High resolution (3 Tesla) MRI-guided conformal brachytherapy for cervical cancer: consequences of different high-risk CTV sizes

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Abstract

Purpose: To evaluate conventional brachytherapy (BT) plans using dose-volume parameters and high resolution (3 Tesla) MRI datasets, and to quantify dosimetric benefits and limitations when MRI-guided, conformal BT (MRIG-CBT) plans are generated.

Material and methods: Fifty-five clinical high-dose-rate BT plans from 14 cervical cancer patients were retrospectively studied. All conventional plans were created using MRI with titanium tandem-and-ovoid applicator (T&O) for delivery. For each conventional plan, a MRIG-CBT plan was retrospectively generated using hybrid inverse optimization. Three categories of high risk (HR)-CTV were considered based on volume: non-bulky (< 20 cc), low-bulky (> 20 cc and < 40 cc) and bulky (≥ 40 cc). Dose-volume metrics of D_{90} of HR-CTV and D_{2cc} and $D_{0.1cc}$ of rectum, bladder, and sigmoid colon were analyzed.

Results: Tumor coverage (HR-CTV D_{90}) of the conventional plans was considerably affected by the HR-CTV size. Sixteen percent of the plans covered HR-CTV D_{90} with the prescription dose within 5%. At least one OAR had D_{2cc} values over the GEC-ESTRO recommended limits in 52.7% of the conventional plans. MRIG-CBT plans showed improved target coverage for HR-CTV D_{90} of 98 and 97% of the prescribed dose for non-bulky and low-bulky tumors, respectively. No MRIG-CBT plans surpassed the D_{2cc} limits of any OAR. Only small improvements (D_{90} of 80%) were found for large targets (> 40 cc) when using T&O applicator approach.

Conclusions: MRIG-CBT plans displayed considerable improvement for tumor coverage and OAR sparing over conventional treatment. When the HR-CTV volume exceeded 40 cc, its improvements were diminished when using a conventional intracavitary applicator.

Purpose

Brachytherapy (BT) has played a central role in radiation therapy for cervical cancer since 1903. The standard of care for cervical cancer is a combination of external beam radiation therapy (EBRT) with concomitant cisplatinum-based chemotherapy and BT. The standard BT treatment technique has been unchanged for decades: 2D orthogonal radiographs are used to specify a dose to a fixed reference point, point A, relative to the intracavitary applicator. The patient anatomy and tumor location, not radiographically visible, are unused in the treatment planning process [1,2]. Recent advances in treatment planning based on 3D imaging enables the delineation of the target volumes and critical structures allowing volume-based inverse planning [3]. As magnetic-resonance imaging (MRI) provides superior soft tissue differentiation relative to computed tomography (CT) [4],

MRI-based treatment planning prior to each BT fraction is preferred. The patient's clinical target volume (CTV) and organs at risk (OARs) can be clearly identified and contoured on MRI datasets [4], allowing radiation delivery to macroscopic tumor volumes, and adaptive planning to account for tumor regression.

The American Brachytherapy Society (ABS) task group for cervical cancer [2] has adopted the Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) recommendations for 3-D imaging based BT planning [5]. The planning method takes the pear-shaped isodose lines of conventional treatment and adjusts dwell times to optimize the minimum dose received by 90%, D_{90}, of the High Risk (HR)-CTV, while restricting the minimum dose to the hottest 2 cc of each OAR, D_{2cc}. Several studies [6-9] have investigated correlations between dose-volume-histogram (DVH) parameters from these op-

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timized treatments and conventional point doses from conventional planning. For example point A and International Commission on Radiation Units and measurements (ICRU) report #38-defined rectum and bladder points [1] using pulsed-dose-rate (PDR) and high-dose-rate (HDR) BT. The goal is to understand the correlation between ICRU report #38-defined points & point A and DVH metrics [6-9]. One center, performing MRI-guided, conformal BT (MRIG-CBT) [10] reports that the mean HR-CTV volume for patients with local recurrence was significantly larger (50 ± 24 cc) than for patients without local recurrence (34 ± 23 cc, $p < 0.05$). Only D_{90} and D_{100} of the HR-CTV had a statistically significant effect on local tumor control, while the doses to intermediate-risk CTV and gross target volume did not [10]. This result implies that more analysis is needed into the dosimetric benefits and limitations of MRIG-CBT plans for different HR-CTV sizes. Previous studies considering HR-CTV size have only classified large and small volumes, and employed lower resolution MRI (< 2 Tesla) [8,9]. There is a need for improved contouring precision [4], accomplished with a high-resolution (3 Tesla) MRI [11]. Even though high-resolution (3 Tesla) MRI is being increas-

ingly used in diagnosis, its use in MRI-guided BT has only recently been introduced in the literature [12-15].

In this study, we retrospectively evaluated conventional plans using GEC-ESTRO recommended [5,16]. DVH parameters, and quantified the dosimetric benefits of MRIG-CBT, both in general and with respect to three different HR-CTV sizes.

Material and methods

Patients and EBRT treatments

We retrospectively studied 55 plans from 14 patients with biopsy-proven cervical cancer, with approval from the institutional review board. The malignancies were rated FIGO (International Federation of Gynecology and Obstetrics) stage Ib1 to IV and were treated in 2009 or 2010. The treatments employed EBRT with concomitant chemotherapy (for all but one patient in which chemotherapy was contraindicated), followed by 3-5 fractions of BT with 5.5-8 Gy fraction size. The institutional protocol specifies eight weeks from the beginning of EBRT to the end of BT; though this time was extended in five cases due to clinical complications. Other pertinent characteristics of the patients, tumors, and treatments are summarized in Table 1. EBRT treatment plans used either a 3-D conformal technique or intensity-modulated radiotherapy (IMRT) generated using the Pinnacle3® treatment planning system (version 7.0, Philips Medical Systems Inc., Madison, WI, USA). The prescription dose of EBRT was 45 Gy in 25 fractions, and, when necessary, a 5.4 to 10 Gy boost in 3 to 5 fractions to the involved paraortic or parametrial regions.

HDR treatments

All 55 plans were treated using a conventional Point A planning technique. Intracavitary HDR started after 3-4 weeks of EBRT, using the ^{192}Ir radioisotope (VariSource iX®, Varian Medical Systems Inc., Palo Alto, CA, USA). Patients were prescribed a total dose of 33-36 Gy_{10} in 5-7 fractions, where Gy_{10} is the equivalent dose in 2 Gy fractions of EBRT (EQD2) using an α/β of 10 Gy. For each fraction, clinical examination was performed under general anesthesia, and a Fletcher-Suit-Declos® T&O applicator (Varian Medical Systems Inc.) was inserted under ultrasound guidance. A titanium applicator was chosen for advantages previously described in the literature [12,17]. Orthogonal digital radiographs were acquired before and after 3.0 Tesla MRI scan to identify applicator displacements during patient transport to the MR scanner (MAGNETOM Trio™, Siemens Medical System Inc., Erlangen, Germany). All conventional plans were clinically generated on MRI not on radiographs, using a previously reported scan protocol [12]. T2- and T1-weighted MR images were used for contouring and source-pathway reconstruction, respectively.

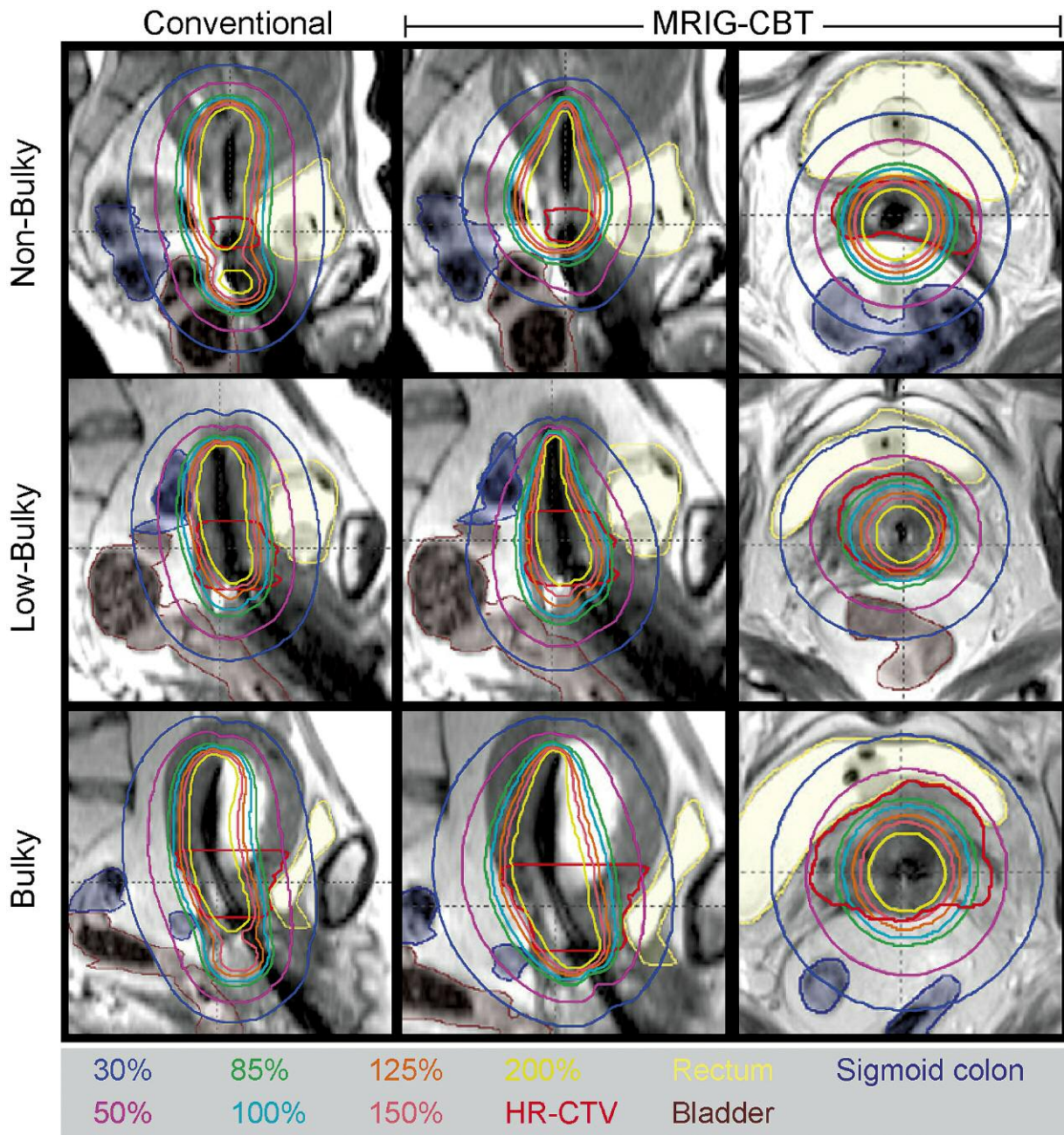### Conventional and MRIG-CBT HDR treatment planning

Conventional point A based planning followed the institute's clinical protocol developed according to ABS guidelines [2] (Fig. 1). The point A was defined by drawing a line

Table 1. Patient and plan characteristics

Patient characteristics	*N*	%
Patients	14	
FIGO stage		
IB-IIB	8	57
III-IV	6	43
Histopathology		
Squamous cell carcinoma	11	79
Adenocarcinoma	2	14
Other	1	7
Lymph node involvement	4	29
3 BT fractions (5.3-7.5 Gy)	5	36
4 BT fractions (5.0-6.0 Gy)	2	14
5 BT fractions (5.5-6.0 Gy)	7	50

		Median	Range
Patient age		58	33-79
EBRT dose (Gy)		50	45-62
BT dose (Gy)		26	16-30

Plan characteristics	*N*	Median	Range
BT (plans)			
Total fractions	58		
Usable fractions†	55		
HR-CTV size (cc)	32	8-145	
Non-bulky (cc)	15	15	8.3-20.0
Low-bulky (cc)	19	27	8.3-39.0
Bulky (cc)	21	74	8.3-145

FIGO – International Federation of Gynecology and Obstetrics, BT – brachytherapy, EBRT – external beam radiotherapy
†For 3 fractions the MRI scanner was unavailable, and patients were imaged by CT instead. These fractions were excluded from the study

Fig. 1. Isodose lines for conventional and MRIG-CBT planning of all three HR-CTV sizes: non-bulky (HR-CTV < 20 cc), low-bulky (20 cc ≤ HR-CTV < 40 cc) and bulky (HR-CTV ≥ 40 cc)

through the center of each ovoid, the radius of the ovoid + 2 cm superiorly along the tandem from the intersection of this line, and 2 cm lateral from the center of the tandem. Optimization lines were generated 0.5 cm lateral from each ovoid surface to specify vaginal doses, in addition to the lines of 2 cm lateral from the center of the tandem to specify point A doses. Source pathway reconstruction [12,17] for T&O was done on T1-weighted MRI (1 mm slice thickness) by importing predetermined shapes from the applicator library (SolidApplicator, BrachyVision™, Varian Medical System Inc.). According to the GEC-ESTRO recommendations

[5,18], the HR-CTV, rectum, bladder and sigmoid colon were retrospectively contoured on T2-weighted MRI of 3 mm slice thickness.

The strategy for volume-optimization was based on a study by Kim *et al.* [12] (Fig. 1) using an hybrid-inverse planning process. Hybrid-inverse planning represents a 3-D volume-optimization plan not solely generated by inverse volume optimization, but generated in a hybrid manner using a conventional point A plan and inverse volume-optimization. The first step is the generation of a conventional point A plan. A planner evaluates the DVH param-

eters according to the total dose limit according to the GEC-ESTRO recommendations [19], the D_{2cc} of an OAR are ≤ 75 Gy_3 of EQD2 for the rectum and sigmoid colon, and ≤ 90 Gy_3 of EQD2 for the bladder. The dose-volume constraints in inverse-volume optimization are set so that all OARs receive equal or lower doses than their limit. Afterward the optimization is iteratively altered with updated dose-volume optimization constraints until three goals are achieved. The three goals are: 1) OAR D_{2cc} values below limits of equation (1) (defined below), 2) HR-CTV D_{90} below 105% of the prescription dose, and 3) if HR-CTV D_{90} was below the prescription dose, at least one OAR D_{2cc} value within 5% of its limit. The isodose lines for each slice on coronal, sagittal, and axial plans were reviewed, and final dose shaping using graphical optimization was performed if necessary.

As a "worst-case scenario", it was assumed that the HR-CTV and all OARs received the EBRT prescription dose, and that each OAR D_{2cc} was in the same location for all BT treatment fractions [20]. The OAR D_{2cc} values from the EBRT boosts were also accounted for and used to determine an OAR limit for each BT fraction:

$$L_i = (D_L - D_{EBRT} - D_{boost}) \frac{D_i}{D_{ET}} \qquad (1)$$

where L_i is the D_{2cc} limit for BT fraction i, D_L is the total dose limit [19] to D_{2cc} of an OAR, D_{EBRT} – the total EBRT dose, D_{boost} – the D_{2cc} dose to the OAR from EBRT boost, D_i is the prescribed BT dose for fraction i, and D_{BT} is the total prescribed BT dose. All OAR quantities were converted to EQD2 values using an α/β of 3 Gy [18].

Analysis

Each plan was analyzed by recording the D_{90} and D_{100} of the HR-CTV, the D_{2cc} and $D_{0.1cc}$ of each OAR, and the doses to point A and the ICRU bladder and rectum points in contrast to those with MRIG-CBT. It has been reported that DVH measurements in MRIG-CBT are highly-dependent on a number of variables, including applicator reconstruction, MRI artifacts, and contouring variation [17]. As both conventional and MRIG-CBT cases employ the same applicator location and contours, the comparison of the two methods was unaffected by these variables. All plans were divided into three volume categories: non-bulky (HR-CTV < 20 cc), low-bulky (20 cc $\leq$ HR-CTV < 40 cc) and bulky (HR-CTV $\geq$ 40 cc). The p values were calculated using a two-tailed t-test assuming homoscedasticity.

Results

Conventional, point A based plans

All 55 conventional plans delivered the prescribed dose to point A with little variation (Table 2). The average doses to right and left point A were 100 ± 1% (mean ± standard deviation) of the respective prescription doses for non-bulky and low-bulky tumors. The plans for bulky tumors showed increased variation in point A dose, at 100 ± 2% of the respective prescription doses. The D_{90} of the HR-CTV for conventional plans was considerably affected by the HR-CTV volume. On average, D_{90} for the HR-CTV for the low-bulky tumors was favorable, at 104 ± 17% (Table 2). However, we found the HR-CTV D_{90} for 47% of the low-bulky tumor plans corresponded to more than 5% overdose, while 42% of the plans received more than 5% under-dose (Table 3). For

Table 2. Conventional plan results

A: Conventional plan results, target coverage			
Target (% Rx)	Pt. A dose	HR-CTV D_{90}	Diff.
All plans	100 ± 1	93 ± 24	−7.1%
Non-bulky	100 ± 1	111 ± 16	10.6%
Low-bulky	100 ± 1	103 ± 16	3.0%
Bulky	100 ± 2	72 ± 17	−28.8%

B: Conventional plan results, OAR sparring					
	ICRU (Gy) Pt.	$D_{0.1cc}$ (Gy)	$D_{0.1cc}/D_{ICRU}$	D_{2cc} (Gy)	D_{2cc}/D_{ICRU}
Rectum					
All plans	3.9 ± 1.5	5.0 ± 1.7	1.3 ± 0.4	3.7 ± 1.1	1.0 ± 0.3
Non-bulky	4.2 ± 1.8	5.1 ± 1.7	1.4 ± 0.5	3.8 ± 1.3	1.0 ± 0.4
Low-bulky	3.9 ± 1.6	5.0 ± 2.0	1.3 ± 0.3	3.7 ± 1.3	1.0 ± 0.3
Bulky	3.8 ± 1.1	4.9 ± 1.5	1.3 ± 0.5	3.7 ± 0.9	1.0 ± 0.3
Bladder (% Lim)					
All plans	4.5 ± 1.8	6.7 ± 2.2	1.7 ± 0.8	5.1 ± 1.4	1.3 ± 0.6
Non-bulky	3.8 ± 1.7	5.9 ± 1.7	1.7 ± 0.4	4.6 ± 1.5	1.3 ± 0.3
Low-bulky	4.6 ± 1.9	7.0 ± 1.8	1.8 ± 0.9	5.3 ± 0.9	1.4 ± 0.7
Bulky	4.7 ± 1.7	7.1 ± 2.8	1.7 ± 0.9	5.4 ± 1.6	1.3 ± 0.7

Rx – prescribed dose, Pt – point, HR-CTV – high-risk clinical target volume, D_{90} – minimum dose to the hottest 90% of the target volume, OAR – organ-at-risk, ICRU Pt – point recommended by ICRU report #38 [1], $D_{0.1cc}/D_{2cc}$ – minimum dose to the hottest 0.1 cc or 2 cc of the OAR volume, DICRU – dose to an ICRU Point. All values are mean ± one standard deviation

non-bulky or bulky tumors, the average HR-CTV D_{90} values were either considerable overdoses (+10.5%) or underdoses (–28.2%), respectively. Regardless of their tumor size, only 16% of conventional plans had HR-CTV D_{90} values within 5% of the prescription dose (Table 3). Of the conventional plans, 52.7%, had at least one OAR with a D_{2cc} value above the GEC-ESTRO limit. The D_{2cc} limits for the rectum, bladder, and sigmoid colon were exceeded in 20%, 29%, and 18% of the conventional plans, respectively (Table 3). The bladder was the most frequently overdosed OAR (29% of plans, Table 3), despite having a higher recommended dose limit than the rectum or sigmoid colon. The mean doses of each OAR across all plans remained below limits for all HR-CTV sizes. When normalized to the fraction D_{2cc} limits of equation 1, mean OAR D_{2cc} ranged from 66 ± 21% for the sigmoid colon in non-bulky geometries to a high of 94 ± 34% for bladder near low-bulky HR-CTVs (Table 4). When the dose distributions for all HDR and EBRT fractions were considered cumulatively, four of the twelve patients for which all HDR fractions were available showed at least one OAR D_{2cc} value over the limit for the entire treatment: one patient had D_{2cc} values over the limit for both rectum and bladder, one patient exceeded only the rectum limit, one only the bladder limit, and one only the limit of the sigmoid colon.

Statistically significant correlation was found between the rectum ICRU point and its D_{2cc} measurements ($r^2 = 0.5449$, $p < 0.001$) (Table 2). The mean ratio of D_{2cc} to D_{ICRU} for the rectum was 1.0 ± 0.3. However, no significant correlation was seen between the bladder ICRU point and D_{2cc} ($r^2 = 0.210$,

$p = 0.125$). The bladder ICRU point underestimated maximal dose (D_{2cc}), i.e. the mean ratio of D_{2cc} to D_{ICRU} was 1.3 ± 0.6.

MRIG-CBT plans

MRIG-CBT plans exhibited significantly higher HR-CTV D_{90} values for non-bulky ($p = 0.002$) and bulky tumors ($p = 0.028$) (Table 4). No MRIG-CBT plans had a D_{90} greater than 5% above the prescription dose. No MRIG-CBT plans exhibited D_{2cc} of any OARs over their GEC-ESTRO limit (Table 3). Thus, no patients showed overall D_{2cc} values over the limits throughout their full HDR treatments. The effect of this restriction was seen in the HR-CTV coverage result: for all plans where HR-CTV D_{90} was less than the prescription dose, at one or more OAR D_{2cc} was within 5% of its limit: this OAR was the bladder in 96% of these plans, the rectum in 20%, and the sigmoid colon in 20%. The average D_{2cc} values of MRIG-CBT plans ranged from 41 ± 16% of the fraction limit for rectum of non-bulky cases and 87 ± 16% for bladder in bulky plans (Table 4). The bladder was the only structure limiting dose in non-bulky and low-bulky plans. For the 16 bulky plans with HR-CTV D_{90} less than the prescribed dose, the bladder D_{2cc} was within 5% of its limit in 81% of the plans, and the rectum and sigmoid D_{2cc} were each dose-restricting in 31% of such cases.

To visually compare volumetric measurements (Fig. 2), the mean success of each plan attribute was plotted on a separate axis; HR-CTV D_{90} is plotted on the vertical axis relative to the prescription dose (Rx). Therefore, the 100% val-

Table 3. Conventional and MRIG-CBT plans. Analysis with respect to tumor coverage and organs-at-risk sparing

Plan characteristics	All sizes (%)		Non-bulky (%)		Low-bulky (%)		Bulky (%)	
	Conv.	MRIG.	Conv.	MRIG.	Conv.	MRIG.	Conv.	MRIG.
Point A								
Over Rx +5%	2	35	0	13	0	37	5	48
Within Rx ±5%	98	16	100	13	100	11	95	24
Under Rx –5%	0	49	0	73	0	53	0	29
ICRU point over 80% Rx								
Rectum ICRU	22	22	33	13	16	21	19	29
Bladder ICRU	42	47	27	13	58	47	38	71
HR-CTV D_{90}								
Over Rx +5%	33	0	53	0	47	0	5	0
Within Rx ±5%	16	56	33	87	11	68	10	24
Under Rx –5%	51	44	13	13	42	32	86	76
D_{2cc} over OAR limit								
Rectum D_{2cc}	20	0	13	0	26	0	19	0
Bladder D_{2cc}	29	0	13	0	37	0	33	0
Sigmoid D_{2cc}	18	0	7	0	5	0	38	0
D_{2cc} within ±5% of OAR limit								
Rectum D_{2cc}	7	9	7	0	0	0	14	24
Bladder D_{2cc}	13	44	20	13	5	47	14	62
Sigmoid D_{2cc}	11	9	13	0	11	0	10	24

OAR – organ-at-risk, D_{2cc}, $D_{0.1cc}$ – minimum dose to the hottest 0.1 cc or 2 cc of the OAR volume, Rx – prescribed dose, HR-CTV – high-risk clinical target volume, D_{90} – minimum dose to the hottest 90% of the volume
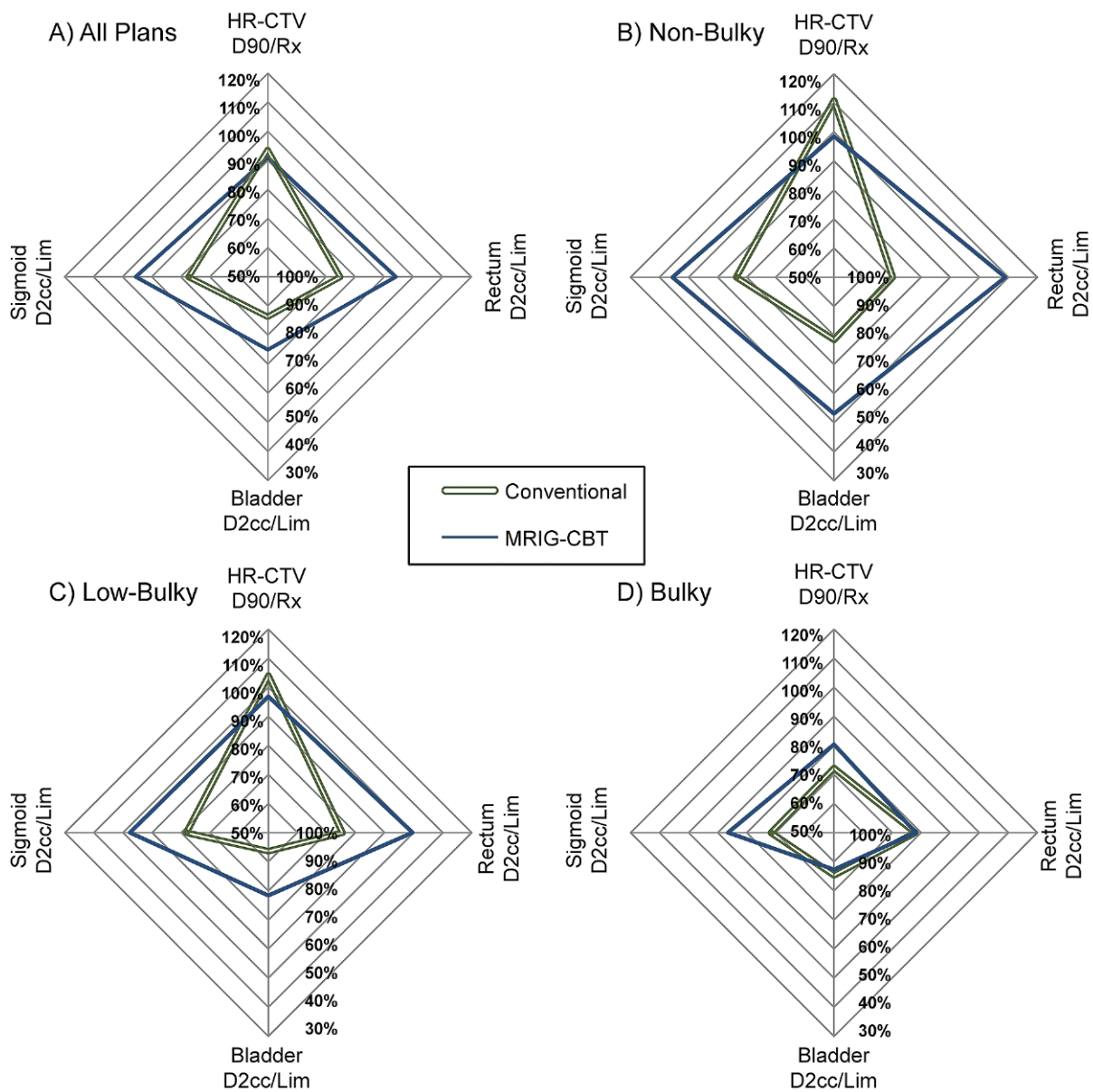
Fig. 2. Average plan attributes for each HR-CTV size. HR-CTV D_{90} is plotted on the vertical axis relative to the prescription dose. Therefore, the 100% of HR-CTV D_{90}/prescription dose (Rx) represents HR-CTV D_{90} receives Rx. The D_{2cc} of each OAR relative to the OAR limit (D_{2cc}/Lim) is plotted on the other three axes, thus smaller % values represent better OAR sparing; these axes are inverted such that OAR sparing increased as the values of sigmoid, bladder, rectum move away from the origin

ue of HR-CTV D_{90}/prescription dose (HR-CTV D_{90}/Rx) on the vertical axis is ideal. For instance, in B panel, conventional plans have 111% Rx at HR-CTV D_{90}, while MRIG-CBT plans deliver 99% Rx. The D_{2cc} of each OAR relative to the OAR limit (D_{2cc}/Lim) is plotted on the other three axes, thus smaller % values represent better OAR sparing; these axes were inverted such that OAR sparing increased as the values of sigmoid, bladder, rectum move *away* from the origin. Thus a larger area of the plotted "diamonds" indicates improved plan characteristics. Large improvements were seen for both low- and non-bulky cases, while mean treatment results of bulky HR-CTV plans remained comparable (Table 3).

Discussion

The dosimetric improvements of MRIG-CBT plans have, when compared to conventional plans, been published for HDR [19], and PDR [6-9] BT when using tandem-and-ring applicator (T&R) [7,9], T&R plus needles [7,9], T&O [6], or tandem only [8]. However, previous studies analyzed the benefits of MRIG-CBT without tumor size classification or with only two tumor size classifications, large and small volumes. In this study, the dosimetric benefits of MRIG-CBT were analyzed for three different HR-CTV groups when using conventional T&O applicators without the use of supplementary needles. For bulky tumors, however, neither

Table 4. MRIG-CBT plan results

A: Conventional plan results, target coverage

HR-CTV D$_{90}$	Conventional (% Rx)	MRIG-CBT (% Rx)	Diff. (%)	*p*-value
All plans	93 ± 24	91 ± 15	−7.6	0.421
Non-bulky	111 ± 16	98 ± 9	−9.2	0.002
Low-bulky	103 ± 16	97 ± 9	−6.2	0.101
Bulky	72 ± 17	80 ± 16	−7.7	0.028

B: Planning comparison, OAR sparring

	Conventional			MRIG-CBT			Diff. of % OAR limits	*p*-value
	D$_{0.1cc}$ (Gy)	D$_{2cc}$ (Gy)	% OAR limit	D$_{0.1cc}$ (Gy)	D$_{2cc}$ (Gy)	% OAR limit		
Rectum								
All plans	5.0 ± 1.7	3.7 ± 1.1	75 ± 34	4.2 ± 1.4	3.1 ± 1.0	56 ± 25	−19.0%	< 0.001
Non-bulky	5.1 ± 1.7	3.8 ± 1.3	80 ± 43	3.6 ± 1.2	2.5 ± 0.7	41 ± 16	−38.7%	< 0.001
Low-bulky	5.0 ± 2.0	3.7 ± 1.3	74 ± 32	3.9 ± 1.3	2.9 ± 0.8	50 ± 19	−24.1%	< 0.001
Bulky	4.9 ± 1.5	3.7 ± 0.9	72 ± 29	4.9 ± 1.4	3.7 ± 1.0	72 ± 26	−0.1%	0.893
Bladder								
All plans	6.7 ± 2.2	5.1 ± 1.4	86 ± 36	6.3 ± 1.7	4.7 ± 1.3	75 ± 25	−11.4%	0.006
Non-bulky	5.9 ± 1.7	4.6 ± 1.5	78 ± 40	4.9 ± 1.6	3.6 ± 1.2	53 ± 28	−25.4%	< 0.001
Low-bulky	7.0 ± 1.8	5.3 ± 0.9	94 ± 34	6.5 ± 1.3	4.8 ± 0.9	78 ± 21	−15.2%	0.009
Bulky	7.1 ± 2.8	5.4 ± 1.6	85 ± 34	7.1 ± 1.6	5.5 ± 1.0	87 ± 16	2%	0.502
Sigmoid								
All plans	5.1 ± 2.2	3.6 ± 1.1	73 ± 31	4.3 ± 1.9	3.0 ± 0.9	54 ± 23	−18.4%	< 0.001
Non-bulky	4.8 ± 1.4	3.5 ± 1.0	66 ± 21	4.0 ± 1.6	2.7 ± 0.9	44 ± 14	−22.0%	< 0.001
Low-bulky	4.7 ± 1.4	3.5 ± 1.1	72 ± 30	3.9 ± 1.3	2.9 ± 0.8	52 ± 21	−19.4%	< 0.001
Bulky	5.6 ± 3.1	3.8 ± 1.3	78 ± 38	4.9 ± 2.4	3.4 ± 1.0	64 ± 28	−14.8%	0.006

OAR – organ-at-risk, D$_{2cc}$, D$_{0.1cc}$ – minimum dose to the hottest 0.1 cc or 2 cc of the OAR volume, Rx – prescribed dose, HR-CTV – high-risk clinical target volume, D$_{90}$ – minimum dose to the hottest 90% of the volume

planning method was able to increase HR-CTV D$_{90}$ to the prescribed dose when the T&O was used. MRIG-CBT resulted in only small improvements for bulky tumors. Therefore, the only use of conformal volume optimization and MRI guidance are limited to appropriately cover bulky tumors when a conventional intracavitary applicator is used. MRIG-CBT applicators for bulky tumors have been developed: T&R plus needles (Vienna applicator) [7,9] and T&O plus needles (Utrecht applicator) [21] and their use is recommended for bulky tumors. Transperineal interstitial implants for MRIG-CBT can be an alternative technique for bulky tumors. As a less invasive approach for bulky tumors, intensity-modulated brachytherapy using intracavitary applicators with electronic brachytherapy source has been under development [22,23].

The MRIG-CBT treatment planning approach showed good HR-CTV D$_{90}$ in all cases where it was not restricted by OAR dose limits. Most of the optimization results were highly dependent on the OAR D$_{2cc}$ limits set by equation (1). In cases where the HR-CTV D$_{90}$ did not reach the prescription dose, one of the three OARs restricted the HR-CTV D$_{90}$, and increasing the limit or allowing a slight overdose could have a large effect on HR-CTV D$_{90}$. This may be pos-

sible by shifting more of the allotted OAR dose to earlier HDR fractions and relying on tumor regression to enable sparing in the corresponding OAR in later treatment fractions. Such a shift in OAR limits would also affect the relative results of the two planning methods. In the present study, the optimization was able to reduce systematic overdoses to the HR-CTV in non-bulky plans, and reduce the D$_{90}$ variance seen in the conventional coverage of low-bulky tumors. Especially, for non-bulky tumors, MRIG-CBT can result in the dose reduction on side wall and nodes. Future studies on nodal doses of MRIG-CBT need to be performed. The studies on how to deliver appropriate radiation dose to nodes through EBRT also are expected to be followed. For instance, a simultaneous boosting to pelvic lymph nodes can be an option using image guided IMRT technique.

As emphasized by Trnková *et al.* [3], large-scale modifications to conventional distributions and/or solely inverse planning should be avoided until an understanding of the relationship between DVH-values and treatment efficacy is established. Thus, hybrid inverse optimization [24] was utilized in this study. What constitutes a "large-scale" modification and how to find improved inverse planning objectives are still open questions.

A low-magnetic-field MR system of 1.5 or 2.0 Tesla has been used for MR-guided BT. However, the signal-to-noise ratio (SNR) of a 1.5 Tesla MR is suboptimal, particularly its ability to accurately delineate the uterine cervix and the macroscopic tumor regions [14,24]. In addition, increased intra-scan motion artifacts exist when using 1.5 Tesla MR due to the extended acquisition time when compared to a 3 Tesla MR (see Fig. 3 in reference [11]). The high resolution (3 Tesla) MR system used in this study has approximately double the SNR of a 1.5 Tesla system, resulting in an image with a higher contrast in the uterine cervix and vagina [11] and a substantially faster image acquisition speed [12,25]. However, caution must be exercised when metal based applicators are used in 3 Tesla MRI-guided BT scans. In this study, a titanium T&O applicator was used with a 3 Tesla MRI. Before any clinical use of 3 Tesla MRI-guided BT, the safety concerns, especially radiofrequency [RF] heat- had been verified first [26]. Once assured of the safety of the process, the artifacts and distortions of the titanium applicator were quantified [12], since the artifact to noise ratio also increases in 3 Tesla MR systems.

Although it has been suggested to replace the BT component of cervical cancer treatment with stereotactic body RT, the unique advantages of BT should not be overlooked. BT offers a significantly higher biologically-effective dose due to the short distance between radiation sources and target volumes, and the sharp fall-off in radiation dose in space allows for higher dose to non-bulky and low-bulky tumor volumes while still retaining adequate sparing of nearby healthy tissues.

Conclusions

HR-CTV D_{90} was considerably affected by tumor size. Only 16% of conventional plans had HR-CTV D_{90} values within 5% of the prescription dose. Mean D_{2cc} values of rectum, bladder, and sigmoid colon were found to be below the GEC-ESTRO recommended limits for the conventional plans. However, in 52.7% of conventional plans at least one of the OARs had a D_{2cc} value over its limit. When all HDR fractions were considered cumulatively, 17% of patients had overall rectum and bladder D_{2cc} values over their limits, while 8% of patients exceeded the limit for sigmoid colon. The MRIG-CBT treatment planning technique was found to improve treatment plans relative to those of the conventional approach with HR-CTV less that 40 cc, bringing the D_{90} dose closer to the prescription value while avoiding overdose to the D_{2cc} of each OAR. Using conventional intracavitary applicators, only small improvements were seen when MRIG-CBT was used for bulky targets (> 40 cc).

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