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REVIEW

Vaginal Cuff Brachytherapy in Endometrial Cancer

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SUMMARY

Endometrial cancer is the most common gynecological cancer in developed countries, and its etiopathogenesis includes obesity, metabolic syndrome and unopposed estrogen effect. Therefore, the incidence is increasing and it is estimated to double in 2030. The main treatment modality is surgery, radiotherapy has role for inoperable patients and adjuvant period. Although adjuvant radiotherapy (external and/or brachytherapy) is possible, there are different literature information about indications and methods of administration. Stage and risk factors are important criteria for adjuvant treatment decision in today's routine clinical practice, grade of tumor, myometrial invasion, lymphatic vascular invasion (LVI (+)), tumor size, lymph node status, extension of tumor to cervix or vagina, age, type of surgery, and other comorbid conditions are all factors under consideration to determine the type and decision of adjuvant therapy. It has been shown that, of molecular markers which are effective on survival, POLE mutation leads to good prognosis and L1CAM and TP53 lead to poor prognosis and increased metastasis rate, and these molecular differences can also be utilized in designing adjuvant therapy in the future. When compared to the risk groups, radiotherapy reduces the risk of recurrence in the low-risk group from 5-6% to 2% and in the moderate-risk group from 12-15% to 3-6%. In the high-moderate risk group, it reduces from 18-26% to 5-6%. Vaginal brachytherapy is a preferred method to prevent the recurrence of vaginal cuff with far fewer side effects than external radiotherapy. The literature review showed that there are 24 different types of single application protocol and 22 different application protocols after external radiotherapy. In the treatment of endometrium cancer, vaginal cuff radiotherapy provides excellent results in disease control with a very low side effect rate, if applied properly and for the correct indication.

Keywords: Brachytherapy; cuff; endometrium.

Introduction

Incidence: In developed countries, endometrial cancer is the most common gynecological cancer with an incidence of 19.1/100000 in the American continent. Its incidence is 12.9–15.6/100000 in Europe and <5/100000 in Central-South Asia and Africa.[1] In general, it accounts for 4.8%–6% of the cancers seen in women, while it is responsible for 1% of cancer deaths in women.[1,2] Since the etiopathogenesis includes obesity, metabolic syndrome, and unopposed estrogen effect, its incidence is rapidly increasing in developed countries, and is estimated to be 42/100000 in 2030.[3]

Subgroups: Type-I is the frequently encountered form of endometrial cancer. It is low grade, endometrioid, diploid, hormone receptor-positive, and has good prognosis. Type II endometrial cancers are non-endometrioid, high grade, aneuploid, TP-53 mutated, hormone receptor negative tumors. They include serous, clear cell, and undifferentiated subgroup, and

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have poor prognosis and high metastasis rates.[4,5] Type-I endometrial cancer is associated with hyperestrogenism and endometrial hyperplasia, and it is mostly seen in the pre-perimenopausal age group, whereas type II is not associated with estrogen, but it develops in advanced age and in the presence of an atrophic endometrium. Type II constitutes 10% of cases, whereas it is estimated that it is responsible for 50% of recurrences.[6,7]

Nowadays, molecular data support that type-I carcinomas are associated with genetic alterations in PTEN, KRAS, CTNNB1, and PIK3CA and MLH1 promoter hypermethylation, whereas serous carcinomas frequently harbor TP53 mutations.[5,8] While L1 adhesion protein (L1CAM) is found to be a strong predictor of distant metastasis, it has an excellent prognosis in POLE mutant endometrial cancers, which may possibly be under unnecessary adjuvant therapy.[9,10]

Since it is not possible to explain all the difference in prognosis with the present dualistic model, the Cancer Genomic Atlas research network has identified four molecular subtypes.[10]

1. (POLE) ultra-mutated tumors
2. Microsatellite unstable tumors
3. Tumors with high number of copy with TP53 mutation
4. The remaining tumors without these alterations

Treatment of Endometrial Cancer

Surgery: Nowadays, surgery is the primary treatment modality in endometrial cancer.[4] A total hysterectomy including both tubes and ovaries is the gold standard for the treatment of stage I endometrial cancer, and this treatment is valid for most cases. This can be done by minimally invasive (laparoscopy or robot-assisted surgery) transvaginal or laparotomic methods. The surgical approach in lymph nodes for surgical staging is one of the most variable subjects around the world. From not doing a nodal evaluation, sentinel nod mapping to complex pelvic±paraaortic lymph node dissection, there is a wide range of approaches. The guiding factors are histological type, preoperative staging, grade, MRI findings, and intraoperative histological findings. To determine myometrial thickness for the decision of lymph node dissection before the operation in patients with stage I, grade 1, and 2 endometrial cancer, it is recommended to perform at least one of the ultrasonographic examination and/or MRI and/or intraoperative pathologic myometrial thickness determination by a specialist.[4] Paraaortic nodal evaluation is recommended, especially for deeply invasive, high grade, and type II disease.[11] The extent of lymphadenectomy varies according to clinical disciplines and surgeons, but it has not yet been demonstrated by a prospective randomized study that a surgical staging by lymphadenectomy provides a survival advantage.

Lymphadenectomy was investigated in two large prospective studies. The MRC ASTEC study has two arms: 704 patients underwent standard surgical treatment [(total abdominal hysterectomy - bilateral salpingo-oophorectomy (TAH+BSO), peritoneal washings and palpation of paraaortic lymph nodes], and 704 patients underwent lymphadenectomy in addition to standard surgery. The five-year overall survival was similar among these arms (81% in standard surgery, 80% in lymphadenectomy, p=0.31). Furthermore, five-year relapse-free survival was better in the standard surgery arm (79% vs. 73%, p=0.017). However, the limitation of this study is that the lymphadenectomy protocol does not include the entire pelvic paraaortic nodal region.[12]

In another Italian prospective study, patients diagnosed with early-stage endometrial cancer were randomized into groups with systemic pelvic lymphadenectomy (264 patients) and without lymphadenectomy (250 patients). While the rate of the diagnosis of nodal involvement was higher in the lymphadenectomy arm (13.3% vs. 3.2%, p<0.001), this result did not affect progression-free survival rate (81.7% vs. 81.7%, p=0.68) and did not change overall survival rate (85.9% vs. 90%, p=0.50). In addition, the rate of complications was lower in women without lymphadenectomy (34 patients vs. 81 patients, p=0.001).[13] Although there is no clear survival advantage proved by prospective randomized trials, older retrospective series had showed survival advantage for survival by lymphadenectomy.[14,15] SEPAL, a Japanese study that evaluated paraaortic lymphadenectomy retrospectively in patients with endometrial cancer, included 671 patients with moderate to high relapse risk treated between 1986 and 2004. In this study, 325 patients underwent standard surgery+pelvic lymphadenectomy and 346 patients underwent pelvic+-paraaortic lymphadenectomy. The overall survival rate was significantly higher in the pelvic paraaortic lymphadenectomy group (p=0.0005).[14]

Standardization of the definition of appropriate lymphadenectomy is still ongoing. The number of lymph nodes removed in most solid tumors is considered to be a marker for the adequacy of lymphadenectomy. In two retrospective reviews, it has been concluded that removal of at least 10 and 12 lymph nodes in the endometrium increases survival.[16,17] Therefore, it is often recommended to remove at least 10 lymph nodes.[16-18] Lymph node sampling has low

sensitivity.[19] The Mayo clinic reported that the rate of isolated paraaortic lymphadenopathy without pelvic lymph nodes is up to 16% in high-risk patients.[11] Surveillance, Epidemiology and End Results (SEER) analyses reported that ≥10–11 lymph node removal provided a limited survival advantage in the low-risk group in 16,995 patients with endometrial cancer, and provided a good survival advantage in the moderate- and high-risk group.[20] However, limb edema was reported as 8%–50% in cases with lymphadenectomy.[21]

Consequently, the European Society for Radiotherapy and Oncology (ESTRO) consensus recognizes that lymphadenectomy is particularly useful in shaping the adjuvant treatment approach.[4] In most national and international guidelines, lymphadenectomy has been excluded from routine practice for patients with low and moderate-risk because of the lack of studies with high levels of randomized evidence on survival advantage and related morbidity rates. However, it remains the focus of interest in high-risk patients.

Radiotherapy: Although radiotherapy has become a major component of treatment for inoperable or recurrent endometrial cancer, adjuvant radiotherapy frequently comes up in operated patients as external beam radiation therapy (EBRT) or vaginal brachytherapy (VBT).

Indication, Risk Determination, and Patient Selection

Stage and risk factors are important criteria. To determine the type and decision of adjuvant therapy, grade of tumor, myometrial invasion, lymphatic vascular invasion (LVI (+)), tumor size, lymph node status, extension of tumor to cervix or vagina, age, type of surgery, and other comorbid conditions are the factors to be considered.

The type of surgery frequently affects the choice of adjuvant therapy. The frequency of external radiotherapy was lower in patients who underwent lymphadenectomy. The decision of external radiotherapy is particularly relevant for patients with moderate-risk for recurrence.

It is necessary to evaluate the main studies to understand the risk factors and groups.

In their study on 540 patients with stage I endometrial cancer (Norwegian study), Aalders et al. applied a low-dose rate (LDR) VBT in one group and added additional EBRT in the other group. They noted that vaginal and pelvic recurrence decreased from 6.9% to 1.9% in the second arm ($p<0.01$). In addition, it was found that metastasis rates were higher, and the addition of EBRT did not increase the five-year overall survival in the second group.

Grade 3, >1/2 myometrial thickness involvement is defined as subgroups in which external EBRT may be advantageous.[22]

Onsrud et al. reported no survival difference ($p=0.186$) in the Norwegian study after a median follow-up of 20.5 years, and, on the contrary, reported higher mortality rates in patients under 60 years of age who applied EBRT. The increase in the incidence of secondary cancer in patients undergoing radiotherapy under 60 years of age is the late result of this study with an HR of 2.02 (95% CI 1.30–3.15).[23]

The PORTEC-1 (Postoperative radiotherapy for endometrium cancer) study was conducted between 1990 and 1997; and 19 out of 20 Dutch oncology centers participated in this study. That study aimed to evaluate the effect of adjuvant pelvic radiotherapy on local recurrence and overall survival in stage I endometrial cancer, and 714 patients were randomized in this study. This study has two arms: TAH+BSO without lymphadenectomy and 46 Gy EBRT in addition to TAH+BSO without lymphadenectomy. The eligibility criteria were endometrial cancer diagnosis, any age, postoperative FIGO stage I and if Grad 1 than deep myometrial invasion (>50%), if Grad 2 than any invasion, or if Grad 3 than superficial invasion. The locoregional control rate was markedly better in the EBRT arm (4% vs. 14%, $p<0.001$). It was also found that 74% of the recurrences are at the top of the vagina. The five-year overall survival rates were similar in the EBRT arm and in the follow-up arm with rates of 81% and 85%, respectively ($p=0.31$). This was attributed to good salvage rates after recurrences. In patients over 60 years of age, a marked increase in locoregional recurrence rates ($p=0.003$) and cancer-related mortality ($p=0.02$) was reported. Subsequently, the 15-year outcomes of PORTEC-1 study were published. At the end of 15 years, locoregional recurrence rate was reported as 5.8% in EBRT arm and 15.5% in follow-up arm ($p<0.001$). At the end of 15 years, overall survival rate was 52% in EBRT arm and 60% in follow-up arm ($p=0.14$).[24,25] In addition, the evaluation of quality of life in the PORTEC-1 study showed that the rate of side effects such as urinary symptoms (urgency, need to be close to the toilet, incontinence) and bowel symptoms (fecal urgency, leakage, diarrhea, restrictions in daily activities because of bowel irritability) increased from 4% to 26% (in fact, most were grade 1) with external RT ($p<0.0001$).[26]

MRC ASTEC and NCIC CTG EN.5 randomized trials (n=905) [27] and Gynecological Oncology Group (GOG)-99 (n=392) [28] also compared postsurgical follow-up and EBRT approaches. Cochrane meta-analysis of these studies showed that although

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there was a decrease in vaginal and pelvic recurrence rates with EBRT, there was no overall survival difference.[29] In the GOG-99 trial, age, depth of myometrial invasion, LVI (+), and grade were found to worsen prognosis.[28] In the light of these studies, postoperative risk groups were defined in endometrial cancer (Table 1).

Today, the ESTRO guideline and the defined risk groups in the guideline are frequently used in treatment management and risk assessment.[4]

Low-Risk (IA Gr 1–2, LVI (-))

The subgroup analyses in the low-risk group included in the large randomized studies showed that adjuvant radiotherapy did not provide an advantage in this group.[4,24,25,27,28] In another randomized study, 645 patients with low-risk endometrial cancer were randomized to post-surgical VBT and follow-up arms. The recurrence rate in the follow-up arm was found to be 5%, indicating that VBT does not provide any benefit.[30] In randomized studies, recurrence rate in low-risk patients is around 4%, indicating that there is no benefit from adjuvant radiotherapy.

Moderate-Risk, High–Moderate-Risk

The GOG-99, PORTEC-1, MRC ASTEC, NCIC CTG EN.5 trials, and Cochrane meta-analysis showed that EBRT reduced pelvic recurrence to one-third, but it did not provide a survival advantage, resulting in increased cost and high toxicity, especially in the gastrointestinal

Table 1 Risk groups in endometrial cancer by study and groups

Study, Group	Risk group			
	Low	**Moderate**	**High-moderate**	**High**
Study Group	Risk group			
	Low	Moderate	High-moderate	High
PORTEC-1	Gr 1-2, MI <50%, EC	Stage I, GI EC and MI≥50% Gr 2 Gr 3 and MI<50%	EC and two of the three factors >60 years old Gr 3 MI≥50%	Stage III–IV Uterine serous or clear cell carcinoma with any stage
PORTEC-2			>60 years old Stage IC, Gr 1–2 Stage IB, Gr 3 Stage IIA (excluding those with MI>50% and Gr3)	
GOG-99 (PRFs) Gr 2-3 LVI (+) MI>2/3	Stage IA, Gr 1–2, endometrioid	≤50 years and ≤2 PRF 50–69 years ≤1 PRF ≥70 years without PRF	Any age and 3 PRF 50–69 years ≥2 PRF ≥70 years and ≥1 PRF	Stage III–IV, any histology and grade Uterine serous and clear cells, Stage IB, Gr 3, endometrioid
ESTRO 2016	Stage I endometrioid Gr 1-2 MI<50% LVI (-)	Stage I endometrioid Gr 1-2 MI≥50% LVI (-)	Stage I endometrioid Gr 3 MI<50% Any LVI or Gr 1-2 LVI (+) Any MI	Stage I endometrioid Gr 3 MI≥50% Any LVI Stage II Stage III endometrioid without residues Non-endometrioid
MRC ASTEC		Stage IA-IB Gr 3, endometrioid Stage IC-IIA, Gr 1–2		Papillary serous and clear cell types Stage IC, Gr 3 Stage IIA, Gr 3 IIB

tract.[24,25,27-29] In the ASTEC study, VBT was applied to 50% of the follow-up arm, although VBT was released in both arms. Vaginal recurrence rates were similar (4% vs. 7%) in patients who underwent and did not undergo EBRT. Kong's Cochrane meta-analysis shows that EBRT provides a 6% reduction in absolute risk, suggesting that each 16.7 treatment rescues one patient from locoregional recurrence.[29]

Then, the PORTEC-2 study, which included only high-moderate-risk patients, investigated 427 patients on whether VBT could replace EBRT with acceptable toxicity and quality of life, and this study confirmed the non-inferiority hypothesis.[31] Similar results were reported from the Swedish study, where Sorbe et al. evaluated endometrial cancer cases in the moderate-risk group (EBRT+VBT vs. VBT).[32]

The PORTEC-2 study was designed as a non-inferiority study aiming to compare two adjuvant radiotherapy schemes as a phase-3 study. Then, 427 patients in the high–moderate-risk group of PORTEC were randomized to EBRT (46 Gy in 23 fractions) or VBT [high-dose rate (HDR) 7 Gyx 3 fractions or LDR 30 Gy, 0.5 cm deep] after TAH-BSO without lymph node dissection. Five-year vaginal recurrence was similar with VBT and BRT, with rates of 1.88% and 1.6% (p=0.74), respectively. The pelvic recurrence rate was higher in the VBT group with a rate of 0.5% compared to 3.88% (p=0.02).[31]

The 10-year outcomes of PORTEC-2 were published in 2018, and vaginal recurrence was still similar in the VBT and EBRT arms, with rates of 3.4% and 2.4% (p=0.55), respectively. The pelvic recurrence was observed in 13 females in the VBT group, and in two females in the EBRT group (6.3% vs. 0.9%, p=0.004). The 10-year distant metastasis rates were 10.4% and 8.9%, respectively (p=0.004). In conclusion, isolated pelvic recurrence rates were similar between groups (2.5% vs. 0.5%, respectively, p=0.10). The 10-year overall survival rate was 69.5% vs. 67% (p=0.72), and the endometrial cancer specific survival rate was 88.2% vs. 90.9% (p=0.42), respectively. According to the central pathology and the re-categorization of the risks, 82.7% of the patients were originally identified in the high-moderate-risk group. Molecular risk factors were also assessed in this evaluation.[33]

Many cohort studies have identified grade 3 and LVI (+) as the greatest risk factors for recurrence. [34, 37] This result is also shown in the current data analysis of PORTEC-1 and 2 trials.[37] However, in the PORTEC-2 trial, most of the patients in the high--moderate-risk group consisted of those with deep myometrial invasion but grade 1–2 and LVI (-) carcinoma, which are nowadays evaluated in the moderate-risk group rather than in the high-moderate-risk group. In both groups, the five-year vaginal recurrence rate was below 2%. The distant metastasis and survival rates were similar. According to the results of this non-inferiority study, VBT is a highly preferred standard treatment with less side effect profile in patients with stage I endometrial cancer, that is in the high-moderate-risk group.[31] Follow-up can be performed with a risk of recurrence up to 20%, but it is reported that patients prefer radiotherapy even if it provides a 5% benefit.[38]

Although there are big randomized trials that have over 900 patients, the power of these studies is still not sufficient to determine the survival advantage. The National Cancer Database (NCDB) demonstrated the survival advantage of postoperative radiotherapy in both high–moderate-risk and high-risk patients in a study that collected data from 1500 centers in the United Nations. They reported that the mortality risk in more than 132.000 patients decreased by 22% with radiotherapy. The presence of radiotherapy has also been shown as an independent factor on overall survival in multivariate analysis.[39] The SEER database showed that EBRT or VBT without lymph node dissection provides survival advantage in both moderate- and high-risk patients.[40] However, further analysis including 58,172 patients revealed that there was no decrease in cancer specific mortality rates.[41] In conclusion, it was observed that RT did not increase overall survival in moderate-risk patients. This recurrence may be explained by the high likelihood of complete survival of the disease with EBRT and VBT, and preferably RT may not be administered to this group. However, it should be kept in mind that the morbidity of rescue therapies will be higher.

In the current classification, tumors with ≥50% invasion, at grade 1–2 and with LVI (+), and with <50% invasion, at grade 3 and with or without LVI (any) are considered in the high-moderate-risk group.

High-Risk Endometrial Cancer

This group has a higher likelihood of pelvic recurrence and distant metastasis, and it includes both endometrioid and non-endometrioid group. This group included advanced-stage patients with≥50% myometrial invasion, at grade 3 and more locoregional recurrence. NCDB reported that VBT increased survival rate in patients with high-risk stage IA.[39] The EBRT+RT boost regimen rather than VBT alone is recommended as a treatment

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protocol in this group, but there are publications with a low level of evidence about the type of radiotherapy. The SEER database reported that radiotherapy (independent of type) provided a survival advantage in patients included in the high-moderate-risk and high-risk groups according to the PORTEC risk grouping.[41]

In the GOG-249 study, both high-moderate-risk and high-risk patients were randomized to three cycles of carboplatin/paclitaxel arms after EBRT and VBT. It was shown that adjuvant chemotherapy did not contribute to progression-free survival. The results were then published as poster presentation.[42] In this group, the opinion that the addition of EBRT to LVI (+) patients who have not undergone surgical lymph node staging, and the use of VBT as adjuvant therapy in the remainder is dominant.

The NSGO-EC-9502/EORTC 55991 and MaNGO-ILIODE III randomized studies investigated the effect of chemotherapy in this group, and the analysis identified an increase in five-year disease-free survival and an increase trend in overall survival.[43]

The PORTEC-3 study, which examined 660 patients with high-risk group of endometrial cancer, randomly administered 48.6 Gy external radiotherapy in one arm and chemotherapy followed by concomitant cisplatin-based chemoradiotherapy in the other arm. Consequently, the addition of chemotherapy had no effect on five-year survival, with even more toxicity.[44]

When compared to the risk groups, radiotherapy reduces the risk of recurrence in the low-risk group from 5%–6% to 2% and in the moderate-risk group from 12%–15% to 3%–6%. In the high-moderate-risk group, it reduces from 18%–26% to 5%–6%.[25,26,28]

Advanced-Stage Endometrial Cancer

Although there were fewer studies on radiotherapy in stage III/IV patients, the SEER retrospective analysis evaluated 1577 patients, and reported a higher five-year overall survival in patients undergoing EBRT or EBRT+VBT.[45]

NCDB revealed that the addition of VBT to EBRT in patients with stage III endometrial cancer and cervical involvement provided a survival advantage (HR 0.86).[46]

Patient Involvement in Determining the Indication

In their study on behalf of Dutch Gynecologic Oncology Group, Kunneman et al. questioned the minimally acceptable level of benefit for the VBT selection to

Table 2 ESTRO Guide for Adjuvant Treatment

Risk Group	Definition	Adjuvant Treatment (Evidence Level, Grade of Recommendation)
Low	Stage I endometrioid, grade 1–2, myometrial invasion <50%, LVI (-)	Follow-up (I, A)
Moderate	Stage I endometrioid, grade 1–2, myometrial invasion ≥50%, LVI (-)	a) Brachytherapy (I, B) b) Follow-up (especially <60y) (II, C)
High-moderate	Stage I endometrioid, grade 3, myometrial invasion <50%, LVI (–), or Stage I endometrioid, grade 1–2, LVI (+) and any myometrial invasion	1. Surgical nodal staging performed, lymph node (-) a) Brachytherapy (III, B) b) Follow-up (III, C) 2. No surgical nodal staging a) External radiotherapy (especially if LVI (+) (III, B) b) Brachytherapy (Grade 3 and LVSI (-)) (III, B) 3. The benefit of systemic therapy is unclear (III, C)
High	Stage I endometrioid, grade 3, ≥50%, LVI (– or +) Stage II Stage III endometrioid, no residual disease	1.Surgical nodal staging performed, lymph node (-) a) Limited area external radiotherapy (I, B) b) Brachytherapy (III, B) c) There are studies about systemic treatment (II, B) 2. No surgical nodal staging a) External radiotherapy (III, B) b) Brachytherapy as a boost (IV, C) c) Sequential adjuvant chemotherapy (II, C) d) Both external radiotherapy and chemotherapy (II, B)
Advanced	Stage III residual disease is available Stage IV	

the patients and health workers. This rate was 0% for patients and 8% for physicians ($p<0.001$). Thus, most patients would like to receive VBT even if there is a possibility of zero benefit.[38] This corresponds to the reluctance to participate in the follow-up arm in the PORTEC-4.[47]

Treatment Recommendations

The American Society for Brachytherapy (ABS) published consensus guidelines on operated endometrium in 2000 and 2012.[48,49]

The American Society of Radiation Oncology has published evidence-based radiotherapy recommendation guidelines in 2014.[50]

In 2016, the ESTRO consensus was published, and Table 2 shows treatment recommendations according to the risk categories of this group.[4]

Treatment Preparation and Applicator Selection

Before radiotherapy, the physician should inform the patient about the risks, benefits, goals, and alternatives treatments. Prior to treatment, it is important to perform pelvic examination and to check that the vaginal apex is healed and the small intestine is not herniated from the vaginal apex. The proposed schedule is not to start before 4 weeks and not to exceed 12 weeks. It should be noted that improvement in robotic- or laparoscopic-assisted vaginal hysterectomy might take more time to heal.[49]

Prior to the placement of the applicator, a vaginal examination should be performed to assess the vaginal structure, width, size, presence and shape of healing (vaginal apex), and presence of recurrence, albeit rarely. Explaining the procedures to the patient and applying lubricant (such as xylocain gel) to the applicator will facilitate the procedure. Rarely, pain relievers, anxiolytics, or moderate sedation are required for brachial brachytherapy. Applying a clip to the apex to check the applicator's full fit and placement in the apex may be an appropriate method, but it does not always give the desired result because of the possibility of the clips falling or being displaced. In deciding the diameter of the cylinder, it is recommended that the physician first places one finger on the vagina and gently presses the perineal muscle to make the patient take deep breaths and relax. After the patient tolerates it and relaxes, the second finger is advanced and rotated to relieve the introitus. If this maneuver can be easily done, the 3.5 cm cylinder will be suitable. If the vagina is too relaxed because of multiparity, then a diameter of 4 cm will be chosen. However, if the entry of the second finger is not allowed, it would be appropriate to select the cylinder with a diameter of 2.5 cm. For the remaining cases, 3-cm cylinder is selected. After the fixation, check must also be done before applying the treatment. The planning tomography (CT) will show the compliance of the vagina and applicator. ABS suggests the largest applicator that can be placed.[49]

Humphrey et al. studied the CT image of 103 patients, and detected 67 air gaps in 38 patients. They reported that this ratio was lowered to 11 patients by placing larger cylinders in spaces larger than 2 mm and required repositioning, and that there is a significant air gap exceeding 2 mm in only 7% of patients.[51] In two other studies, air gaps exceeding 2 mm were reported with a rate of 32% and 72%.[52,53] However, most of them have little clinical significance, and were reported to include only 0.86% of the vaginal surface.

The structure as well as the diameter of the applicator is also important for the implementation of the optimal VBT. In the literature, single-channel cylinders (83.2%) are used for most of the patients.[54] However, a single simple applicator cannot treat all vaginal types and postoperative anatomical variants. In most patients, the vagina is cylindrical in the postoperative period, and it is possible to treat it with a vaginal cylinder of the appropriate size. A vaginal cylinder of a very small diameter than the vaginal size may lead to the formation of air gaps or tissue folds, resulting in dose drops in these regions. It should be kept in mind that multi-catheter cylinders may reduce the rectum and bladder dose, but may cause a dose increase in the vaginal mucosa.[55]

In some cases, the vaginal apex can be seen as a "dog ear" shaped pocket because of the vaginal fornix remnants. These conditions can be best treated with vaginal molds, multichannel applicators, or ovoid applicators.[56,57] (Fig. 1)

Dose Rate

In the past decades, 69% of the patients were treated with HDR, but this rate has reached 96%. Fayed et al. compared the results of HDR and LDR, and revealed that there was no difference between two modality for local control and total survival rates.[58]

Dose Fractionation Schemes

There is a large difference in the fractionation and dose scheme in the literature, and 24 protocols for VBT alone and 22 protocols for boost therapy were recorded. The EQD2 dose is between 36 and 48 Gy for VBT alone and between 57 and 69 Gy in combination with EBRT.[29,54]

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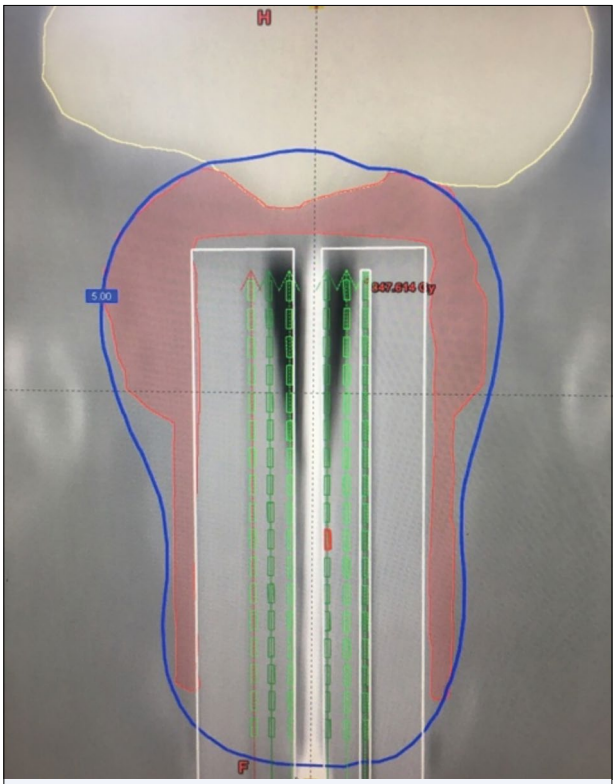

Fig. 1. Better coverage of the lateral regions of apex with the multichannel applicator.

VBT alone: The dose can be varied according to the length and width of the vagina to be irradiated. The recommendation is that the dosing point, line, and volume should be clearly indicated. The doses of 7 Gy in three fractions at 0.5 cm are the frequently preferred scheme in the PORTEC-2 study. MD Anderson Cancer Center prefers 6 Gyx5 fraction scheme, whereas Dana-Farber Cancer Institute 4 Gyx6 fraction scheme on the vaginal surface.[25,54] There is no literature comparing the fractionation schemes or showing the superiority of these schemes against each other.

POTREC-4 is a study designed to determine the optimal dose in VBT alone. The patients with high-moderate-risk endometrial cancer in the postoperative period were randomized to follow-up and VBT arms; and in the VBT arm, a second randomization was performed into 7 Gy and 5 Gy in three fractions at a depth of 0.5 cm. However, because of the bad choice of follow-up arm for high-moderate-risk endometrial cancer, the study has to be closed early. The study is planned to continue in the other two arms.[47] For an optimal schema, there is need for more phase three studies.

VBT after EBRT: Commonly used schemas include 6 Gyx3 (RTOG 0921) regimen after 45 Gy EBRT on the vaginal surface and 6 Gyx2 (RTOG 0418) regimen after 50.4 Gy EBRT on the vaginal surface. If there is a positive margin or disease recurrence, the dose should be increased. It is often useful to reduce the size of the fraction if the diameter of the fitable cylinder diameter is low.

Target and Dose Identification

Length: There are several studies on the size of the treatment area, which often ranges from 1 to 10 cm.[59,60] However, most commonly used protocols were applied to the proximal 3–5 cm of the vagina or proximal 1/3–1/2 of the vagina, while no consensus could be determined. The recommendation of ABS is 3–5 cm proximal to the vagina.[49] The approach to treating the entire vagina is in the process of being discontinued because of the very low rate of distal vaginal recurrences and the increased incidence of side effects.[54] Since the risk of distal vaginal recurrence increases in the presence of papillary serous and clear cell histology and in grad 3 disease or in the presence of extensive lymphovascular invasion, treatment of the entire vagina can be preferred. In their study in which proximal vagina, vaginal apex, proximal half of vagina and whole vagina were treated, Kloetzer et al. reported no difference in survival and vaginal recurrence rates.[61]

Depth: It is known that 50% of the lymphatic channels are located 1 mm below the mucosa, and that 95% of the total is located at a distance of 3 mm below the surface.[62,63] This finding supports the idea that the target is properly covered with the dose defined at the depth of 0.5 cm. When the dose is defined on the surface, the surface dose is more homogenous, whereas the surface dose is more heterogeneous when the dose is defined at depth (81%–172%).

The ABS recommends reporting of both the surface dose and the dose at a depth of 0.5 cm, regardless of where the dose is defined. Furthermore, wherever the dose is defined, it is recommended that the optimization point be placed on both the top and lateral sides in treatment planning.[49]

In the 2014 report of ABS, it was stated that the most preferred VBT alone regimen is three fractions with 7 Gy fraction size at a depth of 0.5 cm, while the most preferred post-EBRT regimen is three fractions with 5 Gy fraction size at a depth of 0.5 cm.[54]

Percentage depth dose has more variability when using 2-cm cylinders. To convert a dose at 0.5 cm depth into a surface dose, a formula as follows can be used.[64]

M (magnification factor)=1.00+0.64/treatment length+1.23/cylinder diameter).

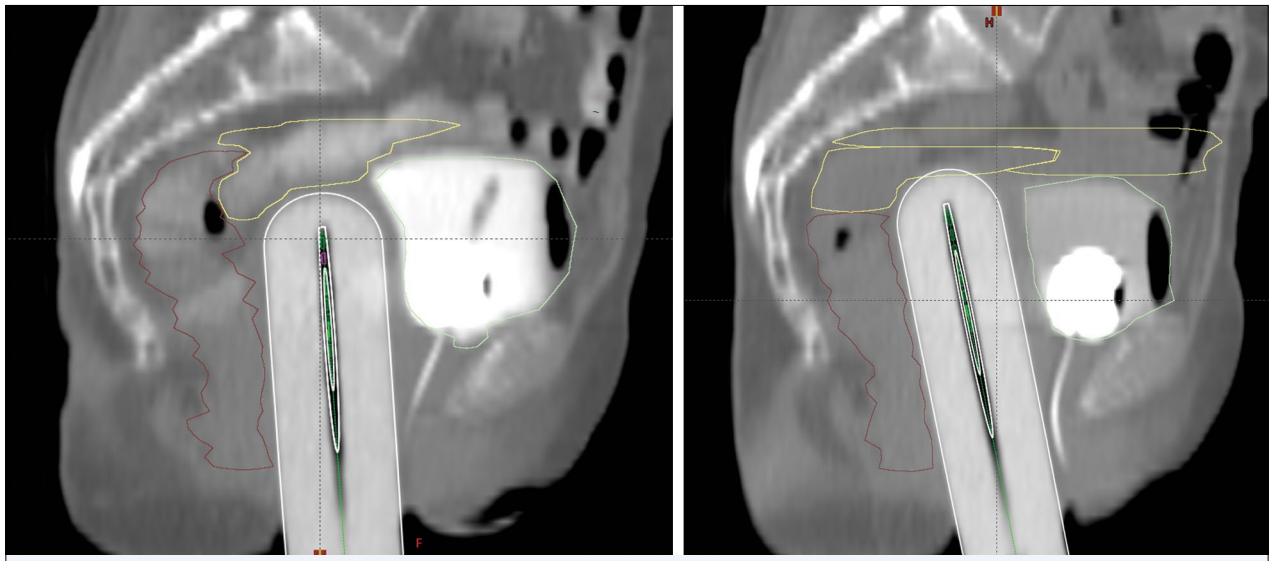

Fig. 2. Sagittal tomography images of the applicator in neutral position and horizontal position in the same patient. In addition, the intestines have been tried to be kept away, increasing the bladder fullness.

Doses of Organ at Risk

A study that analyzed the patient position revealed that treatment of the patient in neutral position lowered the doses of rectum D1cc and 2cc compared to the gynecological position. (4.69 vs. 5.66 Gy and 4.24 vs. 5.14 Gy, respectively).[65]

The placement of the applicator in the horizontal plane is advantageous in terms of both patient comfort and not increasing the dose of rectum or bladder. There are studies reporting the effect of the placement angle of the cylinder on the dose of rectum. In these studies, it has been reported that the positioning of the top of the cylinder toward the rectum increases the dose, but the parallel position of the cylinder to the horizontal axis further decreases the dose of the rectum.[66,67] (Fig. 2)

Although bowel fullness has been reported to increase bowel dose, there was no significant difference in dose parameters in the protocols containing an enema treatment one evening before and one in the morning of treatment.[68,69]

The comparison of the full bladder (180 cc) and empty bladder revealed that the fullness of the bladder reduces D50% values of the bladder and reduces the dose of the small intestine from 36.7% to 21.4%.[70] In another study comparing the full and empty bladder plans in 15 patients, bladder filling was reported to increase the distance between the cylinder and the small intestine from 1.2 to 1.68 cm (p=0.006), but it was observed that this maneuver increased the bladder D2cc by 18.7%.[71] Stewart et al. demonstrated that treatment of a full bladder reduced the maximum dose of the bladder and reduced the volume of bladder that received 70% of the defined dose. In addition, a full bladder allows the adjacent small bowel to move away from the vaginal cylinder.[72] (Fig. 2)

Number of Planning

Today, approximately 80% of the plans are designed as three-dimensional (3D), while up to 75% are carried out only through the plan in the first application.[54] The ABS guide does not recommend planning with every fraction because we have quite a fixed geometry. Creating a plan in each application increases the cost by 35% and does not provide a dosimetric advantage.[73] Studies comparing planning in each fraction versus the first fraction showed that the dose was not reduced in organ at risk, but the cost was increased.[73,74]

Chapman et al. compared magnetic resonance (MRI) and CT images of the patients, and they found that with MRI, a volume of 1 cm3 and more received less than 75% of the defined dose at least in 69% of patients.[75] Low-dose areas often located on the top of the vagina, where the cylinder could not be located exactly because of suture materials.

In a study comparing two-dimensional (2D) and 3D treatment planning, the target dose was the same, while the critical organ doses were reported to be lower with 3D planning.[76]

ABS recommends that there is a clear and written directive, which is dated and signed and has information about treatment area, source, dose defined per

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fraction, total dose, and fractionation scheme. The location of the absorbed dose must be clearly specified. The type of applicator, the shape of the optimization, the dwell position number and position, dwell weights, and isodose distribution should also be documented. The doses of the adjacent organ at risk, especially the bladder and rectum, should also be documented.[49]

Conclusion

In the treatment of endometrium cancer, vaginal cuff radiotherapy provides excellent results in disease control with a very low side effect rate, if applied properly and for the correct indication.

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