

Dosimetric and radiobiological evaluation of treatment plan for cervical cancer high-dose-rate intracavitary brachytherapy

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Abstract

Purpose: The purpose of the study was to consider and calculate dosimetric parameters during treatment planning to improve radiobiological outcomes for cervical cancer patients treated with high-dose-rate (HDR) intracavitary brachytherapy (ICBT).

Material and methods: In the present study, dose volume histograms (DVH) of 30 cervical cancer patients treated with HDR brachytherapy using computer tomography (CT)-based planning were analyzed. High-risk clinical target volume (HR-CTV) was contoured as the main target volume for all the patients, with an assumption that there was no presence of gross tumor at the time of brachytherapy. Values of target coverage volumes (100%, 150%, and 200%) were obtained from DVH, which was used to calculate different quality indices (QIs), including coverage index (CI), dose homogeneity index (DHI), overdose volume index (ODI), and dose non-uniformity ratio (DNR). Values of these QIs were further used to calculate tumor control probability (TCP). Statistical correlation between all QIs with TCP was established. Also, normal tissue complication probabilities for bladder (NTCP_B) and rectum (NTCP_R) were calculated.

Results: The mean values of the various calculated parameters, including CI, DHI, ODI, DNR, TCP, NTCP_B and NTCP_R were 0.92 ± 0.07 , 0.26 ± 0.10 , 0.50 ± 0.10 , 0.74 ± 0.10 , 0.92 ± 0.07 , 0.08 ± 0.25 , and 0.36 ± 0.27 , respectively. Pearson's product moment correlation coefficient between CI, DHI, ODI, and DNR with regards to TCP was $+0.85$, -0.85 , $+0.84$, and $+0.85$, respectively.

Conclusions: The correlation between dosimetric and radiobiological parameters was found statistically significant, which shows the influence of dosimetric parameters on the radiobiological outcome. Therefore, these parameters should be considered during the treatment planning to improve the radiobiological outcome.

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Key words: DVH, quality indices, TCP, NTCP, HDR, intracavitary brachytherapy.

Purpose

Cervical cancer is a major cancer burden and public health concern in developing countries, such as India. India alone accounts for one-quarter of the worldwide burden of cervical cancers [1, 2]. The standard treatment modality and integral part of local control for cervical cancer is external beam radiotherapy (EBRT), followed by brachytherapy.

GEC ESTRO (the Groupe Européen de Curietherapie and the European Society for Radiotherapy and Oncology) has introduced a novel target concept to facilitate image-guided brachytherapy (IGBT) [3, 4]. This study was performed to report our institution's experience with

image-guided high-dose-rate (HDR) brachytherapy in the framework of the current guidelines of the American Brachytherapy Society (ABS) and in light of the recent EMBRACE collaborative results supporting more rigorous dose recommendations [5].

The modern treatment planning system (TPS) provides conformal dose distribution to the target and minimum possible dose to the surrounding normal tissues, with the help of remote control computerized HDR brachytherapy devices. The goal of HDR planning is to produce an acceptable optimized plan that meets the desired dose constraints. These devices have a high activity miniature stepping source, which offers advantages of varying source positions and time to obtain an appropri-

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ate dose distribution and isodose geometry. Improved planning strategies and optimization techniques can reduce normal tissue complications without compromising local control of the disease.

The purpose of the study was to consider and calculate the dosimetric parameters during treatment planning to improve radiobiological outcomes for cervical cancer patients treated with HDR intracavitary brachytherapy (ICBT). Outcomes of the study were clinically correlated with follow-up period of 12 months for all the patients. Scarce and heterogeneous information is available in the literature on correlation between dosimetric quality indices (QIs) [coverage index (CI), dose homogeneity index (DHI), overdose volume index (ODI), and dose non-uniformity ratio (DNR)], which were included in the present study and clinical outcomes of ICBT.

Material and methods

Patients and treatment

This study was performed with 30 patients treated for cervical cancer at the Department of Radiation Oncology, Guru Gobind Singh Medical College and Hospital, Faridkot, Punjab, India, and also approved by the research degree committee of the institute (Baba Farid University of Health Sciences, Faridkot, Punjab, India), with reference number of BFUHS/Ex/PHD/E15/725.

The staging of the disease was done according to the International Federation of Gynecology and Obstetrics (FIGO) staging system. Patients with stage IIB and IIIB were included, and patients with lymph node involvement were excluded from the study. All patients were treated with EBRT of 46 Gy in 23 fractions, followed by ICBT. ICBT was applied with remote afterloading MicroSelectron HDR v.3 (Elekta Medical Pvt. Ltd. System) machine, with iridium-192 radioactive source. The time between completion of EBRT and the first ICBT ranged from 5 to 7 days. The ICBT dose of 22.5 Gy in 3 fractions (7.5 Gy per fraction) was given to all patients. All doses were normalized to a total biological equivalent dose (BED) at 2 Gy per fraction (EQD₂) using a linear quadratic (LQ) model, with $\alpha/\beta = 10$ Gy for target and $\alpha/\beta = 3$ Gy for organs at risk (OARs). Total EQD_{2,10} for EBRT and ICBT was obtained by summation of prescribed EBRT dose (EQD_{2,10}) and fractional ICBT doses (EQD_{2,10}) [6]. Dose constraints for OARs were specified in terms of dose to 2cc (D_{2cc}) as recommended in the EMBRACE-II study [7]. Follow-up was performed up to a period of 12 months after the completion of ICBT, according to the institutional guidelines.

A computer tomography (CT)-compatible Fletcher suit applicator was used for ICBT application, which consists of uterine tandem with various angles (15°, 30°, and 45°), and a pair of ovoids with different diameters (25 mm, 30 mm, and 35 mm). Appropriate vaginal packing was done to fix the applicator's position and to displace the bladder and rectum away from the applicator. To minimize patient's movement during CT scan, every attempt was made to complete the entire process within the shortest time possible.

Treatment planning

Three dimensional (3D) images were acquired using a CT Simulator (GE 580W OPTIMA) machine, with a 2.5 mm slice thickness for ICBT procedure for all patients. All CT slices were transferred to the Oncentra Master Plan, version 4.3 TPS (Elekta Medical Pvt. Ltd. System). Target volume and OARs on each CT slice were contoured. Accurate delineation of high-risk clinical target volume (HR-CTV) requires documentation of gynecological examination at diagnosis and at ICBT. Due to lack of magnetic resonance imaging (MRI) modality and MRI-compatible applicators in the institute, CT-based planning was performed, in which HR-CTV was the main target volume instead of gross tumor volume (GTV); therefore, it was assumed that there was no gross tumor present at the time of brachytherapy. For target delineation, HR-CTV was contoured, including the whole cervix and presumed extra cervical tumor expansion area (if present) upon brachytherapy [8]. The presumed tumor extension was defined by means of clinical examination (visualization and palpation), along with CT findings. Safety margin was chosen according to the tumor size, tumor spread direction, tumor regression, and treatment strategy. The rectum, bladder, sigmoid, and bowel were delineated on each CT slice for the present study. 3D treatment plans were created in TPS. Dose prescription point was Manchester point A in each plan.

Dosimetric parameters

Dose volume histograms (DVH) was utilized for analyzing the plan dosimetrically. For dosimetric analysis, different QIs were calculated in each ICBT plan. All the plans were divided into different regions based on the pattern of dose distribution, to define different QIs. In each treatment plan, the isodose surface of 100%, 150%, and 200% of target volume was generated to find out the respective dose coverage volumes. The QIs analyzed in the present study were defined as:

1. Coverage index (CI): This was the fraction of the target volume that received a dose equal to or greater than the reference dose [9].

$$CI = TV_{D_{ref}}/TV \quad (1)$$

2. Relative dose homogeneity index (DHI): It was defined as the ratio of the target volume, which received a dose in the range of 1.0 to 1.5 times of the reference dose to the volume of the target that received a dose equal to or greater than the reference dose [9].

$$DHI = [TV_{D_{ref}} - TV_{1.5D_{ref}}]/TV_{D_{ref}} \quad (2)$$

3. Overdose volume index (ODI): This was the ratio of the target volume, which received a dose equal to or more than 2 times of the reference dose to the volume of the target that received a dose equal to or greater than the reference dose [9].

$$ODI = TV_{2.0D_{ref}}/TV_{D_{ref}} \quad (3)$$

4. Dose non-uniformity ratio (DNR): This was the ratio of the target volume, which received a dose equal to or greater than 1.5 times of the reference dose to the

volume of the target that received a dose equal to or greater than the reference dose [10].

$$DNR = TV_{1.5D_{ref}}/TV_{D_{ref}} \tag{4}$$

Radiobiological parameters

Radiobiological parameters were calculated using the following dosimetric parameters in this study.

Tumor control probability (TCP): In the case of brachytherapy, it was not possible to obtain a uniform dose distribution as very high radiation dose gradient in the vicinity of the radiation source. Hence, to calculate TCP, the target volume was divided into four different regions based on the pattern of dose distribution.

According to LQ model, TCP for uniform dose distribution within the target volume was given by the following formula [11]:

$$TCP = \exp [-\rho V \exp (-\alpha BED_t)] \tag{5}$$

where ρ , V , α , and BED_t are the clonogenic cell density, target volume, coefficient of lethal damage (radio-sensitivity of lethal damage), and BED (biologically effective dose) for the target, respectively.

The BED in HDR-ICBT for a total dose of D (Gy) delivered with dose d (Gy) per fraction is given by Visser *et al.* [12]:

$$BED = D [1 + G d/(\alpha/\beta)] \tag{6}$$

where α/β is the tissue specific parameter and is used as the coefficient in LQ formalism; G is the factor accounting for incomplete repair of sub-lethal damage during the inter-fraction interval between the fractions.

In this study, it was assumed that the time interval between the fractions was sufficient to allow the full repair of sub-lethal damage, therefore G was considered as 1. The values of ρ and α were assumed to be constant throughout the target volume ($\rho = 10^7$ cells/cc, and $\alpha = 0.35 \text{ Gy}^{-1}$) in the present study, which was also assumed in previous studies in the literature [13, 20]. The assumption of constant ρ throughout HR-CTV could not be expressed due to lack of MRI-based planning. No gross tumor and lymph nodes were present at the time of brachytherapy. Also the influence of cell proliferation rate was assumed to be negligible. The value of α/β ratio was considered as 10 Gy for the target.

Dose distribution in the case of HDR-ICBT within the target was highly non-uniform, so equation (5) could not be applied directly to compute TCP. Hence, the target volume was divided into four regions as described below and shown in Figure 1:

- I. Region receiving a dose less than the reference dose.
- II. Region receiving a dose in the range of 1.0 to 1.5 times of the reference dose.
- III. Region receiving a dose in the range of 1.5 to 2.0 times of the reference dose.

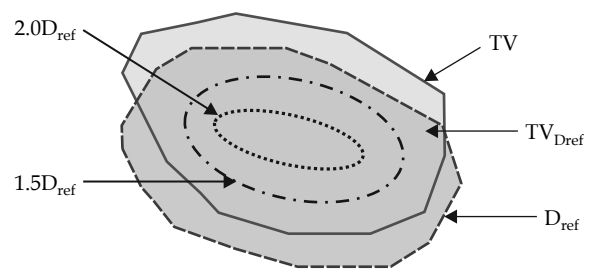


Fig. 1. Drawing showing target volume with different regions

IV. Region receiving a dose equal to or more than 2.0 times of the reference dose.

Each region had its' own BED, but in the present study, BED was replaced by BEEUD (biologically effective equivalent uniform dose) as per the concept provided by Kehwar *et al.* [22]:

$$BEEUD_t = -(1/\alpha) \ln [(1/V) \sum_i v_i \exp\{-\alpha BED_{ti}\}] \tag{7}$$

BEEUD and QIs were introduced into the equation of TCP, which is provided by equation (8).

$$TCP (ICBT) = \exp [-\rho TV_{D_{ref}} \{ (1 - CI)/CI \} \exp (-\alpha BEEUDt1) + DHI \exp (-\alpha BEEUDt2) + (DNR - ODI) \exp (-\alpha BEEUDt3) + ODI \exp (-\alpha BEEUDt4)] \tag{8}$$

$$\text{Total TCP} = TCP (EBRT) \times TCP (ICBT) \tag{9}$$

All dosimetric QIs were used to calculate TCP, and the correlation between these QIs and TCP was observed in the present study.

Normal tissue complication probabilities (NTCP): NTCP of the bladder and rectum was calculated in this study using Niemierko model. In this model, raw data from TPS were converted into a biological equivalent uniform dose, i.e., EQD₂ DVH (EBRT + ICBT). Then, this DVH was converted into DVH of the whole volume of organ (Vi) receiving EUD (equivalent uniform dose), using the DVH reduction method as proposed by Kutcher *et al.* [14]:

$$EUD = [\sum_{i=1}^N (V_i) \cdot (EQD2i)^a]^{1/a} \tag{10}$$

where $EQD2i = EQD_2 (EBRT) + EQD_2 (ICBT)$, 'a' is a parameter describing the response of the structure or organ in relation to the irradiated volume, $a < 0$ for tumors where cold spots are unwanted, and $a > 0$ for healthy tissue where hotspots are undesirable.

NTCP is determined using the following logistic function:

$$NTCP = \frac{1}{1 + [TD50/EUD]^{4\gamma50}} \tag{11}$$

where $\gamma50$ is the slope of sigmoid dose response curve of normal tissue at 50% complication probability.

Parameters used for OARs according to Niemierko model [15] are shown in Table 1.

Table 1. Parameters used for normal tissue complication probabilities (NTCP) calculations

OARs	a	$\gamma50$	TD ₅₀	End point
Bladder	2.00	4	80 Gy	Bladder contracture/volume loss
Rectum	8.33	4	80 Gy	Severe proctitis/necrosis/stenosis/fistula

Follow-up

All the patients underwent follow-up evaluations up to 12 months, according to our departmental protocol. The patients were followed-up with routine investigations, including complete blood counts, chest X-ray, CT, etc. OARs complications were recorded.

Statistical analysis

All parameters of the target and OARs were statistically examined using statistical package for social sciences (IBM SPSS Statistics for Windows, version 26.0; IBM Corp., Armonk, NY, USA). The results were calculated as mean \pm standard deviation (SD). The least square fitting was used and the slope of the curve was noted. The value of the Pearson's product moment correlation coefficient (r -value) was also calculated. The relationship between two variables was generally considered strong and statistically significant, when their r -value was greater than 0.7. The 2D scatter plot representing the correlation was generated.

Results

The median and range of HR-CTV volume at the time of ICBT were 34 cm² and 15-62 cm³, respectively. The to-

Table 2. Dosimetric parameter data for intracavitary brachytherapy (ICBT)

QI	Maximum value	Minimum value	Mean \pm SD
CI	1.00	0.75	0.92 \pm 0.07
DHI	0.50	0.10	0.26 \pm 0.10
ODI	0.68	0.28	0.50 \pm 0.10
DNR	0.90	0.50	0.74 \pm 0.10

CI – coverage index, DHI – dose homogeneity index, ODI – overdose volume index, DNR – dose non-uniformity ratio

Table 3. Radiobiological parameter data for intracavitary brachytherapy (ICBT)

QI	Maximum value	Minimum value	Mean \pm SD
TCP	0.99	0.73	0.92 \pm 0.07
NTCP_B	0.94	0.00	0.08 \pm 0.25
NTCP_R	0.94	0.04	0.36 \pm 0.27

TCP – tumor control probability, NTCP_B – normal tissue complication for the bladder, NTCP_R – normal tissue complication for the rectum

Table 4. The r -values between quality indices (QIs) and tumor control probability (TCP)

Variable parameters	Pearson's product moment correlation coefficient
CI and TCP	+0.85
DHI and TCP	-0.85
ODI and TCP	+0.84
DNR and TCP	+0.85

CI – coverage index, DHI – dose homogeneity index, ODI – overdose volume index, DNR – dose non-uniformity ratio, TCP – tumor control probability

tal EQD2₁₀ (EBRT + ICBT) at point A was 80 Gy on average, and was 83 Gy for D₉₀ HR-CTV when prescription was done at point A. For OARs, the total EQD2₃ (EBRT + ICBT) on average were 71 Gy, 73 Gy, 76 Gy, and 73 Gy for D_{2cc} of the bladder, rectum, bowel, and sigmoid, respectively.

Dosimetric analysis

The maximum, minimum, mean, and SD were calculated for all the dosimetric parameters and are presented in Table 2.

Radiobiological analysis

As shown in Table 3, maximum, minimum, mean, and SD were calculated for all the radiobiological parameters, including TCP for target and NTCP for the bladder and rectum.

The 2D scatter curves were plotted between all QIs and TCP. The r -values (confidence interval: 95%) between CI, DHI, ODI, and DNR with respect to TCP are shown in Table 4.

The relationship between CI and TCP is presented in Figure 2, and indicates that TCP increases in a linear trend as CI increases. The slope of the linear line was 0.94. The r -value between CI and TCP was +0.85, which was statistically significant (confidence interval: 95%). This r -value shows a strong positive relationship between CI and TCP.

Figure 3 shows the relation between TCP and DHI. The curve indicates that TCP decreases linearly with DHI. The slope of the curve was -0.63, which shows the inverse correlation between TCP and DHI. The r -value between DHI and TCP was -0.85, which was statistically significant, and showing negative relationship between DHI and TCP (confidence interval: 95%).

It is clear from Figure 4 that TCP also increases with an increase in ODI. The slope of the curve was 0.62. The r -value between ODI and TCP was +0.84, which was statistically significant (confidence interval: 95%). This r -value showed a strong positive relationship between ODI and TCP.

The curve between TCP and DNR is demonstrated in Figure 5. It was observed that TCP increases linearly with increase in DNR. The slope of the curve was 0.63. The r -value between DNR and TCP was +0.85, which was statistically significant (confidence interval: 95%). This r -value showed a strong relationship between DNR and TCP.

Clinical analysis

Toxicity assessment was evaluated using the Radiation Therapy Oncology Group (RTOG) toxicity assessment scales [16, 17]. There were no recurrences found in all the patients up to 12 months of follow-up. Most of the observed toxicities were grade 1 or 2 in the bladder and rectum. Only two out of thirty patients suffered from radiation proctitis and one from radiation cystitis, but the symptoms did not become apparent until 12 months after the completion of brachytherapy. Supportive medical treatment was applied to the required patients for the

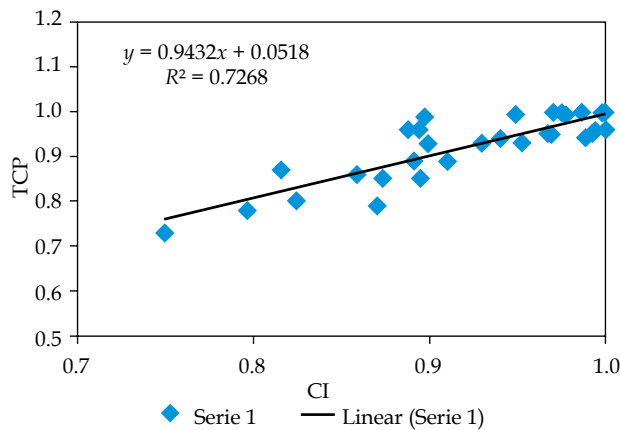


Fig. 2. 2D scatter graph correlating between coverage index (CI) and tumor control probability (TCP)

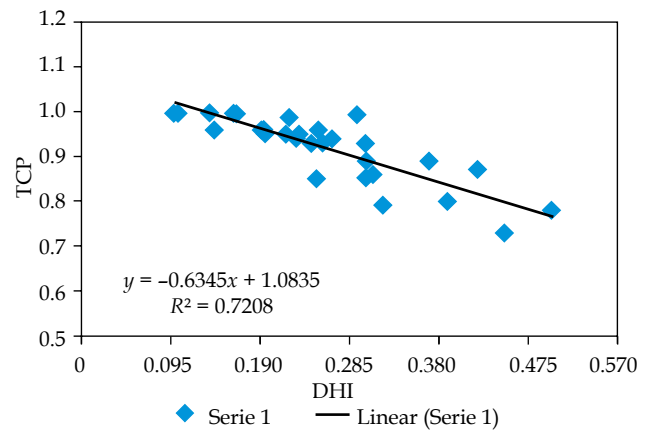


Fig. 3. 2D scatter graph correlating between dose homogeneity index (DHI) and tumor control probability (TCP)

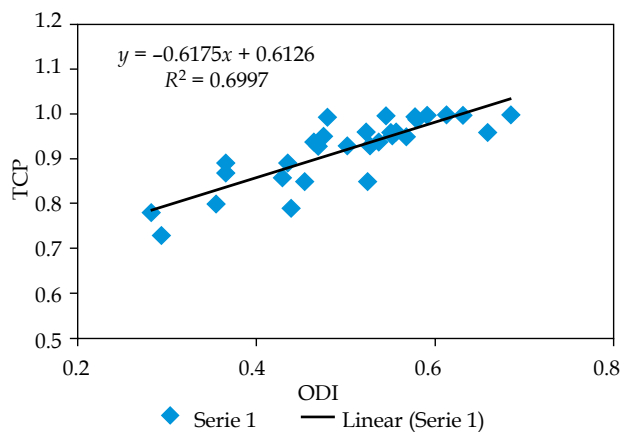


Fig. 4. 2D scatter graph correlating between overdose volume index (ODI) and tumor control probability (TCP)

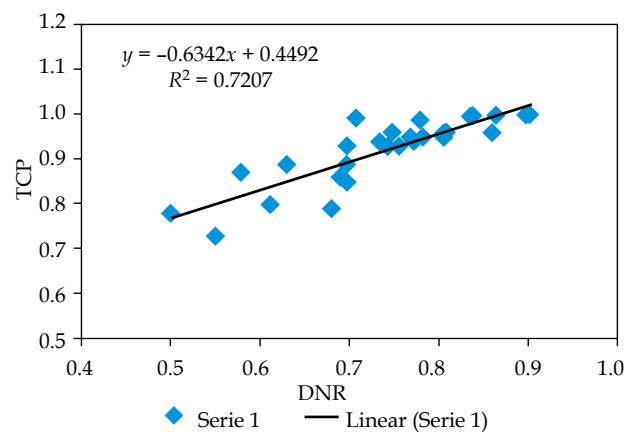


Fig. 5. 2D scatter graph correlating between dose non-uniformity ratio and tumor control probability (TCP)

management of proctitis and cystitis, including hydration, anti-diarrheal, anti-inflammatory drugs, etc.

Discussion

Various QIs have been proposed to evaluate LDR and HDR interstitial implants; for example, DHI and DNR proposed by Saw and Suntharalingam [18, 19] and Saw *et al.*, respectively [10]. Meertens *et al.* defined QIs (CI, DHI, ODI, and DNR for target) for the evaluation of HDR interstitial implants [9]. In this study, we used the QI as defined by Meertens *et al.* Target volume TV was divided into 4 parts to define target related QIs. BEEUD was calculated for these 4 parts of TV and then incorporated into the expression of TCP. The correlation between TCP and QIs was observed.

It was noted that TCP increases with an increase in CI values. This is because the target volume coverage with the prescribed dose was almost full in all the planned cases, which leads to higher TCP. Surega *et al.* in their study observed no correlation between TCP and CI because of statistically insignificant regression coefficient [20]. Their

results are not similar to the present study, which may be because of the institutional dissimilarity from target delineation to treatment plan execution.

DHI is a good indicator of the pattern of dose distribution in a target volume, but it is still unclear what factors are influencing this index. Theoretically, improvement in dose homogeneity and conformity should enhance local control and decrease complications, but there are no studies till date suggesting plans with a better DHI being associated with a better clinical outcome, as compared to such plans with inferior DHI [21]. In the present study, it was found that as DHI increases, TCP decreases. It can happen, as in case of brachytherapy, the dose distribution is highly heterogeneous. Kataria *et al.* in their study reported that DHI increases as prescribed dose increases, and decreases as target volume increases [21].

The present study showed that with an increase in ODI and DNR values, TCP increases, but simultaneously, complications to OARs also increases, which may be manageable. Over-dose region cannot be avoided completely in the case of brachytherapy. Kehwar *et al.* in their study confirmed that higher values of ODI and DNR were

related to higher normal tissue complications, which are in correlation with the present study [22].

In the present study, on follow-up of 12 months, no recurrence was noted within all the patients. Only 2 patients suffered with acute radiation proctitis and 1 with radiation cystitis after the completion of ICBT. On analyzing with dose constraints of DVH, it was found that these patients had higher total EQD₂ (EBRT + ICBT) for the rectum as compared with GEC-ESTRO recommendations [6]. Also, these patients had higher target volumes. Our observations were similar to Tanderup *et al.* study, where they reported that local control depends upon the volume of the target [23].

Conclusions

The correlation between dosimetric and radiobiological parameters was found statistically significant, and shows the influence of dosimetric parameters on the radiobiological outcomes. Therefore, these parameters should be considered during the treatment planning to improve the radiobiological outcomes. This observation can be beneficial for plan evaluation in busy departments, as calculation of TCP and NTCP is not routine work in clinical departments. The radiobiological analysis should be used only for relative comparison between competing plans rather than for assessment of the absolute risk of biological impact. Additionally, this study was performed with a small number of patients and a short follow-up time period, which are the limitations of the study; further follow-up is required. The potential dosimetric results of the present study demonstrated better local control with acceptable toxicities, which are easily manageable.

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Disclosure

The authors report no conflict of interest.

References

1. Ferlay J, Soerjomataram I, Ervik M et al. GLOBOCAN 2012, Cancer Incidence and Mortality Worldwide in 2012. International Agency for Research on Cancer, Lyon, France 2012.
2. Institute for Health Metrics and Evaluation. The Challenge Ahead: Progress in Breast and Cervical Cancer. Institute of Health Metrics and Evaluation. 2011.
3. Prescribing, Recording, and Reporting Brachytherapy for Cancer of the Cervix. Bethesda, MD, USA, International Commission on Radiation Units and Measurements (ICRU report 89). Bethesda 2016.
4. Haie-Meder C, Pötter R, Van Limbergen E et al. Recommendations from Gynaecological (GYN) GECESTRO Working Group (I): concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV. *Radiother Oncol* 2005; 74: 235-245.
5. Viswanathan AN, Beriwal S, De Los Santos JF et al. American brachytherapy society consensus guidelines for locally advanced carcinoma of the cervix. Part II: high-dose-rate brachytherapy. *Brachytherapy* 2012; 11: 47-52.
6. Pötter R, Haie-Meder C, Van Limbergen E et al. Recommendations from gynaecological (GYN) GEC ESTRO working group (II): concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy-3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. *Radiother Oncol* 2006; 78: 67-77.
7. Pötter R, Tanderup K, Kirisits C et al., EMBRACE Collaborative Group (2018). The EMBRACE II study: The outcome and prospect of two decades of evolution within the GEC-ESTRO GYN working group and the EMBRACE studies. *Clin Transl Radiat Oncol* 2018; 9: 48-60.
8. Mahantshetty U, Pötter R, Beriwal S et al. IBS-GEC ESTRO-ABS recommendations for CT based contouring in image guided adaptive brachytherapy for cervical cancer. *Radiother Oncol* 2021; 160: 273-284.
9. Meertens H, Borger J, Steggerda M et al. Evaluation and optimization of interstitial brachytherapy dose distribution. In: Mould RF, Battermann JJ, Martinez AA, Speiser BL (Eds.). Brachytherapy from radium to optimization. Veenendaal. Nucletron International, The Netherlands 1994; 300-306.
10. Saw CB, Suntharalingam N, Wu A. Concept of dose nonuniformity in interstitial brachytherapy. *Int J Radiat Oncol Biol Phys* 1993; 26: 519-527.
11. Nahum AE, Tait DM. Maximising control by customized dose prescription for pelvic tumours. In: Advanced Radiation Therapy: Tumour Response Monitoring and Treatment Planning. Breit A (Ed.). Springer, Heidelberg, Germany 1992; 425-431.
12. Visser AG, Van Den Aardweg GJM, Levendag PC. Pulsed dose rate and fractionated high dose rate brachytherapy: choice of brachytherapy schedules to replace low dose rate treatments. *Int J Radiat Oncol Biol Phys* 1996; 34: 497-505.
13. Anbumani S, Arunai Nambiraj N, Dayalan S et al. A brachytherapy plan evaluation tool for interstitial applications. *Adv Bioinformatics* 2014; 2014: 376207.
14. Kutcher GJ, Burman C, Brewster L. Histogram reduction method for calculating complication probability for three dimensional treatment planning evaluations. *Int J Radiat Oncol Biol Phys* 1991; 21: 137-146.
15. Niemierko A, Goitein M. Modelling of normal tissue response to radiation: The critical volume model. *Int J Radiat Oncol Biol Phys* 1993; 25: 135-145.
16. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys* 1995; 31: 1341-1346.
17. Do NL, Nagle D, Poylin VY. Radiation proctitis: current strategies in management. *Gastroenterol Res Pract* 2011; 2011: 917941.
18. Saw CB, Suntharalingam N. Quantitative assessment of interstitial implants. *Int J Radiat Oncol Biol Phys* 1990; 20: 135-139.
19. Saw CB, Suntharalingam N. Reference dose rates for single plane and double-plane Iridium-192 implants. *J Med Phys* 1988; 15: 391-396.
20. Anbumani S, Anchineyan P, Narayanasamy A et al. Treatment planning methods in high dose rate interstitial brachytherapy of carcinoma cervix: a dosimetric and radiobiological analysis. *ISRN Oncol* 2014; 2014: 125020.
21. Kataria T, Sharma K, Subramani V et al. Homogeneity index: an objective tool for assessment of conformal radiation treatment. *J Med Phys* 2012; 37: 207-213.

22. Kehwar TS, Akber SF. Assessment of tumour control probability for high-dose-rate interstitial brachytherapy implants. *Rep Pract Oncol Radiother* 2008; 13: 74-77.
23. Tanderup K, Fokdal LU, Sturdza A et al. Effect of tumor dose, volume and overall treatment time on local control after radiochemotherapy including MRI guided brachytherapy of locally advanced cervical cancer. *Radiother Oncol* 2016; 120: 441-446.