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Comparison of point a based plans with clinical target volume-based three-dimensional plans using dose–volume parameters in small lesion of cervical cancer brachyterapy

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Objective: Intracavitary brachytherapy (ICBT) is the most critical part of cervical cancer treatment which contains a combination of external and intracavitary radiotherapy. We aimed to compare two different plans normalized to point A and the high-risk clinical target volume (HR-CTV) in terms of the target volume and doses for organs at risk (OARs). *Methods*: Twenty-eight patients with small-residue cervical tumor volume who received CT-based brachytherapy treatment with uterus tandem and double ovoid applicators were included in the study. 3D-ICBT treatment plans normalized to HR-CTV and point A were applied separately to five fractions. We made a total of 280 plans for the two treatment techniques. The patients were given a dose of 5.5 Gy per fraction for a total of 27.5 Gy in 5 fractions. The doses to OAR (rectum, sigmoid, and bladder) and HR-CTV were compared between HR-CTV and point A - based plans. *Results*: In the brachytherapy treatment planning, the mean doses of HR-CTV D_{90} and IR-CTV D_{100} were significantly lower in each fraction and in the total doses when normalized to HR-CTV than when normalized to point A ($p < 0.001$). D_{1cc}, D_{2cc}, and D_{max} values of OAR doses obtained from the brachytherapy treatment planning were significantly lower in each fraction and in the total doses when normalized to HR-CTV than when normalized to point A ($p < 0.001$). *Conclusion*: Our findings revealed that, particularly in small-volume HR-CTV after EBRT, plans normalized to HR-CTV can reduce overdose in the target tissue and avoid unnecessary OAR irradiation compared to the plans normalized to point A.

Keywords

Intracavitary brachytherapy; Cervical cancer; Point A; HR-CTV; Tumor size; Three-dimensional treatment plan; CT scan

1. Introduction

Cervical cancer is the fourth most common cancer type globally with its high prevalence and mortality rates among women [1]. According to the SEER databases, the rate of new cervical cancer cases and deaths due to cervical cancer was 7.5 per 100,000 and 2.2 per 100,000 women per year, in the United States [2]. External and intracavitary radiotherapy is a common therapeutic modality for cervical cancer. Intracavitary brachytherapy (ICBT) is the most critical part of cervical cancer treatment in patients receiving radiotherapy. ICBT delivers the highest dose of radiation onto the tumoral center while relatively sparing the radiation exposure of critical organs, such as the bladder, rectum, and sigmoid colon [3].

Traditionally, according to the International Commission on Radiation Units and Measurement (ICRU) 38 report (1985), the ICBT dose is applied to point A by using two-dimensional (2D) planning based on radiographs [4]. This report includes point A and rectum and bladder reference points using fixed bony landmarks and orthogonal X-ray images. Numerous studies have shown that these points are far from reliable and do not reflect the three-dimensional (3D) anatomy of the patient [5–7].

ICBT planning based on computed tomography/magnetic resonance imaging (CT/MRI) has been increasingly adopted since the emergence of 3D imaging modalities [8]. With 3D-ICBT, spot dose measurements in cervical cancer have been replaced with the determination of volumetric and maximum doses and the evaluation with dose-volume histograms (DVHs), which aim at less toxicity and higher cure rates [9, 10]. Definite doses given to the tumor, bladder, and rectum during 3D-ICBT were not strongly correlated with ICRU reference point estimations, and studies have shown that the dose of point A was excessive in traditional plans, and organ at risk (OAR) doses were underestimated [11]. CT-based 3D-ICBT is frequently used due to its cost-effectiveness and ease of access. Although contouring the OAR is easy with CT images, distinguishing between soft tissue and malignant tissue is poor compared to MRI. This disadvantage of CT-based ICBT is overcome by the fusion of the patient's MRI images to the CT simulation images [12, 13].

Technological advances in radiation oncology have led to a major improvement in treatment outcomes and reduced toxicity. Significant reduction in toxicity, especially in head and neck cancer, has been shown in phase 3 randomized trials with IMRT when compared to 2D or 3D conformal RT

[14]. Therefore, many centers adopted IMRT as a standard treatment modality in majority of tumor sites. Although 3D-ICBT is highly recommended in cervix cancer, many centers are reluctant to adopt the 3D method most probably because they are accustomed to point A calculations and time-consuming contouring and planning [15, 16].

In this study, we examined the dosimetric outcomes in CT-based ICBT treatment planning for small cervical tumors. We aimed to demonstrate dosimetric advantages with 3D-ICBT when compared to point A calculation, especially in small volume disease after EBRT.

2. Materials and methods

2.1 Patients

Between 2020–2021, 28 patients aged 34–80 years, diagnosed with squamous cell cervical cancer by biopsy, above stage IB2, and with a tumor volume below 30 cc after pelvic external beam radiation treatment (EBRT) were included in the study.

2.2 External beam radiation treatment and concomitant chemotherapy

All patients received a combination treatment consisting of EBRT with concurrent weekly cisplatin and ICBT. After the CT simulation, all EBRTs were planned with the volumetric modulated arc therapy (VMAT) technique using a treatment planning system of Monaco 5.1 (Elekta AB PUBL, Stockholm, Sweden). EBRT was applied at a total dose of 45–50.4 Gy with 1.8 Gy per fraction using 6-MV photons. The treatment was applied on a daily cone-beam CT with image-gated RT and an Elekta Synergy Linear Accelerator (Elekta Oncology, UK). After the completion of EBRT, MRI images were obtained to assess the tumor response.

2.3 Patient preparation and intracavitary brachytherapy

During ICBT, the patients were given a special diet and medical treatment in order to keep the rectum as empty as possible. The bladder was inflated with 150 ccs diluted contrast in all patients before each ICBT fraction.

The Fletcher-Suit CT-compatible uterus tandem and double ovoid applicators were used to deliver ICBT. After inserting and fixing the intracavitary applicators, CT scans of the pelvic simulation with a slice thickness of 2.5 mm were performed while the patients were supine by using a CT device, Toshiba Aquilian simulation (Toshiba, Japan). CT images were transferred to the treatment planning system (Gama Med Plus iX® v 15.1, Varian Medical Systems). According to ICRU 38 criteria, point A was defined as 2 cm superior of the cervical os and 2 cm lateral, along the vertical plane to the intrauterine tandem on the patient's CT images. Target volume contouring was performed by fusing EBRT response evaluation MRI images with CT simulation images taken for ICBT. HR-CTV and IR-CTV were created according to the Groupe Européen de Curiethérapie (GEC) and the European Society for Radiotherapy & Oncology (ESTRO) contouring guidelines [3]. The gross tumor volume (GTV) plus the total cervix volume were defined as HR-CTV. An intermediate-risk clinical target volume (IR-CTV) was created with 0.5 cm anterior-posterior and 1 cm safety margin to other directions around the HR-CTV.

The volumes of the bladder, sigmoid colon, and anorectum were contoured as the OAR by the same radiation oncologist. The volumes were contoured had the following features; the sigmoid region included the outer wall of the sigmoid colon approximately 2 cm above the rectosigmoid junction, the anorectum included the segment from the anal wedge to the sigmoid colon to include the outer wall of the rectum, and the bladder included the outer wall from its base to the dome [3, 17–19].

ICBT plans were performed with CT imaging before each fraction by using Gama Med Plus iX® v 15.1, Varian Medical Systems treatment planning system. Dwell positions inside the uterine tandem and ovoids were determined automatically. 3D-ICBT treatment plans normalized to HR-CTV and point A were applied separately to five fractions. We performed a total of 280 plans for the two treatment techniques. The patients were given a dose of 5.5 Gy per fraction for a total of 27.5 Gy in 5 fractions. Planning objectives were 90% of HR-CTV should receive at least 90% of prescribed dose. 100% of IR-CTV should receive 50% of the prescribed dose. For OARs, 1 cc and 2 cc bladder should receive less than 7 and 5 Gy respectively, 1 cc and 2 cc of rectum and sigmoid should receive less than 5 and 3 Gy per fraction DVHs were plotted for all target volumes and OAR. The HR-CTV dose D_{90} covering 90% of the volume and the IR-CTV dose D_{100} covering 50% of the volume were evaluated. The minimum dose received by 1 cc, 2 cc tissue volume, and the maximum dose ($D_{1cc}, D_{2cc}, D_{max}$) values for the bladder, sigmoid colon, and anorectum, as well as HR-CTV D_{90} and IR-CTV D_{100} were noted separately for both plans in each fraction.

Table 1. Patient characteristics and treatment features.

Characteristic	n
Aged (median years)	53 (34–80)
Histology	
Squamous cell carcinoma	28
Stage	
IIA–IIB	13
IIIA–IIIB–IIIC	15
Cisplatin Cycles (cycle numbers)	
3 cycles	2
4 cycles	10
5 cycles	16
Tumor volume (cc)	
Diagnosis (median)	67.3 cc (52–168 cc)
After EBRT (median)	20.1 cc (10–29.8 cc)
EBRT dose (Gy)	
50.4 Gy	10
45 Gy	18

Table 2. The target volume doses and D_{1cc}, D_{2cc}, and D_{max} values of OAR dose when optimized to Point A (Gy).

	Dose parameters for each brachytherapy fraction					
	1st	2nd	3rd	4th	5th	Total
HR CTV D_{90}	7.37 ± 2.04	7.69 ± 2.10	8.79 ± 3.08	7.89 ± 2.86	9.40 ± 3.64	40.82 ± 12.13
IR CTV D_{100}	3.02 ± 0.82	2.90 ± 0.99	3.58 ± 1.19	2.97 ± 0.96	3.66 ± 1.31	16.02 ± 4.46
Rectum D_{max}	10.85 ± 1.75	11.83 ± 3.68	12.70 ± 3.76	10.12 ± 2.96	12.92 ± 5.57	57.98 ± 12.22
Rectum 2 cc	6.59 ± 1.30	6.78 ± 1.41	7.63 ± 1.98	6.66 ± 1.78	7.52 ± 2.10	34.93 ± 5.67
Rectum 1 cc	7.48 ± 1.35	7.65 ± 1.63	8.53 ± 2.19	7.33 ± 2.03	8.29 ± 2.26	39.00 ± 6.32
Bladder D_{max}	10.42 ± 2.24	11.19 ± 2.42	13.73 ± 3.61	11.09 ± 2.33	10.76 ± 3.30	56.82 ± 9.81
Bladder 2 cc	7.24 ± 1.19	7.91 ± 1.43	8.19 ± 2.14	7.39 ± 1.37	7.93 ± 2.43	38.41 ± 6.71
Bladder 1 cc	7.74 ± 1.31	8.47 ± 1.53	8.85 ± 2.33	7.92 ± 1.55	8.49 ± 2.63	41.19 ± 7.26
Sigmoid D_{max}	6.62 ± 2.01	6.14 ± 1.52	5.98 ± 2.54	5.38 ± 1.50	6.06 ± 1.69	25.66 ± 8.17
Sigmoid 2 cc	3.73 ± 0.89	3.71 ± 0.87	3.78 ± 1.58	3.14 ± 0.79	3.91 ± 1.11	15.58 ± 4.64
Sigmoid 1 cc	4.27 ± 1.09	4.15 ± 1.02	4.24 ± 1.77	3.51 ± 0.92	4.31 ± 1.21	17.48 ± 5.29

Abbreviations: HR, high risk; CTV, clinical target volume; D_{90}, dose received by 90% of target volume; IR, intermediate risk; D_{100}, dose received by 50% of target volume; D max, maximum dose; Bladder 2 cc, the minimum dose to 2 cc of bladder receiving the highest dose; Bladder 1 cc, the minimum dose to 1 cc of bladder receiving the highest dose; Sigmoid 2 cc, the minimum dose to 2 cc of sigmoid receiving the highest dose; Sigmoid 1 cc, the minimum dose to 1 cc of sigmoid receiving the highest dose; Rectum 2 cc, the minimum dose to 2 cc of rectum receiving the highest dose; Rectum 1 cc, the minimum dose to 1 cc of rectum receiving the highest dose.

Table 3. The target volume doses and D_{1cc}, D_{2cc}, and D_{max} values of OAR dose when optimized to HR-CTV (Gy).

	Dose parameters for each brachytherapy fraction					
	1st	2nd	3rd	4th	5th	Total
HR CTV D_{90}	4.86 ± 0.70	4.89 ± 0.79	5.14 ± 1.05	5.04 ± 0.79	5.55 ± 1.69	25.30 ± 4.43
IR CTV D_{100}	1.98 ± 0.18	1.84 ± 0.41	2.11 ± 0.37	1.92 ± 0.35	2.17 ± 0.61	9.97 ± 1.52
Rectum D_{max}	6.93 ± 1.30	7.35 ± 1.16	7.48 ± 1.57	6.67 ± 0.76	7.54 ± 2.97	35.72 ± 4.17
Rectum 2 cc	4.98 ± 1.28	4.40 ± 0.46	4.45 ± 0.47	4.37 ± 0.43	4.44 ± 0.33	22.50 ± 2.09
Rectum 1 cc	5.05 ± 0.29	4.92 ± 0.39	4.99 ± 0.50	4.83 ± 0.47	4.90 ± 0.33	24.54 ± 1.43
Bladder D_{max}	7.11 ± 1.77	6.93 ± 0.83	8.15 ± 1.75	7.38 ± 1.09	6.22 ± 0.33	35.58 ± 4.57
Bladder 2 cc	4.92 ± 0.79	4.93 ± 0.41	4.74 ± 0.23	4.83 ± 0.35	4.59 ± 0.22	23.86 ± 1.82
Bladder 1 cc	5.26 ± 0.90	5.28 ± 0.45	5.14 ± 0.29	5.20 ± 0.39	4.91 ± 0.22	25.64 ± 2.06
Sigmoid D_{max}	4.59 ± 1.31	4.10 ± 1.13	3.77 ± 1.45	3.64 ± 1.41	4.22 ± 1.67	17.30 ± 6.67
Sigmoid 2 cc	2.51 ± 0.51	2.54 ± 0.79	2.35 ± 0.84	2.13 ± 0.77	2.70 ± 1.00	10.45 ± 4.00
Sigmoid 1 cc	2.88 ± 0.64	2.82 ± 0.88	2.640 ± 0.96	2.39 ± 0.89	2.99 ± 1.13	11.74 ± 4.53

Abbreviations: HR, high risk; CTV, clinical target volume; D_{90}, dose received by 90% of target volume; IR, intermediate risk; D_{100}, dose received by 50% of target volume; D_{max}: maximum dose; Bladder 2 cc, the minimum dose to 2 cc of bladder receiving the highest dose; Bladder 1 cc, the minimum dose to 1 cc of bladder receiving the highest dose; Sigmoid 2 cc, the minimum dose to 2 cc of sigmoid receiving the highest dose; Sigmoid 1 cc, the minimum dose to 1 cc of sigmoid receiving the highest dose; Rectum 2 cc, the minimum dose to 2 cc of rectum receiving the highest dose; Rectum 1 cc, the minimum dose to 1 cc of rectum receiving the highest dose.

2.4 Statistical analysis

All the statistical analyses were performed with SPSS v.18.0 software (SPSS, Chicago, USA). Dose levels were described by means and standard deviations. Kolmogorov Smirnov test was used for the normality of parameters. Continuous variables were defined as the mean ± standard deviation. Paired sample *t*-test was performed to compare the paired samples. The significance level was determined as $p < 0.05$.

3. Results

The median age of the patients was 53 years (range 34–80). A total of 46% of the patients were diagnosed with stage II cervical cancer, while others were diagnosed with stage III cervical cancer according to the International Federation of Gynecology and Obstetrics (FIGO) classification [20]. The median GTV before EBRT was 67.3 cc (52–168 cc). The median volume of the HR-CTV after EBRT was 20.1 cc (10–29.8 cc). Patient characteristics was given in Table 1.

In all cases, OAR and target volume doses were compared regarding previously defined criteria. D_{1cc}, D_{2cc}, and D_{max} received by the OARs were compared.

In treatment plans, when normalized to point A, the total mean doses for HR-CTV D_{90} and IR-CTV D_{100} were 40.82 Gy and 16.02 Gy, respectively. The target volume doses were overdose of the previously defined criteria.

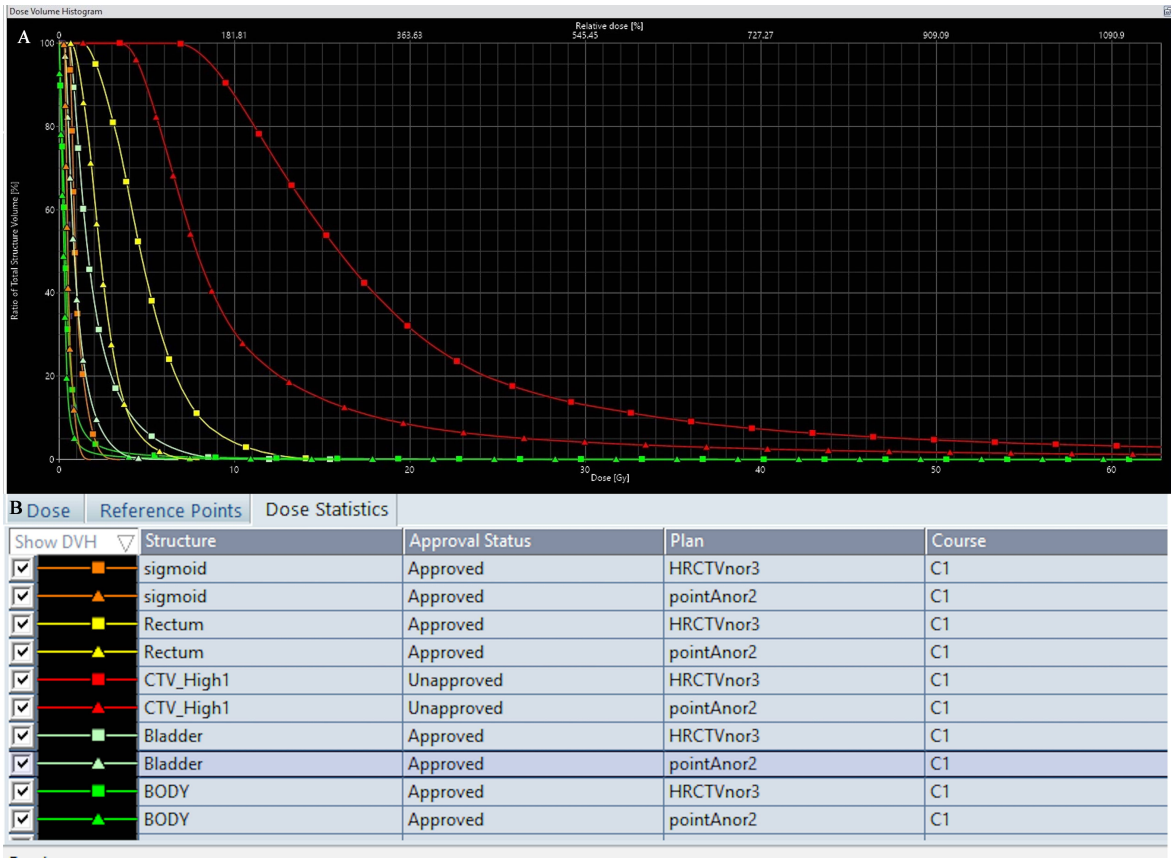

Fig. 1. A comparison of DVH for HR-CTV and OARs according to both optimizations. (A) Comprasion of DVH for HR-CTV and OARs abased on point A vs HR CTV. (B) Distribution of colors and shapes according to DVH (square shape represents plans made according to HR-CTV, triangular shape represents plans made according to point A).

Total D_{max}, D_{1cc}, and D_{2cc} were 57.98 Gy, 39 Gy, and 34.93 Gy for rectum; 56.82 Gy, 41.19 Gy, and 38.41 Gy for the bladder; 25.66 Gy, 17.48 Gy, and 15.58 Gy for the sigmoid, respectively. None of the OAR doses were within the range of clinically acceptable criteria.

In treatment plans, when normalized to HR-CTV; the total mean dose for HR-CTV D_{90} was 25.30 Gy and IR-CTV D_{100} was 9.97 Gy, demonstrating that the target volume doses were reaching the previously defined criteria. Total D_{max}, D_{1cc}, and D_{2cc} were 35.72 Gy, 24.54 Gy, and 22.5 Gy for rectum; 35.58 Gy, 25.64 Gy, and 23.86 Gy for the bladder; 17.30 Gy, 11.74 Gy, and 10.45 Gy for the sigmoid, respectively. Doses at all OARs were within the range of clinically acceptable criteria.

The target volume doses and D_{1cc}, D_{2cc}, and D_{max} values of the OAR dose of both brachytherapy treatment techniques are presented in Tables 2,3.

The mean doses of HR-CTV D_{90} and IR-CTV D_{100} were significantly lower in each fraction and in the total doses when normalized to HR-CTV than when normalized to point A ($p < 0.001$). D_{1cc}, D_{2cc}, and D_{max} values of OAR (rectum, bladder, sigmoid) doses obtained from the brachytherapy treatment planning were significantly lower in each fraction and in the total doses when normalized to HR-CTV than when normalized to point A ($p < 0.001$) (Table 4 and Fig. 1).

When plans for each fraction were compared, only the D_{max} values of the bladder were higher in both plans with reference to point A and HR CTV in the third session (Fig. 2A and 2B).

4. Discussion

Traditionally, 2D planning based on radiographs has been utilized in the treatment of patients with cervical cancer. In these plans, the target volume is optimised according to the anatomical point defined as point A, determined by ICRU 38, and spot dose measurements are used. The reliability of these spot dose measurement values has been the focus of substantial debate. Although the sigmoid colon can be located close to the ICBT source in some patients, there are no safety points in ICRU 38 [12]. Over the last several years, after the introduction of CT/MRI-based image-guided brachytherapy, ICBT planning techniques have improved significantly. The cross-sectional anatomy of the tumor and surrounding organs can be identified in detail with CT/MRI-guided ICBT, and reliable DVH can be plotted.

Traditional ICBT planning based on the ICRU 38 reference points and CT/MRI-guided ICBT planning have been

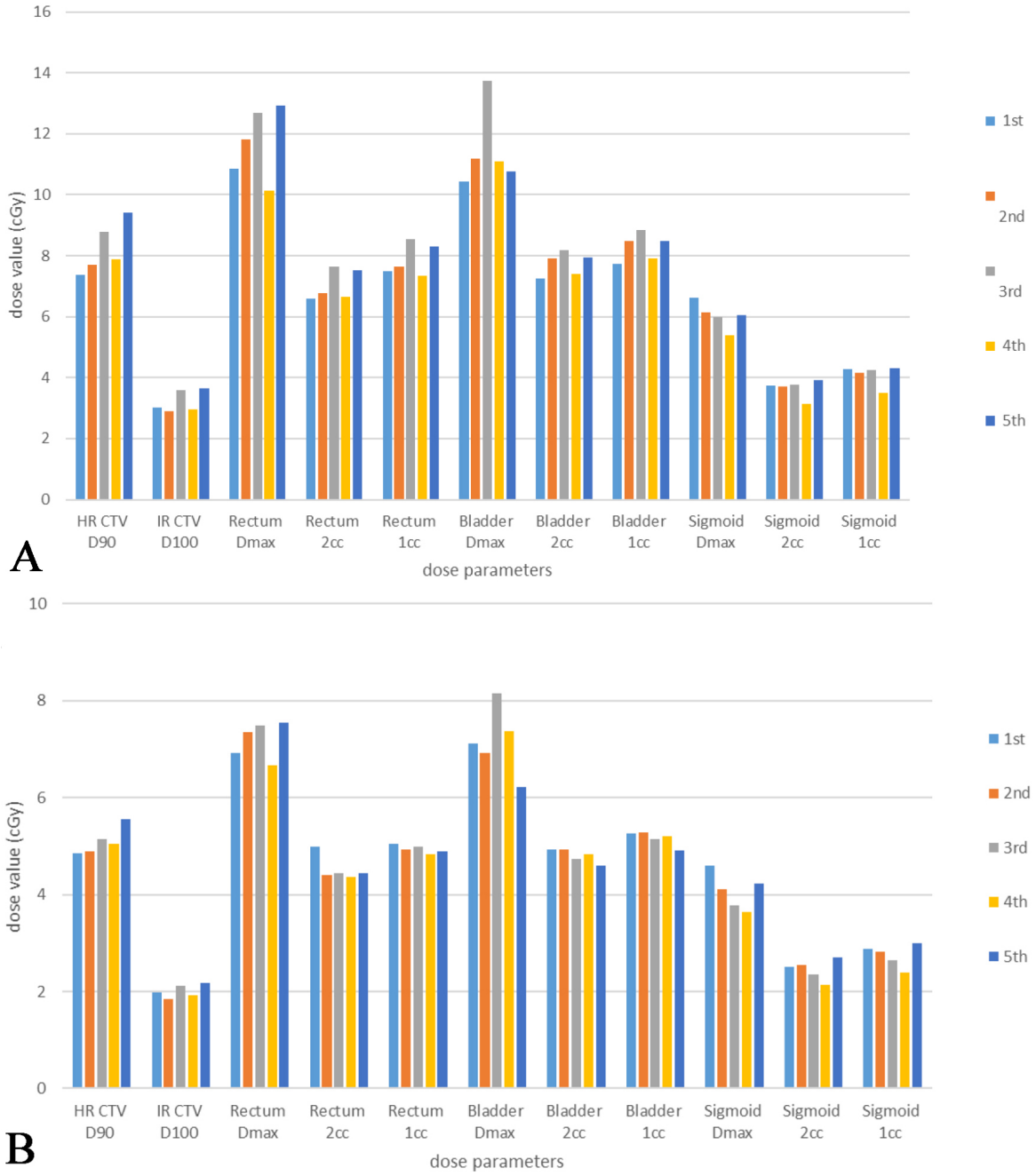

Fig. 2. Dose parameters of the target volumes and OARs for each fraction. (A) The mean target doses and OAR doses of the planning based on point A for each fraction. (B) The mean target doses and OAR doses of the planning based on HR-CTV for each fraction.

evaluated in previous studies that compared 2D plans and 3D plans according to both tumor volume coverage and D_{1cc}, D_{2cc} of the bladder and rectum, and the superiority of 3D plans has been demonstrated [21–24]. In the current study, we compared two different plans normalized to point A and HR-CTV in terms of the target volume and doses for OAR. Although the GEC-ESTRO working group published guidelines that included 3D dose-volume parameters used for the brachytherapy of cervical carcinoma, the high-dose-rate ICBT dose is normalized to point A, defined in reference to the applicator location in several radiation therapy centers [24]. Studies show that this utilization is effective only if the HR-CTV width contains bilateral point A's. However, whether the target volume receives the prescribed dose and OAR are protected with plans normalized to point A is unclear. Goyal *et al.* [24] reported that the dose prescription defined by point A may be below or overdose in terms of the variable size of the tumor and the patients' anatomy. A total of 125 treatment plans of 25 patients (5 fractions/25 patients) were re-analyzed. In each plan, the radiation dose was

Table 4. Total doses of the planning based on point A and based on HR-CTVs (Gy).

Total dose after 5 sessions	Point A	HR-CTV	p^a
HR CTV D_{90}	40.82 ± 12.13	25.30 ± 4.43	0.000
IR CTV D_{100}	16.02 ± 4.46	9.97 ± 1.52	0.000
Rectum D_{max}	57.98 ± 12.22	35.72 ± 4.17	0.000
Rectum 2 cc	34.93 ± 5.67	22.50 ± 2.09	0.000
Rectum 1 cc	39.00 ± 6.32	24.54 ± 1.43	0.000
Bladder D_{max}	56.82 ± 9.81	35.58 ± 4.57	0.000
Bladder 2 cc	38.41 ± 6.71	23.86 ± 1.82	0.000
Bladder 1 cc	41.19 ± 7.26	25.64 ± 2.06	0.000
Sigmoid D_{max}	25.66 ± 8.17	17.30 ± 6.67	0.000
Sigmoid 2 cc	15.58 ± 4.64	10.45 ± 4.00	0.000
Sigmoid 1 cc	17.48 ± 5.29	11.74 ± 4.53	0.000

Abbreviations: p^a, paired samples *t*-test; HR, high risk; CTV, clinical target volume; D_{90}, dose received by 90% of target volume; IR, intermediate risk; D_{100}, dose received by 50% of target volume; D_{max}, maximum dose; Bladder 2 cc, the minimum dose to 2 cc of bladder receiving the highest dose; Bladder 1 cc, the minimum dose to 1 cc of bladder receiving the highest dose; Sigmoid 2 cc, the minimum dose to 2 cc of sigmoid receiving the highest dose; Sigmoid 1 cc, the minimum dose to 1 cc of sigmoid receiving the highest dose; Rectum 2 cc, the minimum dose to 2 cc of rectum receiving the highest dose; Rectum 1 cc, the minimum dose to 1 cc of rectum receiving the highest dose.

originally prescribed to point A (ICRU-38), and the tumor volumes and HR-CTVs were retrospectively remade for all plans. The results showed that the dose prescription of point A relative to HR-CTV caused a risk of a low dose in large tumor sizes or of an overdose in small tumor sizes [24]. In another study, Shin *et al.* [25] demonstrated that CT-guided CTV planning was superior to standard point A planning, according to the consistency of target coverage and avoidance of overdose in normal tissue volume. Paul *et al.* [26] retrospectively analyzed 48 cervical cancer patients with a mean HR-CTV volume of 23 cc who underwent ICBT. The investigators renormalized the point A plans according to the HR-CTV for the high-dose-rate volumetric plans. Although point A plans met the suggested OAR dose limits, they reported that 15% and 17% of patients had genitourinary and gastrointestinal toxicities of grades 3–4, showing the dosimetric advantages of CT planning with the volume-based high-dose rate in providing significant HR-CTV while reducing OAR doses [18]. In another study by Harmon *et al.* [13], twenty-eight fractions obtained from sixteen cervical cancer patients treated with MRI-based high-dose-rate brachytherapy. Lesions were divided into small (<25 cm^3) or large (>25 cm^3) volume. Retrospective plans were optimized and recreated according to point A, and HR-CTV D_{90}. In the small lesion group (<25 cm^3), $D_{0.1cc}$, D_{2cc}, and ICRU points for the bladder, sigmoid, and rectum were significantly higher in plans based on point A compared to HR-CTV plans. Moreover, there were significantly higher doses with HR-CTV D_{90} and D_{100} ($p < 0.05$). However, there were no significant differences in HR-CTV D_{90} dose parameters in the large lesion group (>25 cm^3), demonstrating that there was no dosimetric advantage of HR-CTV D_{90} over Point A in this group [13].

Consistent with the previous studies, the small residual tumor plans were compared based on two different reference points using DVH parameters. In our study, we accomplished better planning objectives with HR-CTV normalized plans than point A normalization in terms of both HR-CTV and OAR. HR-CTV coverage was within planning objectives in most of the fractions mean 25.3 Gy (over 24.75). In addition to the statistical difference, dose values overdose constraints for 1 and 2 cc of bladder and rectum were evident with point A normalization in most fractions. A major strength of the current study was the homogenous population with a small residual tumor after EBRT.

5. Conclusions

Our findings show that particularly in small-volume HR-CTV after EBRT, plans normalized to HR-CTV can reduce overdose in the target tissue and avoid unnecessary OAR irradiation compared to the plans normalized to point A. Today, plans should be evaluated according to 3D volumes in 3D-ICBT planning, even if there is a small tumor. Evaluating plans by looking at traditional point A doses is losing its importance day by day with the increasing literature data.

Author contributions

Concept—EEO, EKU; Design—EEO, MB, EKU; Supervision—EEO, MB, EKU; Materials—EEO, GPS; Data collection &/or processing—EEO, GPS, MF; Analysis and/or interpretation—MF, MKB; Literature search—EEO, MB; Writing—EEO, MB, MKB; Critical review—EEO, MB, EKU.

Ethics approval and consent to participate

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and a local committee on the human investigation was obtained. The study protocol was reviewed and approved by Clinical Research Ethics Committee, decision date-no: 02.11.2020/2020-22-09. Informed written consent forms were read by each patient and signed approvals were obtained before their treatment.

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Conflict of interest

The authors declare no conflict of interest.

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