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MR-versus CT-based high-dose-rate interstitial brachytherapy for vaginal recurrence of endometrial cancer

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Abstract

Purpose—To compare clinical outcomes of MR-based versus CT-based high-dose-rate (HDR) interstitial brachytherapy (ISBT) for vaginal recurrence of endometrioid endometrial cancer (EC).

Methods—We reviewed 66 patients with vaginal recurrent EC; 18 had MR-based ISBT on a prospective clinical trial and 48 had CT-based treatment. Kaplan-Meier (K-M) survival modeling was used to generate estimates for local control (LC), disease-free interval (DFI), and overall survival (OS) and multivariate Cox modeling was used to assess prognostic factors. Toxicities were evaluated and compared.

Results—Median follow up was 33 months (CT 30 months, MR 35 months). Median cumulative EQD2 was 75.5 Gy for MR-ISBT and 73.8 Gy for CT-ISBT ($p=0.58$). MR patients were older ($p=0.03$) and had larger tumor size ($>4\text{cm}$ vs 4cm) compared to CT patients ($p=0.04$). For MR-

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vs. CT-based ISBT, 3-year KM rate for LC was 100% vs. 78% ($p = 0.04$), DFI was 69% vs. 55% ($p = 0.1$), and OS was 63% vs. 75% ($p = 0.81$), respectively. On multivariate analysis, tumor grade 3 was associated with worse OS (HR 3.57, 95%CI 1.25,11.36) in a model with MR-ISBT (HR=0.56, 95%CI 0.16,1.89). Toxicities were not significantly different between the two modalities.

Conclusion—Despite worse patient prognostic features, MR-ISBT was associated with a significantly better (100%) 3-year local control, comparable survival, and improved DFI rates compared to CT. Toxicities did not differ compared to CT-ISBT patients. Tumor grade contributed as the most significant predictor for survival. Larger prospective studies are needed to assess the impact of MR-ISBT on survival outcomes.

Keywords

radiation therapy; interstitial brachytherapy; CT; MRI; endometrial cancer

INTRODUCTION

Endometrial cancer is the most common gynecologic malignancy in the United States (1–4). Approximately 80% of patients with EC present with early-stage disease and undergo a total hysterectomy plus bilateral salpingo-oophorectomy (5–9). Despite the effectiveness of surgery in the management of early-stage disease, relapse is common in those with high-risk features. Pelvic relapse occurs in 10 – 15% of intermediate-risk and 20 – 26% of high-risk patients (1, 5, 10–15). Approximately 75 – 80% of these relapses are confined to the vagina (16–20). Salvage radiation therapy (SRT) in the form of combined external beam treatment (EBRT) and brachytherapy (BT) is the recommended treatment for vaginal recurrence of endometrial cancer (21–23). BT can either be performed using an interstitial or intracavitary technique, depending on the size and location of the recurrence. The advantage of interstitial BT (ISBT) is that it allows for improved dose delivery when the disease cannot be adequately encompassed by the intracavitary technique (24–25).

To ensure significant improvement in locoregional control and to minimize radiation dose to organs-at-risk (OAR), precise placement of interstitial applicators through to use of 3-dimensional (3D) imaging is necessary (26). Imaging in gynecologic radiation planning has resulted in remarkable improvement in the identification and delineation of a target volume (10, 27–29). Three-dimensional imaging modalities currently in use include computed tomography (CT) scan, and magnetic resonance imaging (MRI). MRI has been shown to be superior to CT in delineating gynecologic tumors and normal pelvic structures (19, 26, 30–31). However, no study has compared clinical outcomes and quality of life indices of MR-based to CT-based ISBT for vaginal recurrence of EC. This study was designed to evaluate clinical outcomes of MR-guided to CT-guided ISBT in the treatment of vaginal recurrence of EC.

MATERIALS AND METHODS

Patient and tumor characteristics

A total of 97 patients with biopsy-proven vaginal recurrence of endometrioid endometrial cancer were identified from May 2005 to January 2016 under an Institutional Review Board

(IRB)-approved protocol. We excluded cases of vaginal recurrence of EC treated with low-dose-rate or intracavitary BT (n = 10), cases of initial vaginal involvement of primary EC (stage IIIB) that did not have a hysterectomy (n = 7), cases with aggressive histology of papillary serous, clear cell or carcinosarcoma (n = 13), and one case of vaginal recurrence of EC treated with MR-based Cesium-131 seeds; the remaining 66 patients were treated with HDR MR- (n=18) or CT-ISBT (n=48). MR-ISBT patients were all enrolled on a prospective trial after 8/2011 using 3T MR and not part of a previously published series (32).

All patients received intraoperative general anesthesia, anticoagulant prophylaxis, and antibiotic therapy. Patients were examined under general anesthesia to measure the size of the vagina and evaluate the presence and extent of the tumor (19). Interstitial catheters were placed using an iterative approach of catheter insertion and adjustment with serial CT or MR image acquisition. Except when medically contraindicated, an epidural was placed for the treatment procedure and duration of hospitalization. Additional details about treatment planning and delivery of radiation have been published (19, 22, 33).

Baseline patient and tumor characteristics were recorded for all patients, including date of diagnosis of recurrent disease, age at diagnosis, diagnostic method for recurrence, tumor site, size of recurrent disease at time of brachytherapy, grade, histology, International Federation of Gynecology and Obstetrics (FIGO) primary disease stage, presence of lymphovascular space invasion (LVI), nodal involvement at time of recurrence, and prior chemotherapy and prior radiation treatment. Prior radiation was defined as re-irradiation at least six months after radiation treatment for the same disease. Ascertainment of lymph node involvement was done through the use of CT, MRI or positron emission tomography (PET) scans.

Cumulative radiation dose was converted to biological equivalent dose (BED) in 2-Gy fractions using the quadratic BED equation with an α/β ratio of 10 for the contoured HR-CTV, and an α/β ratio of 3 for normal tissues or organs-at-risk (OAR) (19).

Clinical Endpoints

Biopsy proven evidence of disease recurrence or clinical progression in the true or central pelvis (vagina and adjacent tissues) was defined as local relapse (LR); while relapse in the pelvic nodes or sidewalls was considered pelvic relapse (PR). Regional recurrence was defined as relapse in the inguinal and / or para-aortic nodes; and distant recurrence was defined as overt distant metastasis.

Actuarial estimates of local control (LC), disease-free interval (DFI), and overall survival (OS) were assessed and recorded for both treatment groups. Local control was defined as no evidence of disease in the true pelvis. DFI was defined as the interval from the date of diagnosis of baseline recurrent disease to the date of documented progression, recurrence, or last follow-up. OS was defined as the interval from date of baseline tumor recurrence to the date of death or last contact with the patient. Follow-up time was capped at 6 months for the MR-ISBT patients treated after November 11, 2014.

Treatment-related complications were evaluated and reported as cumulative incidence of grades 1 – 3 rectal and urinary toxicities according to the Common Toxicity Criteria for Adverse Events (v. 4.3) (34). Early complications were defined as those occurring within 90 days of ISBT, and late complications as those occurring more than 90 days after completion of ISBT.

Statistical analysis

We reported median values with range or mean values with standard deviation for numeric variables, and percentages for categorical and ordinal variables. Chi-square analyses comparing the two image-based treatment groups were performed, using Fisher's exact test for binary variables when sample sizes were small, and the likelihood ratio test for categorical variables with multiple groups. Actuarial survival estimates and plots were generated using the Kaplan-Meier (K-M) method and compared using the log rank test. Univariate and multivariate Cox proportional hazards models were built using backwards selection modeling with clinically relevant variables included to identify predictors of LC, DFI, and OS. All statistical tests were two-sided and considered significant for likelihood ratio p-values less than 0.05. All statistical analyses were performed using JMP version 13.0 (SAS Institute Cary, NC) and R version 3.3.2 (35).

RESULTS

Patient and Tumor Characteristics

Overall and group-specific patient and tumor characteristics, as well as details about treatment are summarized in Table 1. Median follow up was 33 months, 30 (rg, 3 – 103) months for CT and 35 (rg, 4 – 56) months for MR subgroups. Compared to patients who received CT-based ISBT, patients treated with MR-based ISBT were significantly older ($p=0.03$), had larger median tumor size (3.6 cm vs 2.1 cm, $p=0.05$), and were more likely to have LVI (78% vs 40%, $p=0.006$).

Treatment characteristics

All patients had hysterectomy for primary disease. Of those who received prior radiation ($n = 24$), 8 (33%) had BT only, 4 (17%) had EB only, and 12 (50%) received a combination of EB+BT. Median interval between primary hysterectomy and salvage radiation for recurrent disease was 20 (rg, 7 – 210) months. Vaginal recurrence of EC was either treated with a combination of EB+BT ($n= 58$; 88%) or BT alone (12%). All patients received 3D image-based HDR ISBT twice daily, with a median of 5 (rg, 3 – 9) fractions and a median dose per fraction of 4.5 (rg, 2.3 – 8.0) Gy. The median cumulative radiation dose in EQD2 to the HR-CTV was 74.2 (rg, 52.2 – 105.6) Gy, and the median D90 was 75.6 (rg, 37.0 – 108.7) Gy.

The median cumulative radiation dose to the HR-CTV in EQD2 among the re-irradiation cases (including prior treatment) was 89.2 (rg, 52.2 – 106.6) Gy versus 74.2 (rg, 64.3 – 79.8) Gy among the non-re-irradiation cases. Among the re-irradiation cases, D90 HR-CTV EQD2 dose (including prior dose) was 78.1 (rg, 37.0 – 108.7) Gy versus 75.5 (rg, 58.7 – 98.1) Gy among non-re-irradiation cases ($p=0.60$). The BT D90 was 41.8 (rg, 10.4 – 77.3) Gy among the re-irradiation cases and 31 (rg, 11.6 – 53.8) Gy among the non-re-irradiation

cases. For re-irradiation cases, 8 had VB in the past and received EB + interstitial brachytherapy at the time of relapse; 2 had EB in the past and received interstitial brachytherapy alone at the time of relapse; 2 had EB in the past and received EB + interstitial brachytherapy at the time of relapse; 6 had EB + VB in the past and received interstitial brachytherapy alone at the time of relapse; 6 had EB + VB in the past and received EB + interstitial brachytherapy at the time of relapse (Supplemental Table 1).

The MR-based treatment group received a median cumulative EQD2 dose of 75.5 (rg, 55.7 – 93.2) Gy, while the CT-based group received 73.8 (rg, 52.2 – 106.6) Gy. In general, 65% of patients received chemotherapy either at diagnosis or at the time of recurrence, and 74% of this subset had platinum-based agents. A statistically significant difference was noted in cumulative radiation dose to the bladder (D_{2CC} bladder) between the MR- and CT-based treatment groups (MR = 72.5 Gy, CT = 64.6 Gy, $p = 0.006$). This may be related to bladder filling and positioning of the Foley bag at the time of the planning scan, and also the larger tumor size of patients in the MR subgroup, compared to the CT (3.6 cm versus 2.1 cm, $p = 0.05$). Compared to patients with tumor size ≤ 4 cm (D_{2cc} bladder = 65.0 Gy), those with tumor size > 4 cm received a higher D_{2cc} bladder (69.2 Gy).

Pattern of tumor relapse

Tumor and treatment characteristics of all patients who experienced relapse are summarized in Table 2. A total of 23 (35%) patients had pathologic evidence of second disease recurrence; of which 9 (39%) were local failures. All 9 patients who experienced local relapse were treated with CT-guided ISBT. Nine recurrences (39%) had been treated with prior RT. The MR-guided ISBT subgroup had 4 (22%) any relapse events, while the CT-based subgroup had a total of 19 (40%) any relapse events.

Local control

Three-year actuarial K-M and Cox proportional hazards local control data are shown in Figure 1 and Table 3a, respectively. There was no significant difference in follow-up lengths between the compared treatment groups. Three-year actuarial K-M LC rate was 84% overall (MR and CT combined), 100% for the MR-based ISBT subgroup, and 78% for the CT-guided ISBT subgroup. The MR-based subgroup had a significantly better 3-year LC rate, with log-rank p -value of 0.04. Three-year LC rate was 71% among those who received prior RT and 92% among those who did not ($p=0.16$). Among those who received prior RT, three-year LC rate was 80% among those who received vaginal brachytherapy previously, 100% among those who received EBRT, and 60% among those who received brachytherapy + EBRT. Receipt of any chemotherapy at the time of recurrence and presence of lymphovascular invasion were significant prognostic predictors of LC in the univariate Cox proportional analysis and associated with improved LC rates. In the multivariable model including both lymphovascular invasion and receipt of any chemotherapy, both remained significant. Brachytherapy imaging status was not included in this model given that there were no local recurrences in the MR-ISBT group.

Disease-free Interval and Overall Survival

Three-year actuarial K-M plots and results of Cox univariate modeling analyses for DFI are shown in Supplemental Figure 1 and Table 3a, respectively. The 3-year actuarial DFI rate was 60% overall, 69% for MR-guided ISBT, and 55% for CT-guided ISBT. The 3-year DFI rate was 52% among those who received prior RT and 65% among those who did not ($p=0.34$). Although there was no statistically significant difference in DFI rates (Log-rank $p=0.1$), there was a trend towards improved DFI for patients who received MR-guided ISBT (HR = 0.44, 95% CI = 0.13, 1.18; $p=0.11$) in the univariate analyses, that was attenuated upon multivariable analysis (HR = 0.62, 95% CI = 0.16, 1.92; $p=0.42$).

In the univariate Cox proportional hazards analysis predicting DFI, cumulative radiation dose to the contoured HR-CTV in 2-Gy fractions (EQD2) (HR = 1.05, 95% CI 1.00, 1.08, $p=0.03$), and cumulative radiation dose to 90% of the contoured HR-CTV volume in 2-Gy fractions (HR = 1.04, 95% CI 1.01, 1.07, $p=0.01$) were significantly associated with DFI, while presence of lymphovascular invasion led to a reduction in risk for progression (HR = 0.38, 95% CI 0.14, 0.94, $p=0.03$). After adjusting for cumulative D90 radiation dose, lymphovascular invasion, and forcing MR-based ISBT into the model, MR-based ISBT reduced risk but was not significantly associated with disease progression or any relapse (HR = 0.62, 95% CI 0.16, 1.92; $p=0.42$) while increasing radiation dose was positively associated with disease progression or any relapse (HR 1.05, 95% CI 1.01, 1.09, $p=0.01$).

The proportion of all-cause mortality observed in the compared treatment groups was similar. The MR-guided ISBT subgroup had a total of 5 (28%) deaths, while the CT-guided ISBT subgroup recorded 15 (31%) deaths. Three-year actuarial OS rate was 72% overall, 63% for the MR-guided ISBT subgroup, and 75% for the CT-guided ISBT subgroup ($p=0.81$) (Figure 2). Three-year actuarial OS rate was 54% among those who received prior RT and 82% among those who did not ($p=0.019$).

MR-guided ISBT was not a significant predictor of OS in the univariate analyses. Only prior radiation therapy, concurrent chemotherapy with EBRT at the time of recurrence, and tumor grade showed statistically significant association with OS on univariate analysis and after backwards selection for multivariate analysis. Based on the univariate OS results shown in Table 3a, there was a trend towards increased risk of death in patients with moderately and poorly differentiated tumors. Compared to patients without prior radiation therapy, patients who had prior radiation treatment were 2.95 (unadjusted) times at-risk of death during the study period. Patients who received concurrent chemotherapy with EBRT at the time of recurrence trended toward a decreased risk in death. In the adjusted multivariable model, again forcing MR-guided ISBT, we sequentially added tumor grade, concurrent chemotherapy, and prior radiation, and found that only tumor grade and concurrent chemotherapy were relevant confounders, therefore included in the final model (Table 3b). In this model, tumor grade remained as a significant determinant of OS, with a HR 3.57, $p=0.02$.

Toxicity and radiation dose to organs-at-risk

Details of observed adverse events are shown in Table 4a. There were a total of 22 grade 3 rectal and urinary toxicities in 20 patients. Three patients were treated with MR-guided ISBT, while 17 received CT-guided ISBT. All 3 patients in the MR-subgroup had late toxicities, which included rectal bleeding (proctitis) and urinary incontinence. Of the 17 CT-patients with grade 3 toxicities, 9 had rectal toxicities only, 6 had urinary toxicities only, and 2 experienced both rectal and urinary toxicities. Three of these were acute and 16 were late toxicities, including proctitis, cystitis, urinary fistula and gross hematuria. Toxicities in re-irradiation cases included 10 grade 3 rectal and urinary toxicities in 8 patients (6 rectal, 4 urinary) compared to 12 grade 3 toxicities in 12 patients that did not have re-irradiation (6 rectal, 6 urinary) (Table 4b, Supplemental Table 1). Despite a statistically significant difference in median radiation dose to the bladder organs-at-risk in the compared treatment groups, there was no difference in resulting urinary toxicities. Compared to CT-based ISBT, MR-based ISBT was associated with fewer cumulative grade 3 urinary and rectal toxicities. There were no grade 4 or 5 toxicities.

DISCUSSION

This study compares clinical outcomes for 66 patients treated with CT or MR-based ISBT for vaginal recurrence of EC. There was no significant difference between the MR- and CT-based treatment groups in terms of median length of follow-up, tumor grade, and primary disease stage. However, patients who received MR-based treatment were significantly older, had larger tumor size, and were more likely to have LVI in the initial hysterectomy specimen. Patients treated with MR-IBST had a better LC than CT, though this did not translate into an improved DFI or OS in this series. This is consistent with the natural history of endometrial cancer. Most recurrences occur in the first 2 years after definitive treatment, but these early recurrences typically do not impact survival until 5 years or more after treatment (1, 16).

Three-dimensional imaging during BT is very important for proper placement of applicators and enables precise contouring of OAR for volume-based dose calculations and treatment. The resultant effect is an optimized radiation dose to the contoured tumor volume, minimized dose to normal tissues, and fewer radiation-related adverse events (26). In a comparison study of CT-versus MRI-based contouring for cervical cancers, CT was noted to be consistently wider in the lateral direction, resulting in significant differences in volume treated to the prescription dose, D_{90} , and D_{100} (36). Another recent publication on CT-versus MR-based contouring by 23 expert gynecologic radiation oncologists showed that mean tumor volume was smaller on MR compared to CT ($p < 0.001$), but there was slightly higher kappa for CT, which shows a higher agreement for CT-based contouring among physicians. This may be partly attributable to the widespread use of CT-based contouring (26). Despite the very high sensitivity and specificity of CT- and MR-based imaging, considerable discordance exists between both modalities when parametrial extension is involved. This could result in significant difference in target dosing when volume-based prescription is adopted.

All patients in this study were treated with either CT- (73%) or MR-guided (27%) ISBT. Median cumulative radiation dose and median D90 received were 74.2 Gy and 75.6 Gy, respectively. These doses are consistent with the American Brachytherapy Society consensus guideline recommendation (37). There was no statistically significant difference in cumulative dose between treatment groups.

Compared to patients who received CT-based ISBT, patients treated with MR-based ISBT had better LC rate and fewer cumulative grades 3 rectal and urinary toxicities as well as an improved DFI. Rectal bleeding is most related to the use of external beam RT (38). Three-year actuarial local control, progression-free, and overall survival rates were 100%, 88%, and 87%, respectively, for patients who received MR-guided ISBT; and 78%, 62%, 84%, respectively, for patients who had CT-based treatment.

Few studies have looked at clinical outcomes of image-based ISBT for vaginal recurrence of EC, and no published data has compared clinical outcomes of CT-based to MR-based ISBT for vaginal recurrence of EC. Among the few studies that have looked at HDR-BT for vaginal recurrent EC, Petignat et al. (17), Vargo et al. (4), Vance et al (23), Lin et al. (2) and Fokdal (39) showed comparable local control, progression-free, and overall survival rates. Petignat et al. reported 5-year LC and DFS rates of 100% and 96%, respectively; for patients treated with HDR-BT for isolated vaginal recurrence of FIGO stage I EC. The relatively higher DFS rate is likely attributable to the inclusion of patients with stage I-only disease at initial diagnosis. In another cohort of 41 patients who received IMRT with HDR-BT for vaginal recurrence of EC, Vargo et al. (4) showed 3-year LC, disease-free, and overall survival rates of 95%, 68%, and 67% respectively. These rates are comparable to results of our study, despite the predominant utilization of IMRT (90%) and cylinder brachytherapy (73%) in this study. Vance et al. (23) reported relatively better 2- and 5-year disease-specific (90%, 77%) and overall survival (84%, 72%) rates among women with early-stage EC (87% FIGO stage I and 13% FIGO stage II disease). Fokdal et al. (38) showed 2-year LC of 92%, with disease-free survival and overall survival rates of 59% and 78% respectively. In contrast, Jhingran et al. (1) showed lower 2-year LC (82%) and OS (69%) rates, when compared to our MR-based ISBT subgroup. The slightly lower rates may be related to the relatively lower proportion of subjects (57%) who received combined EB+BT in this cohort, and there was no image-guidance. The study demonstrated that patients treated with EB+BT had better LC and OS rates than patients treated with EB or BT alone.

Overall, our study showed a relatively higher but comparable cumulative incidence of grade 3 rectal and urinary toxicities over a 3-year follow-up period. MR-based treatment was also associated with lower crude incidence of grade 3 rectal and urinary toxicities. Of the 20/66 (30%) patients who experienced at least one grade 3 toxicity, 3/18 (17%) were treated with MR-guided ISBT, and 17/48 (35%) received CT-guided ISBT. Median cumulative D_{2cc} to the rectum and bladder for patients who experienced grade 3 toxicities were 62.1 Gy and 66.0 Gy, respectively. Amsbaugh et al. (40) reported that 22% of 73 patients who received CT-based ISBT for locally advanced gynecologic cancer had grade 3 toxicities (15.1% urinary and 6.8% rectal). In this study, a dose of 23.1 Gy was related to urinary toxicity. In contrast, Petignat et al. (17) showed that 18% of study patients had grades 3 and 4 toxicities, while Vargo et al. (4) reported grade 3 toxicities among 8% of patients. The significantly

lower incidence of grade 3 toxicities reported by Vargo et al. may be related to the predominant use of IMRT and no prior radiation for initial disease (90%) in this series. We were unable to make objective comparison with published studies because most of these studies utilized different treatment modalities and BT dose rate.

Some limitations of our study include that all patients were treated at a single institution. Prospectively treated patients in the MR-treatment arm were compared to historical CT-cases whose records were reviewed. However, the likelihood of differential ascertainment of prognostic factors, treatment characteristics, and outcome measures was minimal, since standardized clinical methods were used to ascertain baseline patient and tumor characteristics, and outcome measures.

This study is the first to evaluate and compare clinical outcomes of MR- and CT-guided ISBT for vaginal recurrence of endometrial cancer. Despite the worse prognostic features of MR-patients, there was a benefit in local control and less toxicity for patients treated with MR-based HDR ISBT. The impact of image-based ISBT on the overall survival of patients with vaginal recurrence of endometrial cancer should be evaluated within larger prospective study designs. Therefore, future comparative trials are needed to confirm the potential advantage of MR-based ISBT compared to CT-based treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of Abbreviations Used

HDR	High-dose-rate
ISBT	interstitial brachytherapy
EC	endometrial cancer
K-M	Kaplan-Meier

LC	local control
DFI	disease-free interval
OS	overall survival
EBRT	external beam radiation therapy
OAR	organ-at-risk
MRI	magnetic resonance imaging
CT	computed tomography
FIGO	International Federation of Gynecology and Obstetrics
LVI	lymphovascular invasion
PET	positron emission tomography
BED	biological equivalent dose
PR	pelvic relapse
Rg	range

Figure 1. Kaplan-Meier Plot of Local Control

Local control by imaging modality utilized during brachytherapy. There were no local recurrences in the MR-guided ISBT group and 9 local recurrences in the CT-guided ISBT group, resulting in 3-year local control rates of 100% and 78%, respectively.

Figure 2. Kaplan-Meier Plot of Overall Survival

Overall survival by imaging modality utilized during brachytherapy. MR-guided ISBT resulted in 63% 3-year OS while CT-guided ISBT resulted in 75% OS.

Table 1

Patient, Tumor and Treatment Characteristics

Category	All Patients (N = 66)	CT-based ISBT (n = 48)	MR-based ISBT (n = 18)	P-value
Median follow-up (months)	32.5 (2.9 – 103.1)	29.8 (2.9 – 103.1)	35.1 (3.5 – 55.6)	0.58
Median age at diagnosis (years)	65.2 (34.7 – 83.7)	63.3 (34.7 – 83.7)	68.0 (41.2 – 81.2)	0.03
ECOG status				
1	36 (55%)	23 (49%)	13 (72%)	0.09
0	29 (44%)	24 (50%)	5 (28%)	
Not defined	1 (1%)	1 (2%)	0 (0%)	
Year of diagnosis				
2005 – 2010	15 (23%)	15 (31%)	0 (0%)	<0.001
2011 – 2015	51 (77%)	33 (69%)	18 (100%)	
Diagnostic Method				0.002
CT	28 (42%)	25 (52%)	3 (17%)	
MRI	29 (44%)	15 (31%)	14 (78%)	
PET	2 (3%)	1 (2%)	1 (5%)	
Exam	7 (11%)	7 (15%)	0 (0%)	
Tumor size (continuous) cm	2.5 (0.5 – 8.4)	2.1 (0.5 – 6.1)	3.6 (1.3 – 8.4)	0.05
4 cm	52 (79%)	41 (85%)	11 (61%)	0.04
> 4 cm	14 (21%)	7 (15%)	7 (39%)	
Tumor site				
Cuff / Upper 1/3	58 (88%)	44 (92%)	14 (78%)	0.22
Middle 1/3	1 (1%)	1 (2%)	0 (0%)	
Lower 1/3	7 (11%)	3 (6%)	4 (22%)	
Primary disease stage (FIGO)				0.32
I	49 (74%)	34 (71%)	15 (83%)	
II	3 (5%)	3 (6%)	0 (0%)	
III	12 (18%)	9 (19%)	3 (17%)	
IVA	2 (3%)	2 (4%)	0 (0%)	
Histology				
Adenocarcinoma	66 (100%)	48 (100%)	18 (100%)	--
Grade				
1	19 (29%)	15 (31%)	4 (22%)	0.06
2	23 (35%)	19 (40%)	4 (22%)	
3	21 (32%)	11 (23%)	10 (56%)	
Not defined	3 (4%)	3 (6%)	0 (0%)	
LVI present	33 (50%)	19 (40%)	14 (78%)	0.006
Lymph node involved	16 (24%)	11 (23%)	5 (28%)	0.68
Prior hysterectomy	66 (100%)	48 (100%)	18 (100%)	--

Category	All Patients (N = 66)	CT-based ISBT (n = 48)	MR-based ISBT (n = 18)	P-value
Chemotherapy at initial diagnosis^[7]	13 (20%)	7 (15%)	6 (33%)	0.10
Chemotherapy at recurrence	30 (45%)	22 (46%)	8 (44%)	0.92
Concurrent with EBRT	26 (39%)	20 (42%)	6 (33%)	0.53
Prior radiation therapy	24 (36%)	15 (31%)	9 (50%)	0.16
EBRT	4 (6%)	2 (4%)	2 (11%)	
Brachytherapy	8 (12%)	6 (13%)	2 (11%)	
EBRT + Brachytherapy	12 (18%)	7 (27%)	5 (27%)	
Radiation therapy				
EBRT (Yes)	58 (88%)	44 (92%)	14 (78%)	0.14
Techniques				
IMRT	18 (27%)	11 (24%)	7 (39%)	
4-field	26 (39%)	20 (42%)	6 (33%)	
AP/PA	5 (8%)	4 (8%)	1 (6%)	
Others **	4 (6%)	1 (1%)	3 (17%)	
Not defined	13 (20%)	12 (25%)	1 (6%)	
Median dose (EQD ₂) - Gy	44.3 (20.6 – 50.0)	44.3 (30.1 – 50.0)	44.3 (20.6 – 46.0)	0.006
Brachytherapy	66 (100%)	48 (100%)	18 (100%)	---
Median number of fractions	5 (3 – 9)	5 (3 – 9)	5 (4 – 9)	0.85
Median dose per fraction	4.5 (2.3 – 8.0)	4.5 (2.3 – 8.0)	5.0 (3.3 – 6.7)	0.17
Median dose (EQD ₂) - Gy				
Prescription	30.5 (16.1 – 67.7)	29.3 (16.1 – 64.0)	33.8 (17.9 – 57.7)	0.10
D90	32.9 (10.4 – 77.3)	32.4 (10.4 – 62.7)	33.5 (19.7 – 77.3)	0.52
D _{2CC} rectum	17.7 (8.2 – 48.4)	17.0 (8.2 – 48.4)	22.0 (9.4 – 46.6)	0.10
D _{2CC} bladder	22.5 (4.4 – 63.0)	21.3 (7.5 – 49.5)	26.8 (4.4 – 63.0)	0.006
D _{2CC} sigmoid	8.2 (0.0 – 44.3)	8.1 (0.8 – 44.3)	9.0 (0.0 – 33.1)	0.53
Cumulative Dose (EQD₂) - Gy				
EBRT+BT	74.2 (52.2 – 106.6)	73.8 (52.2 – 106.6)	75.5 (55.7 – 93.2)	0.58
70 Gy	17 (26%)	13 (27%)	4 (22%)	0.68
>70 Gy	49 (74%)	35 (73%)	14 (78%)	
D90	75.6 (37.0 – 108.7)	75.2 (37.0 – 104.2)	75.7 (58.6 – 108.7)	0.58
70 Gy	20 (30%)	13 (27%)	7 (39%)	0.36
>70 Gy	46 (70%)	35 (73%)	11 (61%)	
D _{2CC} rectum	60.7 (39.0 – 84.8)	60.1 (39.0 – 79.4)	65.2 (47.9 – 84.8)	0.10
D _{2CC} bladder	65.9 (23.4 – 97.8)	64.6 (23.4 – 88.6)	72.5 (42.4 – 97.8)	0.006
D _{2CC} sigmoid	52.3 (9.4 – 75.5)	51.8 (9.4 – 73.0)	52.8 (27.0 – 75.5)	0.58

*** 3-field, Modified Segmental Boost Technique (MSBT); IMRT: Intensity Modulated Radiation Therapy; EBRT: External Beam Radiation Therapy; Brachy: Brachytherapy;

^[7] Chemotherapy for initial disease

Table 2

Patient, Tumor and Treatment Characteristics of All Recurrences

Age at diag. (yrs)	Histo	Primary stage	Tumor grade	Tumor size (cm)	LVI	Prior RT?	Site of recur.	Time to recur. (mos.)	BT dose (Gy)	Cum. EQD ₂ (Gy)
74	adenoca	IB	3	3.5	yes	yes	iliac, inguinal, hilar LN	13	48.94	93.19
67	adenoca	IB	2	2.3	yes	no	peritoneal, perihaptic	31	35.52	79.77
68	adenoca	IB	3	2.8	yes	no	lung, peritoneal, abd wall	15	27.19	71.43
54	adenoca	IA	3	4.0	no	no	left pelvic sidewall	28	27.56	71.81
57	adenoca	IV	2	1.5	no	no	peritoneal	30	27.20	71.40
54	adenoca	IC	2	1.0	no	yes	lung, mediastinum	6	32.70	76.90
56	adenoca	IA	3	3.0	no	yes	bone (L4 vertebra)	10	29.75	74.30
62	adenoca	IA	2	3.1	no	no	perihaptic, presacral, prevertebral	24	29.40	73.50
61	adenoca	IB	-	2.5	no	no	lung, Hepatic	47	25.10	75.10
79	adenoca	IA	3	2.0	no	no	para-aortic LN	12	35.30	79.60
81	adenoca	IB	2	2.0	no	no	vagina, lung	11	23.30	67.60
74	adenoca	IIIC	3	4.0	yes	yes	Vagina	18	28.80	105.6
54	adenoca	IB	1	2.0	no	no	Vagina	45	25.10	69.40
80	adenoca	IB	1	3.2	no	no	central pelvis (interval increase in size)	16	22.80	73.50
64	adenoca	IIIC	2	1.5	no	yes	peritoneum	16	58.60	102.90
60	adenoca	IA	3	2.9	no	yes	vagina, pelvic node	12	27.20	71.40
56	adenoca	IA	1	5.2	no	no	liver	20	35.30	79.60
57	adenoca	IIIA	2	1.0	no	yes	vagina	22	60.00	102.30
69	adenoca	IA	1	1.8	no	no	vagina	16	31.30	75.50
69	adenoca	IA	1	2.0	no	yes	vagina	20	27.20	66.10
59	adenoca	IB	1	0.8	yes	no	right psoas muscle	38	23.30	67.60
63	adenoca	IIIC	2	6.0	yes	no	abdomen	14	27.20	71.40
61	adenoca	IIIA	1	0.5	no	yes	vagina, vulva, lungs	14	35.50	65.60

Abbreviations: ISBT, Interstitial brachytherapy; Histo, Histology; Adenoca, Adenocarcinoma; Recur, Recurrence; BT, Brachytherapy; abd, abdominal; LN, lymph node; PAN, Para-aortic node; *italicized refers to local recurrence*

Table 3

a: Univariate Cox Analysis						
Category	LC (univariate)		DFI (univariate)		OS (univariate)	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age at diag. (continuous)	1.02 (0.96 – 1.10)	0.49	0.99 (0.95 – 1.03)	0.66	1.05 (1.00 – 1.11)	0.08
Year of Diagnosis						
2010	1.00 (0.25 – 3.77)	1.00	1.16 (0.46 – 2.69)	0.74	1.46 (0.57 – 3.72)	0.43
>2010 *	1		1		1	
Tumor size (cm)						
Continuous	0.72 (1.15 – 1.39)	0.20	0.89 (0.66 – 1.13)	0.36	0.97 (0.70 – 1.26)	0.85
FIGO stage (primary)						
III – IV	1.75 (0.37 – 6.65)	0.45	1.31 (0.47 – 3.17)	0.58	1.11 (0.38 – 2.87)	0.83
I – II *	1		1		1	
Grade						
3	0.36 (0.05 – 1.68)	0.20	1.28 (0.37 – 3.18)	0.89	3.71 (1.19 – 14.33)	0.02
2	0.37 (0.05 – 1.71)	0.21	1.28 (0.46 – 3.64)	0.64	1.05 (0.28 – 4.28)	0.94
1 *	1		1		1	
Lymphovascular invasion						
Yes	0.13 (0.01 – 0.74)	0.02	0.38 (0.14 – 0.94)	0.03	2.29 (0.84 – 6.81)	0.10
Lymph node involvement						
Yes	0.35 (0.02 – 1.94)	0.26	1.35 (0.52 – 3.17)	0.51	1.03 (0.36 – 2.62)	0.95
Chemotherapy at initial diagnosis ^[2]						
Yes	1.21 (0.18 – 5.05)	0.81	2.59 (0.98 – 6.16)	0.06	0.79 (0.19 – 2.39)	0.71
Any chemotherapy at recurrence						
Yes	0.12 (0.01–0.67)	0.01	1.15 (0.51–2.67)	0.72	0.51 (0.18–1.35)	0.18
Concurrent chemotherapy at recurrence						
Yes	0.16 (0.01–0.87)	0.03	0.93 (0.40–2.13)	0.87	0.28 (0.08–0.82)	0.02
Prior radiation therapy						
Yes	2.51 (0.66 – 10.21)	0.17	1.61 (0.67 – 3.71)	0.28	2.97 (1.16 – 7.91)	0.03

a: Univariate Cox Analysis					
Category	LC (univariate)		DFI (univariate)		OS (univariate)
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)
BT imaging status					
MR-guided ISBT	--	--	0.44 (0.13 – 1.18)	0.11	1.13 (0.36 – 3.09)
CT-guided ISBT *	1		1		1
BT dose (EQD ₂) (continuous)	0.99 (0.92 – 1.04)	0.61	1.00 (0.97 – 1.03)	0.93	1.01 (0.97 – 1.04)
Cum. dose (EQD ₂)					
Continuous	1.02 (0.96 – 1.08)	0.42	1.05 (1.00 – 1.08)	0.03	1.02 (0.98 – 1.06)
70.0 Gy	2.25 (0.55 – 8.53)	0.24	0.59 (0.19 – 1.51)	0.29	0.40 (0.09 – 1.21)
>70.0 Gy *	1		1		1
Cum. D90 (EQD ₂)					
Continuous	1.02 (0.97 – 1.08)	0.35	1.04 (1.01 – 1.07)	0.01	1.03 (0.99 – 1.06)
70.0 Gy	0.56 (0.08 – 2.33)	0.45	0.34 (0.10 – 0.92)	0.03	0.47 (0.14 – 1.30)
>70.0 Gy *	1		1		1
2-year K-M rate	84%		70%		85%
3-year K-M rate	84%		60%		72%
5-year K-M rate	79%		46%		53%

b: Multivariable Cox Analysis		
LC (adjusted)		
	HR (95% CI)	p-value
Lymphovascular invasion	0.08 (0.01 – 0.45)	0.001
Any chemotherapy at recurrence	0.07 (0.003 – 0.40)	0.001
DFI (adjusted)		
MR-based ISBT	0.62 (0.16 – 1.92)	0.42
Lymphovascular invasion	0.42 (0.13 – 1.92)	0.09
Cum. D90 (EQD ₂) ^[2]	1.05 (1.01 – 1.09)	0.01
OS (adjusted)		
	HR (95% CI)	p-value

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b: Multivariable Cox Analysis			
LC (adjusted)			
	HR (95% CI)	p-value	
MR-based ISBT	0.56 (0.16 – 1.89)	0.36	
Tumor grade**	3.57 (1.25 – 11.36)	0.02	
Concurrent chemotherapy at recurrence	0.59 (0.15 – 1.88)	0.38	

* Referent group: Diag, Diagnosis; BT, Brachytherapy; ISBT, Interstitial brachytherapy; Adenoca, Adenocarcinoma; Cum, Cumulative;

Chemotherapy for initial disease

** compared grade 3 versus grade 1–2 as referent;

70 vs >70 Gy

Table 4

a: Toxicities (assessed using the Common Toxicity Criteria Version 4.3)						
Characteristics	Grade	CT-based ISBT (n = 48)	MR-based ISBT (n = 18)	p-value		
Rectal	Grade 1	10 (21%)	4 (22%)	0.90		
	Grade 2	9 (19%)	4 (22%)	0.75		
	Grade 3	10 (21%)	2 (11%)	0.36		
Urinary	Grade 1	5 (10%)	5 (28%)	0.08		
	Grade 2	7 (15%)	1 (6%)	0.32		
	Grade 3	9 (19%)	1 (6%)	0.18		

b: Toxicities among reirradiation cases (assessed using the Common Toxicity Criteria Version 4.3)							
Characteristics	Grade	CT-based ISBT re-RT (n = 15)	CT-based ISBT no re-RT (n = 33)	p-value	MR-based ISBT re-RT (n = 9)	MR-based ISBT no re-RT (n = 9)	p-value
Rectal	Grade 1	2 (13%)	8 (24%)	0.94	3 (33%)	1 (11%)	0.92
	Grade 2	0 (0%)	9 (27%)	0.84	1 (11%)	3 (33%)	0.92
	Grade 3	4 (27%)	6 (18%)	0.95	2 (22%)	0 (0%)	0.89
Urinary	Grade 1	1 (7%)	4 (12%)	0.96	3 (33%)	2 (22%)	0.92
	Grade 2	4 (27%)	3 (9%)	0.88	0 (0%)	1 (11%)	0.92
	Grade 3	3 (20%)	6 (18%)	0.99	1 (11%)	0 (0%)	0.92

Abbreviations: ISBT, Interstitial brachytherapy; 2 patients had concurrent grades 3 rectal and urinary toxicities in CT-group
Abbreviations: ISBT, Interstitial brachytherapy; 2 patients had concurrent grades 3 rectal and urinary toxicities in CT-group