

Dosimetric evaluation of Point A and volume-based high-dose-rate plans: a single institution study on adaptive brachytherapy planning for cervical cancer

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Abstract

Purpose: External beam radiation therapy (EBRT) and brachytherapy (BT) with concurrent cisplatin is the standard of care for locally advanced cervical cancer. The applicability of image-guided adaptive volume-based high-dose-rate (HDR) intracavitary brachytherapy planning is an active area of investigation. In this study, we examined whether volume-based HDR-BT (HDR_{VOL}) plans leads to more conformal plans compared to Point A (HDR_{PointA})-based plans.

Material and methods: Two hundred and forty HDR_{PointA} plans from 48 cervical cancer patients treated with chemoradiotherapy were retrospectively collected. Point A plans were renormalized with respect to the high-risk clinical target volume (HR-CTV) for the HDR_{VOL} plans. The doses to organs at risk (OAR; rectum, sigmoid, and bladder), and HR-CTV and the conformal index were compared between HDR_{PointA} and HDR_{VOL} plans.

Results: HDR_{VOL} plans resulted in a 6-12% reduction in the total dose (EBRT + HDR-BT) to 0.1 cc, 1.0 cc, and 2.0 cc of the OAR as well as an 8-37% reduction in the dose to 2 cc of OAR per HDR-BT fraction compared to HDR_{PointA} plans. Differences in the conformal indexes between the two groups of plans showed an 18-31% relative increase per HDR-BT fraction for HDR_{VOL} plans. The D₉₀ of the HR-CTV was reduced by 11% by HDR_{VOL} planning and had a median dose of 86 Gy.

Conclusions: Our study reports the relative improvement in OAR doses per HDR-BT fraction by HDR_{VOL} planning compared to HDR_{PointA} planning and demonstrates the dosimetric advantages of volume-based HDR-BT planning in creating more conformal plans.

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Purpose

Radiation therapy (RT) with concurrent weekly cisplatin consisting of external beam radiation therapy (EBRT) and brachytherapy (BT) is the standard of care for locally advanced cervical cancers [1,2]. Local control rates greater than 80% requires a total biological equivalent dose in 2 Gy per fraction (EQD₂) of 80-90 Gy or more to the high-risk clinical target volume (HR-CTV) [3,4,5,6]. A BT-based approach by low-dose-rate or high-dose-rate (HDR) is most commonly used to achieve a total EQD₂ (EBRT + BT) dose of 80-90 Gy to the HR-CTV [1,2]. The sharp dose fall-off allows for high EQD₂ HR-CTV doses without compromising organs at risk (OAR) doses [1,2,7,8]. Lately, HDR-BT has become more common with the recent report by the quality research in radiation oncology study showing its application in 60-70% of the surveyed facilities [9,10].

HDR-BT for cervical cancer uses the Manchester Point A-based system and has been an effective modality for delivering high-dose radiation to the HR-CTV [7,8,11,12]. The strength of this system is its simplicity in implementation and its reproducibility with respect to the bony anatomy when assessed by radiographs. The main disadvantage of Point A system is related to dose delivery uncertainties due to inter-fraction and intra-fraction geometric disparities in applicator positions, and anatomical variations in rectal and bladder fillings resulting in non-reproducible high- and low-dose areas within the OAR [13,14,15]. Clinically, this could translate into under-dosing and over-dosing of OAR. With the advent of computed tomography/magnetic resonance imaging (CT/MRI) scans and CT/MRI compatible HDR applicators, the accuracy of HR-CTV and OAR dose assessment significantly

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improved since the target and OAR were contoured and used for planning as demonstrated by multiple studies [16,17,18,19]. In recent years, several studies have indicated the benefits of volume-based HDR-BT planning [19,20,21,22,23,24,25]. Volume-based HDR-BT planning creates more conformal treatment plans after careful evaluation of the dose cloud within the context of HR-CTV and OAR contoured from either CT or MRI obtained per HDR-BT fraction [19,20,21]. In this study, we examined the dosimetric outcomes of volume-based HDR-BT (HDR_{VOL}) planning for locally advanced cervical cancers and quantifies the relative difference in OAR doses per HDR-BT fraction between conventional Point A and volume-based HDR-BT planning.

Material and methods

Study population

From January 2008 to July 2015, 124 patient charts with locally advanced cervical cancer treated with concurrent chemotherapy (cisplatin) and RT (EBRT + HDR-BT) were retrospectively screened for the study after approval from the institutional review board. The inclusion criteria used for the screening were: a) CT scan for each HDR-BT fraction (fx); b) five HDR-BT fractions (fxs) using tandem and ring (T&R) or tandem and ovoids (T&O); c) completion of planned radiation treatment; d) absence of metastatic disease; e) availability of electronic HDR-BT planning records. All patients were staged according to the International Federation of Gynecology and Obstetrics (FIGO) classification [26].

Radiation techniques

RT comprised of whole pelvic RT of 45 Gy (1.8 Gy per fraction with five fractions per week) inter-digitated with HDR-BT. Para-aortic chains were treated for patients with either pelvic lymph node or para-aortic node involvement. EBRT was delivered by either intensity modulated RT (IMRT) or three-dimensional RT (3DRT) after delineating the target volumes and OAR on CT scans. MRI and positron emission tomography (PET) scans were fused with the CT images whenever available. Gross nodal involvement received additional boost RT. HDR-BT consisted of twice weekly treatments. CT scans were obtained on a large bore Somatom Sensation CT simulator (Siemens, Malvern, PA, USA) for each HDR-BT fraction after the insertion of CT compatible applicators tandem and ring (T&R) and tandem and ovoid (T&O) with sufficient vaginal packing for ensuring appropriate placements and planning. 60 cc of normal saline was injected into the bladder by Foley catheter before obtaining the planning CT scan and was left in situ for each HDR-BT fraction. The rectum, sigmoid, bladder, and HR-CTV were contoured by a radiation oncologist on 3-5 mm axial CT slices on the CT scan for the respective HDR-BT fx as per the American Brachytherapy Society (ABS) guidelines [1], and was used for HDR-BT planning using Oncentra HDR planning software (Elekta, Stockholm, Sweden). MRI was used for delineating HR-CTV by fusing with the CT image, whenever a second MRI

was obtained during EBRT to assess tumor response as previously described [27]. The prescription points used were either Point A or modified Point A as previously described [2,28,29,30]. Point A was defined as the point 2 cm superior to the external os along the tandem, and 2 cm perpendicular from the intrauterine tandem [2,28,29,30]. Modified Point A plans were chosen when Point A planning resulted in excessive OAR doses for patients with smaller HR-CTV volumes. Modified Point A-based plans were created by changing the prescription point from Point A by altering the lateral distance from the tandem from 2 cm to anywhere between 1.6 cm and 1.9 cm.

High-risk clinical target volume-based high-dose-rate brachytherapy planning protocol

Two hundred forty $\text{HDR}_{\text{PointA}}$ plans from 48 patients with five HDR-BT fractions per patient were reviewed and re-planned with respect to HR-CTV volume for HDR_{VOL} plans. Each plan was re-normalized by scaling the source dwell times and re-optimized by graphically adjusting the isodose lines with objective of lowering OAR doses and at the same time, achieving at a minimum either the D_{95} ($D_{95\text{PRx}}$) or the D_{90} of the HR-CTV ($D_{90\text{PRx}}$) to be the prescription dose. If the initial D_{95} ($D_{95\text{INITIAL}}$) or the initial D_{90} ($D_{90\text{INITIAL}}$) of the HR-CTV were lower than the prescription dose due to the proximity of OAR, an attempt was made to re-optimize by graphically adjusting the isodose lines to achieve maximum OAR sparing followed by re-normalizing to either the $D_{95\text{INITIAL}}$ or $D_{90\text{INITIAL}}$. If the afore mentioned requirements were not met, the respective plans were rejected and the initial Point A plan (Point A) was accepted for analysis. The $D_{0.1(\text{HDR})}$ (dose to 0.1 cc; data not shown), $D_{1.0(\text{HDR})}$ (dose to 1.0 cc; data not shown), and $D_{2.0(\text{HDR})}$ (dose to 2.0 cc) of rectum, sigmoid, and bladder and the $D_{90(\text{HDR})}$ (dose to 90% of HR-CTV; data not shown), $V_{150(\text{HDR})}$ (percentage of HR-CTV receiving 150% of the prescription dose), and $V_{200(\text{HDR})}$ (percentage of HR-CTV receiving 200% of the prescription dose) were collected for both $\text{HDR}_{\text{PointA}}$ and HDR_{VOL} plans per HDR-BT fraction. The total EQD₂ doses $D_{0.1(\text{EBRT+HDR})}$, $D_{1.0(\text{EBRT+HDR})}$, and $D_{2.0(\text{EBRT+HDR})}$ of the rectum, sigmoid, and bladder, and the $D_{90(\text{EBRT+HDR})}$ of the HR-CTV from the combination of EBRT and HDR-BT were calculated for each patient using ABS worksheet ("HDR Radiobiologic Dose Equivalent Worksheets #2", <https://www.americanbrachytherapy.org/guidelines/>) for dose calculations. Conformal index for each HDR-BT plan was calculated as previously described [21]. Conformal index = $(\text{CTV}_{\text{ref}}/\text{V}_{\text{CTV}}) \times (\text{CTV}_{\text{ref}}/\text{V}_{\text{ref}})$. CTV_{ref} is defined as the volume of the HR-CTV receiving $\geq 100\%$ dose. V_{CTV} is defined as the volume of the HR-CTV. V_{ref} is defined as the volume receiving a dose $\geq 100\%$ dose [21].

Statistical analysis

Estimates of proportions are reported with 95% confidence intervals. Estimates of continuous quantities are reported as medians and interquartile ranges (IQR) because of the asymmetry of the frequency distributions. Relative differences of various dosimetric parameters ($D_{0.1(\text{EBRT+HDR})}$, $D_{1.0(\text{EBRT+HDR})}$, $D_{2.0(\text{EBRT+HDR})}$, and $D_{2.0(\text{HDR})}$)

of the rectum, sigmoid, and bladder ($D_{90(EBRT+HDR)}$, $V_{150(HDR)}$, and $V_{200(HDR)}$) of the HR-CTV, and the conformational indexes were calculated as 100 times the difference between HDR_{PointA} and HDR_{VOL} divided by HDR_{VOL} .

Results

Population and radiation therapy characteristics

Forty-eight patients met the inclusion criteria of the study with median follow-up of 13 months. Sixty-four percent of the patients had locally advanced cancer (\geq IIA), whereas 11% and 25% of the patients had IB1 and IB2 disease, respectively. Vaginal involvement was seen in 10% of the patients with either proximal (IIA2, 6%) or distal (IIIA, 4%) vaginal involvement. Parametrial/adnexal involvement was present in 29% (IIB) of the patients. Twenty-three percent of the patients had stage IIIB disease at diagnosis with either pelvic sidewall involvement or hydronephrosis or non-functioning kidney. Patients characteristics are presented in Table 1.

Sixty-seven percent of the patients received fractionated parametrial or sidewall boost RT by 3 DRT with doses ranging from 1.8-9.0 Gy. Fifty-two percent of the patients received fractionated nodal boost RT with doses ranging from 3.6-19.6 Gy. HDR-BT treatments were inter-digitated with EBRT with median total RT (EBRT + HDR-BT) treatment time of 61 days and median total HDR-BT time of 17 days (Tables 2 and 3). RT characteristics are presented in Table 2. 94% and 2% of the patients

Table 1. Population characteristics

Parameters	N = 48
Age at diagnosis (years), median (IQR)	49 (40, 59)
Race	
AA	36 (75%)
Non-AA	12 (25%)
Stage	
IB1	5 (11%)
IB2	12 (25%)
IIA2	3 (6%)
IIB	14 (29%)
IIIA	2 (4%)
IIIB	11 (23%)
IVA	1 (2%)
Pathology	
Squamous cell carcinoma	42 (88%)
Adenocarcinoma	2 (4%)
Others	4 (8%)
Follow-up (months), median (IQR)	13 (6, 27)

N – total number of patients; AA – African American

Table 2. Radiation therapy characteristics

Parameters	N = 48
EBRT dose	
45 Gy	48 (100%)
EBRT modality	
3DRT	24 (50%)
IMRT	24 (50%)
Sidewall boost	
# of patients	32 (67%)
Modality	
3DRT	32 (67%)
Dose (Gy)	
1.8	1 (2%)
5.4	25 (52%)
9	6 (13%)
Nodal boost	
# of patients	25 (52%)
Modality	
3DRT	8 (17%)
IMRT	14 (29%)
3DRT & IMRT	3 (6%)
Dose (Gy)	
3.6	2 (4.2%)
4	1 (2.1%)
6	4 (8.3%)
7.5	1 (2.1%)
8	2 (4.2%)
9	3 (6.3%)
10	1 (2.1%)
10.8	5 (10.4%)
12.6	1 (2.1%)
14	2 (4.2%)
14.4	1 (2.1%)
16	1 (2.1%)
19.6	1 (2.1%)
Duration (days), median (IQR)	
RT (EBRT + brachytherapy)	61 (53, 68)

N – total number of patients, EBRT – external beam radiation therapy, 3D – three dimensional, IMRT – intensively modulated radiation therapy

used T&R and T&O applicators exclusively, respectively. 48% of the patients were treated with '5.5 Gy × 5' HDR-BT fractionation regimen, and 52% of the patients received other commonly used fractionation schemes. Median volumes of HR-CTV, rectum, sigmoid, and bladder from the 240 HDR_{PointA} plans reviewed were 23 cc, 52 cc, 44 cc, and 100 cc, respectively. Treatment characteristics are shown in Table 3. Grade 3-4 gastrointestinal (GI) and genitourinary (GU) toxicities were observed in 17% and 15% of the patients, respectively, with a median follow-up of 13 months, and five (10%) of the 48 patients were lost to follow-up (Tables 1 and 4).

High-dose-rate brachytherapy planning features

Seventy-one percent of the 48 patients had Point A-based prescriptions for all five HDR-BT fractions (Table 3). Twenty-nine percent of the 48 patients used modified point A-based prescriptions as part of the overall brachytherapy fractionation regimen (Table 3). Among the 240 plans reviewed from 48 patients (5 HDR-BT plans per patient), 80% (192/240 plans) were Point A plans and 20% (48/240 plans) were modified Point A plans. Modified Point A prescription points used were 1.9 cm (2/240 plans, 0.8%), 1.8 cm (27/240 plans, 11.3%), 1.7 cm (14/240 plans, 5.8%), and 1.6 cm (5/240 plans, 2.1%). Planning strategies for HDR_{VOL} plans consisted of re-normalizing the prescription dose to D_{95PRx} (176/240 plans, 73.3%), D_{90PRx} (31/240 plans, 13%), D_{95INITIAL} (2/240 plans, 0.8%), and D_{90INITIAL} (2/240 plans, 0.8%). Volume-based planning could not improve OAR doses without compromising initial HR-CTV doses for 12.1% (29/240 plans) of the plans reviewed and thus the initial plan (Point A) was used for analysis.

Point A and volume-based high-dose-rate planning comparisons

The EQD₂ doses D_{0.1(EBRT+HDR)}, D_{1.0(EBRT+HDR)}, and D_{2.0(EBRT+HDR)} was decreased by HDR_{VOL} planning with a relative difference of 8-10% for rectum, 6-9% for sigmoid, and 10-12% for bladder compared to HDR_{PointA} plans (Table 5). The median D_{0.1(EBRT+HDR)}, D_{1.0(EBRT+HDR)}, and D_{2.0(EBRT+HDR)} for HDR_{PointA} and HDR_{VOL} plans were 73 Gy and 63 Gy, 66 Gy and 58 Gy, 63 Gy and 56 Gy for rectum, 76 Gy and 70 Gy, 68 Gy and 62 Gy, 65 Gy and 59 Gy for sigmoid, and 91 Gy and 78 Gy, 79 Gy and 68 Gy, and 74 Gy and 66 Gy for bladder, respectively (Table 5). HDR_{VOL}-based planning decreased the D_{2.0(HDR)} per HDR-BT fx for all the plans with a relative difference of 19-37% for rectum, 10-26% for sigmoid, and 8-23% for bladder compared to HDR_{PointA} plans for fractions 1-5 (Table 5). The median rectal D_{2.0(HDR)} for fractions 1-5 ranged from 2.6 Gy to 3.1 Gy and 1.9 Gy to 2.3 Gy for HDR_{PointA} and HDR_{VOL} plans, respectively (Table 5). The median D_{2.0(HDR)} of sigmoid for fractions 1-5 ranged from 3.1 Gy to 3.3 Gy and 2.5 Gy to 2.7 Gy for HDR_{PointA} and HDR_{VOL} plans, respectively. The median bladder D_{2.0(HDR)} for fractions 1-5 ranged from 3.6 Gy to 4.3 Gy and 3.1 Gy to 3.2 Gy for HDR_{PointA} and HDR_{VOL} plans, respectively (Table 5).

Table 3. High-dose-rate brachytherapy characteristics

HDR-BT parameters	N = 48
HDR-BT applicators by fraction (fx)	
T&R × 5 fx	45 (94%)
T&R × 4 fx and T&O × 1 fx	1 (2%)
T&O × 5 fx	1 (2%)
T&O × 3 fx and T&R × 2 fx	1 (2%)
Fractionation schemes	
5.5 Gy × 5 fx	23 (48%)
Others	25 (52%)
Point A planning strategies:	
Point A (2.0 cm) × 5 fx	34 (71%)
Modified Point A or Point A	14 (29%)
Treatment volumes (cc), median (IQR):	
HR-CTV	23 (18, 33)
Rectum	52 (35, 63)
Sigmoid	44 (33, 64)
Bladder	100 (88, 118)
Duration (days), median (IQR):	17 (14, 22)

HDR-BT – high-dose-rate brachytherapy, N – total number of patients, T&R – tandem and ring, T&O – tandem and ovoids, HR-CTV – high-risk clinical target volume

The relative difference between the D_{90(EBRT+HDR)} of the HR-CTV for HDR_{PointA} (98 Gy) and HDR_{VOL} (86 Gy) plans was 11% (Table 6). The hotspots within HR-CTV were decreased by HDR_{VOL}-based planning for fractions 1-5, with a relative difference of 9-24% for V₁₅₀ and 10-30% for V₂₀₀ compared to HDR_{PointA} plans. The median HR-CTV V₁₅₀ for fractions 1-5 ranged from 72% to 79% and 62% to 65% for HDR_{PointA} and HDR_{VOL} plans, respectively (Table 6). The median HR-CTV V₂₀₀ for fractions 1-5 ranged from 46% to 55% and 39% to 41% for HDR_{PointA} and HDR_{VOL} plans, respectively (Table 6). The conformation indexes of HR-CTV for HDR-BT fractions 1-5 were increased by HDR_{VOL}-based planning with a relative difference of 18-31% compared to HDR_{PointA} plans and ranged from 0.29 to 0.35 and 0.44 to 0.48 for HDR_{PointA} and HDR_{VOL} plans, respectively (Table 7).

Table 4. Gastrointestinal and genitourinary toxicity profile

Status	Grade 3-4 GI toxicities	Grade 3-4 GU toxicities
Present	8 (17%)	7 (15%)
Absent	35 (73%)	36 (75%)
Data missing	5 (10%)	5 (10%)

GI – gastrointestinal, GU – genitourinary

Discussion

The primary objective of HDR-BT in cervical cancer is to provide a biologically significant radiation dose to the HR-CTV without compromising OAR. Current literature

Table 5. Dosimetric parameters of organs at risk

OAR parameters	HDR _{PointA} (Gy) Median (IQR)	HDR _{VOL} (Gy) Median (IQR)	Relative difference (%) Median (IQR)
Rectum			
D _{0.1(EBRT+HDR)}	73 (68, 80)	63 (57, 70)	10 (5, 22)
D _{1.0(EBRT+HDR)}	66 (62, 69)	58 (53, 63)	9 (4, 17)
D _{2.0(EBRT+HDR)}	63 (59, 66)	56 (52, 60)	8 (3, 15)
D_{2.0(HDR)}			
Fraction 1	2.8 (3, 4)	2.3 (3, 3)	19 (2, 57)
Fraction 2	2.9 (2, 3)	2.3 (2, 3)	23 (2, 65)
Fraction 3	3.1 (2, 4)	1.8 (2, 3)	34 (8, 91)
Fraction 4	2.6 (8, 3)	1.9 (8, 2)	37 (8, 76)
Fraction 5	2.6 (8, 3)	1.9 (8, 3)	31 (11, 86)
Sigmoid			
D _{0.1(EBRT+HDR)}	76 (69, 91)	70 (61, 77)	9 (4, 19)
D _{1.0(EBRT+HDR)}	68 (62, 76)	62 (57, 67)	7 (4, 14)
D _{2.0(EBRT+HDR)}	65 (59, 70)	59 (56, 64)	6 (3, 14)
D_{2.0(HDR)}			
Fraction 1	3.3 (3, 4)	2.7 (3, 3)	10 (1, 51)
Fraction 2	3.2 (1, 4)	2.7 (1, 3)	14 (2, 48)
Fraction 3	3.3 (2, 4)	2.6 (2, 3)	19 (5, 49)
Fraction 4	3.3 (5, 4)	2.5 (5, 3)	26 (6, 49)
Fraction 5	3.1 (6, 4)	2.6 (6, 3)	25 (10, 45)
Bladder			
D _{0.1(EBRT+HDR)}	91 (74, 103)	78 (69, 90)	12 (5, 24)
D _{1.0(EBRT+HDR)}	79 (68, 86)	68 (62, 75)	10 (5, 18)
D _{2.0(EBRT+HDR)}	74 (66, 80)	66 (59, 71)	10 (4, 16)
D_{2.0(HDR)}			
Fraction 1	3.8 (4, 5)	3.1 (4, 4)	8 (1, 45)
Fraction 2	4.3 (1, 5)	3.1 (1, 4)	15 (2, 52)
Fraction 3	4.1 (2, 5)	3.1 (2, 4)	21 (4, 53)
Fraction 4	3.6 (4, 5)	3.2 (4, 4)	23 (7, 45)
Fraction 5	4.0 (7, 5)	3.2 (7, 4)	22 (9, 45)

OAR – organs at risk, HDR_{PointA} – conventional Point A or modified Point A plan, HDR_{VOL} – image-guided adaptive volume-based HDR-BT planning, D_{0.1(EBRT+HDR)} – total EQD₂ dose to 0.1 cc from the combination of EBRT and HDR-BT, D_{1.0(EBRT+HDR)} – total EQD₂ dose to 1.0 cc from the combination of EBRT and HDR-BT; D_{2.0(EBRT+HDR)} – total EQD₂ dose to 2.0 cc from the combination of EBRT and HDR-BT; D_{2.0(HDR)} – dose to 2.0 cc per HDR-BT fraction

attributes GI and GU toxicity from gynecological radiation to the high OAR point doses and recommend maintaining the total EQD₂ D_{2cc} of the rectum, sigmoid, and bladder to be < 70 Gy, < 70-75 Gy, and < 90 Gy, respectively [1,2,23,31,32,33]. Despite the Point A plans in our study, meeting the recommended OAR dose constraints, we observed 15% and 17% of patients having grade 3-4 GU and GI toxicities, respectively. The significance of OAR dose limits per HDR-BT fraction in predicting GI and GU toxicities is an unexplored arena with no clear consensus on the OAR dose limits per HDR-BT fraction. Our study for the first time reports the range of D_{2cc} of rectum, sigmoid, and bladder per HDR-BT fraction for Point A plans and its improvement by HDR_{VOL} planning. Our

Table 6. Dosimetric parameters of high-risk clinical target volume

HR-CTV parameters	HDR _{PointA} Median (IQR)	HDR _{VOL} Median (IQR)	Relative difference (%) Median (IQR)
V_{150(HDR)} (%)			
Fraction 1	73 (62, 88)	62 (55, 67)	9 (2, 39)
Fraction 2	73 (60, 90)	63 (58, 67)	12 (1, 38)
Fraction 3	72 (64, 89)	62 (57, 65)	13 (3, 41)
Fraction 4	79 (64, 89)	65 (59, 68)	20 (3, 37)
Fraction 5	79 (71, 89)	63 (58, 67)	24 (5, 44)
V_{200(HDR)} (%)			
Fraction 1	47 (39, 63)	39 (33, 45)	10 (1, 53)
Fraction 2	48 (38, 66)	40 (37, 45)	14 (1, 52)
Fraction 3	46 (40, 58)	40 (35, 43)	15 (0, 51)
Fraction 4	55 (41, 66)	41 (36, 45)	22 (1, 62)
Fraction 5	54 (44, 60)	41 (36, 44)	30 (1, 53)
D _{90(EBRT+HDR)} (Gy)	98 (91, 105)	86 (84, 87)	11 (4, 22)

V_{150(HDR)} – percentage of HR-CTV receiving 150% of the prescription dose per HDR-BT fraction, V_{200(HDR)} – percentage of HR-CTV receiving 200% of the prescription dose per HDR-BT fraction, D_{90(EBRT+HDR)} – dose to 90% of the HR-CTV from the combination of EBRT and HDR-BT

Table 7. Conformal index per high-dose-rate brachytherapy fraction

HDR-BT fraction	HDR _{PointA} Median (IQR)	HDR _{VOL} Median (IQR)	Relative difference (%) Median (IQR)
1	0.35 (0.25, 0.40)	0.44 (0.38, 0.52)	-18 (-46, -1)
2	0.29 (0.22, 0.41)	0.44 (0.39, 0.50)	-28 (-50, -2)
3	0.32 (0.22, 0.39)	0.48 (0.39, 0.54)	-29 (-49, -10)
4	0.29 (0.22, 0.40)	0.47 (0.38, 0.55)	-29 (-48, -6)
5	0.31 (0.25, 0.38)	0.46 (0.40, 0.55)	-31 (-48, -12)

institutional goals for D_{2cc} of the rectum, sigmoid, and bladder per HDR-BT fraction are approximately < 3.0 - 3.5 Gy, < 3.0 - 4.0 Gy, and < 4.0 - 4.5 Gy, respectively. However, such an objective is often not met in clinical scenarios, where HR-CTV is either at sub-centimeter proximity or is flushing the OAR. Under such circumstances, physicians either exceed the OAR dose limits or apply a lower prescription dose on the respective HDR-BT fraction with objective of meeting the total EQD₂ dose constraints. The clinical consequences of such scenarios in terms of GI and GU toxicities are unknown and require an understanding of the OAR dose constraints per HDR-BT fraction within the context of the OAR that are simultaneously recovering from approximately 35-45 Gy of EBRT and receiving the remaining RT. In current era of IMRT, the incidence of grade 3-4 GU and GI toxicities have significantly decreased, compared to conventional AP/PA and four field box techniques [31,33]. 50% of our patients were treated with 3DRT and 67% had a pelvic sidewall boost with AP/PA fields. Furthermore, 52% of our patients had nodal boost by either IMRT or 3DRT or both, which was not used to calculate EQD₂ (EBRT + HDR-BT) doses to the OAR. Thus, the GI and GU toxicities we observed in our study population might have been due to a multitude of factors such as dose per HDR-BT fraction, treatment modality, and total dose.

The evolution of 3D planning from 2D planning resulted in the advent of volume-based HDR-BT planning, where the dose can be prescribed to the HR-CTV delineated by CT and/or MRI scans with close monitoring of OAR doses [7,8]. Accurate target and OAR delineation led to T&R and T&O based dose optimization techniques to create conformal plans by altering dwell times and dwell positions [34,35,36]. Several studies have shown the benefits of image-guided volume-based brachytherapy planning in gynecological malignancies compared to Point A-based plans [20,21,22,23,24,25]. Point A-based plans were compared with volume-based plans by Shin *et al.*, and demonstrated significant improvement in OAR doses and conformal indexes by volume-based planning [21]. In the study by Onal *et al.*, CT-guided volume-based plans showed significant improvement in D_{2cc} and D_{5cc} compared to traditional Point A-based ICRU bladder doses [20]. Similarly, our study demonstrates the advantages of volume-based HDR planning in improving the OAR doses and conformality. In the last decade, many academic institutions have led further advancements in volume-based HDR-BT planning for cervical cancer with the integration of MRI [22,23,24,25,31,32,37,38,39]. The ability of MRI in better defining HR-CTV dimensions and improving the doses to the HR-CTV was demonstrated by Viswanathan *et al.* and Tanderup *et al.* [24,25]. Studies by Pötter *et al.* and Lindegaard *et al.* showed better local control and reduction in toxicities by image-guided volume-based HDR planning compared to historical series [22,23,40,41]. However, most community practices do not have a dedicated MRI scanner available for brachytherapy planning due to financial and infrastructure challenges. Recent reports propose a hybrid CT/MRI approach to circumvent this problem, where an MRI is used for the initial HDR-BT fraction followed by CT

scans for the remaining fractions [27,40,41]. In our study, we used a similar approach where an MRI was obtained 1-2 weeks before the first HDR, which was fused with successive CT scans obtained for each HDR-BT fraction.

Estimating point doses on the walls of hollow structures such as rectum, sigmoid, and bladder are not always precise due to inter-fraction and intra-fraction movements as well as limitations of CT in soft tissue delineation [2]. In our study, we demonstrated improvements in $D_{0.1cc}$, D_{1cc} , and D_{2cc} to the rectum, sigmoid, and bladder by volume-based planning. We did not use D_{5cc} and D_{10cc} because accurate estimation of 5 cc and 10 cc require precise contouring of the rectal, sigmoid, and bladder walls with MRI per HDR-BT fraction [2]. Georg *et al.* demonstrates D_{1cc} and D_{2cc} as significant parameters in predicting rectal toxicity, while $D_{0.1cc}$, D_{1cc} , and D_{2cc} were significant in predicting bladder toxicities [42]. $D_{0.1cc}$, D_{1cc} , D_{2cc} , and D_{5cc} were shown to be predictive of grade 2 or more recto-sigmoidal mucosal changes by Koom *et al.*, whereas Kim *et al.* reports D_{5cc} as predictive of rectosigmoid mucosal changes and late rectosigmoid complications [43,44]. Accurate evaluation of OAR point doses is of paramount importance to prevent GI and GU toxicities after brachytherapy. However, the calculation of EQD₂ (EBRT + HDR-BT)-based point doses to OAR is based on the fundamental assumption of it being on the same anatomical spot during EBRT and brachytherapy despite organ and applicator movements. In addition, current EQD₂ calculations do not account for hotspot locations from the EBRT portion of RT. Thus, our current methods carry the inherent disadvantage of inaccurate anatomical point dose assessments. In recent years, the role of deformable image registration (DIR) has become increasingly relevant in accurately estimating the anatomical point dose when doses from different scans are combined [45,46,47,48]. DIR is still an active area of investigation and further work in this field will help us accurately estimate OAR point doses when EBRT and BT doses are combined.

Twelve percent of the 240 plans re-planned by HDR_{VOL} planning were rejected in our study due to inferior HR-CTV and OAR doses. 20% of the 240 plans reviewed used a modified Point A technique instead of the conventional Point A due to similar reasons. Radiologically, such patients had one or all the following characteristics: 1. parametrial extension; 2. pelvic sidewall extension; 3. OAR (rectum, sigmoid, or bladder) flushing at the surface of HR-CTV. Volume-based planning in such scenarios resulted in either under dosing of the HR-CTV or over-dosing of the OAR compared to Point A plans in our experience. Parametrial and pelvic sidewall tumor extensions impose challenges for HDR-BT planning using conventional CT compatible T&R and T&O. The challenge is in the dosimetric and geometric limitations of the traditional T&R and T&O applicators, where the only variables that can be changed are dwell times and dwell positions, which are restricted to the tandem, ovoid, and ring. Literature indicates limitations of volume-based planning in delivering adequate dose to asymmetrical tumors with diameter greater than 4 cm with conventional T&R and T&O applicators [21]. The study by Shin *et al.* demonstrated similar

results, where volume-based planning led to an increase in rectum and bladder doses in patients where the HR-CTV was not covered by the 100% isodose line [21]. An alternative to the traditional T&R and T&O applicators is the Vienna applicator that has additional channels for needle insertions around the tandem. The Vienna applicator combines an intra-cavitary and interstitial approach and thus adds an additional variable through additional loading channels to attain desirable plans with clinically acceptable HR-CTV doses and lower OAR doses. The studies by Kirisitis *et al.* and Hsu *et al.* have demonstrated the potential of Vienna applicators in HDR-BT treatments of cervical cancer patients in obtaining lowered OAR doses without compromising HR-CTV doses [49,50]. Thus, Vienna applicators are a possible solution for HDR-BT planning in anatomically challenging clinical scenarios.

Point A corresponds to the para-cervical triangle with the uterine vessels and ureter crossing within, where the microscopic and macroscopic disease exist [7,8,11,12]. Historically, EQD₂ doses of 80-90 Gy to the high-risk disease defined by Point A were required to achieve local control rates of 80-90% for cervical cancer [3,4,5,6]. However, in recent years, several studies have demonstrated comparable local control rates with MRI-guided HDR-BT planning for cervical cancer without compromising the total EQD₂ dose to the HR-CTV [2,22,23,37]. Our data clearly demonstrates the potential of HDR_{VOL} planning in achieving the recommended D₉₀ of the HR-CTV with a median dose of 86 Gy. In addition to D₉₀, current guidelines also recommend documentation of V₁₅₀ and V₂₀₀ of HR-CTV [2]. Nevertheless, a biological correlation between HR-CTV hotspots and local control for cervical cancer is unknown. In our study, we could achieve median HR-CTV hotspots of greater than 62% (V₁₅₀) and 39% (V₂₀₀) by volume-based planning and were comparable to the data reported by other studies [51,52].

Conclusions

Volume-based HDR-BT planning allows the physician to create a conformal dose cloud with respect to the HR-CTV after careful CT/MRI-based assessment of the tumor and OAR. Thus, the likelihood of over-estimation and under-estimation of doses to the HR-CTV and OAR, respectively, is lowered. Overall, our study demonstrates the dosimetric benefits of HDR_{VOL} planning in lowering OAR doses and without compromising the recommended D₉₀ of 80-90 Gy to the HR-CTV. The study also underscores the need for prospective studies investigating the OAR dose constraints per HDR-BT fraction and more accurate point dose assessment using DIR.

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Disclosure

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