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Outcomes with Image-based Interstitial Brachytherapy for Vaginal Cancer

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Abstract

PURPOSE—To compare clinical outcomes of image-based versus non-image-based interstitial brachytherapy (IBBT) for vaginal cancer

METHODS AND MATERIALS—Of 72 patients with vaginal cancer treated with brachytherapy (BT), 47 had image guidance (CT=31, MRI=16) and 25 did not. Kaplan-Meier (KM) estimates were generated for any recurrence, local control (LC), disease-free interval (DFI), and overall survival (OS) and Cox models were used to assess prognostic factors.

RESULTS—Median age was 66 and median follow-up time was 24 months. Median cumulative EQD2 dose was 80.8 Gy in the non-IBBT group and 77 Gy in the IBBT group. For non-IBBT versus IBBT, the 2-year KM LC was 71% vs. 93% ($p=0.03$); DFI was 54% vs. 86% ($p=0.04$); and OS 52% vs. 82% ($p=0.35$). On multivariate analysis, IBBT was associated with better DFI (HR 0.24, 95% CI 0.07–0.73). Having any 2 or more of chemotherapy, high-dose-rate (HDR) BT or IBBT (temporally correlated variables) significantly reduced risk of relapse (HR=0.33, 95% CI=0.13–0.83), compared to having none of these factors.

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Conflict of Interest Statement

All authors declare that they have no conflicts of interest.

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CONCLUSION—Over time, the use of chemotherapy, HDR and IBBT has increased in vaginal cancer. The combination of these factors resulted in the highest rates of disease control. Image-guided brachytherapy for vaginal cancer patients maximizes disease control.

Keywords

radiation; brachytherapy; CT; MRI; vaginal cancer

INTRODUCTION

Vaginal cancer is an uncommon gynecologic malignancy. It accounts for 1–2% of all gynecologic malignancies or 0.3% of all invasive cancers among women, and its annual incidence has remained fairly stable since the 1980s [1–3]. The rarity of this disease and the paucity of randomized studies on vaginal cancer have made evaluation of its treatment efficacy difficult. [4, 5]. Established prognostic factors for tumor recurrence include baseline tumor size or volume, disease stage, extent of tumor in the vagina, nodal involvement, histologic subtype and tumor grade [4, 6, 7].

Radiation therapy is currently the standard of care for non-metastatic, advanced vaginal cancer [6–10]. Although organ-sparing surgery may occasionally be considered, vaginal cancers are usually not amenable to surgery, due to proximity of tumor to critical structures, such as the urethral sphincter, bladder and rectum and other patient-related factors [5, 11]. Radiation therapy may be delivered with external beam (EBRT) or brachytherapy (BT) alone or a combination of both. EBRT is used to address potential micro-metastatic nodal disease and to downsize the primary tumor prior to BT [12], studies have shown the effectiveness and superiority of BT in the delivery of curative radiation dose to the gross tumor [4]. BT may either be performed using an interstitial or intracavitary technique. The advantage of interstitial BT is that it allows for improved dose delivery when the disease cannot be adequately covered by the intracavitary technique [12].

For over a decade, evidence supports that 3-dimensional (3D) imaging with ultrasound, CT or MRI in gynecological brachytherapy planning improves the identification and delineation of a target volume [13–15]. The American Brachytherapy Society Consensus Guidelines for interstitial brachytherapy for vaginal cancer recommend the use of image-guided BT to optimize dose delivery to the target tissue and minimize dose to the organs at risk [4, 9]. However, there have been no comparative studies to date of clinical outcomes of image-based interstitial brachytherapy (IBBT) for vaginal cancer that assess the advantages of the addition of imaging. This study was designed and conducted to compare the clinical outcomes of patients treated with IBBT to those of patients treated with non-IBBT for vaginal cancer.

PATIENTS AND METHODS

Data were reviewed under an Institutional Review Board (IRB)-approved protocol with a waiver of consent. Medical records of 102 patients with biopsy-proven primary or baseline recurrent vaginal cancer were identified and retrospectively reviewed. All patients included in the analysis received interstitial BT between December 1973 and 2014. Patients typically

received interstitial implant placement under epidural and general anesthesia followed by iterative insertion under CT- or MR- based contouring, treatment planning, and treatment as an in-patient. Details of treatment planning, including implantation principles and techniques have been described in previous publications [7, 16–18]. Indications for interstitial BT included significant vaginal involvement with tumor thickness greater than 5 mm, bulky disease with poor response to EBRT and/or adjacent organ invasion [4, 12].

Exclusion criteria include cases of vaginal cancer treated with intracavitary BT only (n = 15), cancer involving the cervix or vulva (n = 4), vaginal cancer treated with EBRT only (n = 5), and patients with substantial missing records (n = 6). We reviewed records for each of the 72 patients to ascertain whether or not imaging was used to guide the placement of interstitial implants and the specific imaging modality used. Five patients of the 72 were diagnosed between 1973 – 1980. Baseline patient and tumor characteristics were recorded for all patients, including date of diagnosis, age at diagnosis, body mass index (BMI), tumor site, size, differentiation, histology, disease stage according to the International Federation of Gynecology and Obstetrics (FIGO) 2009 classification, presence of lymphatic vessel invasion (LVI) and lymph node involvement as ascertained through the use of abdominal and pelvic computed tomography (CT), magnetic resonance imaging (MRI) or positron emission tomography (PET) scans.

TREATMENT CHARACTERISTICS

Patients received EBRT followed by an interstitial BT boost. Specific details on radiation dose, EBRT technique, year and duration of treatment, and BT dose rates were obtained from medical records. Data regarding chemotherapy use, type of chemotherapy, prior hysterectomy, and prior use of surgery in the management of the disease were also obtained. HDR was administered twice daily with a median of 5 (3 – 9) fractions and a median dose per fraction of 4.4 Gy. A median LDR of 30 Gy was prescribed over a median of 53 (37 – 75) hours. Cumulative radiation dose was converted to the equivalent dose in 2Gy per fraction (EQD2) using the quadratic BED equation with an α/β ratio of 10.

CLINICAL OUTCOMES

Clinical outcomes in the form of local, regional, and distant relapse; disease-free interval (DFI); overall survival (OS); and organs-at-risk complications or toxicities were assessed and recorded for both the IBBT and non-IBBT groups. Local relapse was defined by direct biopsy- or Papanicolaou smear-proven tumor recurrence and/or clinical progression on physical exam in the vagina or paravaginal area. Regional relapse was defined as recurrence in the pelvic or inguinal lymph nodes as detected on imaging and distant relapse was defined as para-aortic recurrence or overt distant metastasis. DFI was defined as the interval from the date of diagnosis of primary or baseline recurrent disease to the date of documented progression, recurrence, or last follow-up. OS was defined from the date of diagnosis of primary or baseline recurrent disease until death from any cause or last contact with the patient.

Treatment-related complications were recorded according to the Common Toxicity Criteria for Adverse Events (v. 4) [19]. Early complications were defined as those occurring within 90 days of interstitial BT and late complications as those occurring more than 90 days after completion of BT.

STATISTICAL ANALYSIS

We reported median with interquartile range or mean with standard deviation for numeric variables, and percentages for categorical and ordinal variables. Chi-square analyses comparing the two 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 method and compared using the log rank test. Univariate and multivariate Cox proportional hazards models created by backward selection methods were used to identify predictors of disease-free interval (DFI), and OS. All statistical analyses were performed using SAS version 9.3 (SAS Institute Cary, NC). Statistical tests were two-sided and considered significant for p-values less than 0.05.

RESULTS

Medical record review identified 72 patients with primary or recurrent vaginal cancer treated with interstitial BT, 47 (65%) received IBBT and 25 (35%) received interstitial BT without image guidance. Within the IBBT group, 16 (34%) received MR-based interstitial BT and 31 (66%) had CT-based treatment.

Patient and Tumor Characteristics

Details of overall and group-specific patient and tumor characteristics, as well as details of treatment are shown in Table 1. Regarding EBRT technique, 33% of all patients were treated using the 4-field approach and 36% with anteroposterior/posteroanterior (AP/PA) fields. Sixteen patients (22%) were treated with intensity-modulated radiation therapy (IMRT).

CLINICAL OUTCOMES AND PROGNOSTIC FACTORS

The patient, tumor, and treatment characteristics of all cases of relapse are shown in the Supplementary Table. Figure 1 is a graphical illustration of relapse by compared treatment groups. A total of 20 patients (28%) had histologically confirmed evidence of any tumor recurrence following treatment, of which 11 (15.3%) were local-only relapses. Any recurrence occurred in 11/25 patients (44%) in the non-IBBT group and 9/47 (19%) in the IBBT group, whereas local-only relapse occurred in 7 (28%) with non-IBBT and 4 (8.5%) with IBBT. One of the 9 patients in the IBBT group had residual disease. The median time to failure was 22.6 months in the IBBT group and 13.8 months in the non-IBBT group.

Within the IBBT group, 3 patients with baseline FIGO stage II disease developed local relapse and 1 with FIGO stage IVA disease had residual disease. Two patients in the IBBT group with baseline FIGO stage IVA disease developed metastatic spread to the lungs and

adrenals and 2 patients with baseline FIGO stage II disease developed distant recurrence in the small bowel and liver.

In the non-IBBT group, 3 patients with baseline FIGO stages I-II disease had local relapse only, 3 with stages I-III disease had regional relapse, 1 with FIGO stage II disease had distant relapse, 3 with FIGO stages II-IVA disease had a combination of local and regional relapse, and 1 patient with FIGO stage IVA disease had relapse in all three sites (Figure 1). The average tumor size of all cases of relapse was 5.9 cm in the IBBT group and 5.0 cm in the non-IBBT group. The median cumulative dose received by patients who had local relapse was 70.8 Gy (range, 62.5 – 74.3) in the IBBT group compared to 87.6 Gy (range, 78.0 – 95.6) in the non-IBBT group.

Overall, the median follow-up time was 24.0 (13.0 – 83.7) months. There was no significant difference in median follow-up time between the Non-IBBT [23.2 (13.0 – 83.7)] and IBBT [23.8 (14.1 – 36.2)] subgroups. The two-year Kaplan-Meier local control rate was significantly better for the IBBT group (93%) compared to non-IBBT group (71%), ($p = 0.03$) (Figure 2A). When compared to non-IBBT, IBBT was associated with an unadjusted 73% reduction in the risk of local relapse ($HR = 0.27$; 95% $CI = 0.07, 0.90$). The 2-year actuarial DFI rates were 54% for the non-IBBT group and 86% for the IBBT group ($p = 0.04$) (Figure 2B). The median overall survival was 2.3 years for the non-IBBT group and 7.0 years for the IBBT group. Compared to non-IBBT, two-year actuarial OS rates had a 30% difference favoring IBBT (52% vs. 82%), however this difference was not statistically significant ($p = 0.35$; Figure 2D).

In subset analyses, excluding five patients with baseline recurrent disease ($n = 67$), we found no statistically significant difference between the IBBT and non-IBBT subgroups with respect to age at diagnosis, median tumor size, median length of follow-up, stage, histology, and grade. Two-year actuarial rates for LC (93% vs. 71%, $p = 0.048$), and DFI (88% vs. 54%, $p = 0.049$) remained significantly better for IBBT compared to non-IBBT. There was no difference in 2-year OS rates (83% vs. 52%, $p = 0.6$). We compared baseline characteristics and clinical outcomes of CT-guided ($n = 28$) versus MR-guided ($n = 13$) HDR interstitial BT. Two-year actuarial rates did not significantly differ between CT and MR for DFI (CT = 89%, MR = 92%), OS (CT = 78%, MR = 90%), median D_{2cc} rectum (CT = 66.5 Gy, MR = 72.8 Gy), bladder (CT = 70.2 Gy, MR = 73.2 Gy), and sigmoid (CT = 53.2 Gy, MR = 55.5 Gy).

Results of Cox univariate models for LC, DFI, and OS are shown in Table 2. Univariate analyses showed that tumor size >4 cm and the use of IBBT, chemotherapy, HDR BT, and IMRT were all significant predictors of DFI; with the later four also attaining significance for LC. Age was the only significant predictor of OS in the univariate hazard analyses, with older patients having lower survival rates. Given a total of 20 relapse events and a relatively small sample size, a full multivariate adjusted model with all variables included may have limited power to detect a difference between the compared groups, even if one truly exists. On multivariable analysis (MVA) for DFI, compared to non-IBBT, IBBT was associated with a 76% reduction in the risk of relapse ($HR = 0.24$, 95% $CI = 0.07 – 0.73$), adjusting for

stage and size in the model. For OS, the HR was 0.65 (95% CI = 0.31 – 1.33) for IBBT adjusting for age at diagnosis (Table 2).

We observed a time-dependent correlation in the use of IBBT, HDR BT, and chemotherapy. Therefore, although year of diagnosis was not a significant predictor in the univariate analysis, we attempted to include it in a multivariable model to control for possible changes in treatment patterns over time. In that model, after adjusting for tumor size and year of diagnosis, use of IBBT (HR = 0.03, 95% CI = 0.01 – 0.68, $p = 0.033$) was associated with a significantly reduced risk of any relapse. Furthermore, as it was not feasible to tease out the effects of these modern treatment modalities, we then attempted to evaluate the combined impact of IBBT, chemotherapy, and HDR use in the treatment of vaginal cancers, by analyzing different combinations of these treatment modalities, compared to patients who had none. Thus, we assessed in a separate analysis outcomes of patients who received all three, any two, and any one of these treatment modalities, compared to patients who received none. Thirty-five patients (49%) received all three, 12 (17%) received any two, 4 (5%) received any one, and 21 (29%) received none of the three treatment modalities. Compared to patient who had none of these three treatment modalities, the DFI HR for patients who received all three treatment modalities was 0.20 (95% CI = 0.05 – 0.59), HR for patients who received any one or two of these modalities was 0.58 (95% CI = 0.20 – 1.57), and HR for those who received any two or more of these factors was 0.33 (95% CI = 0.13 – 0.83). For OS, the HR for receiving all three factors was 0.50 (95% CI = 0.19 – 1.21), any 1 or 2 factors was 0.93 (95% CI = 0.42 – 2.01), and any 2 or more of these 3 factors was 0.68 (95% CI = 0.32 – 1.47).

Toxicity

A summary of crude incidence rates of observed toxicities are shown in Table 3. A total of nine patients experienced grade 3 genitourinary or gastrointestinal toxicities: eight were in the non-IBBT group and 1 was in the IBBT group. Patients treated with non-IBBT had two acute and three late grade 3 genitourinary toxicities, and one acute and two late grade 3 gastrointestinal toxicities. Observed toxicities in the non-IBBT group included gross hematuria, rectovaginal fistula, overflow incontinence and proctitis. Median cumulative radiation dose received by these patients in 2-Gy fractions was 79.1 Gy (range, 69.0 – 95.1). The only patient with grade 3 toxicity in the IBBT group developed proctitis after receiving a cumulative radiation dose of 88.1 Gy. Compared to the non-IBBT group, IBBT was associated with fewer grade 3 genitourinary and grade 2 gastrointestinal toxicities, respectively.

DISCUSSION

Radiation therapy remains the standard of care for advanced, non-metastatic primary and recurrent vaginal cancer, and brachytherapy is at the core of this definitive management [1, 6, 20]. Our study reports clinical outcomes of 72 patients with primary or recurrent vaginal cancer treated with interstitial brachytherapy, with or without image guidance, at a single institution. Significant prognostic covariates for disease-free interval included image-based BT status, chemotherapy use, tumor size, use of high-dose-rate BT, and use of IMRT.

Compared to non-IBBT, IBBT was associated with a significant reduction in the risk of local relapse, improved disease-free interval, and fewer grade 2 and 3 acute and late toxicities.

At our institution, the management of vaginal cancer has evolved over time. Almost all patients treated before 2002 received low-dose-rate (LDR) brachytherapy, whereas 86% of those treated during or after 2002 received HDR brachytherapy. Prospective randomized trials in cervical cancer do not show significant differences in clinical outcomes between LDR and HDR [20, 21] but do show improved clinical outcomes with concurrent chemo-radiation [20, 22, 23]. By analyzing the combined impact of IBBT, chemotherapy, and use of HDR, we observed that 2-year actuarial disease-free rates were significantly better for patients who received two or more of these modern treatment modalities.

Overall in this study, the 2-year local control, disease-free interval and overall survival rates were 93%, 86% and 82%, respectively, for patients who received image-based interstitial BT, and 71%, 54%, and 52% for patients who underwent non-image-based interstitial BT. There are very few studies on the use of image-based interstitial brachytherapy for vaginal cancer. Most of these have shown comparable but slightly lower local control, progression-free and overall survival rates, except the study by Dimopoulos *et al.* [23], using MR-based brachytherapy. In that study, 13 patients who received MR-based contouring and planning for locally advanced vaginal cancer had 3-year local control, progression-free and overall survival rates of 92%, 85%, and 85% respectively. Beriwal *et al.* [11] reported 2-year locoregional and overall survival rates of 79% and 70%, respectively, in 30 cases of primary and recurrent vaginal cancer treated with three-dimensional image-based HDR interstitial brachytherapy. Samant *et al.* [22] showed 5-year locoregional-relapse-free survival, progression-free survival and overall survival rates of 92%, 75% and 66%, respectively, in 12 patients treated with concurrent chemo-radiation. De Ieso *et al.* [8] showed comparable 2-year local control and overall progression-free survival rates of approximately 74% and 74%, respectively, however, the 2-year overall actuarial survival rate reported by that group was markedly lower (48%).

Disease-free and overall survival rates published in one of the large series by Pingley *et al.* [24] is comparable to outcome results of the non-IBBT subgroup of our study. In this study by Pingley *et al.*, 5- year DFS and OS rates for a subset of 59 patients who received non-image-based BT (intracavitary and Interstitial) for primary vaginal cancer were 53% and 56% respectively. Compared to observed results of our study, most patients had FIGO stage II disease and experienced relapse within the first 2 years of treatment, however, the reported median age of 53, with 66% of patients aged 31 – 60 years shows a much a younger population compared to age ranges reported in most vaginal cancer studies.

Toxicities to organs at risk were reported using the Common Criteria for Adverse Events (v. 4). Compared to the non-IBBT group, IBBT was associated with significantly lower grade 3 and 2 genitourinary and gastrointestinal toxicities, respectively (Table 3). Only one patient in the IBBT group had grade 3 gastrointestinal toxicity (proctitis) compared to three grade 3 gastrointestinal and five grade 3 genitourinary toxicities in the non-IBBT group. Patients with documented grade 3 toxicities received slightly higher cumulative doses to the clinical target volume. The observed difference in toxicity may be attributable to the benefit of

volume-optimized dosimetric planning associated with image-based treatment and IMRT use, which have been shown to minimize radiation dose to organs at risk [25–27]. No grade 4 or 5 toxicity was observed.

In contrast, Dimopoulos *et al.* [23] reported three cases of grade 3 toxicities (vesicovaginal, rectovaginal and periurethral necrosis) among 13 patients who received MR-guided BT with concurrent chemotherapy for locally advanced vaginal cancer. De Ieso *et al.* [8] reported a total of two acute and two late grade 3 genitourinary toxicities, and Samant *et al.* [22] reported severe (grade 3) late gastrointestinal toxicities (fistulae) requiring surgery in 17% of study patients who underwent interstitial BT.

Limitations of our study include its retrospective design, inclusion of patients treated over a long time period encompassing changing treatment techniques, and sample size limiting the power to detect significant differences. In order to account for possible time-dependent variability in treatment approach, we controlled for year of diagnosis in a separate model, despite its insignificance in the univariate Cox model. In that model, use of IBBT remained a significant predictor of DFI after adjusting for year of diagnosis and tumor size.

Despite these limitations, this series stands out as the largest single-institutional analysis, evaluating clinical outcomes for image-guided versus non-image-guided interstitial brachytherapy in vaginal cancer. The results of this study show possible overall benefit in local control, disease-free interval and overall survival and significantly reduced toxicity to organs at risk with the use of IBBT. The impact of image-based interstitial BT on overall survival of patients with vaginal cancer should be evaluated within larger prospective study designs.

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Figure 1.
Sites of relapse in image-based and non-image-based brachytherapy

Figure 2.
Kaplan-Meier curves of A) local control, B) disease-free interval, C) overall survival

Table 1

Patient, Tumor, and Treatment Characteristics

Category	All Patients (N=72)	Non-Image-Based BT (n=25)	Image-Based BT (n=47)	P-value
Median follow-up (months)	23.5 (13.5 – 42.6)	23.2 (13.0 – 83.7)	23.8 (14.1 – 36.2)	0.965
Median age at diagnosis (years)	66.4 (50.0 – 75.0)	65.0 (50.9 – 74.4)	66.5 (49.4 – 75.1)	0.673
Median BMI (kg/m²)	26.4 (22.3 – 30.2)	26.2 (22.3 – 29.3)	26.5 (21.8 – 30.3)	0.952
Median weight (Kg)	69.1 (56.2 – 83.4)	62.1 (56.7 – 88.2)	70.1 (56.2 – 82.4)	0.606
Year of diagnosis				
1973 – 2002	48 (66.7%)	24 (96.0%)	0 (0.0%)	<.0001
2003 – 2015	24 (33.3%)	1 (4.0%)	47 (100.0%)	
Diagnostic imaging				
CT	16 (22.2%)	4 (16.0%)	12 (25.5%)	<.0001
MRI	34 (47.2%)	3 (12.0%)	31 (66.0%)	
PET	3 (4.2%)	0 (0.0%)	3 (6.4%)	
Prior hysterectomy	44 (61.1%)	16 (64.0%)	28 (59.6%)	0.714
Tumor size				
4 cm	36 (50.0%)	12 (48.0%)	24 (51.1%)	0.805
> 4 cm	36 (50.0%)	13 (52.0%)	23 (48.9%)	
Tumor site				
Apex (Cuff)	22 (30.6%)	4 (16.0%)	18 (38.3%)	0.229
Upper 1/3	12 (16.7%)	7 (28.0%)	5 (10.6%)	
Middle 1/3	3 (4.2%)	0 (0.0%)	3 (6.4%)	
Lower 1/3	14 (19.4%)	6 (24.0%)	8 (17.0%)	
Upper 2/3	12 (16.7%)	4 (16.0%)	8 (17.0%)	
Lower 2/3	12 (16.7%)	1 (4.0%)	1 (2.1%)	
Entire	3 (4.2%)	2 (8.0%)	1 (2.1%)	
Unknown	4 (5.6%)	1 (4.0%)	3 (6.4%)	
Vaginal wall involvement^{†**}				
Anterior wall	29 (40.3%)	12 (48.0%)	17 (36.7%)	0.330

Category	All Patients (N=72)	Non-Image-Based BT (n=25)	Image-Based BT (n=47)	P-value
Posterior wall	19 (26.4%)	4 (16.0%)	15 (31.9%)	0.145
Lateral wall	25 (34.7%)	13 (52.0%)	12 (25.5%)	0.025
Stage (FIGO)				
I	3 (4.2%)	2 (8.0%)	1 (2.1%)	0.314
II	39 (54.2%)	15 (60.0%)	24 (51.1%)	
III	16 (22.2%)	6 (24.0%)	10 (21.3%)	
IVA	9 (12.5%)	2 (8.0%)	7 (14.9%)	
Recurrent	5 (6.9%)	0 (0.0%)	5 (10.6%)	
Histology				
Squamous cell	58 (80.6%)	21 (84.0%)	37 (78.7%)	0.310
Adenocarcinoma	13 (18.3%)	3 (12.0%)	10 (21.3%)	
Clear cell	1 (1.4%)	1 (4.0%)	0 (0.0%)	
Grade				
1	5 (6.9%)	4 (16.0%)	1 (2.1%)	0.111
2	28 (38.9%)	10 (40.0%)	18 (38.3%)	
3	26 (36.1%)	6 (24.0%)	20 (42.6%)	
Not defined	13 (18.6%)	5 (20.0%)	8 (17.0%)	
LVI present	13 (18.1%)	2 (8.0%)	11 (23.4%)	0.010
Lymph node involved	26 (36.1%)	8 (32.0%)	18 (38.3%)	0.596
Radiation therapy				
RT dose (EQD2)				
EBRT alone	47.5 ± 5.8 Gy	48.4 ± 6.2 Gy	47.0 ± 5.7 Gy	0.346
BT alone	31.3 ± 8.6 Gy	34.3 ± 11.4 Gy	29.7 ± 6.2 Gy	0.068
EBRT+BT	78.1 ± 8.1 Gy	80.8 ± 9.9 Gy	77.0 ± 6.6 Gy	0.071
Brachytherapy dose rate				
HDR	42 (58.3%)	0 (0.0%)	42 (89.4%)	<.0001
LDR	30 (41.7%)	25 (100.0%)	5 (10.6%)	
Chemotherapy used	44 (61.1%)	4 (16.0%)	40 (85.1%)	<.0001
Concurrent chemo	40(56.6%)	4 (16.0%)	36 (76.6%)	

Category	All Patients (N=72)	Non-Image-Based BT (n=25)	Image-Based BT (n=47)	P-value
Prior Surgery				
Yes	11 (14.3%)	5 (20.0%)	6 (12.8%)	0.436

Table 2

Univariate Cox Analysis

Category	LC (univariate)		DFI (univariate)		OS (univariate)	
	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Age at Diag. (continuous)	1.02	(0.98 – 1.06)	1.01	(0.99 – 1.04)	1.02	(1.01 – 1.05)
Body Mass Index						
Obese	0.82	(0.11 – 5.00)	0.43	(0.06 – 1.86)	0.55	(0.12 – 1.81)
Overweight	0.37	(0.02 – 2.86)	0.32	(0.05 – 1.41)	0.79	(0.29 – 2.10)
Underweight	-		0.88	(0.05 – 5.18)	-	
Normal*	1		1		1	
Year of Diagnosis						
>2002	0.39	(0.11 – 1.31)	0.48	(0.20 – 1.19)	0.78	(0.38 – 1.62)
2002*	1		1		1	
Tumor Size						
>4cm	1.81	(0.55 – 6.89)	3.23	(1.25 – 9.94)	0.94	(0.49 – 1.83)
4cm*	1		1		1	
FIGO Stage (overall)						
Recurrent	-		0.18	(0.01 – 1.90)	0.13	(0.01 – 1.00)
IV	0.90	(0.11 – 18.12)	0.67	(0.14 – 4.67)	0.40	(0.09 – 2.08)
III	0.14	(0.01 – 3.54)	0.12	(0.01 – 1.04)	0.54	(0.16 – 2.43)
II	0.38	(0.06 – 7.16)	0.29	(0.08 – 1.92)	0.34	(0.11 – 1.48)
I*			1		1	
Advanced (III)	0.74	(0.19 – 2.47)	0.83	(0.32 – 2.10)	1.09	(0.53 – 2.17)
Early (I – II)	1		1		1	
Grade						
3	0.28	(0.05 – 2.14)	0.61	(0.14 – 4.17)	1.61	(0.49 – 7.29)
2	0.47	(0.10 – 3.31)	1.03	(0.27 – 6.78)	1.24	(0.39 – 5.58)
1*	1		1		1	
Histology						
Adenoca	0.42	(0.22 – 2.20)	0.42	(0.07 – 1.46)	0.83	(0.31 – 1.88)

Category	LC (univariate) HR (95% CI)	DFI (univariate) HR (95% CI)	OS (univariate) HR (95% CI)
Squamous*	1	1	1
Lymphovascular Invasion			
Yes	1.20 (0.18 – 4.99)	1.29 (0.36 – 3.69)	1.32 (0.48 – 3.11)
Lymph node involvement			
Yes	1.02 (0.26 – 3.39)	1.20 (0.47 – 2.93)	1.46 (0.71 – 2.94)
Prior Hysterectomy			
Yes	7.20 (1.38 – 132.9)	1.46 (0.60 – 3.92)	1.30 (0.67 – 2.55)
Prior Surgery			
Yes	2.37 (0.51 – 8.21)	2.95 (0.90 – 7.49)	0.70 (0.25 – 1.60)
Chemotherapy Use			
Yes	0.21 (0.05 – 0.72)	0.35 (0.14 – 0.85)	0.57 (0.28 – 1.14)
IMRT Use			
Yes	-	0.19 (0.01 – 0.91)	0.39 (0.06 – 1.32)
BT Imaging Status			
IBBT	0.27 (0.07 – 0.90)	0.40 (0.15 – 0.97)	0.71 (0.34 – 1.46)
Non-IBBT*	1	1	1
Brachytherapy Energy			
HDR	0.24 (0.05 – 0.85)	0.29 (0.10 – 0.73)	0.74 (0.35 – 1.53)
Cum. Dose (EQD2)			
Continuous	1.06 (0.99 – 1.14)	1.04 (0.98 – 1.09)	0.99 (0.22 – 1.01)
Multivariable Cox Analysis			
DFI (with size)	HR (95% CI)		
BT Imaging Status (IBBT)	0.24 (0.07 – 0.73)		
FIGO Stage	Multiple groups		
Size	4.21 (1.47 – 14.43)		
DFI (without size)			
BT Imaging Status (IBBT)	0.25 (0.08 – 0.71)		
FIGO Stage	multiple groups		

Category	LC (univariate) HR (95% CI)	DFI (univariate) HR (95% CI)	OS (univariate) HR (95% CI)
Overall Survival			
BT Imaging Status (IBBT)	0.65 (0.31 – 1.33)		
Age at diagnosis	1.03 (1.01 – 1.05)		

Table 3

Toxicities (assessed using the Common Toxicity Criteria Version 4.3)

Characteristics	Grade	Non-IBBT(n=23)	IBBT (n=47)	p-value
Gastrointestinal	Grade 1	5 (22%)	13(28%)	0.594
	Grade 2	10 (44%)	7 (15%)	0.010
	Grade 3	3 (13%)	1 (2%)	0.103
Genitourinary	Grade 1	4 (17%)	15 (32%)	0.259
	Grade 2	5 (22%)	4 (8%)	0.143
	Grade 3	5 (22%)	0 (0%)	0.002

Abbreviations: IBBT, Image-based brachytherapy