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Comparison of outcomes for MR-guided versus CT-guided high-dose-rate interstitial brachytherapy in women with locally advanced carcinoma of the cervix

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Abstract

Objective—The purpose was to compare local control (LC), overall survival (OS) and dose to the organs at risk (OAR) in women with locally advanced cervical cancer treated with MR-guided versus CT-guided interstitial brachytherapy (BT).

Methods—56 patients (29 MR, 27 CT) were treated with high-dose-rate (HDR) interstitial BT between 2005–2015. The MR patients had been prospectively enrolled on a Phase II clinical trial. Data were analyzed using Kaplan-Meier (K-M) and Cox proportional hazards statistical modeling in JMP® & R®.

Results—Median follow-up time was 19.7 months (MR group) and 18.4 months (CT group). There were no statistically significant differences in patient age at diagnosis, histology, percent with tumor size >4 cm, grade, FIGO stage or lymph node involvement between the groups. Patients in the MR group had more lymphovascular involvement compared to patients in the CT group (p<0.01). When evaluating plans generated, there were no statistically significant differences in median cumulative dose to the high-risk clinical target volume or the OAR.

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2-year K-M LC rates for MR-based and CT-based treatments were 96% and 87%, respectively (log-rank $p=0.65$). At 2 years, OS was significantly better in the MR-guided cohort (84% vs. 56%, $p=0.036$). On multivariate analysis, squamous histology was associated with longer OS (HR 0.23, 95% CI 0.07–0.72) in a model with MR BT (HR 0.35, 95% CI 0.08–1.18).

Conclusion—In this population of locally advanced cervical-cancer patients, MR-guided HDR BT resulted in estimated 96% 2-year local control and excellent early survival rates. Squamous cell histology was the most significant predictor for survival.

Keywords

Cervical carcinoma; Interstitial brachytherapy; MR-guidance; Radiation Oncology

INTRODUCTION

Treatment for locally advanced cervical cancer typically involves a combination of concurrent chemoradiation followed by brachytherapy (BT)[1]. BT is a major component of this treatment regimen; the modality has evolved from 2D-based dosimetry using point-based dosing to 3D-based volumetric planning. Volumetric planning can increase the precision of radiation dose delivery by improving the tumor definition and adjacent normal structures, resulting in coverage of the target and sparing of normal tissues. A prospective trial evaluating the efficacy of 3D-based volumetric planning found that 3D BT was associated with improved local relapse-free survival at 24 months compared to 2D imaging (78.5% vs. 73.9%) and with 20% lower global grade 3–4 toxicity (2.6% vs. 22.7%) in patients who received external beam radiation therapy (EBRT) and chemotherapy followed by BT [2].

Technological advances in BT planning include the introduction of magnetic resonance (MR)-guided treatment. MRI allows for assessment of tissue heterogeneity, as well as measurement of the extent of local tumor invasion of the parametria, vagina, uterus, bladder, and rectum. MR imaging arguably permits better visualization of the tumor at the time of BT, thereby allowing better dose distribution that should lead to improved outcomes. MR-based brachytherapy includes MR imaging obtained after the implant is complete, whereas MR guidance allows real-time imaging with adjustment of the catheters during the insertion process. The promise of 3D imaging to aid in tumor delineation led to the publication of MR based post-implant imaging and contouring guidelines by the GEC-ESTRO (Groupe Européen de Curietherapie and the European Society for Radiotherapy and Oncology) [3]. Recently, the results from a retrospective analysis from multiple institutions using 3D imaging after brachytherapy applicator insertion showed that among 731 patients with 43 months of follow-up, 3-year OS, pelvic control, local control (LC), and cancer-specific survival was 74%, 87%, 91%, and 79% respectively [4]. In a prospective trial of MR-guided brachytherapy (EMBRACE, international study on MRI-guided Brachytherapy in Locally Advanced Cervical Cancer) 23% of patients received a combined intracavitary/interstitial approach for at least one BT fraction. A follow-up analysis of rectal toxicities showed that the 3-year fistula risk was 12.5% with D2cc 75 Gy, and patients had a two-fold lower risk of proctitis with D2cc <65 Gy [5].

Patients with large tumors that may benefit the most from MR guidance [6]. We enrolled patients with locally advanced cervical cancer on a prospective clinical trial of MR based brachytherapy (clinicaltrials.gov identified NCT01399658) and compared these to CT based brachytherapy, with the goal of analyzing clinical outcomes as well as evaluating the toxicity profile of each method to determine if there is an advantage using one imaging modality versus the other.

MATERIALS AND METHODS

Patients

Records of 56 patients with biopsy-proven locally advanced cervical cancer who were treated with HDR interstitial BT between 2005 and 2015 were reviewed under an Institutional Review Board-approved protocol. Twenty-nine patients (52%) received 3D MR-guided interstitial catheter placement in a dedicated multimodality operating suite; all 29 were enrolled in a Phase II clinical trial and the treatment and outcome records from that trial were used for this study. The other 27 patients received 3D CT-based treatment planning. The medical records of those CT-based patients were identified and reviewed for patient, tumor, and treatment characteristics and clinical outcomes. Characteristics recorded included date of diagnosis, age at diagnosis, tumor size, grade, histology, International Federation of Gynecology and Obstetrics (FIGO) primary disease stage, and presence of lymphovascular invasion (LVI). Locally advanced disease was defined as stage IB2-IVA.

Treatment Procedures and Data Collection

All patients were treated with EBRT followed by HDR interstitial BT. HDR was administered twice daily, and the 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 high-risk clinical tumor volume (HR-CTV), and an α/β ratio of 3 for normal tissues and organs at risk (OAR).

Details of insertion technique and treatment planning have been described previously [7–9]. Most patients treated with template-based interstitial implants received both epidural anesthesia and general anesthesia, which was initiated on entering the MR or CT unit. Epidural anesthesia continued over the duration of the inpatient hospitalization (approximately 3 days). For patients with an intact uterus, a CT/MR-compatible tandem was placed using ultrasound-guidance. The central obturator (Best Medical International, Springfield, VA) was placed over the distal end of the tandem and advanced the full length of the vaginal canal. A Syed disposable template (Best Medical International, Springfield, VA) was placed over the obturator and sutured to the perineum. Catheters (Pro Guide, Elekta, Stockholm, Sweden) were iteratively inserted with image guidance under physician direction to maximize tumor coverage. Other patients had a ring or ovoids placed with interstitial catheters inserted through preset holes in the applicator. CT imaging (GE CT, 2-mm slices, 120 kVp, 300 mA, 60-cm field of view) or 3T MR (Siemens Verio) T2-weighted fast spin echo (Siemens turbo spin echo or TSE and fat-suppressed 3D gradient echo, Siemens VIBE) as well as RF-spoiled gradient echo (GRE) sequences were performed. Treatment planning (Oncentra workstation, Elekta) calculated the D90 to the clinical target

(CTV) and the D2cc doses to the organs at risk. Other treatment data collected included EBRT technique, number of fractions and dosing; number of HDR fractions; BT dosing; history of previous radiation treatment; and concurrent chemotherapy use, including chemotherapy agents used.

Clinical Endpoints

Patients were followed for outcomes including LC, disease-free interval (DFI) and OS, as well as post-treatment toxicities. In the MR-cohort, patients were seen in follow-up 90 days post-treatment and underwent a pelvic MRI +/- a PET/CT as well as 180 days post-treatment. Follow-up time was capped at 6 months for the MR-ISBT patients treated after November 11, 2014. In the CT-cohort, patients underwent a PET/CT at 90 days, with no further imaging if a complete response was achieved. Patients were examined every 3 months for 2 years. Local recurrence (LR) was defined as biopsy-proven disease or clinical progression in the true or central pelvis (cervix and adjacent tissues). Regional recurrence was defined as relapse in the pelvic nodes or pelvic sidewalls, and distant metastases as recurrent disease outside the pelvis. Treatment-related complications were evaluated according to the Common Toxicity Criteria for Adverse Events (v. 4) [10].

Statistical Analysis

For numeric variables, we reported median with interquartile range or mean with standard deviation, and percentages for categorical and ordinal variables. To compare the two treatment groups, Chi-square analyses were used; Fisher's exact test was used for binary variables when sample sizes were small. The likelihood ratio test was used for categorical variables with multiple groups. The Kaplan-Meier method was used to generate actuarial survival estimates and plots; these were compared using the log rank test. Univariate and multivariate Cox proportional hazards models created by backward selection methods were used to identify predictors of LC, DFI, and OS. All statistical analyses were performed using JMP version 13.0 (SAS Institute Cary, NC) and R version 3.3.2 [11]. Statistical tests were two-sided and considered significant for p -values less than 0.05.

RESULTS

Patients

Fifty-six patients fit the inclusion criteria for this study and were included in the analysis. Twenty-nine patients (52%) received MR-guided interstitial catheter placement, and 27 (48%) received CT-based planning and treatment. The two study groups were well balanced with respect to baseline characteristics (Table 1). All patients in the MR-guided group had received concomitant chemotherapy with the EBRT (87% cisplatin) compared to 26/27 in the CT-guided group (76% cisplatin; p =NS). Median follow-up time was 18.6 months (rg, 1.2–92.8) overall and was 18.4 (rg, 5.5–92.8) months for the CT cohort and 19.7 (rg, 1.2–59.5) months for the MR cohort (p =0.44).

Most patients presented with squamous cell histology (85%) and tumors >4 cm (70%; median, 5.6 cm; range, 0.5–10); these characteristics were not statistically different between the two cohorts. Most patients (94%) had an ECOG performance score ≤ 2 . Sixty-six percent

of patients had lymph node involvement at presentation; 5% had FIGO stage I disease, 20% stage II, 45% stage III, and 30% stage IV. In the MR-guided group, the majority of patients had moderately-differentiated tumors (45%) whereas 60% of patients in the CT-guided group had poorly-differentiated tumors; this difference was not statistically significant. There were no statistically significant differences in FIGO stage or lymph node involvement between the two groups ($p=0.37$ and $p=0.93$, respectively). In addition, there were no statistically significant differences in tumor grade ($p=0.54$) at time of diagnosis. Patients in the MR-guided group were more likely to have LVI ($p<0.01$). Compared to the CT cohort, patients treated with MR-based BT were younger (median age: MR=49.9 years, CT=57.6 years); this was not statistically significant ($p=0.11$). Patients in the MR-based BT group were more likely to have been diagnosed later in the time period reviewed (i.e., between 2011 and 2015 versus 2005–2010, $p<0.01$) and 20 patients in the CT group versus 27 patients in the MR group had MR imaging at diagnosis ($p=0.04$). In the CT cohort, all patients but one had tandem and interstitial BT (without ring or ovoids), while 66% of patients in the MR-based group had tandem and interstitial BT ($p=0.01$).

Dosimetric parameters

With regard to graphic plans generated at the time of BT, there were no statistically significant differences in median cumulative dose to the contoured HR-CTV for any of the following: 2-Gy (EQD2) fractions (MR=80.3 Gy, CT=80.1 Gy, $p=0.79$); D90 tumor (MR=79.8 Gy, CT=81.2 Gy, $p=0.51$); D2cc rectum (MR=69.3 Gy, CT=70.2 Gy, $p=0.43$); D2cc bladder (MR=82.4 Gy, CT=81.8 Gy, $p=0.80$); and D2cc sigmoid (MR=65.6 Gy, CT=66.2 Gy, $p=0.96$) (Table 1).

Local Recurrence and Overall Survival

At the time of analysis, there were 2 LR in the MR-guided group and 3 in the CT-guided group, corresponding to 2-year LC rates of 96% and 87%, respectively ($p=0.65$) (Figure 1). Characteristics of patients with local and distant recurrences are listed in Table 2. Two-year DFI rates were 73% and 65% in the MR-guided versus CT-guided group, respectively ($p=0.87$) (Supplemental Figure S1). There were 3 deaths (10%) in the MR-guided group and 11 (41%) in the CT-guided group. All 3 deaths in the MR-guided cohort were due to disease progression. In the CT-guided cohort, 4 deaths (36%) were due to disease progression, 1 (9%) to infection/sepsis, and 6 (55%) were of unknown cause. Of the 6 with unknown cause, 1 had documented LR and 3 had documented distant metastases. Two-year Kaplan-Meier OS rates were 84% and 56% for the MR and CT groups, respectively ($p=0.036$) (Figure 2).

On univariate analysis, no factors were found to be significantly associated with LC or DFI (Table 3a). For OS, squamous cell histology and MR-guided interstitial BT were associated with a significantly lower risk of death. On multivariate analysis, after adjusting for multiple factors, only squamous cell histology was associated with longer OS (HR 0.23, 95% CI 0.07–0.72, $p=0.0134$) (Table 3b).

Toxicities

There were no significant differences in toxicities comparing CT to MR. Rectal toxicity was noted in 8 patients in the MR-based cohort and 9 in the CT-based cohort. With respect to

toxicity grade, there were 3 vs. 5 grade 1 toxicities ($p=0.38$), 4 vs. 1 grade 2 toxicities ($p=0.17$), and 3 vs. 4 grade 3 toxicities ($p=0.61$) in the MR- and CT-cohorts, respectively; there was no grade 4 rectal toxicity. Urinary toxicity was noted in 8 patients in the MR-based cohort and 6 in the CT-based cohort. Urinary toxicity grades were 6 vs. 4 grade 1 ($p=0.57$), 3 vs. 3 grade 2 ($p=0.93$), and 3 vs. 1 grade 3 ($p=0.32$) in the MR- and CT-cohorts, respectively; no grade 4 urinary toxicity was reported (Table 4).

DISCUSSION

In this study we evaluated outcomes for women with locally advanced cervical cancer treated with either MR-guided brachytherapy or CT-guided BT. The two cohorts were otherwise treated the same way and had no major significant differences in their baseline tumor characteristics or dosimetry, except for the presence of LVI. We found no significant differences between the groups with respect to local recurrence or toxicity. On multivariate analysis, only squamous histology significantly predicted for improved OS with MR resulting in a 65% improvement in survival that was not statistically significant.

Brachytherapy is an essential curative element in the treatment of locally advanced cervical cancer. Advances in imaging and volumetric planning have achieved more precise radiation delivery with a defined outline of the tumor and organs at risk, thereby allowing an accurate estimate of dose delivered. MR-guided BT is arguably an improvement over CT-guided BT, due to the improved visualization of critical soft tissue planes, allowing assessment of local invasion.

MR-based BT guidelines were introduced in 2005 after publication of the GEC-ESTRO guidelines [12]. Our institution began a program of MR-guided interstitial BT in 2002; we prospectively enrolled 25 patients to a clinical trial with a 0.5T MR [8] and described the feasibility and low toxicity rate using MR-guided interstitial brachytherapy [13].

Interstitial BT is necessary for patients with bulky, locally advanced cervical carcinoma, given that LC rates with EBRT and intracavitary BT range from 48–63% for Stage III and 13–18% for Stage IV disease [14]. Syed et al. reported on the use of interstitial BT for locally advanced cancers in 87 patients with Stage III/IV disease, resulting in a 73% overall LC rate and a 5-year DFI of 58%. This study used orthogonal films and image reconstruction to determine dose to tumor and normal tissues. Our study found that MR-guided BT resulted in a higher 2-year LC rate compared to CT-guided BT (96% vs. 87%) that was not statistically significant likely due to the low number of local relapses. MR-guided planning was associated with a significantly improved OS as compared to CT-guided planning. We evaluated upfront characteristics between the two groups, including ECOG status, which was not significantly different between the two groups. Patients in the MR-cohort had a slightly larger median tumor size compared to patients in the CT-cohort (5.8 versus 5.3 cm, respectively) and had significantly more LVI. The MR-guided cohort was enrolled on a prospective trial, and had slightly longer follow up. Most patients relapse in the first two years, though longer follow up will help provide information about late relapses and how this may impact survival after 2 years. Squamous histology predicted for improved

OS on multivariate analysis. This is consistent with previous reports noting that squamous cell histology is a positive prognostic factor for cervical cancer patients [15–16].

Complications from interstitial BT were common in the 2D era. In the aforementioned Syed et al. trial, 10% of the cohort had grade 3 or 4 toxicities and the fistula rate was 4% [14]. The introduction of CT-based guidance for interstitial planning purposes allowed for more accurate dosimetric planning and analysis [17]. The visualization of OARs allowed for better dosimetry, with easier distinction between tumor and normal tissues, thereby leading to lower complication rates [18]. Although rectal and genitourinary grade 1–3 toxicities were noted in both CT and MR groups, there were no grade 4 toxicities. Both CT and MR imaging modalities are excellent at delineating normal tissue if bladder and rectal contrast are used for the CT, therefore we did not expect a significant difference in OAR contouring between the two [19]. MR superiority is with regards to improved tumor visualization [6]. In future studies, if the treated region is limited to just the MR defined tumor volume rather than to the entire cervix, then we would hope for lower doses to the OARs and a difference in toxicity. By covering an HR-CTV in both, the area treated in CT and MR are similar enough that no toxicity difference was observed. Longer follow-up is needed to determine if late toxicities will differ between the MR and CT groups.

There are several limitations to the study that must be recognized. This is a small, single-institutional analysis, with the MR patients enrolled on a prospective trial. Patients on a prospective trial are subject to more rigorous follow-up. In the future, it would be beneficial to study this in a larger trial with longer follow-up. As MR utilization increases in the US and elsewhere, this is becoming feasible to consider. In a survey by the American Brachytherapy Society, the utilization of MRI increased from 2% to 34% between 2007 and 2014 [20]. Given that almost all centers in the United States have access to a CT scanner, 88% of respondents of the survey obtain a CT scan at the first applicator insertion, and 77% get a CT scan at the first and subsequent fractions. An MRI scan may provide crucial details about the tumor, and when obtained a few days before brachytherapy, can still provide important information; this is recommended when an MR immediately after implantation is not feasible.

In conclusion, we found that treatment of locally advanced cervical cancer with MR-guided interstitial BT following EBRT with concurrent chemotherapy was associated with equivalent local control, toxicity and improved overall survival when compared to CT-guided interstitial BT. Squamous histology was the most significant predictor for improved survival. As MR imaging is the gold standard for cervical cancer, more centers may be incorporating MR-guided interstitial BT due to its improved soft-tissue delineation. Future trials should incorporate MR-guided interstitial BT in the treatment of large volume locally advanced cervical cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- MR-guided interstitial brachytherapy results in a 96% local control rate.
- There were no statistically significant dosimetric differences between modalities.
- Histology was a significant predictor for survival.

Figure 1.

Kaplan-Meier Plot of Local Control.

Local control by imaging modality utilized during brachytherapy. There were 2 local recurrences in the MR-guided BT group and 3 local recurrences in the CT-guided BT group, resulting in 2-year local control rates of 96% and 87%, respectively.

Figure 2.

Kaplan-Meier Plot of Overall Survival.

Overall survival by imaging modality utilized during brachytherapy. MR-guided BT was associated with significantly longer overall survival compared to CT-guided BT.

Table 1

Patient, Tumor and Treatment Characteristics

Category	All Patients (N = 56)	CT-guided ISBT (n = 27)	MR-guided ISBT (n = 29)	P-value
Median follow-up (months)	18.6 (1.2–92.8)	18.4 (5.5–92.8)	19.7 (1.2–59.5)	0.28
Median age at diagnosis (years)	55.0 (26.9–77.5)	57.6 (26.9–77.5)	49.9 (29.0–77.0)	0.11
ECOG status				
>2	2 (3%)	0 (0%)	2 (7%)	0.11
2	52 (94%)	25 (93%)	27 (93%)	
Not defined	2 (3%)	2 (7%)	0 (0%)	
Year of diagnosis				
2005 – 2010	11 (20%)	11 (41%)	0 (0%)	<0.01
2011 – 2015	45 (80%)	16 (59%)	29 (100%)	
Diagnostic Method				
MRI	47 (84%)	20 (74%)	27 (93%)	0.04
PET/CT	55 (98%)	27 (100%)	28 (97%)	0.25
Tumor size (continuous) cm				
4 cm	5.6 (0.5–10)	5.3 (2.0–9.1)	5.8 (0.5–10)	0.62
> 4 cm	16 (28%)	8 (30%)	8 (28%)	0.93
> 4 cm	39 (70%)	19 (70%)	20 (70%)	
Not identified	1 (2%)	0 (0%)	1 (2%)	
Primary disease stage (FIGO)				
I	3 (5%)	2 (7%)	1 (3%)	0.37
II	11 (20%)	7 (27%)	4 (14%)	
III	25 (45%)	9 (33%)	16 (55%)	
IVA	17 (30%)	9 (33%)	8 (28%)	
Histology				
Squamous cell	48 (86%)	21 (77%)	27 (93%)	0.25
Adenocarcinoma	6 (11%)	4 (15%)	2 (7%)	
Others *	2 (3%)	2 (8%)	0 (0%)	
Grade				

Category	All Patients (N = 56)	CT-guided ISBT (n = 27)	MR-guided ISBT (n = 29)	P-value
1	4 (7%)	2 (7%)	2 (7%)	0.54
2	21 (38%)	8 (30%)	13 (45%)	
3	29 (52%)	16 (60%)	13 (45%)	
Not defined	2 (3%)	1 (3%)	1 (3%)	
LVI present	29 (52%)	9 (33%)	20 (69%)	<0.01
Lymph node involved	37 (66%)	18 (67%)	19 (66%)	0.93
Chemotherapy use (yes)	55 (98%)	26 (96%)	29 (100%)	0.25
Cisplatin	45 (80%)	20 (76%)	25 (87%)	
Carboplatin	4 (8%)	2 (8%)	2 (7%)	
Cisplatin / Taxol	1 (2%)	1 (4%)	0 (0%)	
Carboplatin / Taxol	1 (2%)	0 (0%)	1 (3%)	
Cisplatin / Gemcitabine	1 (2%)	1 (4%)	0 (0%)	
Not identified / None	3 (6%)	2 (8%)	1 (3%)	
Radiation therapy				
EBRT (Yes)				
Techniques				
IMRT	16 (29%)	7 (26%)	9 (31%)	
4-field	25 (45%)	12 (44%)	13 (45%)	
AP/PA	1 (2%)	0 (0%)	1 (3%)	
Others**	4 (6%)	2 (7%)	2 (7%)	
Not defined	10 (18%)	6 (23%)	4 (14%)	
Median dose (EQD ₂) - Gy	45.0 (45.0–57.6)	45.0 (45.0–57.6)	45.0 (45.0–54.8)	0.15
Brachytherapy				
Brachytherapy Type				0.01
Interstitial #	5 (10%)	1 (4%)	4 (14%)	
Tandem & Interstitial	45 (80%)	26 (96%)	19 (66%)	
Tandem & Ring & Interstitial	4 (7%)	0 (0%)	4 (14%)	
Tandem & Ovoid & Interstitial	2 (3%)	0 (0%)	2 (6%)	
Median number of fractions	5 (2–9)	5 (2–9)	5 (4–9)	0.92

Category	All Patients (N = 56)	CT-guided ISBT (n = 27)	MR-guided ISBT (n = 29)	P-value
Median dose per fraction Gy	5.3 (3.0–9.0)	5.5 (3.0–9.0)	5.0 (3.0–6.0)	0.17
Median dose (EQD ₂) - Gy				
Prescription	35.5 (21.1–45.1)	35.4 (27.2–43.2)	35.5 (21.1–45.1)	0.45
D90	32.9 (11.7–58.9)	32.1 (11.7–58.9)	33.5 (18.6–55.8)	0.96
D _{2CC} rectum	22.2 (5.0–44.5)	23.5 (5.0–44.5)	22.0 (10.4–38.3)	0.33
D _{2CC} bladder	32.6 (14.1–153.1)	31.4 (14.1–89.3)	35.6 (15.5–153.1)	0.18
D _{2CC} sigmoid	18.5 (0.0–41.3)	15.3 (0.0–36.4)	21.5 (3.1–41.3)	0.33
Cumulative Dose (EQD₂) - Gy				
EBRT+BT	80.6 (70.7–94.7)	80.1 (77.1–94.7)	80.3 (70.7–89.4)	0.79
D90	80.7 (57.9–100.2)	81.2 (57.9–100.2)	79.8 (62.8–100.0)	0.51
D _{2CC} rectum	70.1 (56.4–92.5)	70.2 (56.4–92.5)	69.3 (57.3–81.5)	0.43
D _{2CC} bladder	82.1 (58.7–196.3)	81.8 (62.1–185.5)	82.4 (58.7–196.3)	0.80
D _{2CC} sigmoid	66.0 (46.4–87.5)	66.2 (46.4–87.5)	65.6 (48.9–86.2)	0.96

* Histology: Adenosquamous, clear cell;

** 3-field, Modified Segmental Boost Technique (MSBT);

Prior supracervical hysterectomy (no tandem feasible)

Key: IMRT: Intensity Modulated Radiation Therapy; EBRT: External Beam Radiation Therapy; Brachy: Brachytherapy

Table 2

Patient, Tumor and Treatment Characteristics of All Recurrences

Age at diag.(yrs)	Histo	Primary stage	Tumor grade	Tumor size (cm)	LVI	Site of recur.	Time to recur. (mos.)	BT dose (Gy)	Cum. EQD ₂ (Gy)
38	SCC	IIB	2	5.3	Yes	Distant (peritoneum)	7	34	84.92
59	SCC	IIIB	2	6	No	<i>Rectum/anus</i>	57	33.75	82.92
49	Adenoca	IVA	3	8	Yes	Distant (lung)	26	30	81.75
25	SCC	IIB	2	4.7	No	Left SCV LN, RP LNs	17	27.5	83.18
58	SCC	IIIB	1	10	Yes	Aortocaval LN	4	27.5	79.77
41	SCC	IVA	3	4	Yes	Liver, spleen	18	17.6	74.22
33	SCC	IIIB	1	6	Yes	Bone metastases	6	29.75	82.98
29	SCC	IIIB	2	7.3	Yes	<i>Parametrium</i>	5.5	27	82.19
29	SCC	IIIB	3	7.8	Yes	Pelvic LN	1.5	31.5	82.19
52	SCC	IVA	3	6.7	No	Distant (lung)	3	30	84.3
67	SCC	IIIA	3	3	Yes	<i>Cervix, PAN</i>	5	33.5	83.9
60	SCC	IVB	2	7.6	NI	Distant (lung)	2	28	83.9
60	SCC	IIA	2	2.9	NI	<i>Pelvic nodule, bladder</i>	14.5	27.5	79.8
43	SCC	IVA	3	3.6	Yes	<i>Uterus, aortocaval LN</i>	5	27.5	79.8
43	SCC	IVB	NI	7.8	NI	Distant prog NOS	4	31.5	79.4
43	Adenoca	IIB	3	7.3	NI	PAN, RP LNs	5	27	77.9
63	SCC	IIIB	2	7.4	NI	Axillary LN	27	31.5	79.7
34	Adenoca	IB2	3	7.3	NI	PAN	4	33.75	82.9

Key: ISBT, Intersitital brachytherapy; Histo, Histology; SCC, Squamous cell carcinoma; Adenoca, Adenocarcinoma; Adenosq, Adenosquamous; Recur, Recurrent; BT, Brachytherapy; abd, abdominal; LN, lymph node; PAN, Para-aortic node; NI, Not identified; prog, progression; SCV, Supraclavicular; NOS, not otherwise specified; *italicized refers to local recurrence*

Table 3a

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 (0.95–1.10)	0.63		0.97 (0.94–1.01)	0.19		1.01 (0.96–1.06)	0.76	
Year of Diagnosis									
2010	2.18 (0.26–13.98)	0.43		1.93 (0.66–5.06)	0.22		1.97 (0.59–5.94)	0.25	
>2010★	1			1			1		
Tumor size (cm)									
Continuous	1.07 (0.71–1.71)	0.76		1.05 (0.84–1.34)	0.65		1.05 (0.81–1.38)	0.72	
FIGO stage (primary)									
III–IV	1.34 (0.20–26.23)	0.79		0.92 (0.35–2.88)	0.87		0.91 (0.30–3.35)	0.87	
I–II★	1			1			1		
Grade									
3	-	0.25		0.89 (0.21–6.09)	0.89		-	0.07	
2	-	0.31		1.50 (0.38–10.02)	0.59		-	0.07	
I★	1			1			1		
Histology									
SCC	0.44 (0.06–8.91)	0.51		0.60 (0.19–2.60)	0.44		0.19 (0.06–0.58)	0.005	
Others★	1			1			1		
Lymphovascular invasion									
Yes	-	-		1.83 (0.63–6.03)	0.27		1.25 (0.39–4.36)	0.71	
Lymph node involvement									
Yes	0.32 (0.04–1.93)	0.21		1.66 (0.62–5.17)	0.32		1.16 (0.38–3.86)	0.79	
BT imaging status									
MR-guided ISBT	0.65 (0.08–4.13)	0.64		0.92 (0.36–2.41)	0.87		0.27 (0.06–0.90)	0.03	
CT-guided ISBT★	1			1			1		
BT dose (EQD ₂)	0.97 (0.81–1.18)	0.73		1.02 (0.93–1.12)	0.68		1.01 (0.91–1.13)	0.86	

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Category [#]	LC (univariate)			DFI (univariate)			OS (univariate)		
	HR (95% CI)	p-value		HR (95% CI)	p-value		HR (95% CI)	p-value	
Cum. dose (EQD2)	1.00 (0.79–1.23)	0.97		0.97 (0.87–1.09)	0.68		1.04 (0.91–1.17)	0.58	
Cum. D90 (EQD2)	1.03 (0.94–1.14)	0.58		1.02 (0.97–1.08)	0.44		1.01 (0.95–1.07)	0.80	

★ Referent group;

[#] unknown values excluded from the analyses

Key: Diag. Diagnosis; BT, Brachytherapy; ISBT, Interstitial brachytherapy; Adenoca, Adenocarcinoma; Cum, Cumulative;

Table 3b

Multivariable Cox Analysis

OS (adjusted)		
	HR (95% CI)	p-value
MR-guided ISBT	0.35 (0.08–1.18)	0.09
Histology SCC	0.23 (0.07–0.72)	0.013

Key: SCC, Squamous cell carcinoma

Table 4

Toxicities(assessed using the Common Toxicity Criteria Version 4.3)

Characteristics	Grade	CT-guided ISBT (n =27)	MR-guided ISBT (n =29)	p-value
Rectal	1	5	3	0.38
	2	1	4	0.17
	3	4	3	0.61
Urinary	1	4	6	0.57
	2	3	3	0.93
	3	1	3	0.32

Key: ISBT, Interstitial brachytherapy