Chapter

Brachytherapy in Endometrial Cancer

Mehmet Sait Bakir

Abstract

Endometrial cancer is the most common gynecologic cancer in developed countries with the cumulative risk rate of 1.71%. Endometrial cancer standard treatment is surgery. But adjuvant radiotherapy may be recommended for patients in advanced age who have high-grade disease, deep myometrial invasion, LVSI positivity, risk factors such as large tumor diameter, lymph node invasion, and advanced stage disease. Brachytherapy is applied in two ways, namely intra-cavitary or interstitial radiation therapy. Intra-cavitary brachytherapy is the presence of a therapeutic radioactive isotope within the body space, for example, vaginal and intra-uterine brachytherapy. Radioactive isotopes are directly inserted within the tissue in interstitial brachytherapy as in the treatment of cervical or endometrial cancers that have reached the lateral walls. The intra-cavitary brachytherapy technique is the most commonly used technique in gynecologic oncology. Standard treatment cannot be performed in a group of patients due to their medical disorders and clinical performances. In these patients, definitive radiotherapy is applied for clinical stage 1 patients, neo-adjuvant therapy is applied to patients with local advanced stage disease and brachytherapy alone or radiotherapy with addition of EBRT is applied as palliative treatment in patients who have complaints such as bleeding and pelvic pain.

Keywords: endometrial cancer, vaginal brachytherapy, high dose rate (HDR), medically inoperable, vaginal boost

1. Introduction

Endometrial cancer is the most common gynecologic cancer in developed countries with the cumulative risk rate of 1.71% [1]. The median age at the time of diagnosis is 63 years and about 90% of the patients are above 50 years of age. However, 4% of the patients are diagnosed under the age of 40 years [2]. The vast majority (80%) of endometrial cancer patients are diagnosed at early stages and while the 5-year survival rate is 95%, it significantly decreases in patients with local and distant metastases (68 and 17%, respectively) [3]. The standard treatment of endometrial cancer is total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH + BSO). Lymphadenectomy is performed in suitable patients when indicated [4, 5]. Adjuvant radiotherapy may be recommended for patients in advanced age who have high-grade disease, deep myometrial invasion, LVSI positivity, risk factors such as large tumor diameter, lymph node invasion and advanced stage disease (**Table 1**) [6–9].

	PORTEC-1	GOG 99
Age	>60	See below
Grad·	3	2–3
Myometrial invasion	>50% (outer 1/2)	>66.6%·(outer 1/3)
Lvmphvasctilar space invasion	N/A	Present
High-intermediate risk group	At least 2/3 of above	any age, all three of above risk factors age > 50, two of above risk factors age > 70, one of above risk factors

FIGO, International Federation of Gynecology and Obstetrics; PORTEC, postoperative radiation therapy in endometrial cancer; GOG, gynecologic oncology group.

Table 1.
High-intermediate risk groups in FIGO stage I endometrial cancer as defined by PORTEC-1 and GOG 99.

The risk groups had previously been addressed in many studies (PORTEC-1, GOG 99 studies) and finally a consensus was reached by the European Society For Medical Oncology (ESMO), European Society for Radiotherapy and Oncology (ESTRO) and the European Society Of Gynecological Oncology (ESGO) in 2014 (**Table 2**) [9].

In the randomized controlled studies of GOG (Gynecological Oncology Group) 99 and PORTEC-1 (Operative Radiation Therapy in Endometrial Cancer), the patients who had intermediate risk factors were divided to two groups and while one group received external beam radiotherapy (EBRT), the other group was followed-up without treatment. The groups in both studies have been presented in **Table 1** [6, 8].

No effect could be demonstrated on the overall survival in either of the two studies. However, the recurrence rate decreased to 3–6% from 12 to 15% in patients with intermediate risk factors who received EBRT. In the subgroup analyses, while the recurrence rate decreased to 5–6% from 18 to 26% in patients in the high-intermediate (H-I) risk group, it decreased to 2% from 5 to 6% in the low-intermediate risk group. Side effects of radiation therapy were seen at a high rate in both studies despite an excellent local control. While the toxic effect rate was 26% in the EBRT group in PORTEC 1, it was 4% in the untreated group ($p < 0.0001$) [10]. Hematological, genitor-urinary, gastro-intestinal and skin complications were also significantly higher in the GOG 99 study group compared

Risk group	Description
Low	Stage I endometrioid, erade 1–2, <50% myometrial invasion, LVSI negative
Intermediate	Stage I endometrioid, grade 1–2, ≥50% myometrial invasion, LVSI negative
High-intermediate	Stage I endometrioid, grade 3, <50% myometrial invasion, regardless of LVSI status Stage I endometrioid. 1–2, LVSI unequivocally positive, regardless of depth of invasion
High	Stage I endometrioid, grade 3, ≥50% myometrial invasion, regardless of LVSI status Stage II Stage III endometrioid. no residual disease Non-endometrioid (serous or clear cell or undifferentiated carcinoma, or carcinosarcoma)
Advanced	Stage III residual disease and stage IVA
Metastatic	Stage IVB

Table 2.
New risk groups to guide adjuvant therapy use.

to the untreated group [6]. In the long-term quality of life data of the PORTEC-1 study, urinary and intestinal functions were found to be poorer compared to the untreated group [11]. Local radiation therapies have come to the foreground due to the high incidence of the toxic effects of pelvic EBRT and their significance has gradually increased. Brachytherapy is applied in two ways, namely intra-cavitary or interstitial radiation therapy. Intra-cavitary brachytherapy is the presence of a therapeutic radioactive isotope within the body space, for example, vaginal and intra-uterine brachytherapy. Radioactive isotopes are directly inserted within the tissue in interstitial brachytherapy as in the treatment of cervical or endometrial cancers that have reached the lateral walls. The intra-cavitary brachytherapy technique is the most commonly used technique in gynecologic oncology.

2. Vaginal brachytherapy

2.1 Vaginal brachytherapy (VB) application

2.1.1 Vaginal applicators

Various vaginal applicators are available in gynecologic oncology depending on the location of the radiation source and whether it contains a cover or not. The Fletcher-Suit-Delclos system is among the most commonly used (**Figure 1**). Vaginal ring applicators are mostly used in HDR. Cylinder vaginal applicators, i.e., Delclos dome cylinder are used in patients undergoing hysterectomy (**Figure 2**).

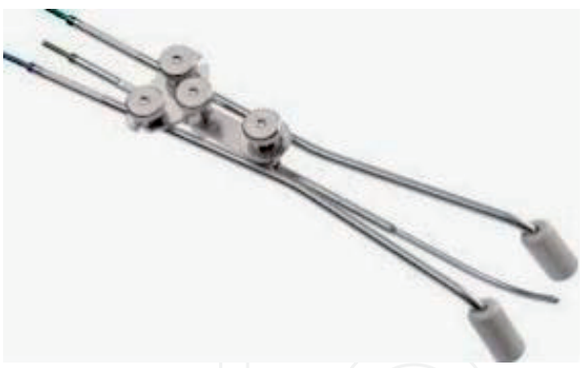

Figure 1.
Vaginal ring applicator.

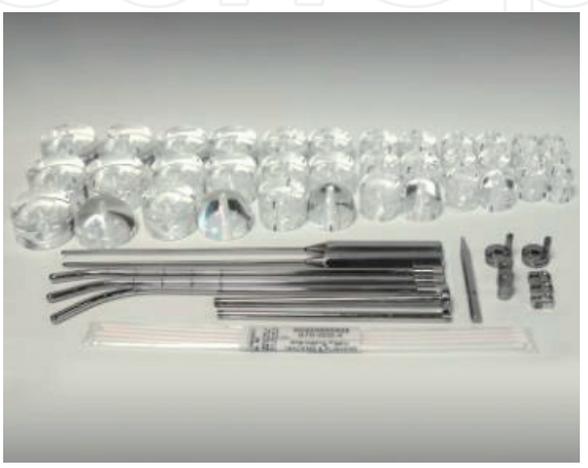

Figure 2.
Cylinder vaginal applicators (Delclos dome cylinder).

Single-channel cylinder applicator is among the most commonly used applicators; it minimizes the toxic effects as it is simple and since it covers the whole of the vaginal surface [12]. Multi-channel vaginal cylinder applicators are less harmful to neighboring tissues through providing asymmetrical dose radiation; however, they have a higher effect on the vaginal mucosa [13, 14].

Despite the presence of variable applicators, they have similar efficiency in the prevention of vaginal recurrence.

2.1.2 Dose depth

Despite the absence of a standard dose depth, vaginal lymphatics were reported to proceed 3 mm beneath the mucosa and treatment covering this depth was reported to be sufficient. Normally, a 1 cm depth is targeted. The most common monotherapy is a 0.5 cm depth and 7 Gy 3 fraction [12]. The doses effective in the vaginal surface when used as vaginal boost treatment have been reported by the Radiation Therapy Oncology Group [15].

2.1.3 Vaginal length

There is no consensus on the vaginal length to be treated. It has been reported that the proximal vagina can be treated between 1 and 10 cm [16]. The American Brachytherapy Society (ABS) has reported that the proximal vagina should be treated 3–5 cm or including 1/2–1/3 of the vagina [17]. Due to the possibility of high toxic doses causing vaginal stenosis and due to the decreasing frequency of distal vaginal recurrence, the treatment modalities that cover the whole vagina are gradually decreasing [12].

2.1.4 Dose rate

All vaginal brachytherapy applications had been carried out as LDR before the introduction of HDR [4]. Historically, low dose hourly 60 cGy had been used widespread in most brachytherapy regimens. This treatment modality given as LDR was taking long and it required hospitalization. About 96% of brachy therapists have switched to this method through the introduction of HDR applicators [17]. The advantages of HDR include less radiation exposure of the health staff and visitors as it enables remote control, thrombo-embolic events are less frequently encountered as the patients are treated in the outpatient setting and long-term immobilization is avoided. There is no difference between LDR and HDR with regard to recurrence and the overall survival [18].

2.1.5 Treatment plan

There are many ways for an accurate treatment plan in VB applications. When 2D and 3D CT-based treatment plans were compared, the 3D method was found to be superior as it reached the clinical target volume and produced less harm to neighboring tissues [19]. Many brachy therapists use the 3D treatment plan and its application at every session separately was not found to be superior to single session application, except for being expensive [20]. The CT-based treatment plan reveals the air between the vaginal cuff and the applicator effectively and enables a more effective treatment [21].

2.1.6 Dose and duration of vaginal brachytherapy

The toxic dose that emerges during VB is related to the amount of the total dose, dose velocity, total vaginal length, dose depth and the fraction time. In a study, the

patients who received VB with HDR were allocated to four groups as 4 fractions of 9.0 Gy, 5 fractions of 6.0 Gy, 6 fractions of 5.0 Gy and 6 fractions of 4.5 Gy. A 1 cm depth from the vaginal surface was utilized. Vaginal, urinary bladder and rectal toxicity were found to increase as the amount of the dose increased along with the fraction [22]. In another study, no grade 2 or above vaginal, urinary bladder and rectal toxicity were encountered when 6 fractions of 4.0 Gy VB was applied targeted only to the vaginal surface [23]. The ABS recommends HDR VB as 24 treatment schemes as monotherapy and the 22 treatment scheme as boost dose [12]. In the PORTEC-4 study conducted for standardization of the dose and the fraction amount, the patients with H-I risk, early stage endometrial cancer were divided into treatment and observation groups; the treatment group was randomized as 3 fractions of 7.0 Gy or 3 fractions of 5.0 Gy. However, the study was terminated early as the patient collection and the untreated group were not proper. Therefore, further studies are required for standardization of the dose amount and the duration of fraction.

2.1.7 Protection from vaginal toxicity

Vaginal toxicity is a significant complication of VB and it impairs the quality of sexual life due to vaginal atrophy, shortness and narrowness. The sexual activity frequency and satisfaction are reduced in patients undergoing surgery and VB [24]. In a study, having sexual intercourse during the VB treatment was reported to prevent vaginal shortness and narrowness; however, atrophy-related dyspareunia was reported in 2/3 of the patients and furthermore, it was emphasized that the distal 2/3 of the vagina was more susceptible to toxic effects rather than the proximal 1/3 of the vagina [22]. Use of vaginal dilator for 6 months following radiotherapy was shown to decrease the vaginal stenosis [25]. In the Cochrane database, use of vaginal dilator during radiotherapy was not shown to have sufficient evidence. However, it accepts the observational studies suggesting that use of the regular vaginal dilator may improve the vaginal stenosis rates reported by the patients [26]. Estrogen cream is another option for protection of the vagina. Despite the absence of sufficient and strong evidence about the use of estrogen creams, they were shown to prevent vaginal atrophy in small studies [27]. A selection should be made after discussing the benefits and harms of this treatment option with the patient.

3. Adjuvant vaginal brachytherapy treatment

3.1 Adjuvant vaginal brachytherapy as monotherapy

As reported above, we know that pelvic EBRT reduces the recurrence; however, it leads to severe side effects compared to follow-up without treatment in endometrial cancer. Radiotherapy via the vaginal route was considered to be more proper as vaginal recurrences are seen most in post-operative endometrial cancer patients. Similarly, with pelvic EBRT, VB treatment was not shown to be effective on the overall survival. However, while the vaginal recurrence rate is 0–3.1% in VB, the pelvic recurrence rate is 0–4.1% [28–30]. These rates are similar with pelvic EBRT and related to the lower toxic effects.

In the randomized controlled PROTEC-2 study comparing the effectiveness of pelvic EBRT and VB treatment, all patients were H-I risk endometrial cancer patients who had undergone TAH + BSO, but not lymphadenectomy. The patients were allocated to three groups as the group that received 23 fractions 46 Gy as pelvic EBRT, the high dose rate (HDR) group that received 7 Gyx3 fractions and the low dose rate (LDR) group that received 30 Gy VB. While the 5-year vaginal recurrence

was 1.8% with VB, it was 1.6% in the pelvic EBRT group (p = 0.74). The pelvic recurrence rate was higher in the VB group (3.8% vs. 0.5%, p = 0.02). However, the gastrointestinal side effects were significantly lower in the VB group compared to the EBRT group [30].

3.2 Adjuvant vaginal brachytherapy as boost

A better loco-regional control can be achieved by adding VB to pelvic EBRT and the rate of vaginal recurrence would be seen as 0–2.7% and the rate of pelvic recurrence as 0.3–4.0% [29, 31–33]. Despite the absence of EBRT+/-VB randomized controlled study, boost VB may be added in the treatment of high risk patients whose vaginal recurrence is high and who receive low dose EBRT (45 Gy at 1.8 Gy/fractions). There are randomized controlled studies comparing EBRT + boost VB and VB alone. In one of these studies, while the total pelvic recurrence rate was 0.4% in EBRT + boost VB group, it was 5.3% in the VB only group (p = 0.013). No difference was found between the groups with regard to vaginal recurrence and overall survival; however, the radiation toxicity was lower in the VB group [33]. In the studies of RTOG, applying 5–6 Gy VB boost only onto the vaginal surface as 45 Gy EBRTx3 fractions or 50.4 Gy EBRTx2 fractions is recommended [34, 35].

3.3 Vaginal brachytherapy and chemotherapy

The effect of adding chemotherapy (CT) to VB was investigated particularly in high risk endometrial cancer patients who had the likelihood of distant metastasis. In a study conducted by Landrum et al., the 2-year progression-free survival was 91% in 23 patients including H-I risk early stage endometrial cancer, uterine serous carcinoma (USC) and clear cell carcinoma (CCC). Vaginal recurrence occurred in one patient (4.2%); this patient also had distant metastasis [36]. The effect of VB + CT was investigated in the GOG 249 randomized controlled study. In that study, while one group received EBRT, another group received VB + CT (3 cycles of carboplatin and paclitaxel). The study included the GOG 99 H-I risk patients, patients with stromal invasion and stage 1–2 USC and CCC. While the overall survival was 92% in the EBRT group, it was 92% in the VB + CT group at the end of the 2-year follow-up (p = NS). There was no significant difference between the vaginal recurrence rates in the two groups. While hematologic toxicity, neuropathy and fatigue were more common in the VB + CT arm, grade 2 diarrhea was more common in the EBRT arm [37].

4. Vaginal brachytherapy treatment in high-risk histology

More aggressive treatments are used in uterine serous cancer (USC), clear cell carcinoma (CCC) and carcino-sarcoma (CS), which are the high risk histologies of endometrial cancer [38]. Most of the large studies including PORTEC-1, GOG 99 and PORTEC-2 [6, 8, 30] included early stage endometrial cancer patients and not high-risk patients. However, in the GOG 249 study, 20% of the patients were USC and CCC patients [37]. In a study conducted by Creasman et al., the outcomes of stage 1 high risk patients were found to be similar to those of grade 3 endometrioid type adeno-carcinoma patients [39]. Despite the presence of vaginal recurrence at a rate of 0–2.7% in stage 1–2 patients with high risk histology, the pelvic recurrence rate was found to be 0–9% [40–43]. In a study investigating USC patients, while the 5-year survival rate was 94% in patients who received VB + CT, it was 65% in patients who received LDR + EBRT but not CT [40]. In another study, USC patients

received VB + CT (six cycles of carboplatin and paclitaxel) and the vaginal, pelvic and distant metastasis rates were found to be 0, 9, and 10%, respectively, and the 5-year survival rate was 90% [41]. The effectiveness of VB alone was investigated in endometrial cancer patients with high risk histology. Some authors reported that CT did not have a great contribution [42, 43].

4.1 Brachytherapy for treatment of medically inoperable endometrial cancer

As mentioned above, the standard treatment of endometrial cancer is TAH + BSO (total abdominal hysterectomy + bilateral salphingo-oopherectomy) and lymphadenectomy when indicated, however, this standard treatment cannot be performed in a group of patients due to their medical disorders and clinical performances. In these patients, definitive radiotherapy is applied for clinical stage 1 patients, neo-adjuvant therapy is applied to patients with local advanced stage disease and brachytherapy alone or radiotherapy with addition of EBRT is applied as palliative treatment in patients who have complaints such as bleeding and pelvic pain. While LDR VB+/−EBRT has been used recently in the treatment of these patients, HDR VB+/−EBRT is widely used today [44, 45]. The treatment of medically inoperable endometrial cancer patients is planned better and more effectively through advancements in radiology.

4.1.1 Patient characteristics

Medically inoperable endometrial cancer patients should be meticulously evaluated pre-operatively by a gynecologic oncologist. Most of these patients have cardiac diseases, pulmonary diseases, hypertension, diabetes mellitus, cerebro-vascular disease, renal disease, syndromes such as Marfan syndrome, advanced age and other malignancies. Morbid obesity is a relative contra-indication for the operation depending on the experience of the surgeon and the condition of the patient. Clinical performance of the patients is of vital importance as a pre-operative parameter. All of these patients should be evaluated pre-operatively for local or general anesthesia by experienced anesthetists. The hormone therapy (progestin, aromatase inhibitors) option is also available besides the radiotherapy option for clinical stage 1, grade 1 patients who are not eligible for surgery, for patients with endometrioid type endometrial cancer, for those below the age of 40 years and those willing to have a child [46]. Regression has been detected in 55% of the patients treated in this way [47].

Levonorgestrel-releasing intra-uterine devices (LNGIUDs) may be added to treatment of patients who have precancerous and stage 1, grade 1 endometrioid type endometrial cancer [48]. The patients are meticulously evaluated with CT or MRI with regard to tumor diameter, myometrial invasion depth, cervical involvement, ovarian involvement and pelvic para-aortic lymph node involvement if hormone therapy is planned, as oral regimens have the likelihood of recurrence at a rate of 25% despite the 50% or above success rates [49]. While endometrial cancer staging is done surgically according to the recent International Federation of Gynecology and Obstetrics (FIGO) 2009 classification, clinical staging is used in medically inoperable patients (**Table 3**) [50].

The patients should be meticulously evaluated for pelvic examination and distant metastasis if clinical staging would be used. Vagina, cervix and the uterus are evaluated, presence of a mass lesion is examined and the search for parametrium involvement is attempted through bimanual (rectal-vaginal) examination. Computed tomographies of the thorax, abdomen and the pelvis are performed for distant metastasis and MRI is used for assessment of the uterus and the pelvis as the negative predictive value is >85% for myometrial invasion in contrast-enhanced T2-weighted

IA-Uterine cavity sounds to <8 cm
IB-Uterine cavity sounds to >8 cm
Stage II-Involves the corpus and cervix
Stage III-Parametrium, adnexa, or vagina but confined to true pelvis
Stage IVA-Involving local structures (rectum/bladder)
Stage IVB-Metastatic

Table 3.
Clinical staging system for endometrial cancer.

Structure	Image data set	Definition
Gross tumor volume	T2-wcightcd MRI	Visible abnormality if present Entire uterus, cervix,
clinical target volume	MRI or CT	and upper 1–2 cm of the vagina
Organs at risk	MRI or CT	Sigmoid, rectum, bladder, bowel, and uninvolved lower third of the vagina

CT, computed tomography; MRI, magnetic resonance imaging.
Note. MRI is required if a gross tumor volume is to be contoured. The clinical target volume includes the entire uterus, cervix, and upper vagina. Organs at risk include bladder, rectum, and sigmoid.

Table 4.
Recommended structures for volume-based planning in medically inoperable endometrial cancer.

MRI and the positive predictive value is low [51]. 18-F-fluoro-deoxyglucose positron emission tomography (PET) is used for lymph node involvement [52, 53]. In a study conducted with PET-CT, the pelvic node involvement rate was 63% and the para-aortic lymph node involvement was 95% [54].

4.1.2 Dose standards and technical properties

The target volume has been defined as the whole uterus, cervix and the upper 3–5 cm of the vagina for inoperable endometrial cancer in the 2000 ABS guideline and mainly MRI, and if MRI is not available, CT was recommended for the treatment plan [55]. The risks for the neighboring organs should be considered when performing volume-based treatment through MRI or CT [56] (**Table 4**).

In a study of Gill et al., 38 inoperable endometrial cancer patients underwent volume-based treatment and the gross tumor volume (GTV) and the clinical target volume (CTV) were determined with MRI in 19 patients and with CT in the remaining 19. While 20 patients received a mean 37.5 Gy VB in 4–5 fractions, 20 patients received 45 Gy EBRT followed by 25 Gy boost VB treatment. While the local control rate was 90.6% for 2 years, the overall survival rate was 94.4%. Hemorrhage developed in only one patient during the applicator placement and she received blood transfusion. No patients had grade 3 or acute and late complications [57]. The patients should be referred to centers where MRI or CT is available or their treatment should be attempted by using ultrasonography and radiography.

4.1.3 Treatment

1. HDR VB may be used alone in patients who have clinical stage 1, grade 1–2 myometrial invasion of less than 50 [56]%. GTV is specified in the course of brachytherapy with MRI and the whole uterus and its serosa are irradiated (CTV). For minimal harm to the neighboring tissues (OAT), the limit is 70–75 Gy for the rectum and the sigmoid, and 80–100 Gy for the urinary bladder. The HDR dose schemas for these patients have been presented in **Table 5**.

2. Pelvic EBRT+HDR VB is recommended for clinical stage 1 patients with myometrial invasion >50%. EBRT is applied 45–50 Gy so as to include all pelvic lymph nodes, the whole uterus and 1–2 cm proximal of vagina. Dose schemas are presented in **Table 6** for these patients.

3. Patients with clinical stage 2 endometrial cancer are given pelvic EBRT + HDR VB. This treatment modality is also valid for clinics that do not have MRI. The doses presented in **Table 6** are used.

4. Higher doses of pelvic EBRT (including all lymphatic regions) up to 65 Gy + HDR VB are given to patients with clinical stage 3 endometrial cancer. The doses presented in **Table 6** are used.

4.1.4 Management of recurrent disease after definitive radiation

Radiotherapy options are quite limited in biopsy-proven recurrences after definitive radiation treatment. It may only be used for palliative purposes in vaginal hemorrhage and pelvic pain. Hormone therapy and chemotherapy options should be considered in patients with recurrence [58].

4.2 Treatment-related toxicity from the use of radiation therapy for endometrial cancer

In the literature, radiotherapy was shown to have been used in 60% of cervical cancers, 45% of endometrial cancers and 100% of vaginal cancers [59, 60]. Healthy cervical and uterine tissues are known to tolerate radiation therapy (RT) well. Although pregnancy is known to have occurred in women receiving 20–30 Gy RT for the uterus, an atrophic uterus improper for pregnancy develops in women

HDR total dose (Gy)	HDR dose fractionation	EQD_2 (Gy)
36	6 Gy × 6	48
38.4	6.4 Gy × 6	52.5
363	7.3 Gy × 5	52.6
34	8.5 Gy × 4	52.4
40–50	5 Gy × 9–10	50–62.5

Table 5.
HDR dose table.

EBRT (Gy)	HDR total dose (Gy)	HDR dose fractionation	EQD_2 (Gy)
45	19.5	6.5 Gy × 3	71.1
45	18.9	6.3 Gy × 3	69.9
45	20.8	5.2 Gy × 4	70.6
45	25	5 Gy × 5	75
45	17	8.5 Gy × 2	70.5
50.4	12	6.0 Gy × 2	65.6
50.4	22.5	3.75 Gy × 6	75.3

Table 6.
EBRT and HDR dose schemas.

receiving 40–50 Gy. The toxic effect of RT depends on the age for ovaries; exposure to 20 Gy usually results in ovarian insufficiency in an adult woman. The influence of RT on the vagina depends on the location (superior, medial, inferior, posterior or the anterior wall). While the proximal vagina seems to be resistant to high doses (>100 Gy), the distal and the posterior walls are susceptible to atrophy and stenosis. While the rectum and the urinary bladder can be treated with low risk with 45–50 Gy RT, the small intestine shows severe toxic effects against <30 Gy, depending on the treated volume. These toxic effects of RT are known to be related to the treated tissue amount, fraction number and dose, previous surgeries, concurrent chemotherapies, co-morbid conditions and the smoking status [61].

Acute toxicity is defined as conditions that develop in the course of RT.

Sub-acute toxicity is defined as conditions that develop between 4 and 12 weeks after termination of RT.

Late toxicity is defined as the irreversible reactions that develop 3 months after termination of the treatment.

4.2.1 Genito-urinary (GU) system toxicity

The patient is asked to come to the treatment with a full urinary bladder with the aim of moving away the bowels as the urinary bladder can tolerate RT relatively better than the bowels.

4.2.1.1 Acute radiation cystitis

This is among the most common RT-induced complications. The patients present with urinary symptoms (dysuria, frequency, urgency and nocturia). Infectious cystitis should be excluded. The symptoms usually recover spontaneously within 1–2 weeks. Genitor-urinary complaints were reported to be seen less frequently when adjuvant therapy was performed with intensity-modulated radiation therapy (IMRT) [62].

4.2.1.2 Late genito-urinary toxicity

This toxic effect of RT emerges as the urinary bladder epithelium and the micro-vascular circulation are affected. Fibrosis and collagen accumulate under the epithelium and the muscle layer, and the urinary bladder capacity decreases. This effect leads to over-activity and contraction of the urinary bladder resulting in urge incontinence. In the PORTEC-1 study, while grade 3–4 toxicity was not observed, the rate of grade 1–2 genito-urinary complication was 5% higher [11].

Hematuria and ulcer formation are the late GU findings. Recurrent urinary bladder stones may be formed. Ureto-vaginal or vesico-vaginal fistulae may also develop following brachytherapy [63].

4.2.2 Gastro-intestinal (GI) toxicity

Gastro-intestinal toxicity may develop during RT or later and impair the quality of life of the patients through leading to restrictions in the daily lives of the patients.

4.2.2.1 Acute RT toxicity

As the small intestine epithelium shows a rapid proliferation, it is affected to a higher extent by RT. While nausea and vomiting are seen at the beginning of the

treatment, abdominal cramps and diarrhea are experienced during the following 2–3 weeks. This effect is considered to result from the disappearance of small intestine crypts and the inability to restore them in a short while [64]. The acute effects in the colon include fecal urgency and tenesmus. Acute colonic problems are seen in approximately 50% of the patients who receive 45–50 Gy as adjuvant; however, acute grade 3 toxicity is lower than 3% [10, 30]. There are randomized studies reporting that these acute effects may be significantly reduced by using IMRT [65].

4.2.2.2 Late GI toxicity

Late effects may develop between 6 months and several years in most patients. The pathophysiology includes chronic enteropathy with mucosal atrophy and loss of mucin-producing goblet cells. Fibrosis in the intestinal walls causes dysmotility and acute obstruction. There are no techniques that do not cause late intestinal complications, including IMRT. The late toxic intestinal effects include chronic diarrhea, malabsorption, recurrent ileus, mucosal ulcer, telangiectasias and rectal proctopathy.

4.2.3 Vaginal toxicity

Vaginal complications are commonly seen both during pelvic EBRT and VB. This toxic effect impairs the quality of life of the patients by leading to sexual dysfunction. Vaginal toxicity above grade 2 was not reported when the vaginal cuff was treated with HDR VB alone in a study [23].

4.2.3.1 Acute vaginal mucositis

Erythema and superficial ulcers develop as a result of vaginal surface epithelium injury in patients receiving brachytherapy. This leads to exudative vaginal discharge and may result in secondary infections.

4.2.3.2 Vaginal ulceration and necrosis

This complication is particularly seen when interstitial brachytherapy is used for treatment of full-thickness vaginal mucosa involvement [66].

4.2.3.3 Vaginal stenosis

This is a common late complication of both pelvic EBRT and VB. Dyspareunia is common due to reduced vaginal length. Vaginal stenosis and complete closure should be prevented to achieve a satisfactory follow-up. Stenosis usually develops 3–6 months after therapy. Vaginal dilators with proper thickness and length are used for the primary repair in these patients. While some authors propose that the use of vaginal dilators after RT reduces the stenosis, some others propose that it is not much effective [67].

Author details

Mehmet Sait Bakir
Division of Gyneacologic Oncology, Department of Gyneacology Obstetrics, Akdeniz University, Antalya, Turkey

*Address all correspondence to: sabakcil@gmail.com

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