finally, the vagina is packed or a mould is introduced, to keep the applicators in place.

Two or three channel-applicators (Y-shaped)

One of the two curved Rotte 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 by a screw clamp on the applicator stem. The whole applicator is stabilized by vaginal packing.

One channel-applicator

The intrauterine 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.

The applicators will require fixation with a bandage (e.g. the Elastoplast BrachySlip) or corset as used for an intrauterine tube.

9. TREATMENT PLANNING

9.1.1 Imaging for treatment planning: postoperative
Although post-hysterectomy vaginal brachytherapy is a simple treatment technique, imaging with applicator in place should be performed to verify and document the size and position of the applicator and to determine the dose to the organs at risk (OAR) [36]. Whilst vaginal vault brachytherapy was not included in the ICRU recommendations 38 or 50, analogous rectal and bladder points may be used to assess dose to the organs at risk using plain radiographs.. PDR treatment will require an indwelling catheter which is used to define a bladder reference point for dosimetry but in HDR this will require catheterisation for dosimetry which is not usually undertaken for each fraction. Rectal doses may be measured using a rectal reference point but the large PORTEC trials did not use bladder or rectal dosimetry and there are no clear guidelines with regard to dose constraints. The use of CT has obvious advantages, giving better information on the exact position of the organs at risk, identifying air pockets and avoiding the use of catheters and markers. MRI again gives more anatomical detail in the area of the surgical scar and increases the resolution between the vaginal wall, the bladder and rectum.

9.1.2 Treatment planning: postoperative
The majority (90%) of the recurrences are located cranially, in the vaginal cuff and vaginal morbidity is higher if more of the length is included. This is most apparent when the whole length or the distal third is included. To avoid excess vaginal morbidity, the target volume for postoperative brachytherapy has been limited to only the upper third of the vagina. The resulting typical target length is 3 - 4 cm.

Historically there have been two methods to specify the dose, either at 5 mm depth or at the surface of the applicator. The aim of treatment planning would be to have the 100% isodose run parallel to the cylinder surface and the loading pattern in the cylinder is symmetrical in the cranio-caudal direction. Prescribing at 5 mm from the surface of the applicator is most frequently used, as shown in an ABS survey and this was also the prescription practice in both randomized trials [23][24]. Typically the prescription point is placed at the mid- point of the length of the activated dwell positions however this does not guarantee that the prescribed dose will follow parallel along the cylinder at 5mm, especially at the curved apex. The distance of the first dwell position to the apex, the radius or degree of curvature of the apex and an8isotropy along the longitudinal axis of the source are factors that compromise an ideal dose distribution along the surface of the apex. For commercial applicators the range for the distance of the first dwell position to the apex is between 5 and 6.5 mm. It is also important to recognise that with varying diameters of vaginal cylinders and a fixed prescription dose point at 5 mm, the dose at the surface increases with decreasing cylinder diameters. In contrast, when prescribing at the surface of the applicator, this is more representative of the maximal dose to the mucosal surface and the dose at 5 mm decreases with a smaller diameter cylinder.

Recommendations for dose prescription and reporting
Standard treatment plans
For quality assurance and clinical workflow purposes a library of standard plans per applicator type, diameter and target length will be used. Traditionally the dose (100%) is prescribed to a point 'P', located 5 mm from the applicator surface laterally, at the mid-point of the length of the activated dwell positions as shown in figure 15.7.

In order to achieve the same dose at the apex central point it will be necessary to increase the dwell times in the distal positions of the source passage. Additional dose points can be used at 5 mm from the surface, along the lateral wall of the applicator. The aim is to have 100% of the prescribed dose in these points. However, due to curving at the apex it is accepted that the dose in the most cranial point is somewhat lower.

If standard 'library' plans are used it is sufficient to report the diameter of the cylinder, the prescription dose and the active source length for each individual. In addition it is recommended to record the length of the vagina (depth to which the cylinder is inserted as measured from the introitus) and dose to organs at risk. Depending on which type of imaging is used for treatment planning, dose to organs at risk can be reported either as point doses (ICRU rectum, bladder and additional points for bowel if necessary) or as DVH parameters (e.g. D2cc of rectum and bladder).

A summary of these recommendations is shown in table 15.2.

Individualized treatment planning
Most outcome data for the use of postoperative brachytherapy for endometrial cancer is based on the use of single channel cylinder brachytherapy using a fixed prescription depth. As shown when using CT or MRI, the vaginal mucosa can be thin, and especially in the dorsal direction and the anterior rectal wall can lie within 5 mm depth of the cylinder surface. The varying thickness of the vaginal wall may be taken into consideration for individualized treatment planning, particularly if the wall is very thin. In one study of 217 patients with an individual customized prescribed isodose depth chosen at 3, 4, or 5 mm from the applicator surface, estimated by inspection and palpation, the incidence of mainly grade 2 complications decreased when compared with a standard prescribed isodose at 5 mm from the vaginal surface [37]. The reduction was greatest for late bladder reactions, dropping from 10% to 1% and was also significant for the vagina: 34% in the standard treatment versus 18% with the individualized treatment.

CT and MRI studies have shown that not only is there considerable individual variation in vaginal wall thickness, but also air bubbles between the applicator surface and the mucosa may contribute to uneven distribution. Standard single channel treatment plans can be individualized by adjusting the prescription depth. Alternatively a multichannel cylinder can be used to create an asymmetrical treatment plan. However in the absence of prospective clinical data using individualised treatment plans and the excellent results using standard treatment plans at 5 mm, there is currently little rationale to push the 100% isodose further than 5 mm from the surface of the applicator, thereby increasing the dose at the surface of the applicator.

Table 15.2: Dose prescription and reporting recommendations for vaginal vault brachytherapy

CONVENTIONAL CLINICAL PRESCRIPTION BASED ON DOSE POINTS; DOSE REPORTING IS IDENTICAL TO PRESCRIPTION

Points at 5 mm from the applicator surface
Prescription point: at the mid-point of active source length 100%
Cylinder: Central apical point ..... >90%
Ovoids: apex 5mm from ovoid surface..... >90%
Additional points at other positions along the applicator 100%
(may be used for dose optimisation avoiding the Havanna cigar effect…)

Clinical reporting
Applicator diameter
Treated length
Treatment time
Optional: vaginal length

Dose to prescription point
In case prescription defined above is not used, the reference dose at 5 mm from the surface

Surface dose at prescription point
Optional: doses at other points

Dose to rectum (ICRU point or D2cc)
Dose to bladder (ICRU point or D2cc)

In addition the physics parameters (e.g. type of source, source activity, dose rate, Al system) have to be reported (see physics chapter)

Figure 15.7: Prescription points for vaginal vault brachytherapy using a vaginal cylinder applicator

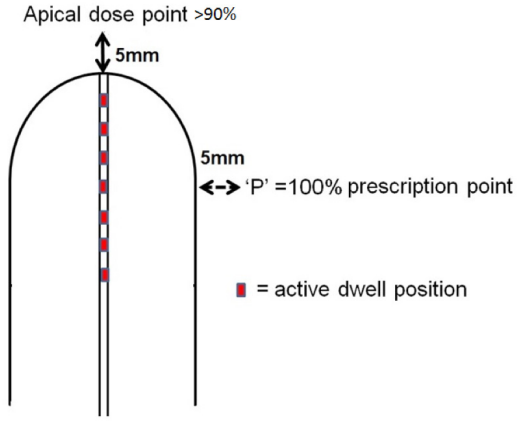
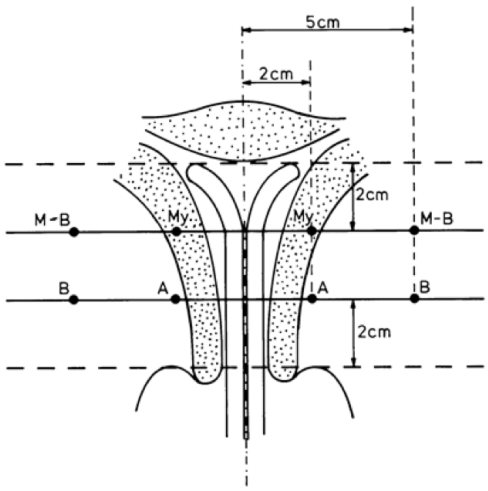


Figure 15.8 Dose prescription points for point based dosimetry: the prescription point is point My; dose should also be reported to the other points as defined.



9.1.3: Imaging for treatment planning: uterus in situ

Optimal planning will require 3D cross-sectional imaging with the applicators in situ; preferably this will be MR but if not available or if MR compatible applicators have not been used then CT or ultrasound can be used. These images should be used to define the GTV and CTV cross-referencing to the results from the diagnostic EUA, ultrasound and MR. Individual image-based CTV definition and treatment planning is then possible.
Two isocentric orthogonal radiographs (AP and lateral view) may be taken immediately at the end of the application with the woman in the same position as during the insertion to document their position and for later quality assurance, particularly in HDR where fractionated treatments will be required. In a modified Heyman packing, x-ray imaging should be performed additional to 3D imaging in order to guide the reconstruction of the individual applicators. Specific radiographic markers may also be introduced into the catheters so that it becomes possible to recognize individual catheters in the AP-view as well as in the lateral view. If at this point the applicator position is suboptimal, it should be changed and new radiographs taken.

9.1.4: Treatment planning: uterus in situ

There is a general move to volume based planning and use of standard reference points is not encouraged except for reporting.

There is no consensus on which standard reference points should be used. The "point My" (Myometrium) has been described located 2 cm caudal to the top of the highest applicator and 2 cm laterally. The "A-line" may also be used which is 2 cm from the tip of the applicator laterally. Additional reference points on the surface of the uterine cavity and at the macroscopic tumour margin are added as shown in figure 15.8 as well as organs at risk. For the bladder this is along its posterior wall, not primarily at the bladder neck.

Similarly for image guided brachytherapy there are no international guidelines but one proposal is shown in figure 15.9 [29].

Figure 15.9 Proposed dose prescription volumes for image guided brachytherapy. Using CT (a) it is not possible to define the tumour accurately and the CTV is the entire uterus; with MR (b) accurate definition of the GTV enables subvolumes of GTV, HRCTV which is the GTV with a margin including adjacent uterine walls and the IR CTV which is the entire uterus (equivalent to the CTV when using CT)

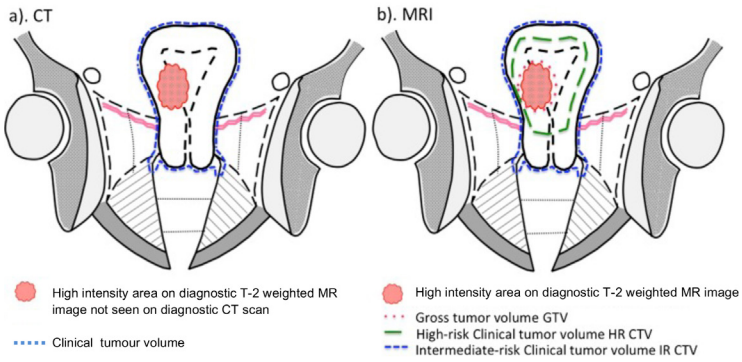


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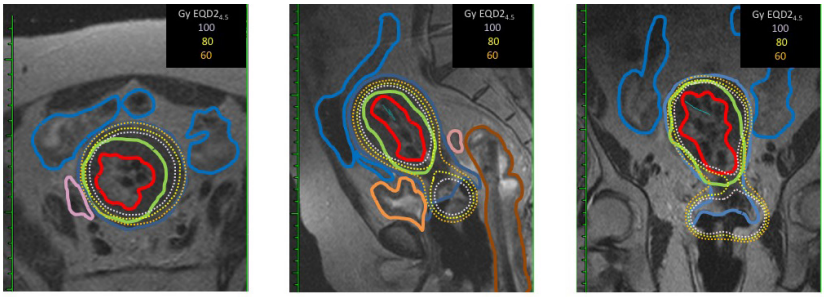
Figure 15.9 (c) MR scans demonstrating planning volumes as defined in (b) above



Delineated structures: GTV (red), LR CTV entire uterus + upper vagina (blue), HR CTV=GTV+margins (green), bowel (blue), sigmoid (pink), bladder (yellow), rectum (brown).
Isodoses (dotted lines) correspond to 60 (orange), 80 (yellow) and 100 (violet) Gy EQD2 (α/β=4.5Gy) for 6 fractions of brachytherapy alone.
Obese patient (51 years), ECOG 3, Endometrium Cancer FIGO stage II, with diabetes, hemiplegia (cerebral ischemia) and heart transplantation, 17 Heyman catheters, HDR BT, 2005; no radiation related adverse side effects and no evidence of disease after 10 years.

GTV	(34 cm^3), D_{98}:	116.3 Gy EQD2$_{4.5}$	Sigmoid	D_{2cm^3}:	48 Gy EQD2$_3$
HR CTV	(131 cm^3), D_{90}:	83.1 Gy EQD2$_{4.5}$	Bowel	D_{2cm^3}:	45 Gy EQD2$_3$
LR CTV	(243 cm^3), D_{90}:	59.7 Gy EQD2$_{4.5}$	rectum	D_{2cm^3}:	20 Gy EQD2$_3$
			bladder	D_{2cm^3}:	53 Gy EQD2$_3$

Dose optimisation should be based on individual delineations of the GTV and the CTV which will encompass the entire uterus. Organs at risk are the bladder, rectum and sigmoid as defined for cervical cancer. [27][28][29][34][37]. DVH-parameters should be used for dose prescription, e.g. the D90 the dose to 90% of the volume. For the OAR the minimum dose to the most exposed 2cm3 (D2cm3) should be evaluated and reported. A typical example with Norman Simon capsules is shown in figure 15.6.

The ability to optimise the plan with sufficiently high CTV D90 and OAR dose below the constraints is closely related to the size of the uterus, the location of the OAR and the type of applicator used.

10. DOSE, DOSE RATE AND FRACTIONATION

10.1 Postoperative vaginal brachytherapy

With HDR, a wide variation of schedules can be found in the literature with a broad range of doses when converted to 2 Gy fractions (EQD2), with additional variation introduced by differing prescription points, typically either surface dose or at 5mm depth. Most studies are institutional series including a majority of low-risk patients. A frequently used schedule is 21 Gy in 3 fractions of 7 Gy prescribed at 5 mm from the cylinder surface as was used in PORTEC-2. This schedule aims for to deliver a dose required for potential microscopic disease

There is considerable uncertainty with regard to the correct α/β ratio for endometrial cancer. In the past a value of 10 has been used however biologically it is an adenocarcinoma which is more likely to have characteristics similar to breast and prostate cancer. These tumours have been shown to have a much lower α/β and whilst the extreme estimates for prostate cancer of around 1.5 are perhaps not appropriate a figure around 4.5, similar to breast cancer is most likely.. Using an α/β of 4.5 for tumour the EQD2 of 21Gy in 3 fractions is 37.2Gy at 5 mm and presuming approximately 150% at the surface the EQD2 will be 55.8 Gy. Compared to external beam the brachytherapy is given in a shorter time span, a factor not included in the EQD2 calculation. With α/β of 3 for OAR this is 42.0 Gy at 5 mm and 63 Gy at the surface, explaining the increased rate of mild to moderate

vaginal mucosal atrophy compared to external beam radiotherapy in PORTEC-2. Somewhat equivalent schedules are 4 fractions of 6.0 Gy and 5 fractions of 5.0 Gy. Alternative schedules at 5 mm depth reported in the literature include those with a total dose between 15 and 24 Gy applied in 3 to 4 fractions: 3 - 4 x 5-5.5 Gy, 3 - 4 x 6 Gy [34][38], corresponding to EQD2 of 21.9 – 38.8Gy for an α/β of 4.5 and 24 – 43 Gy with an α/β of 3. Again presuming 150% at the surface, the overall range of EQD2 at the vaginal surface is between 32.8 and 58.2 Gy for an α/β of 4.5. The time interval between fractions varies in the literature, in PORTEC-2 there was a week interval between each fraction. Due to these variations, the different schedules are not directly comparable even if the EQD2 values are calculated.

Treatment delivery 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.

For PDR brachytherapy alone the schedules also vary. Some centres deliver 50 Gy at 5 mm from the vaginal mucosa in one application within 4 - 5 days. Such a schedule is equivalent to an EQD2 of 50 Gy with an α/β of 10 if pulses of 0.5 Gy per hourly are used. Another schedule is reported delivering a total dose of 40 Gy in two fractions with 1 Gy per hourly pulse [39], This corresponds to a EQD2 of 46.4 Gy with an α/β of 10.

In general as a result of the PORTEC 2 trial brachytherapy in addition to external beam is not used in the postoperative setting however it is still recommended by some centres for high risk endometrial cancer where there is also cervical involvement. If brachytherapy is combined with external beam radiotherapy (45-50 Gy in 2.0-1.8 Gy per fraction), it is performed at the end of external beam irradiation. The dose of brachytherapy depends on the dose previously given by external beam irradiation, but aims towards a total dose of 60 Gy EQD2 at 5 mm depth. Again there is a range in schedules reported with HDR; 2 fractions of 5 or 5.5 Gy at 5 mm depth (EQD2 of 2 fractions of 5.5 Gy is 19.5Gy and 25.4 Gy at the surface with an α/β of 4.5; EQD2 of 18.7 Gy and 28.1 Gy at the surface with an α/β of 3) or 3 x 5 Gy at 5 mm depth (EQD2 of 32.9Gy at the surface with an α/β of 4.5; EQD2 of 36 Gy at the surface with an α/β of 3).

In PDR brachytherapy the dose at 5 mm depth ranges between 19Gy EQD2 ($\alpha/\beta_{4.5}$) single dose and 28Gy EQD2 ($\alpha/\beta_{4.5}$) in two fractions delivered at 50 cGy per fraction per hour

10.2 Radiotherapy alone with the uterus in situ

The overall aim is to treat the macroscopic tumor ie the GTV with at least 80Gy EQD2. The total dose and fractionation schedule for the brachytherapy depends whether or not there is subclinical disease in lymph nodes that require external beam treatment. The GTV can however only be visualized on MRI with an applicator in situ which explains why most series not using MRI prescribe dose to a CTV that includes the whole uterus, however the macroscopic tumour volume receives an unknown higher dose.

For PDR brachytherapy alone, a clinical target dose of 60-65Gy EQD2 is proposed for the uterus (outer contour) and 45 - 50Gy for the upper third of the vagina, which is usually delivered in one or two sessions one week apart. If there are risk factors for pelvic disease, pelvic radiotherapy is recommended with 45 to 50 Gy followed by 25-30Gy EQD2 ($\alpha/\beta_{4.5}$) to the CTV (whole uterus) and 35-50 Gy EQD2 ($\alpha/\beta_{4.5}$) given additionally by endocavitary brachytherapy to the GTV +/-margins.

For HDR brachytherapy alone, 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 [24], 42 Gy "point-A line" [41,42] and 50 Gy "point My" [70] in 5 to 6 fractions. When using image guided brachytherapy with a defined GTV and CTV then an equivalent dose of 60Gy should be given to the entire uterus and 45-50 Gy to the upper vagina with the GTV +/- margins receiving in excess of 80Gy. This will equate to a prescription of 36-42Gy in 6 fractions, (corresponding to 58.2 to 74.3 Gy EQD2 ($\alpha/\beta_{4.5}$). Technique, dosimetry and prescription and reporting practice are not homogenous (see section 8).

When 2 fractions of PDR are administered 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) followed by brachytherapy delivering 3-4 fractions of 7Gy. (37.2 -49.5 Gy EQD2 ($\alpha/\beta_{4.5}$))

11. MONITORING

In principle, monitoring is similar to that of patients with cervix cancer brachytherapy. A regular review with vaginal examination is recommended although the probability of vaginal relapse is small and the need for intense follow up in these patients is debatable. Post hysterectomy there is no role for routine imaging or vaginal smears.

Treatment of uterine cancer with the uterus in situ may be followed by MR scan performed at 3 months after treatment and then annual ultrasound. Clinical evaluation is often difficult particularly in the obese patient.

12. RESULTS

Overall, results are dependent on patient, treatment and tumor characteristics. The most important prognostic factors are stage, type of histology, grade of tumor differentiation, depth of myometrial invasion lymphovascular space invasion, and age. In historical published series, usually retrospective, there is often no clear correlation between risk factors, treatment strategy and outcome in terms of local (vagina, pelvis) and distant failure. In addition, often pelvic failure is reported, without discerning vaginal from regional nodal relapse, and frequently it is not clear if only isolated pelvic or vaginal failures or total events including those with distant or pelvic failure are reported.

The overall five-year survival rate according to the FIGO Annual report 26 [5] is shown in figure 15.1.

12.1 Surgery

Due to heterogeneity in patient-, tumor- and treatment characteristics, variable rates of vaginal and pelvic failures after surgery alone have been reported.

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 (all grades, all ages), 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. 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 [40].

In a series of 811 FIGO stage I and 116 stage II endometrial cancers, hysterectomy was the sole treatment in 492 patients [40]. 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 other series reported [41], nearly 45% of the patients with a vaginal recurrence died from cancer within one year and 77% within 5 years.

Results for surgery alone from the randomised trials introduced in chapter 5.1 can be summarised as follows: In the Dutch PORTEC I trial [20] after surgery alone the actuarial ten-year probability of locoregional relapse was 14% and actuarial ten year survival after surgery alone was 73%, no different from the group that received radiotherapy. Vaginal relapse was the most common event (75%) after surgery alone. Successful salvage was seen in those that relapsed with a five year survival of 70% in those relapsing in this group. For patients with high-intermediate risk features the locoregional relapse rate was 20% at 5 years after surgery alone, again with approximately 75% being vaginal relapses. In the GOG-99 trial [21] the cumulative incidence of recurrence at 2 years is reported for surgery alone (including lymphadenectomy); this was 12% overall and 26% for patients with high-intermediate risk features. There were 18 patients with a locoregional relapse in the 202 patients in the surgery only arm of which 13 were isolated vaginal recurrences.

Finally, in the ASTEC Study [22] with brachytherapy used in 50% of the observation after surgery patients, the rate of isolated vaginal or pelvic at 5 years was 6.1%. In total 24 patients presented with isolated vaginal recurrences of which 17 were included in the observation arm.

The risk of lymph node involvement increases with stage and grade. Lymph node sampling is frequently recommended for grade 3, clear cell and papillary serous tumours. Two large randomised trials found no evidence that lymph node surgery [various forms of sampling or dissection) contributes to a decrease in pelvic lymph node recurrence [42,43]. In the ASTEC trial which randomised patients undergoing hysterectomy for endometrial cancer to a control group or lymph node removal five year survival was 80% in the control group and 77% in the lymphadenectomy group [43].

12.2 Adjuvant radiotherapy

The role of external beam radiotherapy has been studied in three large randomised trials that included intermediate risk patients and were carried out by the GOG in the US, PORTEC in the Netherlands and ASTEC by the MRC in the UK. These results shown consistently that radiotherapy contributes significantly to a threefold reduction in locoregional relapse (both vaginal and pelvic) but has no effect on survival. Again the largest benefit in reduction of locoregional recurrence was found in high-intermediate risk patients (PORTEC-1 5-year 20% with no additional therapy vs. 5% after pelvic external beam radiotherapy; GOG-99 cumulative incidence of relapse 26% without vs 6% with adjuvant radiotherapy). These results have been subject to a Cochrane meta-analysis [44] which confirms a benefit for local control (figure 15.10a) but no impact upon survival (figure 15.10b)

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% [45,46,47,48]

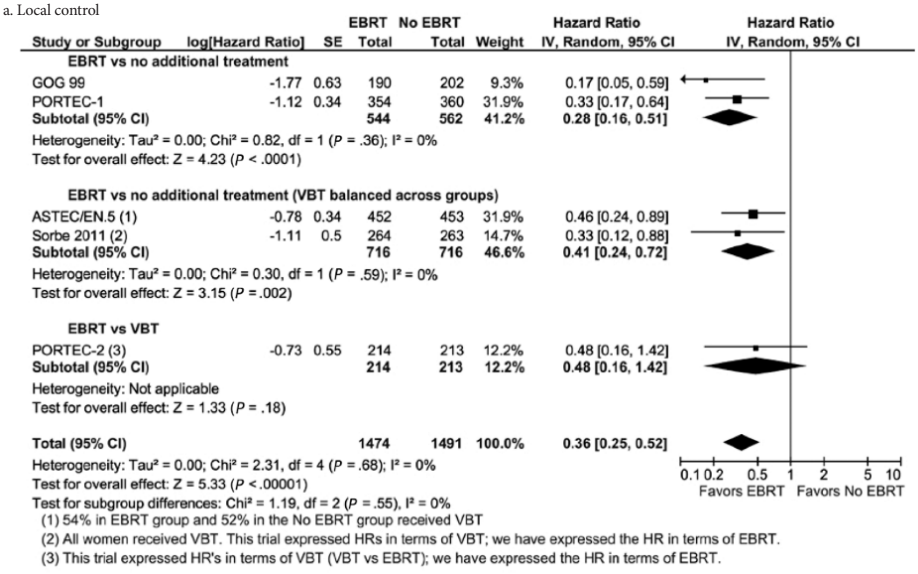
The PORTEC 2 trial randomised 427 high-intermediate risk patients to receive either external beam radiotherapy or vaginal vault brachytherapy [23]. A significant improvement in quality of life scores was seen in the brachytherapy group, in particular social functioning, diarrhoea, faecal leakage and need to remain close to a toilet were considerably worse in patients receiving external beam. Published 5-year results with a median follow-up of 45 months found a low risk of vaginal recurrence in both arms (EBRT 1.9% vs VBT 1.5% p=0.74) reliably excluding a clinical relevant difference in vaginal recurrence risk between both treatments. Updated results published as abstract with a median follow-up of 89 months confirm the low risk of vaginal recurrence (EBRT 1.9% at 5 years and 2.4% at 8 years, compared to 2.4% and 2.9% after VBT) [23]. Although the rate of total regional nodal recurrences was higher after vaginal brachytherapy 4.7% compared to 0.9% at 5-years, there was no difference in isolated nodal recurrences (0.5% vs 1.5%) with the majority of patients having simultaneous nodal and distant relapse. There was no difference in rate of distant metastasis (7.2% versus 9.3% at 5 years) or overall survival (83.9% in both arms at 5 years) between both arms.

The findings of PORTEC-2 have later been confirmed in a Swedish trial in which 527 medium risk patients were randomised between vaginal brachytherapy (HDR 6x3Gy or 3x5.9Gy; LDR 20Gy) or external beam radiotherapy combined with the same vaginal brachytherapy. The crude rate of vaginal recurrence in the brachytherapy only arm was 2.7% compared to 1.9% in the combined treatment arm. While the 5-year rate of locoregional relapse was 5% after VBT alone, this was 1.5% after combined EBRT and VBT p=0.013, with similar overall survival 90% vs 89% at 5 years [24].

The GOG-249 trial [49] randomised 601 high-intermediate and high risk stage I-II patients between pelvic external beam radiotherapy and vaginal brachytherapy followed by 3 cycles of adjuvant paclitaxel carboplatin. Results with a median follow-up of 24 months have been published as abstract and find for EBRT vs. VBT+chemo: 5 vs 3 vagina, 2 vs 19 pelvic and 32 vs 24 distant failures with a similar 2-year relapse free survival rates (93% vs

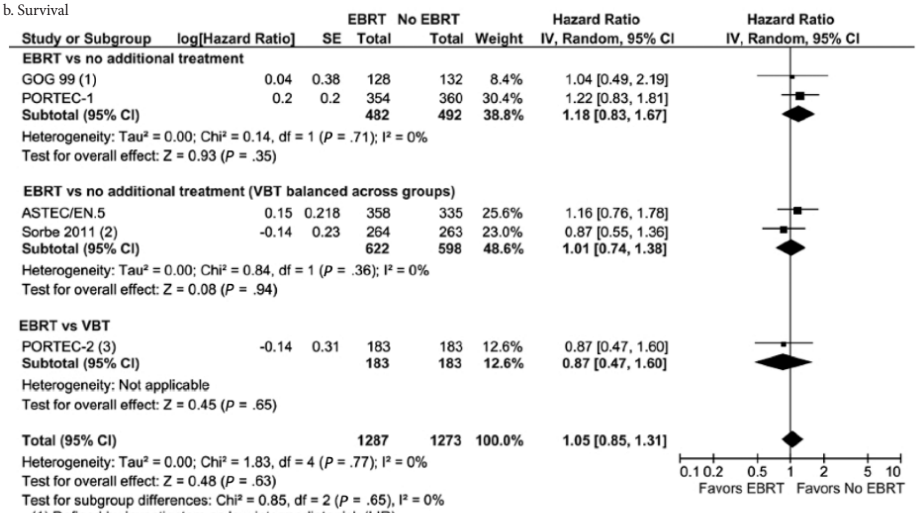
Figure 15.10: Meta-analysis of randomised trials for Local control and Survival after postoperative radiotherapy for endometrial cancer. (from ref 44)

a. Local control



(1) 54% in EBRT group and 52% in the No EBRT group received VBT
(2) All women received VBT. This trial expressed HRs in terms of VBT; we have expressed the HR in terms of EBRT.
(3) This trial expressed HR's in terms of VBT (VBT vs EBRT); we have expressed the HR in terms of EBRT.

b. Survival



(1) Defined by investigators as low-intermediate risk (LIR)
(2) All women received VBT. This trial expressed HRs in terms of VBT; we have expressed the HR in terms of EBRT.
(3) True high-intermediate risk after pathology review (N=366). HR expressed in terms of EBRT.

92%). In contrast VBT+ chemo was associated with more acute toxicity. The authors conclude that combined VBT with chemotherapy is not superior to EBRT in these high-intermediate to high risk patients.

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. In contrast, 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 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 intra-abdominal spread and haematogenous 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.

Because of the higher risk of distant metastasis in high-risk patients the role of adjuvant chemotherapy is under investigation. Two trials randomised high risk patients between EBRT and adjuvant chemotherapy and did not show a benefit in overall or disease free survival [50,51]. In contrast an analysis that combined patients from NSGO 9501/EORTC 55991 and MANGO–ILIADE III randomised trials in which EBRT was compared to EBRT with 4 cycles of adjuvant chemotherapy (paclitaxel carboplatin) [52], found an improved 5-year progression free survival (78% vs 69%, p=0.009), but only a trend for an improved overall survival (82% vs 75%, p=0.07) [51]. PORTEC-3 randomised high risk

Table 15.3: Results of definitive brachytherapy +/- EBT

Author	N° pts	Stage	Treatment	Survival	%	Recurr. %	Complic.	%
Churn [53]	37	I to II	B	DSS	68	-	Gr 2-3	8
Knocke [54]	280	I to III	A-B	DSS	77	25	Gr 3	5
Kupelian [55]	152	I to IV	A-B	DSS I II	86	I II 14	Gr 3	5
Landgren [56]	124	I-II	A-B-C	III IV	49	22	Gr 3	7
Lehoczy [57]	171	I	A	OS	68	23	Gr 3	0
Pernot [58]	139	I to III	A-B	DSS	74	17	15	
Rouanet [59]	119	I-II	B	OS	55	24	Gr 3	8
Varia [60]	73	I-II	A-B	DSS	65	40	Gr 3	10
Shenfield [61]	44	I	A-B	OS	43	11.4	Gr 2-4	7
Wegener [62]	26	I-II-III	A-B	OS	54	8	Gr 2	8

Legends:
Treatment
A: Brachytherapy alone
B: EBRT + Brachytherapy
C: EBRT alone

Survival
OS Overall Survival
DSS Disease Specific Survival

patients between EBRT and EBRT combined with concurrent Cisplatin and adjuvant paclitaxel carboplatin has finalized accrual and results are awaited. The same is true for GOG 258 in which high-risk patients are randomised between the same EBRT combined with concurrent and adjuvant chemotherapy schedule as in PORTEC-3 and 6 cycles of paclitaxel carboplatin. This trial will show if there is a role for external beam radiotherapy at all in patients at high risk for distant relapse.

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 [6]. The natural history of these tumours is for early dissemination particularly within the peritoneal cavity. Chemotherapy therefore is increasingly recommended in this group either alone or in combination with radiotherapy, despite which results so far in small patient (subgroup) populations reported do not show a benefit. Again, these patients represent subgroups in ongoing trials like PORTEC-3 and GOG-258, which may help to inform whether adjuvant chemotherapy is of benefit in these patients.

12.3 Definitive radiotherapy with the uterus in situ

Where radiotherapy alone has been given, the reported results based on clinical staging are inferior to those of definitive surgery based on pathological staging. More accurate staging with MRI is now possible but mature series of patients staged in this way are not yet reported. The overall local control rates reported are about 75% (60 - 92%), the disease specific survival is about 65% (49 - 86% (Table 15.3)

Survival in this group of patients is mainly related to their co-morbidity with death from non-cancer causes predominating in defining their overall survival

13. ADVERSE SIDE EFFECTS

13.1 Adjuvant radiotherapy in combination with surgery

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

Surgery

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 [63]. Total laparoscopic hysterectomy is associated with less pain, a decreased length of hospital stay, faster resumption of daily activities and improved quality of life compared to TAH-BSO [64,65,66]. However, pelvic lymphadenectomy increases the risk of complications, especially in the sub-group of patients who receive additional external irradiation. In multivariate analysis, pelvic lymphadenectomy was an independent significant factor for complications (p=0.0049) [67]. The risk of complications with a treatment combining pelvic lymphadenectomy and irradiation has been shown to increase with age [68].

External Beam Therapy alone

The risk of severe complications mostly gastro-intestinal after treatments combining external irradiation and surgery ranges between 5.5% [54] and 7.8% [69]. In the PORTEC 1 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 [70]. 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.

Detailed quality of life was prospectively studied in the PORTEC 2 trial [22] comparing external beam radiotherapy with vaginal vault brachytherapy in intermediate risk patients. After external beam 15.4% of patients reported 'quite a bit' of diarrhoea and 7.3% 'very much' diarrhoea compared to 2.8% and 2.8% with VBT. The rates of diarrhoea decrease with longer follow-up but remained at a higher level compared to EBRT and to an age-controlled Dutch normal population. In addition, 10% of EBRT patients reported an increase in faecal leakage and 22% had limitation of daily activities because of bowel symptoms compared to 2% and 6% of the patients treated with VBT. The Swedish trial that randomised patients between VBT and EBRT combined with the same VBT found a similar negative effect of EBRT on gastro-intestinal symptoms.

Long-term quality of life was investigated in the PORTEC-1 trial with a median follow-up of 13.3 years [71]. This analysis confirmed increased gastrointestinal symptoms impacting on limitations in daily activities and physical functioning with longer follow-up after EBRT. In addition there was an increased rate of urinary incontinence and increased use of pads after EBRT (day and night use 43% vs 15% after no additional therapy). Of importance approximately 30% of patients were treated with parallel opposing fields in this trial. So far no increased rate of urinary incontinence was found with shorter follow-up in PORTEC-2 in which all patients received 3D conformal EBRT

Vaginal brachytherapy
Acute side effects are limited and may result from vaginitis, mild cystitis and/or proctitis during or immediately following brachytherapy, complaints which may in part be caused by the applicator or urinary catheter insertion itself, particularly in PDR where they will be retained for a long period. These symptoms usually disappear spontaneously within a few days.

The main late side effects are mild to moderate vaginal dryness, shortening and less frequently consequential stenosis. Chronic cystitis, proctitis, sigmoiditis and enteritis are less frequently reported, and only rarely have grade 3 events such as bowel obstruction, necrosis and fistula (between bladder, vagina, rectum) been reported.

When HDR brachytherapy is used the dose per fraction appears to be a significant factor for complications. In an older study that used different dose fractionation schedules, 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 x 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; all doses are at 5mm.. 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 [24]. In another 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 [58]. The incidence of grade 1 and 2 vaginal complications was 15.3%, bladder complications 5.6% and rectal complications 2.1%.

The individualization of the depth of the prescription dose according to the vaginal thickness reduces the risk of late complications as discussed in section 7.1.4.

Another important factor is the length of the vagina treated, with a significant increase in complications seen when the whole vagina is included [72]. The change in the mean age of this population towards younger and sexually active patients may highlight the importance of vaginal changes after brachytherapy and counseling for post-treatment vaginal dilatation.

In the PORTEC 2 trial 3 fractions of 7 Gy were prescribed at 5 mm from the surface of the cylinder and the target volume consisted of the proximal half of the vagina. One year after treatment mild to moderate mucosal atrophy on gynaecological examination was found in 36% of the patients treated with VBT compared to 14% after EBRT, and grade 3 atrophy with shortening was seen in 2% after VBT and <1% after EBRT. This higher rate of vaginal atrophy with vaginal brachytherapy can be explained by the higher dose at the surface of the cylinder (EQD2 approximately 63 Gy). Importantly the increased rate of mucosal changes did not lead to a difference in sexual activity or patient reported vaginal symptoms between both arms of the trial. In fact sexual activity increased in the first six months in most patients except those older than 75 years. It should be noted that the majority of these patients are elderly and quite a few indicated they were widowed. When compared to an age matched Dutch normal population, sexual activity in both treatment groups was a little lower, which might be explained by the diagnosis and surgery for a gynaecological malignancy. In contrast, mild to moderate gastro-intestinal toxicity was more frequent after EBRT 21% at one year compared to 9% after VBT (remaining at baseline level) , and grade 3 toxicity was found in 2% after EBRT compared to <1% after VBT. The increase rate of gastro-intestinal toxicity with EBRT compared to VBT was confirmed by the Swedish trial which reported an incidence of all grades GI toxicity in 14.5% in the external beam arm and only 2.7% in the brachytherapy arm [24].

If external beam radiotherapy is combined with a vaginal brachytherapy boost, the dose to the vagina and surrounding organs at risk (rectum, sigmoid, bowel and bladder) is higher. Although there is no randomised trial that has compared EBRT and EBRT with a VBT boost, cohort studies do suggest a higher rate of complications with the combined EBRT with VBT boost. However, complications from the small and large bowel (except the rectum) reported in different series are usually related to the dose and volume treated by external beam therapy.

13.2 Definitive radiotherapy with the uterus in situ

Brachytherapy alone
Patients who have brachytherapy alone are often high risk patients with serious comorbidities. In this setting acute toxicity may be dominated by cardiovascular and thromboembolic complications of the procedure rather than radiation effects themselves. Severe acute side effects are not expected but grade 1 and 2 urinary toxicity may be seen in around 40% [74]. The incidence of grade 3 or more late effects varies reflecting the retrospective nature and small number of patients in most series between <5% and 38% [73,74]. This reflects predominantly grade 1 and 2 vaginal dryness or shrinkage and urinary urgency. More severe complications are rare but both proctitis and rectal bleeding and haematuria are reported and vesicovaginal fistula has been described.

External beam in combination with brachytherapy

The incidence of late complications after definitive brachytherapy for uterine cancer is reported variously between 2% to 17.5%. In the series from Nancy using LDR brachytherapy, grade 1 complications were reported in 10% of the patients, grade 2 in 4.3%, grade 3 in 3% and grade 4 in 1.4% [58]. The complications were mostly located in the rectosigmoid. The complication rate has decreased significantly with the use of new techniques and computerized dosimetry. Similar experience has been 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% [75]. With the systematic use of 3 D image based treatment planning and the Heymann packing method in Vienna, the rate of side effects has been was significantly reduced in the last decade [74].

14. KEY MESSAGES

- Vaginal vault brachytherapy is indicated post-hysterectomy for intermediate risk endometrial cancer.
- Vaginal vault brachytherapy is indicated post-hysterectomy for high risk endometrial cancer in combination with external beam therapy when there has been cervial involvement
- Vaginal vault brachytherapy reduces local recurrence but may have no effect upon survival
- Vaginal vault brachytherapy has a low toxicity profile, the most common late effect being vaginal dryness and stenosis.
- Intrauterine brachytherapy using capsules or a Y applicator is indicated for stage I or II endometrial cancer in patients unfit for hysterectomy.
- Intrauterine brachytherapy using capsules or a Y applicator is indicated with external beam therapy in stage III endometrial cancer.

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