

## Consensus statement for brachytherapy for the treatment of medically inoperable endometrial cancer

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### ABSTRACT

**PURPOSE:** The purpose of this consensus statement from the American Brachytherapy Society (ABS) is to summarize recent advances and to generate general guidelines for the management of medically inoperable endometrial cancer patients with radiation therapy.

**METHODS:** Recent advances in the literature were summarized and reviewed by a panel of experts. Panel members participated in a series of conference calls and were surveyed to determine their current practices and patterns. This document was reviewed and approved by the full panel, the ABS Board of Directors and the ACR Commission on Radiation Oncology.

**RESULTS:** A transition from two-dimensional (2D) to three-dimensional (3D) treatment planning for the definitive treatment of medically inoperable endometrial cancer is described. Magnetic resonance (MR) imaging can be used to define the gross tumor volume (GTV), clinical target volume (CTV), and the organs at risk (OARs). Brachytherapy alone can be used for medically inoperable endometrial cancer patients with clinical Stage I cancer with no lymph node involvement and no evidence of deep invasion of the myometrium on MR imaging. In the absence of MR imaging, a combined approach using external beam and brachytherapy may be considered.

**CONCLUSIONS:** Recent advances support the use of MR imaging and 3D planning for brachytherapy treatment for medically inoperable endometrial cancer. © 2015 American Brachytherapy Society. Published by Elsevier Inc. All rights reserved.

**Keywords:** Endometrial carcinoma; Magnetic resonance imaging; Brachytherapy

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### Introduction

Carcinoma of the endometrium is the most common gynecologic malignancy in the Western world, but unlike other cancers in women, the incidence and mortality rates for endometrial cancer continue to rise (1). The American Cancer society estimates that there will be 52,630 new diagnoses and 8590 deaths from this disease in 2014 (2). The standard of care for newly diagnosed endometrial cancer is surgery, which includes total abdominal hysterectomy with bilateral salpingo-oophorectomy with or without

Table 1

Results of low-dose–rate brachytherapy alone and in combination with external beam radiotherapy for the treatment of medically inoperable endometrial cancer

Author	Year	Stage	No. of patients	Type radiation	LC %	DFS/DSS %	Late complications (%)	DICD (%)
Fishman (1996)	1975–1992	I	39	LDR		80.0	0	83.3
		II	15	LDR ± EBRT		85.0		
Chao (1996)	1965–1990	I	101	LDR ± EBRT	90	84.0 <sup>a</sup>	5.0	62.0
Kupelian (1993)	1960–1986	I	120	LDR ± EBRT	84	87.0	4.5 <sup>b</sup>	
		II	17		87	88.0		
Rouanet (1993)	1967–1986	III–IV	15		68	49.0		
		I	108	EBRT + LDR	77.8	63.9	3.3	16.2
		II	11		72.7	63.6		
III	59		73.0	57.2				
Lehoczy (1991)	1976–1981	I	171	LDR	79.5	74.8	0	22.0
Taghian (1988)	1975–1984	I	79	EBRT + LDR	87.6	72.2	17.3	
		II	15					
Grigsby (1987)	1960–1983	III–IV	10					
		I	69	LDR ± EBRT	87	88.1	16.3	36.2
Varia (1987)	1969–1980	I	41	LDR ± EBRT	65.9	57.0	9.6	26.0
		II	32		53.1	26.0		
		III–IV						
Wang (1987)	1960–1979	I	35	LDR ± EBRT	78.0	76.0	5.0	54.0
		II	6					
Jones (1986)	1965–1970	I	123	LDR	77	64.5	0	
		II	23		79	39.7		
		III	14		22	14.2		
Patanaphan (1985)	1962–1977	I	32	LDR ± EBRT	87.5	72	2.0	
		II	10		80.0	40		
		III–IV	10		40.0	20		
Andersen (1983)	1950–1979	I	61	LDR ± EBRT	69.2	64.4 <sup>a</sup>	3.4	51.0
		II	42			42.3 <sup>a</sup>		
		III–IV	14			12.9 <sup>a</sup>		
Rustowski (1982)	1952–1971	I	196	LDR ± EBRT		51.5 <sup>a</sup>		
		II	74			50.0 <sup>a</sup>		
		III	218			37.1 <sup>a</sup>		
Abayomi (1982)	1968–1977	I–II	50	EBRT + LDR	92	78.0 <sup>a</sup>	15.2	
		III–IV	16		50	37.0 <sup>a</sup> (3 years)		
Fayos (1980)	1955–1974	I	56	LDR ± EBRT	95.0	65.0 <sup>a</sup>	4.0	
Landgren (1976)	1948–1969	I	86	LDR ± EBRT	87	68.0 <sup>a</sup>	7.3	45

PC/UC = 5-year estimate of pelvic control/uterine control (except as noted); DFS/DSS = 5-year disease-free survival estimate (except as noted); DICD = death from intercurrent illness.

Note. Results from the literature previously reported and reproduced with permission from Nguyen and Petereit (30).

<sup>a</sup> Survival estimate.

<sup>b</sup> Actuarial data.

evaluation of pelvic and para-aortic lymph nodes. External beam radiotherapy, brachytherapy, and/or chemotherapy are added in the adjuvant setting based on individual risk factors to reduce the risk of recurrence and to prevent the development of distant metastatic disease.

Although the standard of care for endometrial cancer is upfront surgery, a fraction of newly diagnosed patients are unable to undergo surgery because of medical comorbidities and/or tumor-related factors that preclude surgery. In this setting, radiation therapy can be used for definitive management of early stage disease, for preoperative treatment for locally advanced disease, or for the palliation of symptoms, such as bleeding or pain associated with the primary tumor. Historically, low-dose–rate (LDR) brachytherapy was used alone or combined with external beam radiotherapy for the treatment of medically inoperable endometrial cancer

(Table 1) (3). More recently, high-dose–rate (HDR) techniques have been used in combination with external beam radiotherapy and alone in appropriately selected patients with excellent results (Table 2) (4). Recent advances in imaging and radiation therapy technology have allowed for a more precise definition of tumor targets and the potential for increased accuracy of dose delivery. The purpose of this consensus statement from the American Brachytherapy Society is to summarize recent advances and to generate general guidelines for the management of medically inoperable endometrial cancer patients with radiation therapy. Panel members participated in a series of conference calls and were surveyed to determine their current practices and patterns. This document was reviewed and approved by the full panel, the ABS Board of Directors, and the ACR Commission on Radiation Oncology.

Table 2

Results of high-dose–rate brachytherapy alone and in combination with external beam radiotherapy for the treatment of medically inoperable endometrial cancer

Author	Year	Stage	No. of patients	Type radiation	PC/UC %	DFS/DSS %	Late complications (%)	DID (%)
Wegner (2010)	1997–2008	I	19	HDR ± EBRT	75%	73 (3 yrs)	8	NR
		II	5					
		III	2					
Inciura (2010)	1995–1998	I	14	HDR ± EBRT	72%	73	0	48
		II	9					
		III	6					
Coon (2008)	1997–2007	I	42	HDR ± EBRT	93%	87	0	30
		II	5					
		III	2					
Niazi (2005)	1984–2003	I	29	HDR ± EBRT	71%	90	8	37
		II	9					
Nguyen (1998)	1989–1997	I	36	HDR	88.0 (3 years)	85.0 (3 years)	14.7 <sup>a</sup> (3 years)	53.3
Kucera (1998)	1981–1992	I	228	HDR	82.5	85.4	4.6	NR
Knocke (1997)	1981–1992	I–II	272	HDR	75.4	76.6	5.2 <sup>a</sup>	37.1
		IA	116					
		IB	119					
		II	37					
Nguyen (1995)	1984–1992	I–II	27	HDR ± EBRT	85.0	76.0	11.0	
		I	20					
		II	7					
Rotte (1990)	1972–1988	I–III	227	HDR		74.0		
		I	103					
		II	109					
		III	15					
Sorbe (1989)	1977–1986	I	91	HDR	88.0	72.4	6.6 <sup>b</sup>	

DFS/DSS = 5-year disease-free survival estimate (except as noted); DICD = death from intercurrent illness; PC/UC = 5-year estimate of pelvic control/uterine control (except as noted); late complications = Grade 3 or greater reported at the time of the original publication was completed except as noted.

Note. Results from the literature from 1998 forward have been added to summary tables previously reported and reproduced with permission from Nguyen and Peterit (30).

<sup>a</sup> Actuarial data.

<sup>b</sup> Late complications Grade 3 or greater in this series of patients are combined with results from patients who received radiation followed by hysterectomy. Late complication rate is reported for the entire series and is related to dose per fraction, 0% in the group of patients who were treated with 7 Gy or less per fraction and 15% in the group of patients who were treated with 12 Gy per fraction.

### Patient characteristics

Medically inoperable patients are defined as patients whose medical comorbidities preclude primary surgery after assessment by their gynecologic oncologists and other qualified health professionals. This status is determined based on an assessment of operative and perioperative risks associated with the operative intervention, which would be hysterectomy plus or minus surgical staging. The reasons for classification as medically inoperable can be medical comorbidities such as cardiovascular disorders, pulmonary disease, cerebrovascular accidents, venothromboembolic disease, renal disease, or other more rare conditions, including Marfan syndrome, hemophilia, other malignancies, or age. Increasingly, patients are deemed to be medically inoperable because of morbid obesity. This designation may relate to the surgeons' experience in operating on such patients and may be a relative contraindication rather than a strict contraindication. It is worthwhile to evaluate patients for surgery in a tertiary care setting where significant support is available for high-risk patients. Performance status is also a key factor in determining a patient's suitability for anesthesia.

All patients considered medically inoperable should be evaluated by a high-risk anesthesia team. Options such as the use of regional, rather than general, anesthesia may be used in concert with light i.v. sedation to help secure adequate pain control in appropriately selected patients. These same anesthesia concerns may also limit the feasibility of brachytherapy. Use of a paracervical block along with light i.v. or oral sedation may be needed for patients to be able to undergo brachytherapy, even when they are considered medically inoperable.

In some patients where surgery is not feasible because of risk secondary to comorbid conditions, the use of progestin therapy may be considered to treat early stage well-differentiated endometrioid endometrial cancer (5–8). Much of the data for treatment of endometrial cancer by progestin therapy is extrapolated from studies in younger women (age <40 years) desiring fertility preservation. One prospective study cites regression in 55% of patients with presumed early stage disease (9). In addition to oral progestins, levonorgestrel-releasing intrauterine devices (LNG-IUDs) have been used as part of a fertility-sparing regimen for both precancerous and Grade 1 endometrial

adenocarcinoma (10, 11). Their use may also be considered in selected cases of inoperable endometrial cancer patients. The endometrial drug concentration has been found to be 100 times higher compared with that found in the endometrial lining after oral progestin therapy (12). Use of LNG-IUD and oral micronized progesterone may be associated with slightly less risk of venous thromboembolic events than medroxyprogesterone acetate or megestrol acetate. In the morbidly obese patient, a combination of LNG-IUD and lower dose oral progestin combined may provide a temporizing bridge until weight loss interventions can be pursued and surgery ultimately considered. In patients who have significant comorbid conditions who otherwise meet the above criteria, hormonal manipulation may be considered as a therapeutic option if surgery or radiation is considered unsafe.

When using hormonal therapy, imaging (computer tomography [CT] or preferably magnetic resonance imaging [MRI]) should suggest no evidence of cervical invasion, pelvic or aortic lymphadenopathy, or involvement of the ovaries. Oral regimens have noted response rates  $\geq 50\%$ ; however, this can be associated with recurrence rates of 25% and higher (13). LNG-IUD proved to be effective in early endometrial cancers in 75% of cases after 12 months (14). A comprehensive meta-analysis published by Baker *et al.* (5) cites specific studies and outcomes for various regimens and may serve to assist in counseling patients as there are currently no randomized controlled trials for using these drugs for conservative management of medically inoperable endometrial cancer. Aromatase inhibitors have had some success in treating recurrent endometrial cancers (15), but no clinical studies have shown durable response in early endometrial cancers. Theoretically, aromatase inhibitors may have effect in morbidly obese patients whose peripheral conversion of androgens to estrogens is higher than those with normal adiposity.

### Patient evaluation

Endometrial cancer is staged surgically according to the International Federation of Gynecology and Obstetrics (FIGO). FIGO first recommended comprehensive surgical staging with pelvic and para-aortic lymph node dissection in 1988 and recently updated stage classifications in 2009. For patients who cannot undergo surgery, the clinical staging system can be used (Table 3) (16). This staging system relies

Table 3  
Clinical staging system for endometrial cancer

• Stage I—confined to the uterus
– 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 IV
– A—Involving local structures (rectum/bladder)
– B—Metastatic

Note. See text for details.

on the results of a complete pelvic examination to determine disease extent. Sounding the uterus can provide an approximation of the size of the endometrial cavity (Stages IA and IB). The cervix and vagina are examined to rule out gross disease, which would make the case Stage II or III, respectively. Rectal/bimanual examinations evaluate the parametria (i.e., Stage III) and assess adjacent organs for tumor spread (i.e., Stage IV). Accurate and complete pelvic examination is also necessary to determine the feasibility of performing brachytherapy implants in medically inoperable patients.

Anatomic and functional imaging techniques can provide additional data regarding disease extent in medically inoperable patients. CT scanning can be used to rule out distant metastasis (i.e., lung) in advanced and early stage endometrial cancers but is not the most sensitive imaging technique for evaluating disease extent within the pelvis. MRI can be used to assess the depth of myometrial invasion within the uterus, and several authors have published MRI protocols for this purpose (17). In a pooled analysis of prospective MRI studies, contrast-enhanced and T2-weighted MRI had negative predictive values  $>85\%$  for identifying deep myometrial involvement; however, the positive predictive values were significantly lower, suggesting that MRI may be best used to rule out deep myometrial invasion in medically inoperable patients with presumed organ-confined disease (18).

An important task in the workup of medically inoperable endometrial cancer patients is to identify involved lymph nodes or estimate the probability of lymph node involvement. CT is less accurate than  $^{18}\text{F}$ -fluoro-deoxy-glucose—positron emission tomography (PET) or MRI for identifying nodal metastasis (19–21). In a recent meta-analysis, the pooled estimates for sensitivity and specificity for  $^{18}\text{F}$ -fluoro-deoxy-glucose—PET and PET/CT in the detection of pelvic and para-aortic lymph node metastasis in endometrial cancer were 63% and 95%, respectively (22). Similar results have been published for MRI (21). The American College of Radiology published appropriateness criteria for pretreatment evaluation and followup of endometrial cancer. They concluded that in patients who need pretreatment evaluation, MRI was preferred over CT and ultrasound (US). The addition of PET imaging allows the most accurate means of assessing adenopathy (23).

The presence of deep myometrial invasion on MRI can also be combined with tumor grade on biopsy and used to estimate probability of lymph node involvement using surgicopathologic data Gynecologic Oncology Group 33 (GOG 33) (24). More recently, Kang *et al.* (25) have developed a system to identify endometrial cancer patients at very low risk of developing lymph node metastasis using a combination of serum CA-125 levels and MRI data.

### Applicators and insertion techniques

Patients are first positioned in the dorsal lithotomy position, and an examination under anesthesia is performed to

evaluate the position of the uterus and cervix and the capacity of the vagina. Residual cervical and vaginal involvement is documented and whether the uterus is anteverted, retroverted, or midplane. Pain control during applicator insertion is important for patient comfort both during and after the procedure; this may also help to avoid large shifts in blood pressure, pulse, and oxygenation during and after applicator insertion. Often, lower risk sedation options are used such as conscious sedation or paracervical block because of the risks related to more traditional general or regional anesthesia in these patients. Spinal or epidural anesthesia can be associated with more dramatic drops in blood pressure that may be a challenge in the setting of cardiovascular disease. Additionally, patients with bleeding disorders may not be candidates for such interventions. Having a dedicated anesthesiologist or nurse anesthetist with the patient throughout the procedure is recommended.

Ultrasound guidance can be used during the insertion to help guide dilation of the endocervical canal and evaluate placement of the uterine applicators. With a Foley balloon in place, filling of the bladder assists with optimal US imaging of the uterus. For patients treated with HDR, LDR, or pulsed-dose–rate techniques, there are a variety of applicators available for uterine brachytherapy. These can include a single tandem with ovoids or a vaginal cylinder. Dual and triple tandem applicators with or without a vaginal cylinder are also available. Typically, having a tandem in each cornu better covers the endometrial surface compared with a single tandem. The cervix will need to be dilated to 14 mm with sequential cervical dilators to accommodate 2 tandems. Two 15-degree tandems can be rotated laterally 30–45° and placed in the uterine cavity with flanges positioned so that they approximate the cervix.

It is important for patients with endometrial cancer that the tandem extends to the uterine fundus to ensure that the entire endometrial lining is treated. Modified Heyman capsules used with remote afterloading and plastic catheters can also be used within the uterus in an umbrella or “parapluie” configuration. The available tandem and ring applicators have fixed-length tandems that may not extend to the tip of the uterine fundus. Having a variable tandem length gives the operator the ability to place the tandem to the tip of the fundus. In the survey of panel members, the most commonly used applicator is a combination of 1–2 tandems and a vaginal cylinder. Some panel members preferred a single tandem, Simon–Heyman capsules, and/or tandem with vaginal ovoids depending on the tumor geometry.

Advantages and disadvantages to the different applicator systems require that the most appropriate applicator be selected based on the individual patient and tumor anatomy. Beriwal *et al.* (26) used a Y-applicator and found comparing plans based on CT images to orthogonal radiographic–based recalculated plans that the mean dose to uterine points was 99% of that prescribed, but the clinical target volume (CTV) coverage was only 62%, and optimization on three dimension to improve target coverage was

not always feasible given the applicator geometry (27). Similarly, Mock *et al.* compared different applicators and achieved 70% coverage of the target volume with Heyman capsules vs. an average of 47% for one-channel applicators. Thus, coverage of the entire target by the prescription isodose may not be achievable given the applicator geometry. A small dosimetry study, using Point A–based and CTV-based treatment plans with single, dual, and triple tandem applicators demonstrated that optimal coverage was dependent on the type of applicator and the anatomy, that is, size and shape of the uterus and its location relative to critical organs (28). The triple tandem applicator provided the greatest latitude in dose and anatomic uterus coverage compared with either single or dual tandem applicators. This was found to be the case when using either point or volumetric-based normalization (28).

Once the applicator is in place, and if there is no vaginal cylinder, vaginal packing is inserted to displace the bladder and rectum and secure the applicator. The applicator can be secured in a stable position with a perineal bar, external base plate and clamp, sutures, or an alternative fixation device. Radiographic-based, CT-based, or MR-based brachytherapy imaging techniques for dosimetry should be performed for each insertion. With CT and MR, a CTV can be defined to help guide dose specification.

Most panel members are currently performing CT imaging after each insertion for treatment planning. CT may be performed for each insertion or for each fraction, depending on whether the patient has one insertion and multiple fractions in 1 week as an inpatient with at least 6 h between fractions or, in contrast, if the patient has multiple insertions, with one fraction per insertion. In the latter situation, the CT can be fused to a first-fraction MRI to assist with treatment planning. Repeat CT imaging may be performed with each insertion to ensure that the tandem has not perforated or that there is no applicator movement requiring repositioning or revised planning. Imaging allows for an assessment of applicator position including possible perforation with repositioning and modification of the treatment plan after detection.

## Dose specification, dosimetry, and quality assurance

### *Recommendations for brachytherapy facilities with access to MRI or CT*

The ABS guidelines for HDR brachytherapy treatment of endometrial cancer published in 2000 defined the target volume for inoperable primary endometrial cancer as the entire uterus, cervix, and upper 3–5 cm of vagina (29). The 2000 ABS guidelines recommended the use of CT, MRI, or US to determine the uterine wall thickness. As of 2014, we recommend the use of MRI, and if unavailable, CT, for a volume-based approach for brachytherapy planning. Although point doses may still be tracked and used for optimization purposes, we recommend that

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

Structure	Image data set	Definition
Gross tumor volume	T2-weighted MRI	Visible abnormality if present
Clinical target volume	MRI or CT	Entire uterus, cervix, 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.

brachytherapy facilities also extend the planning process to include doses to normal tissue structure volumes (organs at risk [OAR]; Table 4).

Although specific contouring guidelines do not exist, the panel recommends contouring a CTV, which includes the entire uterus, cervix, and upper 1–2 cm of the vagina (Fig. 1). If MR is available, the tumor itself should be contoured as a gross tumor volume (GTV). GTV is defined as visible abnormality on T2-weighted MRI. It is recommended that the bladder, rectum, sigmoid, vagina (not included in the CTV), and bowel be contoured for OAR dose calculations.

The serosal point dose is not reflective of volumetric dose, and the coverage of the entire uterus to doses prescribed in the past to points may not be feasible without

exceeding the tolerance of adjacent critical structures (17). A 1998 study by Nguyen and Peterit (30) of 36 Stage I endometrial cancer patients treated with HDR brachytherapy alone for a total dose of 35 Gy to Point W (serosal point) found increased acute and late complication rates, most likely because of underestimation of critical organ doses by point-based dosimetry. Clinical outcomes using a volume-based approach with volumetric image-based (CT or MR) planning and optimization for HDR brachytherapy for endometrial cancer using mainly Heyman capsules were published (31). The median  $D_{90}$  to CTV was 40.8 Gy, isoeffective with respect to 2-Gy fractions ( $EQD_2$ ), with 68% of the CTV covered by the prescribed dose of 60 Gy. For OARs, the maximum 2-cm<sup>3</sup> dose was not to exceed 75–80 Gy for rectum or sigmoid colon and 90 Gy for the bladder. Twelve patients treated with curative intent had complete remission, and no severe acute or late (Grade 3 or 4) side effects were observed. After a median followup of 47 months, 5 patients were alive without evidence of disease and 7 patients died of intercurrent disease after a mean duration of 21 months. MRI provided more accurate delineation of the GTV and the small bowel and sigmoid colon. Notably, 1 of 2 patients with a  $D_{90}$  of 50 Gy to GTV had a recurrence, whereas there were no recurrences among patients with a  $D_{90}$  of  $\geq 68$  Gy to the GTV. Their findings suggest that GTV may be a useful target volume to prescribe dose for inoperable endometrial cancer to reduce the risk of central recurrence.

Gill et al. (32) recently published initial clinical outcome data for 38 medically inoperable endometrial

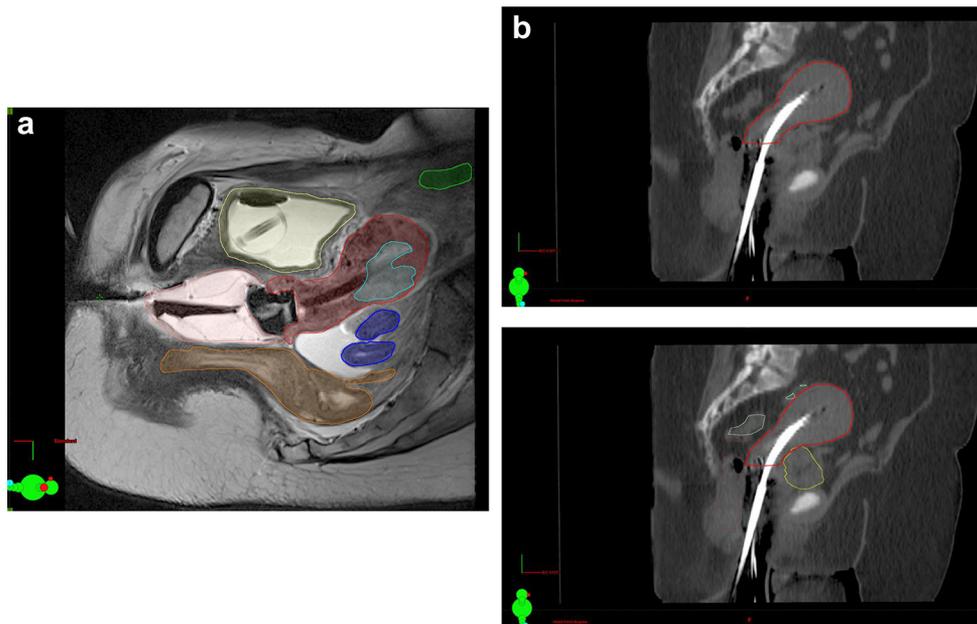


Fig. 1. Contouring for medically inoperable endometrial cancer using intraoperative magnetic resonance imaging (MRI) or computer tomography (CT). (a) Sagittal slices of T2-weighted MRI showing gross tumor volume (light blue) and clinical target volume including uterus, cervix, and upper vagina (red) with adjacent sigmoid colon (dark blue), rectum (orange), bowel (green), and bladder (yellow). (b) Sagittal view from a CT image data set displaying the uterus (red) for a tandem and ovoid implant with Heyman capsules displayed without and with the surrounding organs at risk, that is, sigmoid (light green), bladder (yellow), and rectum (brown).

cancer patients treated with image-guided brachytherapy. Nineteen patients underwent MRI-based planning where an MRI was performed after applicator placement; 19 underwent CT-based planning with 13 of these having a diagnostic MRI before brachytherapy to assist in identifying the GTV; 20 patients were treated with brachytherapy alone to a median dose of 37.5 Gy in five or six fractions; 18 were treated with a combination of external beam radiation to 45 Gy followed by an additional 25 Gy in four to five fractions with brachytherapy. After a median followup of 15 months, 2-year local control was 90.6%, and overall survival was 94.4%. One patient developed bleeding after applicator insertion requiring blood transfusion. Otherwise, no other Grade 3 or greater acute or late toxicities were observed. Mean CTV  $D_{90}$  EQD<sub>2</sub> was  $48.6 \pm 5.6$  Gy for brachytherapy alone. In contrast, mean GTV  $D_{90}$  EQD<sub>2</sub> was  $172.3 \pm 59.6$  Gy for brachytherapy alone. Mean CTV  $D_{90}$  EQD<sub>2</sub> was  $72.4 \pm 6.0$  Gy for external beam plus brachytherapy patients. In contrast, mean GTV  $D_{90}$  EQD<sub>2</sub> was  $138.0 \pm 64.6$  Gy for external beam plus brachytherapy. Given the excellent local control rates observed in this study, these results suggest that high doses to the CTV are not necessary to control disease, particularly in Stage I patients, provided that the GTV receives adequate dose. Longer followup and supporting data from a multi-institutional setting are needed to validate these results (32).

Based on the best available evidence, this panel recommends that patients with Stage I endometrial cancer should receive an EQD<sub>2</sub> of at least 48 Gy for brachytherapy alone and at least 65 Gy for the combination of external beam plus brachytherapy to 90% of the ( $D_{90}$ ) CTV volume encompassing the whole uterus, depending on tumor-specific (i.e., presence or absence of deep invasion on pretreatment MRI) and patient-specific (inability of the patient to undergo pretreatment MRI) factors (see “Clinical Scenarios”). A GTV may also be defined using T2-weighted MRI and may be prescribed a dose of  $\geq 80$  Gy (Fig. 1). Although MRI-based planning provides superior information for contouring GTV, obtaining an MR can be logistically difficult as most radiation oncology departments do not have a dedicated MRI unit. In addition, a subset of patients may not receive an MRI because of metallic fragments or implanted medical devices, medical comorbidities, or obesity. In this situation, target-based planning is limited to the CTV alone, which can still be defined on CT as described earlier for MRI and used for planning.

The dose prescribed within this range should be decided on the basis of tumor features while not exceeding established parameters for normal tissues dosimetry. It should be emphasized that patients with medically inoperable endometrial cancer may not be able to undergo surgery as a means of managing radiation-induced toxicities. For this reason, the panel encourages practitioners to limit doses to the OAR when performing brachytherapy for medically inoperable endometrial cancer. Data for maximum tolerated doses to the OAR specifically in medically inoperable endometrial cancer are

lacking. The best available data recommend that the  $D_{2CC}$  to the sigmoid and rectum be limited to 70–75 Gy and  $D_{2CC}$  to the bladder of 80–100 Gy (33). A dose limit of 65 Gy to the  $D_{2CC}$  to the bowel may be considered.

#### *Recommendations for brachytherapy facilities without MRI or CT*

##### *Point-based approach*

For the treatment of medically inoperable endometrial cancer in the absence of imaging capabilities, one should consider referral to a center with MRI or CT access. A radiographic-based approach can be used, but this severely limits one to a point-based approach using the applicator geometry as a surrogate for the target. Historically, film-based planning for LDR brachytherapy treatment of endometrial cancer required the use of standard loadings similar to cervical cancer, using approximately 5 mg RaEq per centimeter of uterine tandem with up to 10 mg RaEq per centimeter in the upper 2 cm of the tandem to increase dose to the endometrial cavity. Bladder and rectal doses could then be evaluated according to the International Commission on Radiation Units and Measurements (ICRU) 38 definitions.

With dose optimization capabilities available for HDR brachytherapy, the 2000 ABS guidelines recommended defining a dose specification point at 2 cm from the central axis at the midpoint along the Y-shaped uterine applicator, where the isodose is widened at the uterine fundus and was optimized to a 0.5-cm depth within the vaginal mucosa (the mucosa being defined as the surface of a vaginal cylinder). The 2000 ABS guidelines recognized that in some cases one may need to place additional dose optimization points depending on the geometry of the applicator, start with a computer optimized plan, and then manually adjust the dwell weights to produce the desired isodose distribution (Fig. 2). The bladder and rectal dose reference points were to be defined as specified in ICRU 38, and sigmoid colon localization was to be performed to obtain an estimate of the sigmoid dose.

We recommend that if a point-based approach must be used, one should consider uterine wall thickness and uterine size, which may vary significantly between patients. As an example, the Madison system used midmyometrial dose points where the distance between the midmyometrium and the uterine midline was fixed at average values for small vs. large uteri based on surgical specimens (34). The practice evolved into using US of the uterus at the time of the procedure to determine the anatomical dimensions. In the Madison system, dose is specified in four regions around a vaginal cylinder paired with either one or two tandems (depending on uterus size), where in the latter the tandems are pointed away from each other, and the tips fall into the cornu. The four regions were represented by points: a “superior” Point S (defined at about two-thirds thickness of the fundus, superior to the tip of tandem), “wall” Points W (defined as 2 cm inferior to tip of the tandem and



Fig. 2. Optimization of a magnetic resonance (MR)—based treatment plan using points. Coronal MR with dual tandem and superimposed dose distribution. The optimization points (blue + symbols) were placed in accordance with the computer tomography—defined uterine wall thickness along the course of the tandems and the location of the adjacent recto sigmoid and bladder. In this example, optimization points were placed laterally from each tandem in the following manner: for dwells 1 to 9, at a distance of 15 mm, and for dwells 12 to 15, at a distance of 10 mm. Optimization and prescription were performed by the planning software to make the average of the optimization points equal to the prescription and to minimize the standard deviation of the points compared with the average.

two-thirds of the thickness of uterine wall, lateral to the tandem), Points M (defined similarly to Point A except it lies at the lateral extent of the cervical wall), and a point defining the vaginal mucosa at the surface of the cylinder.

#### *Integrated reference air kerma—based approach*

As another option, an integrated reference air kerma—based approach for HDR brachytherapy, can be based off the classical LDR brachytherapy experience. For many decades, the LDR brachytherapy prescription for endometrial brachytherapy was empirical and based on the original method of Heyman with the addition of Fletcher-Suit tandem and ovoids. The Heyman method was developed around the 1940s in which short metallic capsules containing Ra-226 sources were inserted into the uterus (35). Patients were implanted with as many capsules as possible to increase the activity in the uterus and also to stretch and thin the uterine wall. Calculations converting the integrated reference air kerma for LDR to HDR may be performed.

#### **Postprocedure dosimetry and QA**

The previously published recommendations by ABS for quality assurance of endometrial cancer treatments using HDR brachytherapy should also be in place for QA of medically inoperable endometrial cancer using HDR (29). The ABS recommends the use of AAPM Task Group reports 56 (Brachytherapy Code of Practice), 41 (QA of HDR Devices), 53 (QA of Treatment Planning Systems), and 59 (HDR Treatment Delivery, Training and Staffing) to provide guidelines

for HDR brachytherapy in general. Also, the previously published ABS recommendations for cervix cancer HDR brachytherapy can also be applied to the treatment of medically inoperable endometrial cancer (36). Quality assurance recommendations for the dose prescription, applicators and corresponding source guide tubes, applicator localization, dosimetry (pre-calculated vs. patient specific), dwell time/position optimization, and treatment have been summarized previously by the ABS and are readily applicable to medically inoperable patients receiving HDR brachytherapy (29).

#### **Applicator reconstruction and source position localization**

The localization of treatment dwell positions using X-ray—based imaging modalities (radiographic and CT) may be different from that using an MRI. As an example, for X-ray—based imaging, radio-opaque markers must be inserted into the applicator for visualization and reconstruction of the applicators on the images. Identification of the most distal length of the applicator and of the dwell positions will be relative to the tip of the radio-opaque marker. Because of the lack of commercially available and robust markers for MRI-based brachytherapy, identification is based generally on the outline of the signal void representing the boundaries of the applicators. Thus, identification of dwell positions will be determined relative to the tip of the applicator. The procedure for applicator reconstruction and source position localization will be dependent on the results of applicator QA performed at the time of commissioning, that is, measurement of applicator plus guide tube length, determination of dwell position distances, and how these dwell positions are defined on the images, for example, either relative to an X-ray marker on CT or the applicator itself on MRI.

#### **Postimplant management**

Guidelines for the followup of endometrial cancer patients offer a general framework for the postimplant management of these patients (37–40). In general, relapses most often occur within the first 3 years after treatment. For this special population of medically inoperable patients treated with definitive radiation, salvage options with curative intent are extremely limited. Most of these patients will succumb to their medical comorbidities, and surveillance should be straightforward and primarily consists of pelvic and speculum examinations every 3 to 6 months for assessment of disease status and to monitor for late sequelae of treatment. There are no data to support or to refute the routine use of radiographic surveillance, Pap smear, or routine blood work, such as Ca-125, in this setting. It is recommended that all patients receive counseling about potential recurrence symptoms as the majority of recurrences are symptomatic; symptoms can include any of the following, not limited to unexplained

vaginal bleeding or discharge, detection of a mass, abdominal distension, persistent pain, especially in the abdomen or pelvic region, fatigue, diarrhea, nausea or vomiting, persistent cough, swelling, and weight loss. Any symptoms that persist >2 weeks after completion of radiation therapy should be evaluated.

Patients with medically inoperable endometrial cancer may be at high risk of disease progression after definitive radiotherapy depending on clinical factors. A prudent follow-up plan would include routine pelvic examinations every 3 months. Vaginal cytology followed by biopsy may be useful if visible residual tumor is seen. Documentation of a complete response, especially if other adjuvant therapies are considered, is desirable. The optimal timing for pelvic imaging is unknown. In the general endometrial cancer population, after 5 years of recurrence-free follow-up, patients may consider return to annual population-based general physical and pelvic examination as the majority of recurrences are symptomatic and occur within the first 5 years. In the medically inoperable population, this same concept is reasonable.

### Potential complications and their management

In one study of acute complications by Chao *et al.* (41) from the Washington University in 96 patients who underwent LDR implants for medically inoperable uterine cancer, there were four serious morbidities in the first 30 days: 2 patients had myocardial infarctions, 1 congestive heart failure, and 1 patient had a pulmonary embolus. Two of these patients died. Anesthesia poses high risks in this patient population, and these patients should be managed by an experienced team. It should be noted that medically inoperable patients may not be able to undergo surgical management of complications. As such, prevention of complications is extraordinarily important. Optimal DVT prophylaxis is essential to prevent PE and DVT, particularly in the setting of inpatient LDR and pulsed-dose-rate techniques treatments.

Uterine perforations may occur during the applicator insertion process. In a prospective study from the University of Toronto in cervix cancer patients, the CT-detected rate of uterine perforation was 13.7% (42). Radiation oncologists were asked to rate their confidence in whether the uterus was perforated. The uterine perforation rate was still 8.2% when radiation oncologists were confident that the uterus had not been perforated, indicating that clinical impression of uterine perforation is of somewhat limited predictive value. Two recent studies have documented a low uterine perforation rate of 3% and 1.4% when intraoperative US was used (43, 44). If uterine perforation is thought to have occurred during cervical dilation with a blunt instrument, the risk of vascular or visceral injury is low, and close observation may be sufficient. Observing serial hematocrit values postprocedure may offer reassurance that there is no significant blood loss. If perforation is identified with the applicator in place, the applicator should be removed, repositioned, and

reimaged to verify proper placement. Antibiotic prophylaxis with coverage of gram-negative and anaerobic bacteria is recommended in selected cases (45, 46).

Late complications have been well documented in the literature for both LDR and HDR brachytherapy in this population (Tables 1 and 2). Toxicity rates increase when external beam is added to brachytherapy. Late toxicities from radiotherapy include bowel injury such as obstruction and fistula formation, proctitis, sigmoid stricture, hemorrhagic cystitis, bladder contracture, pelvic fracture, chronic diarrhea, vaginal stenosis and agglutination, and secondary malignancies. In 16 studies using LDR brachytherapy, the range of late complications was 0–17.3% (30), and in 10 studies using HDR brachytherapy, the range of late complications was 0–14.7% (30). As noted previously, medically inoperable patients by definition cannot undergo surgical management of complications, and as such, prevention is the best option. There is significant promise for image-based brachytherapy to reduce the rate of late complications in this population.

### Management of recurrence disease after definitive radiation

In patients with a suspected recurrence of endometrial cancer, the American College of Radiology recommends imaging (23). However, before launching into an extensive and costly restaging workup, the realistic options for salvage or palliative therapy should be reviewed with the patient. Biopsy to establish diagnosis of recurrence may be sufficient. For patients with symptomatic recurrence, limited use of palliative re-irradiation may be beneficial for severe bleeding or pain; however, these decisions are made on a case-by-case basis. Hospice care should be considered and encouraged for patients with symptomatic recurrent disease and a limited life expectancy.

If disease progresses or recurs in patients with tumors that are positive for the estrogen or progesterone receptor, frontline treatment is hormonal therapy including progestational agents, tamoxifen, aromatase inhibitors, or megestrol and tamoxifen. Chemotherapy may be an option in some patients, and if tolerated, a multiagent combination of cytotoxic agents can be considered (47). In rare situations, uterine artery embolization can be used to control vaginal bleeding. In some cases, if a patient's medical status has improved, surgery can be reconsidered.

### Clinical scenarios

1. What is the best treatment for a Stage I (uterine confined) Grade 1 or 2 endometrial cancer with initial MRI demonstrating minimal myometrial invasion?
  - a. Brachytherapy alone can be used (Fig. 3).
  - b. The GTV target can be delineated on MRI at the time of brachytherapy and will include any visible



Fig. 3. Magnetic resonance (MR)–based planning for brachytherapy alone for Stage I endometrial cancer confined to the uterus. T2-weighted sagittal MR image displaying the isodose distribution for a tandem and ovoid implant with Heyman capsules. The patient was prescribed to receive a dose of 36.0 Gy in six fractions to the uterine serosa using high-dose–rate brachytherapy alone. Prescription isodose (100%) is shown in green, and the 50% isodose line is in blue. Uterus contour is displayed in red. Note the proximity of the sigmoid to the uterus.

gross disease and the endometrial lining. A CTV will be defined, which encompasses the whole uterus extending out to the uterine serosa.

- c. The goal will be to deliver an EQD<sub>2</sub> of 80–90 Gy to the GTV. The CTV will receive a D<sub>90</sub> EQD<sub>2</sub> of 48–62.5 Gy.
- d. Dose limits for normal tissues have not been established for treatment with brachytherapy alone. Because prescribed doses for brachytherapy alone are lower than combined treatment with external beam and brachytherapy for cervical cancer, doses should be well within the following constraints. D<sub>2CC</sub> to the rectum and sigmoid should not exceed an EQD<sub>2</sub> of 70–75 Gy. D<sub>2CC</sub> to the bladder should not exceed an EQD<sub>2</sub> of 80–100 Gy.
- e. Acceptable dose and fractionation schemes for the CTV using HDR in this setting based on the literature and clinical experience of the panel include

HDR total dose (Gy)	HDR dose fractionation	EQD <sub>2</sub> (Gy)
36	6 Gy × 6	48
38.4	6.4 Gy × 6	52.5
36.5	7.3 Gy × 5	52.6
34	8.5 Gy × 4	52.4
40–50	5 Gy × 9–10	50–62.5

- 2. What is the best treatment for a Stage I (uterine confined) endometrial cancer with MRI evidence of deep myometrial invasion?
  - a. A combination of external beam and brachytherapy is recommended. External beam radiation (EBRT) 45–50 Gy is used to treat the entire uterus and the nodal areas at risk (obturator, internal, external, and common iliac).
  - b. A GTV target will be delineated on MRI to encompass any gross residual disease at the time of brachytherapy and the endometrial lining. A CTV will be defined, which encompasses the whole uterus out to the serosal surface including the cervix and the upper 1–2 cm of the vagina.
  - c. The goal will be to deliver an EQD<sub>2</sub> of 80–90 Gy to the GTV. A CTV extending out to the serosa will receive a D<sub>90</sub> EQD<sub>2</sub> of 65–75 Gy.
  - d. The D<sub>2CC</sub> to the rectum and sigmoid should not exceed an EQD<sub>2</sub> of 70–75 Gy, and the D<sub>2CC</sub> to the bladder should not exceed an EQD<sub>2</sub> of 80–100 Gy.
  - e. Acceptable dose and fractionation schemes for HDR in this setting based on the published literature and the clinical experience of the panel include

EBRT (Gy)	HDR total dose (Gy)	HDR dose fractionation	EQD <sub>2</sub> (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

- 3. What is the best treatment for a Stage I (uterine confined) endometrial cancer when CT but not MRI is available?
  - a. A combination of external beam and brachytherapy is indicated. EBRT 45–50 Gy is used to treat the entire uterus and the nodal areas at risk (obturator, internal, external and common iliac).
  - b. A CTV will be defined, which will include the entire uterus to the serosa.
  - c. The dose to the CTV will deliver a total EQD<sub>2</sub> of 65–75 Gy to the CTV D<sub>90</sub>. A higher dose to the uterine serosa is recommended when MRI is not available because of uncertainty about the depth of myometrial invasion.
  - d. The D<sub>2CC</sub> to the rectum and sigmoid should not exceed 70–75 Gy and the D<sub>2CC</sub> to the bladder should not exceed 80–100 Gy.

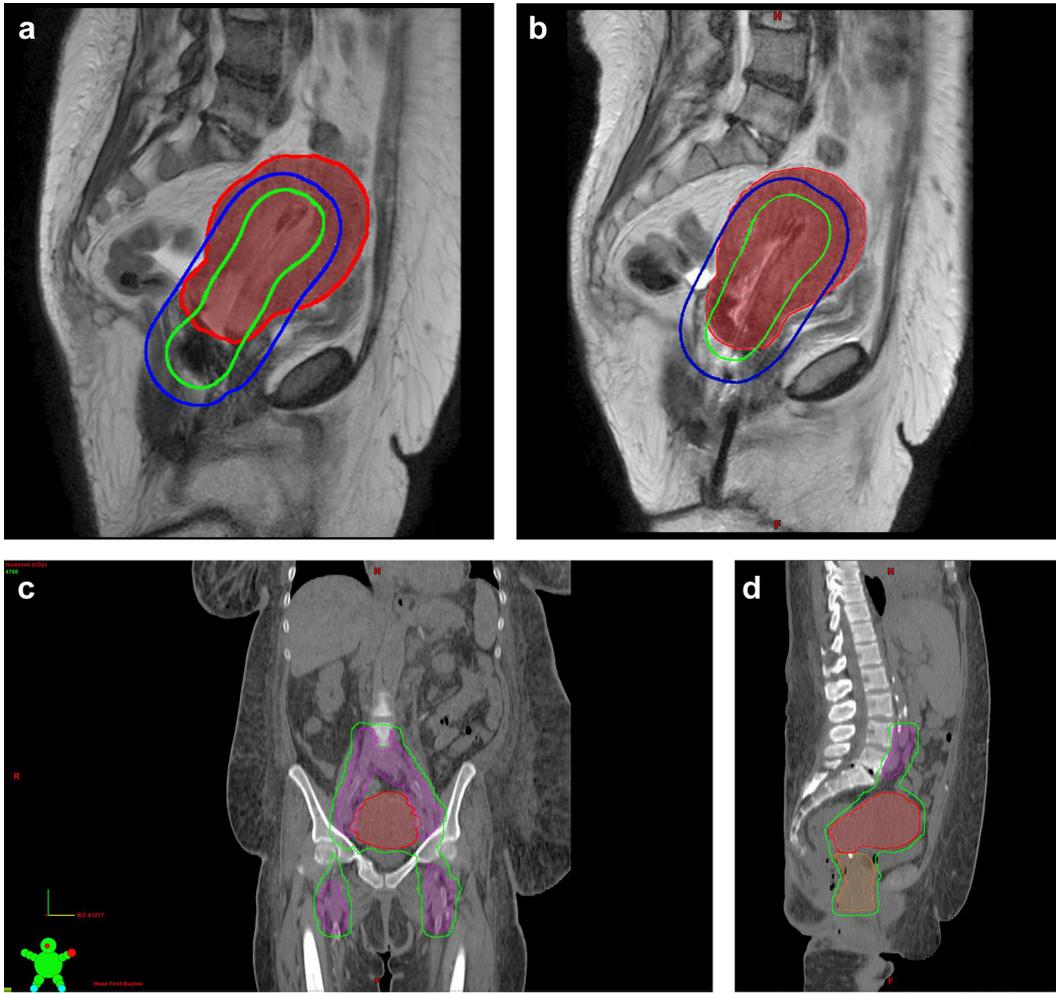


Fig. 4. Magnetic resonance (MR)–based planning for brachytherapy plus external beam for Stage III endometrial cancer presenting with parametrial and vaginal involvement. T2-weighted sagittal MR images displaying the brachytherapy isodose distributions for a tandem and ovoid implant with Heyman capsules at time of fractions 1 (a) and 6 (b) for a Stage III patient prescribed to receive combined external beam therapy (helical tomotherapy) and brachytherapy. For the high-dose–rate brachytherapy portion of the treatment, the patient was prescribed to receive a dose of 22.5 Gy in six fractions to the uterine serosa. Prescription isodose (100%) is shown in green, and the 50% isodose line is in blue. The uterus contour is displayed in red. Note the decrease in size of the uterus at Fraction 6. Coronal (c) and sagittal (d) views of a computer tomography image data set displaying the tomotherapy intensity-modulated radiation therapy isodose distribution. The patient was prescribed 50.4 Gy in 28 fractions via tomotherapy to a planning target volume, which was a 0.5-cm expansion about the CTVs, which are displayed for the uterus (red), the pelvic and groin nodes (magenta), and the vagina for this patient who presented with vaginal involvement (orange, shown in sagittal view only). The 95% isodose is shown in green.

e. Acceptable dose and fractionation schemes for HDR in this setting based on the published literature and the clinical experience of the panel include

EBRT (Gy)	HDR total dose (Gy)	HDR dose fractionation	EQD <sub>2</sub> (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	17	8.5 Gy × 2	70.5
45	25	5 Gy × 5	75
50.4	12	6.0 Gy × 2	65.6
50.4	22.5	3.75 Gy × 6	75.3

4. What is the best treatment for a Stage II endometrial cancer (involving the cervix)?

- a. A combination of external beam and brachytherapy is indicated. EBRT 45–50 Gy is used to treat the entire uterus and cervix and the nodal areas at risk (paracervical, obturator, internal, external, common iliac ± presacral LN).
- b. Applicators including ring and/or vaginal ovoids will be selected to deliver prescription dose to the cervix. A GTV target will be defined, which will encompass any gross residual disease, the endometrial lining, and the cervix. A CTV target will be defined, which will encompass the whole uterus

out to the serosal surface, the cervix, and the upper 1–2 cm of the vagina.

- c. The goal will be to deliver an EQD<sub>2</sub> of 80–90 Gy to the GTV. The CTV will receive a D<sub>90</sub> EQD<sub>2</sub> of 70–75 Gy. The D<sub>2CC</sub> to the rectum and sigmoid should not exceed an EQD<sub>2</sub> of 70–75 Gy and the D<sub>2CC</sub> to the bladder should not exceed an EQD<sub>2</sub> of 80–100 Gy.
- d. Acceptable dose and fractionation schemes for HDR in this setting based on the published literature and the clinical experience of the panel include

EBRT (Gy)	HDR total dose (Gy)	HDR dose fractionation	EQD <sub>2</sub> (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	17	8.5 Gy × 2	70.5
45	25	5 Gy × 5	75
50.4	22.5	3.75 Gy × 6	75.3

5. What is the best treatment for Stage III endometrial cancer (disease has extended outside the uterus but is regionally confined to pelvis)?

- a. A combination of external beam and brachytherapy is indicated (Fig. 4). EBRT is used to treat the entire uterus, involved regional structures and the nodal areas within the pelvis. Additional EBRT with intensity-modulated radiation therapy boost dose (up to 65 Gy) (48) can be considered to treat enlarged lymph nodes, respecting surrounding normal tissue tolerances, including a dose limit to the small bowel (55 Gy < 5 cm<sup>3</sup>) (49).
- b. A GTV target will be defined, which will encompass any gross residual disease, the endometrial lining, and the cervix. A CTV target will be defined, which will encompass the whole uterus out to the serosal surface, the cervix, and the upper 1–2 cm of the vagina.
- c. The goal will be to deliver an EQD<sub>2</sub> of 80–90 Gy to the GTV. A CTV extending out to the serosa will receive an EQD<sub>2</sub> of 70–75 Gy. The D<sub>2CC</sub> to the rectum and sigmoid should not exceed an EQD<sub>2</sub> of 70 Gy and the D<sub>2CC</sub> to the bladder should not exceed an EQD<sub>2</sub> of 90 Gy.
- d. Brachytherapy prescription is delivered to a volume, CTV, that encompasses the whole uterus and any residual gross disease after EBRT if EBRT is delivered first.
- e. Acceptable dose and fractionation schemes for HDR in this setting based on the published literature and the clinical experience of the panel include:

EBRT (Gy)	HDR total dose (Gy)	HDR dose fractionation	EQD <sub>2</sub> (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	22.5	3.75 Gy × 6	75.3

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