Chapter 27
Endometrial Cancer

Brittaney-Belle E. Gordon, Orit Kaidar-Person, Mahesh Varia, and Ashley A. Weiner

Hypofractionation in the radiotherapeutic management of endometrial cancer has an important but selective role, mainly in terms of postoperative vaginal cuff HDR brachytherapy. SBRT is used for oligometastatic disease, rarely as a boost technique with EBRT and for palliation. These data have mostly been reported from retrospective cohort studies that include other gynecological malignancies as discussed in the cervical cancer chapter. Surgery [total hysterectomy with bilateral salpingo-oophorectomy (BSO)] with or without nodal assessment (sentinel lymph node biopsy or nodal dissection) is the primary treatment of endometrial cancer. Recommendations for adjuvant radiotherapy are based on surgical pathology. Factors considered include depth of invasion, grade, lymphovascular space invasion, and nodal involvement. The use of postoperative vaginal cuff brachytherapy for high-intermediate-risk early-stage endometrial cancer is increasing in the recent years after reports indicating its efficacy in local control and favorable toxicity profile compared to pelvic EBRT.

B.-B. E. Gordon
University of North Carolina School of Medicine, Chapel Hill, NC, USA

O. Kaidar-Person
Department of Radiation Oncology, University of North Carolina School of Medicine, Chapel Hill, NC, USA

Oncology Institute Radiation Oncology and Neuro-Oncology Unit, Rambam Medical Center, Haifa, Israel

M. Varia · A. A. Weiner (✉)
Department of Radiation Oncology, University of North Carolina School of Medicine, Chapel Hill, NC, USA
e-mail: ashley_weiner@med.unc.edu

O. Kaidar-Person, R. Chen (eds.), *Hypofractionated and Stereotactic Radiation Therapy*, https://doi.org/10.1007/978-3-319-92802-9_27

27.1 Pearls

- Uterine cancer is the most common gynecologic malignancy in the USA and the sixth most common cancer diagnosis in women worldwide.
- Mostly diagnosed in postmenopausal women (median age 63 years); 4% of the women are younger than 40 years.
- It is most common in white women followed by African-Americans, Hispanics, and Asian women. Notably, African-American women experience poorer prognosis, regardless of stage, pathology, socioeconomic status, and treatment.
- Risk factors include excess (unopposed) estrogen exposure: early age at menarche, nulliparity, late age at menopause, obesity, estrogen-secreting tumors, tamoxifen therapy, and estrogen-progestin postmenopausal hormone therapy. Diabetes mellitus and high-fat diet are also considered risk factors.
- Genetic predisposition: Lynch syndrome, BRCA1 mutation.
- The most common presenting symptom is postmenopausal uterine bleeding (75–90%).
- Most diagnoses occur at an early stage: disease confined to the uterus (67–80%), spread to regional lymph nodes and organs (21%), and distant metastases (12%).
- Histology: Adenocarcinoma (i.e., endometrioid cancer) is the most common subtype (90–95%). Type 1 cancers (75–80%) are estrogen-dependent, low-grade, and uterus-confined cancers that typically occur in postmenopausal women and have favorable prognosis. Type 2 cancers (10–20%) are estrogen-independent, non-endometrioid (serous, clear cell, mixed histology, undifferentiated, carcinosarcoma) cancers with poorer prognosis. Uterine sarcoma ~ 5%.
- **Patterns of spread:**
  - Local spread is through invasion of the myometrium or the cervix and less commonly to uterine serosa, parametria, or vagina.
  - Extrauterine spread of endometrioid cancer primarily occurs through lymphatic drainage to locoregional lymph nodes (pelvic, iliac, obturator, presacral, and para-aortic) and the adnexa.
  - Surgical series have described several pathologic risk factors for lymphatic spread including depth of invasion, tumor grade [1], tumor sizes [2], and lymphovascular space invasion (LVSI) [3].
  - Hematogenous dissemination to the lungs and liver is less common. Uterine sarcoma can spread to the lungs.
- **Medical workup:**
  - Physical exam including a pelvic exam with speculum and bimanual examination. For women with postmenopausal vaginal bleeding, the American College of Obstetricians and Gynecologists recommends initial evaluation with either endometrial biopsy or transvaginal ultrasonography. Endometrial thickness of greater than 4 mm on ultrasound requires a biopsy. Non-diagnostic endometrial biopsy should be followed by dilation and curettage.
  - Laboratory tests: CBC, serum chemistries, LFTs, and renal function tests. CA-125 is optional for high-grade endometrioid histology, advanced stage, and serous or clear cell histology.

  - Though the majority of women diagnosed are postmenopausal, fertility consultation should be considered for patients of childbearing age.

- **Imaging studies:**
  - For patients, who will have surgical staging and primary treatment, preoperative imaging is reserved for those with high-grade or non-endometrioid cell types or suspected advanced stage on clinical evaluation.
  - Suspected/gross cervical involvement: contrast abdomen and pelvis MRI is recommended to evaluate extent of disease.
  - Suspected extrauterine disease: MRI/CT/PET as clinically indicated.

- Operable patients undergo initial hysterectomy (open, laparoscopic, or robotic) with BSO ± adjuvant treatment based on age, stage, and pathologic risk factors.
- The highest-risk site of disease recurrence after surgery is at the vaginal cuff.
- Adjuvant therapy primarily includes EBRT and/or vaginal brachytherapy (VBT). Chemotherapy may be administered for advanced disease. Recent data showed that VBT is as effective as EBRT in reducing vaginal recurrences in select FIGO stage I intermediate- to high-intermediate-risk patients, who have a low risk of lymph node involvement [4].
- Patients with FIGO stage II endometrial cancer may be candidates for VBT ± EBRT based on other pathologic risk factors.
- Patients with FIGO stage III endometrial cancer typically receive chemotherapy with pelvic EBRT.
- Medically inoperable patients with early-stage disease without risk factors per MRI (positive LN, deep myometrium involvement) can be treated by intracavitary brachytherapy alone or EBRT + brachytherapy [5]. Hormone therapy (either systemic or via a hormonal intrauterine device) alone can be considered for unfit patients [6].
- Patients with unresectable disease (e.g., invasion of the vagina, bladder, rectum) or with extrauterine pelvis disease are candidates for EBRT + brachytherapy ± chemotherapy, or neoadjuvant chemotherapy or chemoradiotherapy followed by surgical resection or chemotherapy alone.
- Treatment for locoregional recurrences is dependent on primary cancer treatment as well as site of recurrence. Patients without prior RT are treated with EBRT ± brachytherapy. Recurrences at the vaginal cuff are amenable to intracavitary or interstitial brachytherapy, while nodal or pelvic sidewall recurrences are typically treated with EBRT alone. Patients, who recur in or adjacent to a prior RT field, are treated with surgical exploration with resection ± intraoperative radiotherapy (IORT) and/or systemic therapy.
- Limited nodal recurrence may be amenable to hypofractionated radiotherapy using SBRT with good efficacy and favorable toxicity in retrospective review [7] and in single-institution prospective evaluation [8], though further evaluation of this strategy may be warranted.
- Regardless of tumor type, the estimated 5-year OS is 85–90% for stage I, 75–85% for stage II, 50–65% for stage III, and 20–25% for stage IV (FIGO 26th report).

27.2 AJCC and FIGO Staging

Primary tumor (T)		
T category	**FIGO stage**	**T criteria**
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	I	Tumor confined to the corpus uteri, including endocervical glandular involvement[a]
T1a	IA	Tumor limited to the endometrium or invading less than half the myometrium
T1b	IB	Tumor invading one half or more of the myometrium
T2	II	Tumor invading the stromal connective tissue of the cervix but not extending beyond the uterus. Does NOT include endocervical glandular involvement
T3	III	Tumor involving serosa, adnexa, vagina, or parametrium
T3a	IIIA	Tumor involving the serosa and/or adnexa (direct extension or metastasis)
T3b	IIIB	Vaginal involvement (direct extension or metastasis) or parametrial involvement
T4	IVA	Tumor invading the bladder mucosa and/or bowel mucosa (bullous edema is not sufficient to classify a tumor as T4)
Regional lymph nodes (N)		
N category	**FIGO stage**	**N criteria**
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N0(i+)		Isolated tumor cells in regional lymph node(s) no greater than 0.2 mm
N1	IIIC1	Regional lymph node metastasis to pelvic lymph node
N1mi	IIIC1	Regional lymph node metastasis (greater than 0.2 mm but not greater than 2.0 mm in diameter) to pelvic lymph nodes
N1a	IIIC1	Regional lymph node metastasis (greater than 2.0 mm in diameter) to pelvic lymph nodes
N2	IIIC2	Regional lymph node metastasis to Para-aortic lymph nodes, with or without positive pelvic lymph nodes
N2mi	IIIC2	Regional lymph node metastasis (greater than 0.2 mm but not greater than 2.0 mm in diameter) to Para-aortic lymph nodes, with or without positive pelvic lymph nodes
N2a	IIIC2	Regional lymph node metastasis (greater than 2.0 mm in diameter) to Para-aortic lymph nodes, with or without positive pelvic lymph nodes
Suffix (sn) is added to the N category when metastasis is identified only by sentinel lymph node biopsy		

Distant metastasis (M)			
M category	**FIGO stage**	**M criteria**	
M0		No distant metastasis	
M1	IVB	Distant metastasis (including metastasis to inguinal lymph nodes, intraperitoneal disease, lung, liver, or bone) (it excludes metastasis to pelvic or Para-aortic lymph nodes, vagina, uterine serosa, or adnexa)	
Prognostic state groups			
When T is…	**And N is…**	**And M is…**	**Then the stage group is…**
T1	N0	M0	I
T1a	N0	M0	IA
T1b	N0	M0	IB
T2	N0	M0	II
T3	N0	M0	III
T3a	N0	M0	IIIA
T3b	N0	M0	IIIB
T1-T3	N1/N1mi/N1a	M0	IIIC1
T1-T3	N2/N2mi/N2a	M0	IIIC2
T4	Any N	M0	IVA
Any T	Any N	M1	IVB
Histologic grade (G)			
G	**G definition**		
GX	Grade cannot be assessed		
G1	Well differentiated		
G2	Moderately differentiated		
G3	Poorly differentiated or undifferentiated		
Histopathology: Degree of differentiation			
Cases or carcinoma of the corpus uteri should be grouped according to the degree of differentiation of the endometrioid adenocarcinoma			
G	**G definition**		
G1	5% or less of nonsquamous or nonmorular solid growth pattern		
G2	6–50% of a nonsquamous or nonmorular solid growth pattern		
G3	More than 50% of a nonsquamous or nonmorular solid growth pattern. Papillary serous, clear cell, and carcinosarcoma are considered high grade		

NOTES on pathologic grading

1. Notable nuclear atypia exceeding that which is routinely expected for the architectural grade increases the tumor grade by 1 (i.e., 1 to 2 and 2 to 3)
2. Serous, clear cell, and mixed mesodermal tumors are *high risk* and considered grade 3

Adenocarcinomas with benign squamous elements (squamous metaplasia) are graded according to the nuclear grade of the glandular component

Used with permission of the American College of Surgeons, Chicago, Illinois. The original course for this information is the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing

[a]Endometrial intraepithelial carcinoma (EIC) should be considered a T1 cancer

27.3 Patient Selection

Adjuvant setting (after hysterectomy/BSO) : FIGO stage I–II

- Surgical pathology must be fully assessed to determine recommendations for adjuvant radiotherapy.
- For patients with FIGO stage I endometrioid cancer, three risk factors are considered: high grade (grade 2–3), deep (>66%) myometrial invasion, and LVSI. Adjuvant treatment is recommended for patients with age <50 years with all three risk factors; 50–70 years with two risk factors; and 70 years and older with any one risk factor. These risk factors for recurrence were initially described in GOG 99 [9].
- Low-risk patients, who do not meet the above criteria, need only close surveillance.
- Patients meeting the above "high-intermediate"-risk criteria are recommended to receive adjuvant EBRT or VBT.
- Many of these patients are candidates for VBT alone; however, some patients have substantial risk of occult nodal involvement (i.e., G3 disease with deep myometrial invasion, extensive LVSI) warranting EBRT to target the at-risk nodal basins in addition to the vaginal cuff.
- Occasionally, a patient may have risk factors that warrant EBRT but have additional risk factors for recurrence at the vaginal cuff (positive surgical margins, FIGO stage II – cervical stromal invasion), and a VBT boost is administered.
- Initiate brachytherapy after the vaginal cuff is healed, usually at least 4–6 weeks postsurgery (within 12 weeks postoperatively).
- Brachytherapy dose depends on whether EBRT is indicated.

FIGO stage IIIC1/2

- Patients with lymph node involvement will typically receive 6 cycles of chemotherapy and pelvic EBRT. EBRT will generally occur between cycles 3 and 4 of chemotherapy ("sandwich") or after completion of chemotherapy. VBT boost may be warranted if there are additional risk factors for vaginal cuff recurrence.

Definitive radiotherapy in patients who are not surgical candidates:

- Patients with early stage but medically inoperable disease are treated with EBRT and/or intracavitary brachytherapy or hormone therapy.
- Patients with unresectable disease (e.g., invasion of the vagina, bladder, rectum) or extrauterine pelvic disease are candidates for EBRT + brachytherapy ± chemotherapy, chemoradiotherapy followed by surgical resection, neoadjuvant chemotherapy, or chemotherapy alone.

Recurrent disease:

- Patients with recurrent disease should only be considered for surgery if gross tumor resection can be achieved [4, 6]. RT with curative intent is indicated in

patients with isolated pelvic relapse after surgery alone for initial disease (no prior RT) [8].

- Brachytherapy technique for vaginal cuff recurrence (intracavitary vs. interstitial) is based on the depth of vaginal wall invasion and the distribution of the disease. In cases of superficial (<5 mm) recurrences, VBT may be selected. For lesions invading ≥5 mm, VBT provides inadequate dose at depth compared with interstitial techniques [10–13]. For recurrences in the pelvic lymph nodes or pelvic sidewall not amenable for brachytherapy, EBRT is given with a boost to the region of gross involvement. SBRT can be considered for low volume recurrences.

27.4 Treatment Planning

Vaginal brachytherapy:

Timing	Brachytherapy should be started within 12 weeks after surgery. We recommend once weekly intracavitary brachytherapy if administered during EBRT. VBT can be administered twice weekly as a monotherapy or after EBRT completion
Analgesia	Consider premedication with anxiolytics, pain medication, or mild sedation [11]. However, these are often not necessary with VBT
Position	Dorsal lithotomy position
Pelvic exam	Perform a visual inspection and manual examination with care to ensure that the vaginal cuff is well healed and that there is no recurrence at the vaginal apex or vaginal cuff dehiscence. In a subset of patients, the placement of a vaginal applicator may be difficult (postoperative changes, pain, etc.)
Preparation and procedure	• Placement of a radiopaque marker at the vaginal cuff can assist in verifying that the applicator is in contact with the vaginal mucosa. Typically three markers are placed – One at the apex and two laterally • A vaginal cylinder is commonly used for postoperative VBT. The choice of applicator depends on patient's anatomy and physician's experience. In many patients, the postoperative vagina is cylindrical, and it can be treated adequately with a properly sized vaginal cylinder. In some situations, ovoids may provide better dosimetry due to the remnants of the vaginal fornices. The applicator should be lubricated prior to placement. After placement of the applicator, a visual check is done to verify that the applicator is midline and not tilted laterally, anteriorly, or posteriorly • The treatment target is the submucosal lymphatics of the vagina, and in most situations only the proximal vagina must be targeted [11, 14–16]. The proximal vagina is limited to the upper 1/3–1/2 of the vagina (upper 3–5 cm of the vagina) [11, 15]. Increased treatment length can result in increased toxicity • To allow an optimal dose distribution, the vaginal mucosa needs to be in contact with the applicator surface (no air pockets). The ABS recommends use of the largest diameter cylinder that can comfortably fit into the apex of the vagina [6, 11] to reduce mucosal dose

Treatment planning	Treatment planning can be 2D (x-ray) and/or 3D (CT, MRI) based. For treatment planning optimization, points should be placed around both the apex and the lateral aspects of the applicator [11, 15]
Documentation	Documentation of brachytherapy is essential and should include the type of isotope and source; description of the target (including size and shape); prescription depth, target dose, dose per fraction, and the fractionation plan; the applicator type and size, and the treatment plan documentation (dose distribution to dose the target and OAR)

Intact uterus:

Timing	Brachytherapy should be started as soon as possible. We recommend once weekly intracavitary brachytherapy if administered during EBRT. Brachytherapy can be administered twice weekly as a monotherapy or after EBRT completion
Analgesia	Analgesia options include general, spinal, intravenous sedation and/or oral pain medication. Our practice is to use titrated doses of fentanyl, starting with 50 micrograms IV, and lorazepam with 1 mg IV, 20–30 min prior to start of the procedure
Position	Dorsal lithotomy position
Pelvic exam	Examination under anesthesia – a bimanual examination to document any residual nodularity, the cervix size and, the size of the vaginal fornices (i.e., disease extension/response to treatment). The uterus is sounded to aid in selection of the appropriate tandem applicator. Insertion of radiopaque markers in the cervix aids localization of the cervix on imaging. We generally avoid inserting the seed at 3, 6, 9, and 12 o'clock position on the cervical os so that the seeds are not masked by the applicator on AP and lateral orthogonal images
Procedure	• A Foley catheter is inserted into the bladder, and the balloon is inflated with dilute contrast • Tandem and ovoids are commonly used for brachytherapy in this setting. Other applicators include tandem and ring applicator. Simon-Heyman capsules can be used to further distribute dose to the uterus • After selection of appropriate applicators (including angle of the intrauterine tandem and size of ring or ovoids), cervical os is dilated to enable accommodation of Simon-Heyman capsules (if used). Ultrasound guidance can be used during applicator insertion to help guide dilation of the endocervical canal and evaluate placement of the uterine applicators. A tenaculum may be placed on the cervix to provide countertraction for placement of the intrauterine tandem. A ring or ovoids can be used if lateral cervical dosing is needed • It is important that the tandem extends to the uterine fundus to ensure that the entire endometrial lining is treated • Radiopaque vaginal packing is used to displace the bladder base anteriorly and the anterior rectal wall posteriorly away from the intracavitary applicator. Packing also serves to prevent the displacement of the tandem from the uterus and to secure the positioning of the entire applicator • We do not routinely use a smit sleeve, but they can be useful for anatomically difficult implants • Imaging (CT, MRI, plain radiographs) is done for each implant immediately following the placement of the applicator and is essential for treatment planning of each procedure • 3D imaging allows for accurate contouring of the tumor, cervix, uterus, and OAR

Treatment planning	Treatment planning can be 2D (X-ray) and/or 3D (CT, MRI) based. Brachytherapy is prescribed to the uterine serosa
Documentation	Documentation of brachytherapy is essential and should include the type of isotope and source; description of the target (including size and shape), target dose, dose per fraction, and the fractionation plan; the applicator type and size and the treatment plan documentation (dose distribution to dose the target and OAR)

27.5 Common Dose/Fractionation Scheme

Vaginal brachytherapy alone:

- At UNC, VBT is typically prescribed to a dose of 7 Gy at 0.5 cm depth × 3 fractions for VBT alone after hysterectomy. The goal is to achieve an LDR equivalent of 30 Gy at 0.5 cm depth and 65 Gy at the surface.

Common vaginal brachytherapy doses [11, 15]

Dose and fractionation	Prescription depth
7 Gy × 3	0.5 cm depth
4 Gy × 6	Vaginal surface
6 Gy × 5	Vaginal surface
5.5 Gy × 4	0.5 cm depth

EBRT followed by vaginal brachytherapy:

- If EBRT is given, the total dose is 45–50.4 Gy. Midline block (at ~40 Gy) can be used [11].
- Involved unresected lymph nodes can be boosted during EBRT with 1.8 Gy daily fractions for a total of 59.4 Gy [11].
- At UNC, VBT is typically prescribed to a dose of 5 Gy to the vaginal surface x 3 fractions when administered in conjunction with EBRT.

Common vaginal brachytherapy doses (combined with EBRT, 1.8 Gy × 25–33 fx) [6, 12]

Dose and fractionation	Prescription depth
5 Gy × 3	Vaginal surface or 0.5 cm depth
6 Gy × 2	Vaginal surface or 0.5 cm depth
6 Gy × 3	Vaginal surface

RT for inoperable patients:

Inoperable patients with stage I grade 1–2 endometrial cancer with minimal myometrial invasion can be treated with brachytherapy alone. All other patients should receive EBRT in conjunction with brachytherapy. The CTV encompassing

the whole uterus extending to the serosal surface should receive an EQD2 of at least 48 Gy for tandem/ovoids (intracavitary brachytherapy alone) and at least 65 Gy for combination of EBRT plus VBT. A GTV may also be defined using T2-weighted MRI and may be prescribed a dose of ≥80 Gy [5].

Common brachytherapy doses (without EBRT) for inoperable endometrial cancer [5]

Fractionation prescribed to uterine serosa	EQD2(Gy) to the tumor (point A with $\alpha/\beta = 10$ Gy)
6 Gy × 6	48
6.4 Gy × 6	52.5
7.3 Gy × 5	52.6
8.5 Gy × 4	52.4

Common brachytherapy doses (combined with EBRT, 1.8 Gy × 25 fx) [5].

Fractionation prescribed to uterine serosa	EQD2(Gy) to the tumor (point A with $\alpha/\beta = 10$ Gy)
6.5 Gy × 3	71.1
5.2 Gy × 4	70.6
5 Gy × 5	75

27.6 Normal Tissue Tolerance

- EBRT + VBT:
  - Upper vagina mucosa 150 Gy, mid-vagina mucosa 80–90 Gy, lower vagina mucosa 60–70 Gy. *NOTE: the proximal vagina is a target in VBT
  - Small bowel <45–50.5 Gy
  - Rectal point dose <70 Gy
  - Bladder <75 Gy

Dose constraints to organs at risk for brachytherapy

Organ at risk	Radiographic (ICRU point)	3D imaging (D2cc)
Bladder	5× < 3.7 Gy	<90 Gy[a]
Rectum	5× < 3.7 Gy	<70–75 Gy[a]
Sigmoid	–	<70–75 Gy[a]
Ureters	–	<70 Gy

[a]Max point dose defined as <0.035 cc

27.7 Patient Management Considerations

- After completion of treatment, patients should be given a vaginal dilator to prevent scar tissue and adhesions within the vagina. Patients are instructed to place the dilator within the vagina for 10–15 min several times per week.

Acute toxicity

Due to the conformal dosimetry of vaginal cuff brachytherapy, toxicity to bowel, bladder, and rectum are low. There are generally minimal acute toxicities during treatment with vaginal cuff brachytherapy alone.

Late toxicity

Late toxicity is also rare with vaginal cuff brachytherapy alone. The most common side effect is stenosis and atrophy of the vagina, which can result in vaginal shortening or narrowing. Incidences of severe bowel, rectum, and bladder toxicity have been reported including rectovaginal fistula, radiation colitis or cystitis, and vaginal or bladder necrosis, but these reports are rare and appear to be more common when VBT is administered with EBRT.

27.8 Follow-Up

- H&P including pelvic exam should be completed every 3–6 months for the first 2–3 years, then every 6 months for 5 years, and then annually.
- Ca-125 is optional, useful for follow-up if preoperative level was elevated.
- Imaging only if clinically indicated and/or if extrauterine spread was present at initial surgery.

27.9 Relevant Literature

PORTEC-1 and GOG-99, which established the role of postoperative EBRT (conventional fractionation), are outside the scope of this chapter.

Postoperative vaginal brachytherapy vs. vaginal brachytherapy + EBRT				
Randomized control trials				
Study	**Arm 1: VBT alone**	**Arm 2: VBT + EBRT**	**Median follow-up**	**Outcomes**
Onsrud (2013) [17] Stage I	(n = 280) 60 Gy LDR	(n = 288) 60 Gy LDR + 40 Gy EBRT	20.5 years	Median OS 20.48 years (VBT) vs. 20.5 years (EBRT+VBT) (p = 0.186)

Aalders (1980) [18] Stage I	(n = 277) 60 Gy LDR	(n = 263) 60 Gy LDR + 40 Gy EBRT	3–10 years	5-year OS 91% (VBT) vs. 89% (EBRT+VBT) (p = NS) Vaginal/pelvic recurrences 6.9% (VBT) vs. 1.9% (EBRT+VBT) ($p < 0.01$) Grade 3+ toxicity 0.7% (VBT) vs. 1.1% (EBRT+VBT)
Sorbe (2012) [19] Stage I	(n = 263) 3 Gy × 6 fx (HDR) 5.9 Gy × 3 fx (HDR) , or 20 Gy (LDR)	(n = 285) VBT + 46 Gy EBRT	62 months	5-year OS 90% (VBT) vs. 89% (EBRT+VBT) (p = NS) Pelvic recurrences 5.3% (VBT) vs. 0.4% (EBRT+VBT) ($p < 0.001$) Vaginal recurrences 2.7% (VBT) vs. 1.9% (EBRT +VBT) ($p = 0.55$) Grade 3 toxicity 0.8% (VBT) vs. 1.9% (EBRT+VBT)
Postoperative vaginal brachytherapy vs. EBRT				
Randomized control trial				
Study	**Arm 1: VBT**	**Arm 2: EBRT**	**Median follow-up**	**Outcomes**
Nout (2010) [20] (PORTEC-2) Stage I–II	(n = 213) 7 Gy × 3 fx at 0.5 cm (HDR) or 30 Gy at 0.5 cm (LDR)	(n = 214) 46 Gy EBRT	45 months	5-year OS 84.8% (VBT) vs. 79.6% (EBRT) (p = NS) Pelvic recurrences 3.8% (VBT) vs. 0.5% (EBRT) ($p = 0.02$) Vaginal recurrences 1.8% (VBT) vs. 1.6% (EBRT) (p = NS) Grade 3 toxicity <1% (VBT) vs. 3% (EBRT)

Selected studies of postoperative HDR-VBT alone

Study	Patients	Treatments	Median follow-up	Outcomes
Prospective				
Sorbe (1990) [21] Stage I	404	5.0 Gy × 6 fx 4.5 Gy × 6 fx 6.0 Gy × 5 fx 9.0 Gy × 4 fx	NA	5-year OS 92% Pelvic/vaginal recurrences 1.7% Vaginal recurrences 0.7% Acute toxicity 30.9%, late toxicity 15.8% The high-dose group 9 Gy × 4 had a higher rate and grade of late complications
Retrospective				
Weiss (1998) [22] Stage IA–II	122	7.0 Gy × 3 fx	25.6 months	Pelvic recurrence 4.1% Vaginal recurrence 1.6% Recurrence occurred in 3.8% of patients with moderate risk and in 20.5% of patients with high risk No grade 3–4 toxicity
Petereit (1999) [23] Stage IB	191	16.2 Gy × 2 fx prescribed to surface	38 months	4-year OS 95% Pelvic recurrence 0.5% Vaginal recurrence 0% 0.5% developed colo-vaginal fistula 4% asymptomatic vaginal cuff necrosis
Horowitz (2002) [24] Stage IB–II	164	7 Gy × 3 fx at 0.5 cm	65 months	5-year OS 87% Pelvic recurrence 0.6% Vaginal recurrence 1.2% No grade 3–4 toxicity
Alektiar (2005) [16] Stage IB–IIB	382	6.0–7.0 Gy × 3 fx	48 months	5-year OS 93% Pelvic recurrence 3% Vaginal recurrence 0.8% No grade 3–4 toxicity
Diavolitsis (2012) [25] Stage IA	169	7.0 Gy × 3 fx 5.5 Gy × 4 fx at 0.5 cm	103 months	5-year OS 95.5% 5-year RFS 94.4% Pelvic recurrence 0.5% Vaginal recurrence 0.5% No grade 3–4 toxicity

Selected studies of postoperative pelvic EBRT and HDR-VBT

Study	Patients	Treatments	Median follow-up	Outcomes
Retrospective				
Lybeert (1989) [26] Stage I–IV	291	40 Gy EBRT + 5Gy × 4 fx at 0.5 cm HDR	NA	5-year RFS Stage I:88% Stage II:68% Stage III/IV:50% Pelvic recurrence 2.7% Vaginal recurrence 2.7% No grade 3–4 toxicity
Nori (1994) [27] Stage I	300	40 Gy EBRT + 7Gy × 3 fx at 0.5 cm HDR	12 years	PFS 96.6% Pelvic recurrence 0.3% Vaginal recurrence 2% No grade 3–4 toxicity
Algan (1996) [28] Stage I/II	81	45 Gy EBRT + 4 Gy × 3 fx at 0.5 cm HDR Or 30 Gy LDR to surface	NA	5-year OS 83% Pelvic recurrence 3% Vaginal recurrence 4% Grade 3 toxicity 3%
Cannon (2009) [29] Stage II	50	45–51 Gy EBRT + more than 4 different fractionations for HDR (most common 5 Gy × 5 fx or 7.8 Gy × 2 fx)	5.2 years	5-yearr OS 82% 5-year DFS 82% Pelvic recurrence 4% Vaginal recurrence 0% Grade 3 toxicity 2%, grade 4 toxicity 2%

References

1. Creasman WT, Morrow CP, Bundy BN, Homesley HD, Graham JE, Heller PB. Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group Study. Cancer. 1987;60:2035–41.
2. Schink JC, Rademaker AW, Miller DS, Lurain JR. Tumor size in endometrial cancer. Cancer. 1991;67(11):2791–4.
3. Cohn DE, Horowitz NS, Mutch DG, Kim SM, Manolitsas T, Fowler JM. Should the presence of lymphovascular space involvement be used to assign patients to adjuvant therapy following hysterectomy for unstaged endometrial cancer? Gynecol Oncol. 2002;87(3):243–6.

4. Kong A, Johnson N, Kitchener HC, Lawrie TA. Adjuvant radiotherapy for stage I endometrial cancer: an updated cochrane systematic review and meta-analysis. J Natl Cancer Inst. 2012;104(21):1625–34. https://doi.org/10.1093/jnci/djs374.
5. Schwarz JK, Beriwal S, Esthappan J, et al. Consensus statement for brachytherapy for the treatment of medically inoperable endometrial cancer. Brachytherapy. 2015;14:587–99. https://doi.org/10.1016/j.brachy.2015.06.002.
6. Colombo N, Creutzberg C, Amant F, et al. ESMO-ESGO-ESTRO consensus conference on endometrial cancer: diagnosis, treatment and follow-up. Int J Gynecol Cancer. 2016;26:2–30. https://doi.org/10.1097/IGC.0000000000000609.
7. Higginson DS, Morris DE, Jones EL, Clarke-Pearson D, Varia MA. Stereotactic body radiotherapy (SBRT): technological innovation and application in gynecologic oncology. Gynecol Oncol. 2011;120:404–12. https://doi.org/10.1016/j.ygyno.2010.11.042.
8. Kunos CA, Brindle J, Waggoner S, et al. Phase II clinical trial of robotic stereotactic body radiosurgery for metastatic gynecologic malignancies. Front Oncol. 2012;2:181. https://doi.org/10.3389/fonc.2012.00181.
9. Keys HM, Roberts JA, Brunetto VL, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. Gynecol Oncol. 2004;92:744–51. https://doi.org/10.1016/j.ygyno.2003.11.048.
10. Baek S, Isohashi F, Yamaguchi H, et al. Salvage high-dose-rate brachytherapy for isolated vaginal recurrence of endometrial cancer. Brachytherapy. 2016;15(6):812–6. https://doi.org/10.1016/j.brachy.2016.08.005.
11. Small W, Beriwal S, Demanes DJ, et al. American Brachytherapy Society consensus guidelines for adjuvant vaginal cuff brachytherapy after hysterectomy. Brachytherapy. 2012;11(1):58–67. https://doi.org/10.1016/j.brachy.2011.08.005.
12. Jhingran A, Burke TW, Eifel PJ. Definitive radiotherapy for patients with isolated vaginal recurrence of endometrial carcinoma after hysterectomy. Int J Radiat Oncol Biol Phys. 2003;56(5):1366–72.
13. Lin LL, Grigsby PW, Powell MA, Mutch DG. Definitive radiotherapy in the management of isolated vaginal recurrences of endometrial cancer. Int J Radiat Oncol. 2005;63(2):500–4. https://doi.org/10.1016/j.ijrobp.2005.02.004.
14. Wahl AO, Gaffney DK, Jhingran A, et al. ACR appropriateness criteria® adjuvant management of early-stage endometrial cancer. Oncology (Williston Park). 2016;30(9):816–22.
15. Harkenrider MM, Grover S, Erickson BA, et al. Vaginal brachytherapy for postoperative endometrial cancer: 2014 Survey of the American Brachytherapy Society. Brachytherapy. 2016;15:23–9. https://doi.org/10.1016/j.brachy.2015.09.012.
16. Alektiar KM, Venkatraman E, Chi DS, Barakat RR. Intravaginal brachytherapy alone for intermediate-risk endometrial cancer. Int J Radiat Oncol Biol Phys. 2005;62:111–7. https://doi.org/10.1016/j.ijrobp.2004.09.054.
17. Onsrud M, Cvancarova M, Hellebust TP, Tropé CG, Kristensen GB, Lindemann K. Long-term outcomes after pelvic radiation for early-stage endometrial cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2013;31(31):3951–6. https://doi.org/10.1200/JCO.2013.48.8023.
18. Aalders J, Abeler V, Kolstad P, Onsrud M. Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma: clinical and histopathologic study of 540 patients. Obstet Gynecol. 1980;56(4):419–27.
19. Sorbe B, Horvath G, Andersson H, Boman K, Lundgren C, Pettersson B. External pelvic and vaginal irradiation versus vaginal irradiation alone as postoperative therapy in medium-risk endometrial carcinoma--a prospective randomized study. Int J Radiat Oncol Biol Phys. 2012;82(3):1249–55. https://doi.org/10.1016/j.ijrobp.2011.04.014.
20. Nout RA, Smit VT, Putter H, et al. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. Lancet. 2010;375:816–23. https://doi.org/10.1016/S0140-6736(09)62163-2.

21. Sorbe BG, Smeds AC. Postoperative vaginal irradiation with high dose rate afterloading technique in endometrial carcinoma stage I. Int J Radiat Oncol Biol Phys. 1990;18(2):305–14.
22. Weiss E, Hirnle P, Arnold-Bofinger H, Hess CF, Bamberg M. Adjuvant vaginal high-dose-rate afterloading alone in endometrial carcinoma: patterns of relapse and side effects following low-dose therapy. Gynecol Oncol. 1998;71(1):72–6. https://doi.org/10.1006/gyno.1998.5155.
23. Petereit DG, Tannehill SP, Grosen EA, Hartenbach EM, Schink JC. Outpatient vaginal cuff brachytherapy for endometrial cancer. Int J Gynecol Cancer. 1999;9(6):456–62.
24. Horowitz NS, Peters WA, Smith MR, Drescher CW, Atwood M, Mate TP. Adjuvant high dose rate vaginal brachytherapy as treatment of stage I and II endometrial carcinoma. Obstet Gynecol. 2002;99(2):235–40.
25. Diavolitsis V, Rademaker A, Lurain J, Hoekstra A, Strauss J, Small W. Clinical outcomes in international federation of gynecology and obstetrics stage IA endometrial cancer with myometrial invasion treated with or without postoperative vaginal brachytherapy. Int J Radiat Oncol Biol Phys. 2012;84(2):415–9. https://doi.org/10.1016/j.ijrobp.2011.12.010.
26. Lybeert ML, van Putten WL, Ribot JG, Crommelin MA. Endometrial carcinoma: high dose-rate brachytherapy in combination with external irradiation; a multivariate analysis of relapses. Radiother Oncol. 1989;16(4):245–52.
27. Nori D, Merimsky O, Batata M, Caputo T. Postoperative high dose-rate intravaginal brachytherapy combined with external irradiation for early stage endometrial cancer: a long-term follow-up. Int J Radiat Oncol Biol Phys. 1994;30(4):831–7.
28. Algan O, Tabesh T, Hanlon A, Hogan WM, Boente M, Lanciano RM. Improved outcome in patients treated with postoperative radiation therapy for pathologic stage I/II endometrial cancer. Int J Radiat Oncol Biol Phys. 1996;35(5):925–33.
29. Cannon GM, Geye H, Terakedis BE, et al. Outcomes following surgery and adjuvant radiation in stage II endometrial adenocarcinoma. Gynecol Oncol. 2009;113(2):176–80. https://doi.org/10.1016/j.ygyno.2008.12.029.