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American Brachytherapy Task Group Report: A pooled analysis of clinical outcomes for high-dose-rate brachytherapy for cervical cancer

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Abstract

PURPOSE—Advanced imaging used in combination with brachytherapy (BT) has revolutionized the treatment of patients with cervical cancer. We present a comprehensive review of the literature for definitive radiation with high-dose-rate (HDR) BT. In addition, we investigate potential outcome improvement with image-based brachytherapy (IBBT) compared to studies using traditional Point A dosing. This review extensively investigates acute and late toxicities.

METHODS AND MATERIALS—This study reviews the literature from 2000 to 2015 with an emphasis on modern approaches including concurrent chemotherapy (chemoRT), radiation, and HDR BT and IBBT. Descriptive statistics and pelvic control (PC), disease-free survival (DFS), and overall survival (OS) outcomes were calculated using weighted means to report pooled analysis of outcomes.

RESULTS—Literature search yielded 16 prospective, 51 retrospective studies that reported survival outcomes, and 13 retrospective studies that focused on acute and late toxicity outcomes regardless of applicator type. There are 57 studies that report Point A dose specification with 33 having chemoRT, and 10 studies that use IBBT, 8 with chemoRT. Patients receiving radiation and chemoRT with HDR BT in the prospective studies, with >24 months followup, rates of PC were: for RT: 73%, SD: 11; CRT: 82%, SD: 8; DFSdRT: 55%, SD: 10; CRT: 65%, SD: 7; OSdRT: 66%, SD: 7; CRT: 70%, SD: 11. In the retrospective studies, the PC rates (weighted means) for the

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radiation and chemoradiation outcomes are 75% vs. 80%, and for DFS, the values were 55% vs. 63%, respectively. Comparing patients receiving chemoRT and IBBT to traditional Point A dose specification, there is a significant improvement in PC ($p < 0.01$) and DFS ($p < 0.01$) with IBBT. The range of genitourinary late toxicity reported for radiation was Grade 3: 1–6% and for chemoRT 2–20%. The range of late gastrointestinal toxicity for radiation was Grade 3: 4–11% and for chemoRT, 1–11%. For the late gynecologic toxicity, only 1 of the 16 prospective trials report a Grade 1–2 of 17% for radiation and 9% for chemoRT effects.

CONCLUSIONS—We present concise outcomes of PC, DFS, OS, and toxicity for cervical cancer patients treated with chemoradiation and HDR BT. Our data suggest an improvement in outcomes with the use of IBBT compared with traditional Point A dose prescriptions. In conclusion, HDR BT is a safe, effective modality when combined with IBBT.

Keywords

Cervical cancer; Radiation; Image guidance; Brachytherapy; HDR

Introduction

Cervical cancer affects over 12,000 women in the United States and accounts for more than 4200 deaths annually. Advanced stage disease (Stage IIB) continues to be an important cause of morbidity and mortality (1). Definitive irradiation, with both external beam radiation and brachytherapy (BT), has been the mainstay of curative treatment of locally advanced cervical cancer for more than half of a century. BT is a key component in the treatment of cervical cancer as it allows for dose escalation to the tumor while minimizing the dose to surrounding critical organs at risk (OAR) such as the sigmoid, bladder, and rectum. Patterns of care studies established the essential role of BT in the management of cervical cancer and linked its use to improvements in pelvic control (PC) and disease-free survival (DFS) (2).

In 1999, the National Cancer Institute issued a practice changing statement mandating that the new standard of care includes the addition of concurrent chemotherapy (chemoRT) to radiation therapy due to significant outcome improvements. This consensus statement revolutionized the management and clinical outcome of locally advanced cervical cancer (3–8). While the integration of systemic therapy in the treatment paradigm of locally advanced cervical cancer has evolved, radiation treatment options have also significantly progressed over time. In the late 1990s, radiation therapy centers around the globe started a major transition from the routine use of low-dose-rate BT to high-dose-rate (HDR) BT (9). Furthermore, within the last decade, the advent of image-based brachytherapy (IBBT) for both applicator insertion and treatment planning has increased the procedural implantation and treatment planning options for the treatment of cervical cancer (10). With the widespread use of sophisticated imaging modalities in radiation oncology departments, the use of three-dimensional (3D) imaging for contouring and treatment planning for gynecologic BT is increasing (11–17). In 2008, the American Brachytherapy Society published a practice patterns survey regarding 3D imaging in gynecologic BT (18). Of the survey responders, 70% obtained a CT scan during the implantation process (18) whereas in 2014, 95% report using CT (Grover *et al.* IJROBP accepted, personal communication). An

increasing number of radiation centers have switched over the past decade from two-dimensional (2D) treatment planning to IBBT (11, 13–22). Use of image guidance is more complex and time consuming and, resultantly, has not been universally adopted (23, 24). The use of MRI-based BT has also increased to 34% compared to the 2007 survey (Grover *et al.*, IJROBP accepted). The benefit of MRI in the planning process is the superior soft tissue delineation that permits targeting of the residual tumor volume with BT. In addition, MRI-based BT is used to determine the parametrial involvement or areas of gross tumor response known as the “gray zones” that are not in the gross tumor volume but need to be included in the high risk clinical target volume. This delineation can allow for dose escalation to the primary tumor and targeting of response after chemoRT with external beam (13–15).

Unfortunately, with the advent of more sophisticated external beam radiation modalities, the increasing use of image-based radiation requiring advanced technical skills for competency, and the increased complexity with HDR, the use of BT for cervical cancer has declined. In a recent SEER review, the BT utilization rate for cervical cancer has decreased from 83% in 1988 to 58% in 2009 ($p < 0.001$), with a corresponding decline in overall survival (OS) (25).

There is a plethora of data reporting outcomes in cervical cancer after definitive radiation. The purpose of this comprehensive review is to present the recent PC, DFS, and OS outcomes in the era of chemoRT and HDR BT for locally advanced cervical cancer. Furthermore, we sought to explore potential outcome differences that exist between IBBT and traditional Point A dosing and 2D planning in the available literature with chemoRT. In addition, we also examine acute and late gastrointestinal (GI), genitourinary, and gynecologic toxicity outcomes after definitive therapy.

Methods and materials

We define inclusion criteria for the literature search using the Population, Intervention, Control, Outcome, Study Design (Table 1) approach (26). We searched the published English medical literature from January 2000 until May 2015 in MEDLINE and PubMed using the terms “cervical cancer,” “high-dose-rate,” “radiation,” and “brachytherapy.” This search yielded 649 published articles. Of those, both prospective and retrospective studies with at least 40 patients with at least 24 months of reported followup (FU) were included for this analysis. Case reports, abstracts, dosimetric studies, special populations, low-dose-rate, MDR, small studies less than 40 patients, short FU <24 months reported, redundant study populations, chemoRT/study drug objectives, posthysterectomy, review article, non-cervical cancer studies, and specific studies on applicator molding were excluded. The abstract refinement then yielded 150 full text articles. Eighty-seven articles met the inclusion criteria: 16 prospective outcomes, 0 prospective toxicity, 51 retrospective outcomes, and 13 retrospective toxicity studies as shown in Fig. 1. We then performed an in-depth review for analyses of primary clinical outcomes PC, DFS, OS, and acute and late toxicities. For the IBBT group, there were 10 prospective and retrospective studies and 57 that used Point A dosing. We then examined the eight studies that used chemoRT and IBBT, and 33 investigations that report on chemoRT outcomes using Point A prescriptions.

Given the heterogeneity of the patients reported, some studies describe a percentage of patients being treated with radiation vs. chemoRT. We therefore report the outcomes of radiation and chemoRT patients separately in the descriptive tables. In addition, for the toxicity results, several studies do not specify a toxicity scale. Most of the acute and late toxicity reports use the radiation therapy oncology group (RTOG), Common Terminology Criteria for Adverse Events version 3 or 4, European Organisation for Research and Treatment of Cancer, or Late Effects Normal Tissue Task Force (LENT)-Subjective, Objective, Management, Analytic (SOMA) scales. We combined rectal and bowel toxicity to report GI toxicities together. For a comprehensive analysis of outcomes and creation of figures, we included all retrospective and prospective studies. The outcomes in terms of PC, DFS, or OS are reported as actuarial or median FU time. For the acute and late toxicities, we constructed graphs of median number with toxicity outcomes and severity using a toxicity scoring system. In the data analysis of toxicity, we note that most studies use RTOG criteria for grading late toxicity. For the IBBT group, we include studies that use CT- or MR-based planning as a comparison to the group that prescribed dose to Point A.

Statistical analysis

For comprehensive analysis of outcomes and creation of figures, we include all retrospective and prospective studies. Descriptive statistics were calculated using SAS 9.4 (Cary, NC). We note that reported DFS, OS, and PC rates differ among those treated with radiation (RT) vs. chemoRT (CRT), and several studies have a combination of treatment groups. The outcomes in terms of PC, DFS, or OS are reported at an actuarial or a median FU time. We construct plots of PC, DFS, and OS around a weighted mean of outcome. Using a pooled analysis and patient numbers in the studies examined, we provide weighted means calculated using the statistical software, R version 3.2.1 (open source) and corresponding Forest plots with the pooled SD and 95% confidence intervals (CIs). Time points chosen for the weighted means calculation were greater than 24 months as reported study outcomes. Ideally, we would be able to report outcomes at various specific time points, but the data set did not allow for this specification. The reported FU time in the data set is actually the mean of all subjects' FU times in the included studies. To compare the IBBT and the Point A prescription studies using chemoRT, we compared the weighted means, with the 95% CI, calculated as each individual study. To compare the results, a Student's *t*-test was used with the SD representing the SD for the sample mean. For the Forest plots, the width of the line shows the confidence, with the area of the horizontal box representing the weight given to the studies included. For the acute and late toxicities, we constructed graphs of median number of articles with toxicity outcomes and severity using a toxicity scoring system with weighted means. In data analysis of toxicity, we note that most studies use RTOG criteria for grading toxicity. Given the variation in the scoring scale and time points reported of the studies, we report crude toxicity percentages vs. a weighted mean analysis.

Pelvic control

The literature search yielded 16 prospective studies reporting on local control for radiation or chemoRT and HDR BT for cervical cancer (10, 27–41). Local control is defined as no recurrence in the pelvis. Of the studies, six report outcomes with radiation and 12 report chemoRT outcomes. For those patients, the weighted mean PC at 24 months for RT: 74%,

SD: 11 (95% CI: 52, 95) and CRT: 81%, SD: 9 (95% CI: 64, 99). For the 51 retrospective studies reviewed that met our criteria, 28 studies reported PC outcomes for radiation and 28 for chemoRT with HDR BT (42–92). The weighted mean PC rate at 24 months for RT was 75%, SD: 18 (95% CI: 40, 110) and for CRT was 81%, SD: 16 (95% CI: 49, 112).

Disease-free survival

Nine prospective studies report DFS outcomes for cervical patients treated with HDR BT with radiation and chemoRT. The weighted DFS means at 24 months for the patients treated with RT: 55%, SD: 9.6 (95% CI: 36, 74) and CRT: 65%, SD: 7 (95% CI: 51, 80). For the retrospective studies, the weighted DFS means at 24 months for the patients treated with RT: 56%, SD: 20 (95% CI: 16, 96) and CRT: 63%, SD: 21 (95% CI: 22, 104).

Overall survival

For the prospective studies, the weighted mean at 24 months for OS for the RT: 66%, SD: 7 (CI: 52, 80) and CRT: 65%, SD: 7 (CI: 51, 80). For the retrospective series, there are 37 studies provide a weighted mean OS for the RT: 54%; SD: 18 (18, 90) and CRT: 66%, SD: 17 (33, 99).

Tables 2 and 3 display the prospective and retrospective studies, respectively, with the study characteristics and outcomes for PC, DFS, and OS for the radiation and chemoRT patients. Table 6 depicts the weighted means and outcomes for the prospective and retrospective studies with a corresponding forest plots in Figs. 2 and 3.

IBBT vs. Point A dose prescription

We examined the eight studies using chemoRT and IBBT with the 35 studies using chemoRT and Point A dose prescriptions. Table 6 shows the weighted means and comparisons of PC, DFS, and OS between the groups. PC and DFS were significantly increased in the IBBT studies, $p < 0.01$ and $p < 0.01$, respectively. The mean improvement in PC and DFS in the era of chemoRT is 3%. The OS of the groups were statistically different, with the mean OS better in the Point A dose group vs. the IBBT group, $p < 0.01$. The weighted means and comparisons are shown in Table 6 with corresponding comparison of the standardized mean differences in Fig. 4.

Toxicity

From our review, of the 16 prospective studies, only six report acute toxicity outcomes using the RTOG scale ($n = 4$), NCIC ($n = 1$), or the LENT/SOMA ($n = 1$). There is little data reporting for Grade 3 or higher toxicity in the prospective studies for GU toxicity for RT alone patients. For the late effects, the 14 of the 16 prospective studies report toxicity scales using the RTOG ($n = 9$), NCIC ($n = 2$), or not specified ($n = 3$). Of the 64 retrospective studies reviewed, 13 have a primary outcome of late toxicity reporting. Forty of the 51 retrospective outcome series report late effects after RT or CRT.

Acute toxicity

For radiation and chemoradiation treatment, in the prospective and retrospective series, the range of GU acute toxicity reported is RT: Grade 2: 1–54%, Grade 3: 1–3%, and Grade 4:

0%; CRT: Grade 2: 2–53%, Grade 3: 1–3%, and Grade 4: 0%. The range of acute GI toxicity is RT: Grade 2: 15–48%, Grade 3: 3–11%, and Grade 4: 5%; CRT: Grade 2: 5–62%, Grade 3: 1–25%, and Grade 4: 1–2%. As seen in Tables 4 and 5, only two of the IBBT studies report acute toxicity.

Late toxicity

For radiation and chemoRT treatment, in the prospective and retrospective series, the range of GU late toxicity reported is RT: Grade 2: 3–8%, Grade 3: 1–5%, and Grade 4: 2–5%; CRT: Grade 2: 2–7% and Grade 3: 1–14%, with heterogeneity of the grouping of Grade 4 toxicity per Table 2. The range of late GI toxicity is RT: Grade 2: 4–6%, Grade 3: 3–11%, and Grade 4: 0–11%; CRT: Grade 2: 1–13%, Grade 3: 1–4%, and Grade 4: 1–5%. For the late gynecologic (GYN) toxicity, only 1 of the 16 prospective trials report a Grade 1–2 of 17% for radiation and 9% for chemoRT effects. For the retrospective studies, seven studies report GYN vaginal late toxicity. The range of late GYN toxicity is RT: Grade 2: 2–23%, Grade 3: 1–10%, and Grade 4: 0–6%; CRT: Grade 2: 29–61%, Grade 3: 3–7%, and Grade 4: 3% and otherwise unspecified from other studies. For the IBBT studies, nine report late toxicity. The range of late GU toxicity is Grade 4: 1–4%; late GI toxicity Grades 3–4: 2–4%; and late GYN toxicity Grades 3–4: 3%.

The acute and long-term GI, GU, GYN toxicity with scale for radiation and chemoRT patients are illustrated in Tables 4 and 5 (93, 95–100, 102–105), with nine of the IBBT reporting late toxicity.

Discussion

Outcomes in cervical cancer are shaped by several clinical and pathologic risk factors. This pooled analysis demonstrates the improvement in PC and DFS seen in the era of chemoRT with IBBT compared to the Point A dose reports. Therefore, our article suggests that with refinement in technique that is offered with IBBT, there is a reasonably small, but probably still significant, marginal improvement in cervical cancer outcomes. Historically, cervical cancer risk stratification is largely based on International Federation of Gynecology and Obstetrics (FIGO) staging, presence of pelvic or para-aortic lymphadenopathy, and patient performance status. Various definitions of risk factors and the use of the nonspecific FIGO system to stratify patients explain a wide variation in outcome results across the studies we report. In addition, there may be selection bias for treatment or other confounders in the articles reviewed. The main goal of our review is to define a summary result for chemoRT and HDR BT and to compare IBBT to non-IBBT series in the era of chemoRT.

Image-based BT

This investigation of pooled data analysis augments the individual outcomes reports in the literature that IBBT improves local control and DFS. This analysis reported a mean improvement in PC of 3% for patients treated with CRT. For DFS, studies with IBBT showed a mean increase in the CRT group of 3%. The difference in PC and DFS with IBBT is noteworthy, as estimates of the impact of concurrent systemic therapy which lead to the NCI statement in 1999 are 9% and 8%, respectively. To reflect on series in the literature that

was used in our analysis, mono-institutional IBBT series of 156 and 140 patients from the Medical University of Vienna and Aarhus University Hospital, respectively, have demonstrated excellent outcomes with 3-year actuarial local control rates of >90% (10). Pötter *et al.* (10) reported local control rates of 100% for Stage IB, 96% for Stage IIB, and 86% for Stage IIIB cervical cancers. Compared with earlier patients treated without image guidance, patients treated with IBBT appeared to have higher survival rates and less major morbidity (10). In addition, in a prospective trial of locally advanced cervical cancer with chemoradiation and low-dose-rate or pulse-dose-rate BT to either 2D vs. 3D treatment planning, there was an improvement in local control with half the toxicity observed with 3D image guidance for treatment planning (107). Our analysis of the studies shows a higher OS in the Point A group vs. the IBBT group in patients treated with chemoRT. The difference could be related to a multitude of factors including various stages of patients in the studies and confounding of systemic failure in patients with locally advanced cervical cancer.

Furthermore, IBBT is an advancement and technological augmentation of an existing treatment with BT. Therefore, the increase in outcome improvements is likely due to advancement in imaging sophistication to better and more appropriately define the target volume, treatment planning, and dose escalation. Importantly, much of the benefit of IBBT is likely related to enhanced target volume coverage and further escalating that dose, if need be, with the addition of needles, in the case of interstitial BT. With the advent of IBBT techniques and delivery, a major advantage is better assessment of the surrounding OAR such as the bladder, sigmoid, rectum, and vagina. IBBT allows for more precise placement of the applicator and optimization of the dose to avoid in part the OAR to decrease serious late effects. The Groupe Européen de Curiethérapie and the European Society for Radiotherapy & Oncology (GEC-ESTRO) has studied the relationship between volume-based dose constraints and long-term outcomes using a model system (10). The International Commission on Radiation Units and Measurements Report 38 advocated a standardized system of dose reporting using critical organ doses at specified reference points. However, in the era of IBBT, a more detailed volumetric and dosimetric account is appreciated during the treatment planning phase to potential avoid high-grade toxicity (94, 101, 106). In addition, GEC-ESTRO sponsored a trial entitled “A European Study on MRI-Guided Brachytherapy in Locally Advanced Cervical Cancer” known as the EMBRACE Trial. The name was later changed to “An International Study on MRI-Guided Brachytherapy in Locally Advanced Cervical Cancer,” as international institutions began participating. As the study results develop from this trial, we will continue to enrich our understanding of IBBT and cervical cancer outcomes.

Toxicity outcomes

There are various reporting systems for acute and late toxicity. The majority of studies report acute toxicity using the clinical trials Common Terminology Criteria for Adverse Events and the LENT/SOMA or RTOG/European Organisation for Research and Treatment of Cancer toxicity scales. For acute effects, cervical cancer patients face genitourinary symptoms such as cystitis, urethritis, hematuria, dysuria, and increased risk of urinary tract infections. For gastrointestinal acute effects, there is a risk of bleeding, pain, mucus discharge, irregular bowel habits, food intolerances, nausea, and vomiting. Among late adverse events, the most

feared complication is fistula between the bladder, vagina, or rectum requiring surgical repair. In addition, vaginal toxicity may include vaginal dryness, vaginal narrowing, foreshortening, ulceration, potential necrosis, and pain with intercourse. In our study, we found a mean acute late GU toxicity for the CRT studies as 3% and 5%, with a mean GI acute and late toxicity of 5% and 5%. The mean late GYN toxicity was 16% in the RT treatment and 3% in those treated with chemoRT. There is a lack of acute toxicity reporting in the IBBT studies, with more reporting of late toxicity. Therefore, as BT programs grow in IBBT, prospective outcome toxicity reporting and patient reported toxicity outcomes are needed.

Conclusions

We present modern era outcomes of PC, DFS, OS, acute, and late toxicities in the era of chemoradiation and image-based techniques for HDR BT. Our study suggests that IBBT improves PC and DFS compared to studies with conventional 2D-based imaging technology in patients treated with chemoRT. Although IBBT is not a treatment of itself for cervical cancer, the advance in imaging may lead to improved outcomes. We need to develop more user friendly techniques to incorporate IBBT for centers with even a low volume of cervical cancer patients. This review presents a summary of reported outcomes to aid the clinician in discussions regarding efficacy and prognosis after HDR BT, as the adoption of IBBT increases.

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Fig. 1.
Search results. LDR = low-dose-rate; MDR = medium-dose-rate.

Fig. 2.

Forest plot for the outcomes for the prospective studies. DFS = disease-free survival; OS = overall survival.

Fig. 3. Forest plot for the outcomes for the retrospective studies. DFS = disease-free survival; OS = overall survival.

Fig. 4.

Forest plot comparison for the IBBT and non-IBBT studies. Comparison of chemoRT mean differences of the IBBT vs. Point A dosing studies for pelvic control (Study 1), DFS (Study 2), and OS (Study 3). IBBT = image-based brachytherapy; CI = confidence interval; DFS = disease-free survival; OS = overall survival; SMD = standardized mean difference.

Table 1**Population, Intervention, Control, Outcome, Study Design (PICOS) inclusion criteria**

Population	Females with FIGO stage IB1–IVA cervical cancer
Intervention	Primary radiation or chemoradiation followed by HDR brachytherapy, defined as radiation that is delivered as 1–6 fractions (typically, 4–5), at 5.5–7 Gy per fraction after EBRT
Control	Either no control group (i.e., HDR BT as a single-arm study) or a multiarm study that contains an HDR BT arm
Outcomes	
Efficacy	Primary clinical (surrogate outcomes) for all studies: local control, disease-free survival, and overall survival
Toxicity	Late LENT/SOMA, RTOG, CTCAE v 4: GU, GYN, GI toxicities; sexual toxicity
Study design	
Efficacy	All prospective and retrospective studies, >40 patients, with one or more arms, >24 month FU
Toxicity	All prospective and retrospective studies, >40 patients, with one or more arms, >24 month FU

BT = brachytherapy; EBRT = external beam radiation therapy; HDR = high-dose-rate; FU = followup; GI = gastrointestinal; GU = genitourinary; GYN = gynecologic; RTOG = radiation therapy oncology group; LENT = Late Effects Normal Tissue Task Force; SOMA = Subjective, Objective, Management, Analytic; CTCAE = Common Terminology Criteria for Adverse Event.

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Study	Stage	WPRT	PM boost	HDR dose/fx	Fx #	Total HDR	HDR Rx	Median f/u	F/u mo	Stage	Pelvic control (RT)	Pelvic control (CRT)	DFS (RT)	DFS (CRT)	OS (RT)	OS (CRT)
R fx schema	1b1-4a	45		3	10	30	A	46	36					88	76	
	2b-41	41.4-50.4		5	5	25							59			
	2b-41	41.4-50.4		6	5	30	A	44	48		89				70	
R fx schema T and RT)	1b-4a	39.6	5.4	6	4	24	A	57	60		80			55	47	65
	2b-4a	40		10	2	20	CT	23	36		62					
	2b-4a	40		7	5	35	A									

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Overall survival; FU = follow-up; WPRT = whole pelvic radiation therapy; PM = parametria; CRT = chemoradiation; RT = radiation; CRT =

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Table 3

Stage	WPRT	PM boost	HDR dose/fx	HDR fx	Total HDR	Rx HDR	Median f/u	F/u mo	Stage	Pelvic control (RT)	Pelvic control (CRT)	DFS (RT)	DFS (CRT)	OS (RT)	OS (CRT)
Ia-4a	30-50		5.5-7.5	4-6	30 Jan	A	96	60				54		68	
1-4	48.6-50		7	3-4	21-28	A	34	36	78			69		58	
	45	9	6	4	24	A	38	60	62			53		54	
1-4	50		4.5-7	3-6	21-27	A		60	76			63		65	
1-4b	42	6-8	7	5-6	35 or 42	A	70	36						58	
1b-4b	40-45	5-13	7.2	4	28										
	44-53		6		24										
			6	5	30	A	60	60				63		60	
	54		8	3	24	A	60	60	73			53		45	
1b-3b	45	9	8	3	24	A	28	36	100		90			90	78
			9.6	1	9.6										
			10	1	10										
2a-3b	30		8	4	32	A	40	60			69				89
			6	5	30										
1-4a	45		6	5	30	A	82	58				71		62	
1-3	40-50		6	4	24	A	70	60	65			56		55	
1b-4b	40-50		6	4	24	A	264	120	78					Stage 1b-74%	Breaks down by stage
			5	3	15									Stage 2-52%	
														Stage 3-42%	
1b-4b	40-46		9	2	18	A	60	60						Stage 4a-17%	

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Stage	WPRT	PM boost	HDR dose/fx	HDR fx	Total HDR	Rx HDR	Median f/u	F/u mo	Stage	Pelvic control (RT)	Pelvic control (CRT)	DFS (RT)	DFS (CRT)	OS (RT)	OS (CRT)
1b-4a	45		8	3	24	A	50	60		75		62		62	
														57	
								120						52	
2b-3	45	6-12	6	4	24	A	52	48		85				47	
										85	87			68	74
2b-3	45		6	4	24	A	59	36		76		59		55	
			6	5	30										
1b-3b	45-50		5	5	25	A		60		95		54		53	
2b-3b	45						45	60		71		51		55	
			7.5	2	15	A	59	60	1	42		58		58	
1-4	50-54								2			44		49	
									3			33		37	
									4			15		23	
2-4	45-50		6	3	18	A	59	60		81		71		69	
1b2-4	45	9-14	9	2	18	A	42	60			83		74		
1b2-4a						A	42	60			82		77		69
1b-4a	45-50		7	4	28	MRI	51	36		82	85	85	85	58	58
2b-4a	41.4-50.4		5	6	30	A	39	48					69		66
1b2-4a	45	9-12.6	5	7	35										
			5	6	30	A	49	48	1b2-2a		100		92		82
			6	5	30				2b		92		78		
									3		81		51		
1b2-4	30				24	A			1b2-2	91	100	76	74	81	82

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Stage	WPRT	PM boost	HDR dose/fx	HDR fx	Total HDR	Rx HDR	Median f/u	F/u mo	Stage	Pelvic control (RT)	Pelvic control (CRT)	DFS (RT)	DFS (CRT)	OS (RT)	OS (CRT)
3b	40-60		5	6	30	A	44	60	4a		80		60		20
1b2-4a	41.4-50.4	10-15	5	6	30	A	52	60					74		52
1b2-4a	45		7	4	28	A	60	60			84		76		67
3-4a	50	6-10					58	60			83		69		65
2b-4a	50.4		6	6	36	CT	35	36			85		68		72
1b-4a	30.6-50.4		6	4	24	A	48	60			61		60		58
1b-4a	20-40		6	4	24	A		60		86		81			44
			5	4	20			2		7		89			65
			5	5	25			3				52			
			7.5	5	37.5			4				15			
1b2-3b	50.4	5.4-9	6	6	36								69		85
			6	4	24	A	28								
			6	5	30										
1b2-3	45-54				20-33.5	A	42	48			92		67		74
1b1-4a	45		5	6	30	A	24	24			92		82		88
			5	5	25										
1b-4a	40		7	3	21	A	56	60	1b	88		88		72	
			6	4	24				2a	90		85		80	
									2b	80		67		67	
									3b	76		45		45	
									4a	74		0		25	
1b-4b	36-45		5	6	30	CT		36			97				
			7	4	28										
			6	4	24										

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HDR = high-dose-rate; DFS = disease-free survival; FU = followup; LDR = low-dose-rate; EFRT = extended field radiation therapy; IMRT = intensity modulated radiation therapy.

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Table 4

Prospective and retrospective series acute and late effects

Author	Reference	No pts	Phase	Arms	Stage	WPRT	PM boost	HDR dose/tx	Fx #	Total HDR	HDR Rx	Median f/u	F/u mo	Scale
Pearcey <i>et al.</i> , 2002	(37)	259	3	RT vs. CRT (cis)	1b–1va	45		8	3	24	A	82	36	NCIC CTG
Lorvidhaya <i>et al.</i> , 2003, 2000	(35, 69)	926	3	RT vs. RT (MMC 5 FU)	2B–4a	50	10–16	7–7.5	4	28	A	89	60	
Brachytherapy				4 arms, reporting 2										
Chirapapaglu <i>et al.</i> , 2004	(27)	44	3	RT vs. CRT (cis)	2b–3b	46–50		10	2	20	A	40	60	
Lanciano <i>et al.</i> , 2005	(33)	316	3	CRT (cis) vs. CRT (5 FU)	2b–4a	45	4–9	6	5	30	A	40	48	
Yoon <i>et al.</i> , 2006	(40)	43	1, 3	CRT (cis and 5 FU) (RT 6 days/wk)	1b–3b	45	5.4	4	6	24	A	37	36	RTOG
Kim <i>et al.</i> , 2005, 2008	(31, 32)	158	3	CRT (wk cis) vs. CRT (cis 5 FU month)	2B–4a	40–50		5	6–7	30–35	A	39	48	RTOG
Taira <i>et al.</i> , 2012	(39)	72	2		3–4a	30–40.1		5.5–6	2	11	A	28	24	NCI CTCEA v3
Huang <i>et al.</i> , 2013	(29)	267	3	CRT 2 HDR fx schema	1b–4a	39.6–45		4.5–6	4–6	24	A	57	60	
Kato <i>et al.</i> , 2013, 2010	(30, 60)	120	2		2b–3b	30–40	10	6–7	4	24–28	A	64	60	
Zuliani <i>et al.</i> , 2014, 2010	(41, 92)	147	3	RT vs. CRT	3b	45					A	43	36	RTOG
Hirayama <i>et al.</i> , 2002	(28)	151	3	RT LDR vs. RT HDR	2–3b	30–50		5.8	5	29	A		60	
Potter <i>et al.</i> , 2011, 2006, 2007, 2000	(10, 14, 81, 82)	156	2	RT HDR plus CT		45–50.4		5.75–7.6	3, 4	23				
Lertsangansinchai <i>et al.</i> , 2004	(34)	112	3	RT (LDR vs. HDR)	1b1–3b	45–50	4–9	7.5	3	22.5	A	37	36	
Nam <i>et al.</i> , 2004	(36)	46	3	HDR fx schema	1b1–4a	45		8.3	2	16.6				
								3	10	30	A	46	36	
								5	5	25				

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Author	Reference	No pts	Phase	Arms	Stage	WPRT	PM boost	HDR dose/tx	Fx #	Total HDR	HDR Rx	Median f/u	F/u mo	Scale
Kim <i>et al.</i> , 2005, 2008	(31, 32)	61	3	CRT 5 FU cis vs. CRT cis	2b-4i	41.4-50.4		6	5	30	A	44	48	RTOG
Sharma <i>et al.</i> , 2011	(38)	42	2	CRT (interstitial)	2b-4a	40		7	5	35	A			
Huang <i>et al.</i> , 2013	(29)	267	3	HDR fx schema (CRT and RT)	1b-4a	39.6	5.4	6	4	24	A	57	60	
Lorvidhaya <i>et al.</i> , 2003, 2000	(35, 69)	2063		RT	1a-4a	30-50		5.5-7.5	4-6	30 Jan	A	96	60	Not spec
Poster <i>et al.</i> , 2011, 2006, 2007, 2000	(10, 14, 81, 82)	189		RT	1-4	48.6-50		7	3-4	21-28	A	34	36	
Ferrigno <i>et al.</i> , 2001, 2005	(52, 53)	138		RT		45	9	6	4	24	A	38	60	
Hama <i>et al.</i> , 2001	(56)	124		RT HDR fx	1-4	50		4.5-7	3-6	21-27	A		60	Not spec
Rodriguez <i>et al.</i> , 2001	(64)	189		RT HDR	1-4b	42	6-8	7	5-6	35 or 42	A	70	36	
Chen <i>et al.</i> , 2006	(48)	295		RT elderly	1b-4b	40-45	5-13	7.2	4	28				
								6		24				
Chen Y., 2003	(74)	442		RT		44-53		6	5	30	A	60	60	RTOG/EORTC
Okkan S., 2003	(75)	293		RT		54		8	3	24	A	60	60	Not spec
Spiegel <i>et al.</i> , 2003	(85)	54		RT	1b-3b	45	9	8	3	24	A	28	36	Not spec
								9.6	1	9.6				
								10	1	10				
Meyer <i>et al.</i> , 2004	(70)	210		RT	2a-3b	30		8	4	32	A	40	60	Not spec
								6	5	30				
Chouda <i>et al.</i> , 2004	(76)	146			1-4a	45		6	5	30	A	82	58	
Ferrigno <i>et al.</i> , 2001, 2005	(52, 53)	118			1-3	40-50		6	4	24	A	70	60	
Nakano <i>et al.</i> , 2005	(71)	1148			1b-4b	40-50		6	4	24	A	264	120	
								5	3	15				
Patel <i>et al.</i> , 2005	(79)	121		RT	1b-4b	40-46		9	2	18	A	60	60	
Souhami <i>et al.</i> , 2005	(87)	282		RT	1b-4a	45		8	3	24	A	50	60	
													120	
													180	

Author	Reference	No pts	Phase	Arms	Stage	WPRT	PM boost	HDR dose/fx	Fx #	Total HDR	HDR Rx	Median f/u	F/u mo	Scale
Chen <i>et al.</i> , 2015	(47)	171		RT vs. CRT (weekly cisp)	2b–3	45	6–12	6	4	24	A	52	48	
Falkenberg <i>et al.</i> , 2006	(51)	57		LDR vs. HDR	2b–3	45		6	4	24	A	59	36	
Gerszten <i>et al.</i> , 2006	(54)	107	(44% RT got chemo)	LDR vs. HDR	1b–3b	45–50		6	5	30			60	
Atahan <i>et al.</i> , 2007	(43)	183	49% chemo	RT vs. CRT (weekly cisp)	2b–3b	45		5	5	25	A	45	60	RTOG/EORTC
Brady <i>et al.</i> , 2007	(57)	214		RT	1–4	50–54.4		7.5	2	15	A	59	60	
Kocher <i>et al.</i> , 2007	(61)	106		RT	2–4	45–50.4		6	3	18	A	59	60	
Niivetsky <i>et al.</i> , 2007	(73)	77		CRT (cisp)	1b2–4	45	9–14	9	2	18	A	42	60	
Osararan <i>et al.</i> , 2007	(77)	76		CRT (weekly cisp)	1b2–4a						A	42	60	
Parker <i>et al.</i> , 2011, 2006, 2007, 2000	(10, 14, 81, 82)	145		RT and CRT (55% weekly cisp)	1b–4a	45–50.4		7	4	28	MRI	51	36	
Kim <i>et al.</i> , 2005, 2008	(31, 32)	158		CRT 3 monthly 5Fu plus 5 days of cisplatin vs. weekly cisplatin	2b–4a	41.4–50.4		5	6	30	A	39	48	Not spec
Lang <i>et al.</i> , 2008	(68)	148		CRT weekly cisp	1b2–4a	45	9–12.6	5	7	35	A	49	48	
Saitata <i>et al.</i> , 2008	(83)	226		CRT vs. RT	1b2–4	30		6	5	30	A			etc v2
Kim <i>et al.</i> , 2009	(62)	51		CRT (weekly cisp)	1b1–4a	40–50.4		7	4	28	MRI	24	24	etc v3
Parker <i>et al.</i> , 2009	(78)	92		CRT (weekly cisp)	1b2–4a	45		6	4	24	CT		24	
Azad and Choudhary, 2010	(44)	342		CRT	1–4	45		6.5	3	19.5	A	36	60	
Kato <i>et al.</i> , 2013, 2010	(30, 60)	84		RT		50		6	4	24	CT	44	60	
Niibe <i>et al.</i> , 2010	(72)	61		RT and CRT	3b	40–59.4		6	5	30	A		60	
Sorbe <i>et al.</i> , 2010	(86)	131		CRT (weekly cis) some without chemo	1–4	50–60		6	5	30	A		60	RTOG/EORTC
								6	3	18				

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Author	Reference	No pts	Phase	Arms	Stage	WPRT	PM boost	HDR dose/fx	Fx #	Total HDR	HDR Rx	Median f/u	F/u mo	Scale
Teh <i>et al.</i> , 2010	(88)	120		CRT (cispl weekly)	1b2-4a	46-50.4		6	3	18	A		60	
Zuliani <i>et al.</i> , 2014, 2010	(41, 92)	155		CRT	3b	40-50.4		5	4	20				
Beriwal <i>et al.</i> , 2011	(45)	44		CRT (weekly cisp)	1b1-3b	45-50.4		5	5	25	MRI	8	24	
Das <i>et al.</i> , 2011	(49)	286		RT	2b-4a	40	10-20	6	5	30				
Shamid <i>et al.</i> , 2011	(84)	265		CRT and RT				7	3	21	A		24	
Konnan <i>et al.</i> , 2012	(59)	47		CRT (interstitial only)	2b-4a	45		3.75	5	18.75	CT	17	24	
Kim <i>et al.</i> , 2012	(63)	174		CRT (weekly cis, or cis FU, or cis palitaxel)	1b1-4a	45	5.4	5	6	30	A	30	60	
Kuroda <i>et al.</i> , 2012	(66)	131		CRT (weekly cisp)	3b	40-60		5	6	30	A	44	60	
Lee <i>et al.</i> , 2013, 2012	(67, 93)	209		CRT (cispl)	1b2-4a	41.4-50.4	10-15	5	6	30	A	52	60	
Al Asiri <i>et al.</i> , 2013	(42)	74		CRT	1b2-4a	45		7	4	28	A	60	60	
Kadaka <i>et al.</i> , 2013	(65)	99		CRT (weekly cisp vs. q 3 cisplatin)	3-4a	50	6-10					58	60	
Pinn-Bingham <i>et al.</i> , 2013	(80)	116		CRT (interstitial only)	2b-4a	50.4		6	6	36	CT	35	36	
Yamashita <i>et al.</i> , 2013	(90)	118		CRT (<40 yo)	1b-4a	30.6-50.4		6	4	24	A	48	60	CTCAE v 3 Not spec
Chatani <i>et al.</i> , 2014	(46)	218		RT diff HDR (A vs. B)	1b-4a	20-40		6	4	24	A		60	
Zhang <i>et al.</i> , 2014	(91)	45		EFRT IMRT	1b2-3b	50.4	5.4-9	6	6	36	A	28		RTOG
								6	5	30				

Author	Reference	No pts	Phase	Arms	Stage	WPRT	PM boost	HDR dose/fx	Fx #	Total HDR	HDR Rx	Median f/u	F/u mo	Scale
Chen <i>et al.</i> , 2015	(47)	125		IMRT (weekly cis)	1b2-3	45-54				20-33.5	A	42	48	CTCAE v 3
Gill <i>et al.</i> , 2015	(55)	128		CRT	1b1-4a	45		5	6	30	A	24	24	
Wong <i>et al.</i> , 2003	(89)	220		RT	1b-4a	40		5	5	25				
Kang <i>et al.</i> , 2010	(58)	97		CRT (weekly cis)	1b-4b	36-45		7	3	21	A	56	60	
Nishida <i>et al.</i> , 2007	(94)	93		RT	1b-4b		6	4	24	A				
Fujikawa <i>et al.</i> , 2001	(95)	232	RT-GI and GU tox	1-4	45-60			3-5	15-29	A		24+		
Han <i>et al.</i> , 2002	(96)	228	RT-pelvic insuff	1b-3b	50.4-55.8		4	6	24	A				
Cheng <i>et al.</i> , 2003	(97)	187	RT-rectal toxicity	1a-4a	40-45		5	4	20	A				
Chan <i>et al.</i> , 2004	(98)	213	RT-rectal tox	1b1-4a	45	6-8	4	7	28	A	39			
Chen <i>et al.</i> , 2006, 2010	(48, 99)	451	RT GU and GI tox	1b1-3b	45	5-14.4	6	4	24	A				
Takumaru <i>et al.</i> , 2012	(100)	RT-p53ic insufficiency	1b1-32b		50		7.2	3	21.6					
Tchiletti <i>et al.</i> , 2015	(101)	85	RT-GI toxicity	1b2-2b	45	9-10	5.5	5	27.5	CT	15			
Yang <i>et al.</i> , 2012	(102)	1518	RT-GU and GI toxicity	1b-3b	32-36	12-15	5	6	30	A				
Yoshida <i>et al.</i> , 2015	(103)	57	HDR-interstitial and TR	1b-4a	30	20	7.5	4	30		36			
Kirchheiner <i>et al.</i> , 2014	(104)	CRT-88	aginal stenosis	1b-4a	45		6	5	30					
Bohr Mordhorst <i>et al.</i> , 2014	(105)	134	CRT	1-4	50-60		7	4	28	MRI	15	24		
Georg <i>et al.</i> , 2013	(106)	225	CRT	1b-4a	45-50.4		7	4	28	MRI	44	60	RTOG	

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HDR = high-dose-rate; FU = followup; RTOG = radiation therapy oncology group; LDR = low-dose-rate; CTCAE = Common Terminology Criteria for Adverse Event; GI = gastrointestinal; GU = genitourinary; LENT = Late Effects Normal Tissue Task Force; SOMA = Subjective, Objective, Management, Analytic; NCIC CTG = National Cancer Institute of Canada Clinical Trials Group; EORTC = European Organisation for Research and Treatment of Cancer.

acute and late effects with scale toxicities

Toxicity grade (acute)	GU (RT)	GI (CRT)	GYN (RT)	GYN (CRT)	Scale	Toxicity scale (late)	GU (RT)	GI (RT)	GYN (RT)	GYN (CRT)
3	3	11	1		NCIC CTG	3	5	6	1	
4	0	5	0			4	5	7	5	
					RTOG	3	4	4	3	3
						4				
2	12	33			RTOG	2				7
3	0	1				3	2		2	
2	7	20			RTOG	2	2		4	
3	0	0				3	1		2	
3 Not spec					NCI CTCEA v3	2	7		8	
						3	2		0	
					Not spec	2-4 (est)	7		22	
					Not spec	2-4 (est)	12		26	
1-2	54	31	4	10	RTOG	Grades 1 and 2	22	69	17	9
				Spec Vagina: 28	RTOG	Grade 3	4	6		
2	2	5								
					RTOG	2	8	6		
						3	1	5		
					RTOG	2-4				13
2	5	51			RTOG	2	0		0	
3	0	2				3	2		2	
4	0	0				4	0		0	
					Not spec					
						2				
						3			5	
						4				
					RTOG	2 to 3	1			HDR 4: 19 vs.

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Toxicity grade (acute)	GU (RT)	GU (CRT)	GI (RT)	GI (CRT)	GYN (RT)	GYN (CRT)	Scale	Toxicity scale (late)	GU (RT)	GU (CRT)	GI (RT)	GI (CRT)	GYN (RT)	GYN (CRT)
				HDR 6: 10										
							RTOG	Grade 3/4		3.5		4.8		
							RTOG	Grade 3/4		0		11		
							Not spec	2		3		12		
							RTOG/EORTC	1–2		2		6		
								3–4		0.2		2		
								5		0		0.2		
							Not spec	2–4		21		21		
3														
Not spec							Not spec	Not spec			13		25	
							RTOG	2	3					
								3	1					
								4	2					
							RTOG/EORTC	2						
								3						
								4				2		
								5				1		
							RTOG	3–5		1		7		
							RTOG	2		2		1		
								3		2		0		
							RTOG	3						
								4				1.5		
							Not spec	4				5		
							Not spec	3 and 4	4			4		

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	Toxicity grade (acute)	GU (RT)	GU (CRT)	GI (RT)	GI (CRT)	GYN (RT)	GYN (CRT)	Scale	Toxicity scale (late)	GU (RT)	GU (CRT)	GI (RT)	GI (CRT)	GYN (RT)	GYN (CRT)
2	2	15	48					RTOG/EORTC	2		2		13		
3	3	1	3						3		8		4		
4	4								4		2		2		
								RTOG	1-4		7		9		
								RTOG	4				1		
								RTOG	3 and 4	6					
								RTOG	2					2	
									3						
								LENT/SOMA	3 and 4		4	4	4	4	3
2	2			26				Not spec	2			4		4	
3	3			2.5					3			0		2	
4	4			1					4			0		0	
2	2	1	0	15	0			Not spec	2-4	15 (RT)					
3	3	0	0	0	0					35 (CRT)					
4	4	0	0	0	0			ctc v3	2			4		7	
2	2	15	0	10	0	0			3			0		2	
3	3	0	0	0	0				4			0		0	
4	4	0	0	0	0			ctc v3	3-4			1		1	
								RTOG	2			5		5	
									3			1		1	
									4			0		0	
								RTOG/EORTC	2				8		
									3				0		
									4				0		
2	2	2	1					Not spec	2-4	13					
3	3							RTOG/EORTC	2			5		18	
4	4								3			3		5	
									4			6		6	

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Toxicity grade (acute)	GU (RT)	GU (CRT)	GI (RT)	GI (CRT)	GYN (RT)	GYN (CRT)	Scale	Toxicity scale (late)	GU (RT)	GU (CRT)	GI (RT)	GI (CRT)	GYN (RT)	GYN (CRT)
							RTOG/EORTC	2			0			
								3			0		3	
								4			0		1	
							RTOG/EORTC	2					4	
							RTOG	2		2		2		
								3		2		2		
							RTOG	3					1	
								4					1	
							ctc v3	Not spec			15		18	
							Not spec	3	5					
							RTOG	3			1			
								4					2	
2	3	8					ctc v3	2			3		8	
3	0	1						3			6		10	
								4			1		1	
2	0	5					Not spec	2			2		2	
3	3	3						3			4		9	
4	0	2						4			0		0	
2	53	62					RTOG	2			2		4	
3	2	7						3			0		6	
4	0	0						4			0		0	
2		10					CTCAE v 3	2			11		6	
3		2						3			1		2	
4		1					Not spec	4			4		4	
								3	1					

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Toxicity grade (acute)	GU (RT)	GU (CRT)	GI (RT)	GI (CRT)	GYN (RT)	GYN (CRT)	Scale	Toxicity scale (late)	GU (RT)	GU (CRT)	GI (RT)	GI (CRT)	GYN (RT)	GYN (CRT)
							RTOG	3–4					2	
							RTOG	2			4			RTOG
								3			0			
								4			0			
							Not spec	3–4		20	15			
							Not spec							
							RTOG	2 or higher					23	
							LENT.SOMA	2			8			
								3			1			
								4			0			
								2–4	5	15	10	15		
									6		14			
								etc v3	2	10				
								3	5					
							etc v4	3–4					6	
								3		2.3	3.8			61
							Not spec	2						7
								3						29
							EORTC/RTOG	2						4
								3						
							RTOG	2			5		18	
								3			11		5	
								4			11		3	
								LENT.SOMA	2		8.9			6.2

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GU = genitourinary; GYN = gynecologic; LENT =
 Common Terminology Criteria for Adverse Event; GI = gastrointestinal; GU = genitourinary; GYN = gynecologic; LENT =
 Subjective, Objective, Management, Analytic; NCIC CTCEA = National Cancer Institute Common Terminology Criteria for Adverse Events.

Table 6

Weighted means and outcomes for the prospective, retrospective, IBBT, and non-IBBT studies

Treatment	Prospective			Retrospective			IBBT with chemoRT			Point A dose chemoRT		
	Mean	SD	Lower bound	Upper bound	Mean	SD	Lower bound	Upper bound	Mean	SD	Lower bound	Upper bound
Pelvic control (RT)	73.49	11.17	51.59	95.39	74.82	17.70	40.13	109.51				
Pelvic Control (CRT)	81.27	8.84	63.95	98.59	80.51	16.08	49.00	112.03	83.84	9.17	65.88	101.80
DFS (RT)	55.23	9.60	36.41	74.05	55.72	20.46	15.62	95.82				
DFS (CRT)	65.44	7.37	50.99	79.89	63.02	20.94	21.98	104.06	69.51	9.26	51.35	87.66
OS (RT)	66.06	7.26	51.84	80.28	54.05	18.14	18.49	89.61				
OS (CRT)	70.15	10.58	49.41	90.89	66.19	16.72	33.43	98.96	73.36	10.64	52.49	94.23

IBBT = image-based brachytherapy; DFS = disease-free survival; OS = overall survival.

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