

Impact of different dose prescription schedules on EQD₂ in high-dose-rate intracavitary brachytherapy of carcinoma cervix

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Abstract

Purpose: To observe the effect of different high-dose-rate (HDR) intracavitary brachytherapy dose schedules on equieffective dose in 2 Gy per fraction (EQD₂).

Material and methods: It is a retrospective study involving 50 cervical cancer patients, who received external radiotherapy of 45 Gy in 25 fractions and underwent intracavitary brachytherapy (ICBT). Computed tomography (CT) simulation was done after insertion of the applicators. High-risk clinical target volume (CTV_{HR}) and organs at risk (OARs) such as bladder, rectum, and sigmoid were contoured. Four different plans were generated for each patient, with dose prescriptions of 5.5 Gy × 5 fractions (plan A), 6.5 Gy × 4 fractions (plan B), 7 Gy × 4 fractions (plan C), and 9 Gy × 2 fractions (plan D), delivered to CTV_{HR}. The total EQD₂ for 0.1 cm³ and 2 cm³ of bladder, rectum, and sigmoid as well as dose received by 90% of the CTV_{HR} (D₉₀) and point A were calculated. The values were analyzed and compared with available literature.

Results: The mean CTV_{HR} volume was 47.12 ± 13.8 cm³. All plans delivered similar EQD₂ for 0.1 cm³ and 2 cm³ of sigmoid. Plan D delivered lesser EQD₂ compared to other plans for bladder, rectum, D₉₀ CTV_{HR}, and point A (*p* = 0.0001). Plan C delivered higher EQD₂ to OARs compared to other plans (*p* = 0.001). Plan A, B, and plan C delivered similar EQD₂ for D₉₀ CTV_{HR} and point A.

Conclusions: EQD₂ of bladder, rectum, sigmoid, D₉₀ CTV_{HR}, and point A were similar with 5.5 Gy × 5 fractions, 6.5 Gy × 4 fractions, and 7 Gy × 4 fractions, whereas EQD₂ of 9 Gy × 2 fractions was significantly unfavorable compared to other schedules. Further clinical studies are recommended to observe clinical outcomes.

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Key words: brachytherapy, EQD₂, cervical cancer.

Purpose

Cervical cancer is the fourth most common cancer among women in terms of incidence and mortality [1]. Majority of patients present in locally advanced stage, and need external beam radiotherapy (EBRT) and brachytherapy (BT) as well as concurrent chemotherapy. Brachytherapy plays an important role in the treatment of cervical cancer. Low-dose-rate (LDR) brachytherapy is replaced by high-dose-rate (HDR) brachytherapy, which is more convenient for patient, with no risk of radiation exposure to the staff and most importantly, with the advantage of dose optimization [2]. Most of the institutes follow similar dose prescription pattern for LDR brachytherapy; however, there is a wide range of discrepancy in HDR brachytherapy dose prescription. In the literature, we have observed different institutions

following different HDR brachytherapy schedules such as 5.5 Gy × 5 fractions, 6 Gy × 4 fractions, 7 Gy × 3 fractions, and 9 Gy × 2 fractions, probably because of the availability of the resources and logistic problems. In our institute, we follow 6.5 Gy × 4 fractions for two consecutive days, after 45 Gy EBRT. Since the local control and toxicities are determined by the dose per fraction, it is important to know the EQD₂ for different dose prescription schedules for HDR brachytherapy. EQD₂ or equieffective dose is also referred as equivalent dose in 2 Gy fractions [1,3,4,5,6].

The aim of this work is to investigate different HDR brachytherapy dose schedules of EQD₂ for high-risk clinical target volume (CTV_{HR}) and organs at risk (OARs), and also comparing dose schedules with available literature.

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Material and methods

In this retrospective study, cervical cancer patients with stage IB2 to IIB treated from January 2017 to December 2017 were included. Fifty patients who underwent intracavitary brachytherapy (ICBT) were included, and patients who underwent combination of ICBT with interstitial needles were excluded from the study.

Procedure

Around 10-15 days after the completion of EBRT, ICBT applicators (uterine tandem with flange and two vaginal ovoids) were inserted under spinal anesthesia or mild sedation. To ensure the emptiness of the rectum, sodium phosphate enema was given two hours before the procedure. Computed tomography (CT) scan simulation without intravenous contrast was completed after the insertion of applicators. During CT simulation, bladder was filled with 50 ml of normal saline and rectum was filled with 20 ml of rectal contrast. Axial CT slices of 3 mm thickness were taken from the upper border of third lumbar vertebra to the middle of shaft of the femur. The CT images were transferred to treatment planning system (HDR Plus, Bebig, Eckert and Ziegler, Germany) compliant with the Task Group 43 (TG-43) algorithm.

Planning and evaluation

The OARs such as bladder, rectum, sigmoid, and CTV_{HR} were contoured according to the guidelines published by Viswanathan *et al.* [7]. CTV_{HR} was defined based on the findings of examination under anesthesia and CT scan image. Intermediate-risk clinical target volume (CTV_{IR}) was created by giving 10 mm margin to CTV_{HR}. Applicators were digitized using the applicator library and verified with digitally reconstructed radiograph (DRR) before activating the dwell positions. At that

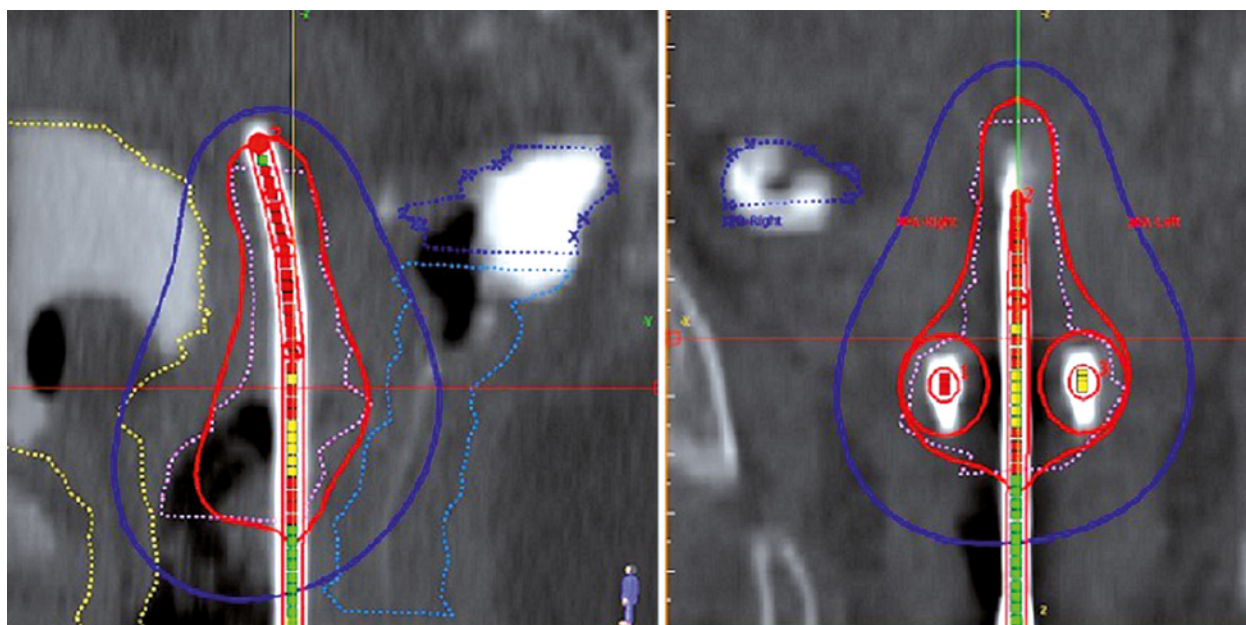
point, CTV_{HR} surface control points were generated and dose prescribed to CTV_{HR}. The dose-volume histogram (DVH) parameters were evaluated and isodose reshapener tool was used to maintain the pear shape dose distribution with maximum possible D₉₀ (dose received by 90% of the CTV_{HR}) and restrict the dose to OARs within the permissible limits. Figure 1 shows the dose distribution of intracavitary brachytherapy. Even though the dose was prescribed to CTV_{HR}, we also calculated the dose received by point A, which was marked 2 cm superior to external os and 2 cm perpendicular to the uterine tandem.

Dosimetric details

Four different plans were generated for each patient, with dose prescriptions of 5.5 Gy × 5 fractions (plan A), 6.5 Gy × 4 fractions (plan B), 7 Gy × 4 fractions (plan C), and 9 Gy × 2 fractions (plan D) to CTV_{HR}. The EQD₂ for 0.1 cm³ and 2 cm³ of bladder, rectum, sigmoid, point A, and D₉₀ were calculated for all plans, using the formula $BED = nd(1 + d/\alpha/\beta)$ and $EQD_2 = BED/[1 + (2/\alpha/\beta)]$, where n is the number of fractions and d is the dose per fraction. The α/β ratio was considered as 3 for normal tissues and 10 for the tumor [8]. The values were tabulated and analyzed by the statistical software SPSS version 18.0 (SPSS Inc., IBM, Chicago, USA). One-way ANOVA test was used to compare the values. The values were considered to be statistically significant when $p \leq 0.05$.

Results

A total of two hundred plans were generated for different dose prescriptions. The mean EQD₂ for OARs, D₉₀ CTV_{HR}, and point A is summarized in Tables 1 and 2, and Figure 2. The mean CTV_{HR} volume was 47.12 ± 13.8 cm³. We have observed that plan D delivered lower EQD₂ to 0.1 cm³ and 2 cm³ of bladder compared to other plans



bladder – yellow, rectum and sigmoid – blue, CTVHR – pink, 100% isodose line – red, 50% isodose line – solid blue

Fig. 1. Dose distribution of intracavitary brachytherapy

Table 1. The total EQD₂ (EBRT + BT) of organ at risks for different dose prescriptions (mean and standard deviation)

Plan (dose × fractions)	Bladder (Gy ₃)		Rectum (Gy ₃)		Sigmoid (Gy ₃)	
	0.1 cm ³	2 cm ³	0.1 cm ³	2 cm ³	0.1 cm ³	2 cm ³
Plan A (5.5 Gy × 5)	88.67 ±13	74.06 ±7	81.39 ±10	67.43 ±6	64.45 ±13	54.56 ±7
Plan B (6.5 Gy × 4)	88.27 ±14	73.75 ±8	82.08 ±10	67.57 ±5	64.25 ±14	54.43 ±7
Plan C (7 Gy × 4)	93.22 ±15	77.26 ±9	88.65 ±12	71.11 ±6	66.30 ±14	55.44 ±7
Plan D (9 Gy × 2)	75.20 ±12	68.58 ±7	79.59 ±11	64.82 ±5	60.60 ±12	52.14 ±6

EQD₂ – equieffective dose in 2 Gy

(*p* = 0.001). There was no difference in the mean EQD₂ for 0.1 cm³ and 2 cm³ of bladder for plan A, B, and C (*p* = 0.8, *p* = 0.1, and *p* = 0.07). Plan C delivered higher EQD₂ to 0.1 cm³ and 2 cm³ of rectum compared to other plans (*p* = 0.001). There was no significant difference in the mean EQD₂ for 0.1 cm³ of rectum for plan A, B, and D (*p* = 0.9, *p* = 0.3, and *p* = 0.2). The mean EQD₂ for 2 cm³ of rectum was lower for plan D compared to plan A and B (*p* = 0.001, *p* = 0.002). There was no significant difference in the mean EQD₂ for 0.1 cm³ and 2 cm³ of sigmoid for all the plans. The mean EQD₂ of D₉₀ CTV_{HR} and EQD₂ of point A was similar for plan A, B, C, but plan D delivered lower EQD₂ to D₉₀ CTV_{HR} and point A compared to other plans (*p* = 0.0001).

Discussion

This retrospective dosimetric study was conducted to compare 6.5 Gy × 4 fractions of ICBT that we follow with the other fractionation schedules available in the literature. An attempt was made to compare the EQD₂ of D₉₀ CTV_{HR} and OARs. In the literature, we found different dose schedules like 5 Gy × 5 fractions, 6 Gy × 4 fractions, 7 Gy × 4 fractions, 7.5 Gy × 3 fractions, and 9 Gy × 2 fractions being applied in practice [9,10,11,12,13,14,15,16]. The choice of fractionation schedule of a particular oncology center mainly depends on the number of patients, availability of the staff, cost effectiveness, etc. At our center, we follow single application of ICBT with four fractions of 6.5 Gy, with 6-hour gap between the fractions, on two consecutive days, two weeks after the completion of EBRT of 45 Gy in 25 fractions by 3DCRT technique, along with concurrent chemotherapy. Image-guided intensity modulated external beam radiochemotherapy and MRI-based adaptive brachytherapy in locally advanced cervical cancer (EMBRACEII) study recommends MRI-based brachytherapy for better delineation of OARs and CTV_{HR} [7,9]. In our institute, we practice CT-based brachytherapy because of limitation of the resources. We have summarized the EQD₂ of OARs and D₉₀ CTV_{HR} of different studies in Table 3. In these studies, the EQD₂ for 2 cm³ of bladder, 2 cm³ of rectum, and 2 cm³ of sigmoid are in the range of 79.7-88.2 Gy, 57.5-82.8 Gy, and 61-73.9 Gy, respectively. According to the ICRU 89 and the American Brachyther-

Table 2. The total EQD₂ (EBRT + BT) of D₉₀ CTV_{HR} and point A for different prescriptions (mean and standard deviation)

Plan (dose × fractions)	D ₉₀ CTV _{HR} (Gy ₁₀)	Point A (Gy ₁₀)
Plan A (5.5 Gy × 5)	85.9 ±3	64.36 ±6
Plan B (6.5 Gy × 4)	84.67 ±2	63.49 ±6
Plan C (7 Gy × 4)	89.03 ±2	65.24 ±7
Plan D (9 Gy × 2)	69.16 ±4	55.86 ±5

EQD₂ – equieffective dose in 2 Gy, CTV_{HR} – high-risk clinical target volume, D₉₀ – dose received by 90% of CTV_{HR}

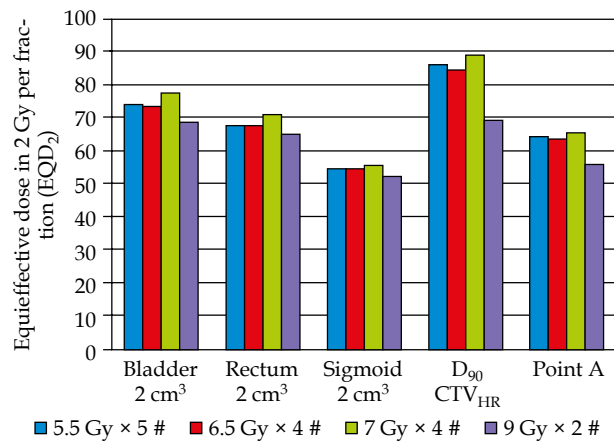


Fig. 2. The mean equieffective dose in 2 Gy per fraction (EQD₂) of organs at risk (OARs), D₉₀ CTV_{HR}, and point A

apy Society (ABS), the recommended EQD₂ for 2 cm³ of bladder and rectum is ≤ 90 Gy and ≤ 75 Gy, respectively, and it is also recommended to achieve 85 Gy EQD₂ for D₉₀ CTV_{HR} [3,4]. In the present study, the range of EQD₂ for 2 cm³ of bladder, 2 cm³ of rectum, and 2 cm³ of sigmoid is 68.58-77.27 Gy, 64.82-71.11 Gy, and 52.14-55.44 Gy, respectively. Although volume-based prescription is the standard practice, most of the centers still follow the X-ray-based point A prescription. Ghosh *et al.* in their

Table 3. Equieffective dose in 2 Gy in available literatures

Literature	Year of study	No. of patients	EBRT dose (Gy)	BT dose × fractions	Bladder 2 cm ³ (Gy ₃)	Rectum 2 cm ³ (Gy ₃)	Sigmoid 2 cm ³ (Gy ₃)	D ₉₀ CTV _{HR} (Gy ₁₀)
Pötter <i>et al.</i> [9]	2011	156	50.4	7 Gy × 4	86	65	64	93
Jamalludin <i>et al.</i> [10]	2016	A	48.6	7 Gy × 4	80.8	81.7	73.9	–
		B	45.4	7.5 Gy × 3	80.4	82.8	65.9	–
Kirisits <i>et al.</i> [11]	2005	22	45	7 Gy × 4	83	64	63	87
Beriwal <i>et al.</i> [12]	2011	44	45	5-6 Gy × 4	79.7	57.5	66.8	83.3
Tharavichitkul <i>et al.</i> [13]	2013	47	45	6.5-7 Gy × 4	88.2	69.6	72	93.1
Nomden <i>et al.</i> [14]	2013	46	45	7 Gy × 4	83	66	61	84
Wang <i>et al.</i> [15]	2016	42	46	5 Gy × 5	86	72.9	73.27	73.82
Present study		50	45	5.5 Gy × 5	74.06	67.43	54.56	85.9
			45	6.5 Gy × 4	73.75	67.57	54.43	84.67
			45	7 Gy × 4	77.27	71.11	55.44	89.03
			45	9 Gy × 2	68.58	64.82	52.14	69.16

EBRT – external beam radiotherapy, BT – brachytherapy, D₉₀ – dose received by 90% of the CTV_{HR}

study based on X-ray-based planning observed higher incidence of late toxicities of bladder and rectum in patients treated with 9 Gy × 2 fractions compared to 7 Gy × 3 fractions [16]. Mazon *et al.* reported increased grade 3 and higher rectal complications for dose > 75 Gy for 2 cm³ of rectum [17]. Georg *et al.* reported in their study that there is an increased probability of grade 3 rectal toxicities for dose greater than 88 Gy and 76 Gy for 0.1 cm³ and 2 cm³ of the rectum, respectively [18]. In a retrospective study by Manir *et al.* on correlation of rectal toxicity and dose, it was recommended to restrict the dose between 75 to 81 Gy for 0.1 cm³ of the rectum and between 64 to 69 Gy for 2 cm³ of the rectum to avoid grade 3 proctitis [19]. In our study, we have observed EQD₂ in the range of 80 to 89 Gy for 0.1 cm³ of the rectum and 65 to 71 Gy for 2 cm³ of the rectum by all the four plans. All the dose fractionation schedules were in compliance with the ICRU 89 recommendation for OARs. The EQD₂ of D₉₀ CTV_{HR} in different studies are in the range of 73.82-93.1 Gy. Studies have shown better local control with EQD₂ of D₉₀ CTV_{HR} in the range of 80 to 90 Gy [3,5]. Tanderup *et al.* in their study reported better local control rate with D₉₀ CTV_{HR} ≥ 85 Gy [20]. Dimopoulos *et al.* reported lower incidence of local recurrence and better local control in patients who received more than 87 Gy EQD₂ for CTV_{HR} [21]. In the present study, the mean EQD₂ of D₉₀ CTV_{HR} of plan A, B, C, and D were 85.9 Gy, 84.67 Gy, 89.03 Gy, and 69.19 Gy, respectively. Even though we have prescribed the dose to CTV_{HR}, we calculated the dose received by point A. The EMBRACE II study aimed at achieving 65 Gy EQD₂ to point A [5]. In our study, mean EQD₂ of point A with plan A, B, C, and D were 64.36 Gy, 63.49 Gy, 65.24 Gy, and 55.86 Gy, respectively. Overall, plans A, B, and C were better in terms of EQD₂ for D₉₀ CTV_{HR} and point A. We are in the process of comparing our clinical data

with different institutions practicing different dose fractionation schedule of HDR ICBT for cervical cancer. The limitation of the present study is that we have used CT-based planning, which might have overestimated the CTV_{HR} volume as reported by few studies [12,22]. In future, we plan to adopt MRI-based brachytherapy for cervical cancer.

Conclusions

EQD₂ of bladder, rectum, sigmoid, D₉₀ CTV_{HR}, and point A is similar with dose fractionation schedule such as 5.5 Gy × 5 fractions, 6.5 Gy × 4 fractions, and 7 Gy × 4 fractions. EQD₂ of 9 Gy × 2 fractions was significantly unfavorable compared to other schedules. Since it is a dosimetric study, further clinical studies are suggested to analyze the clinical outcome.

Disclosure

Authors report no conflict of interest.

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