Original Article

Tumor Control and Normal Tissue Complications in High-dose-rate Brachytherapy for Cervical Cancer Patients Using Ir-192 Radioactive Source

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Abstract

Introduction: The purpose of the study was to calculate, tumor control probability (TCP) and normal tissue complication probability (NTCP) in cervical cancer patients and to clinically correlate the outcomes with a follow-up period of 24 months. **Materials and Methods:** One hundred and fifty patients were included in the present study who received 46 Gy/23 fractions/4½ weeks of external beam radiotherapy with concurrent cisplatin chemotherapy, followed by intracavitary brachytherapy of 3 different fractionations regimens, i.e., 9.5 Gy per fraction of two fractions (50 patients in Arm1), 7.5 Gy per fraction of three fractions (50 patients in Arm2), and 6.0 Gy per fraction of four fractions (50 patients in Arm3). **Results:** The median TCP value for Arm1, Arm2, and Arm3 was 99.6%, 94%, and 98.1%, respectively, ($P < 0.01$). The median NTC*P* value for bladder in Arm1, Arm2, and Arm3 was 0.17%, 0.04%, and 0.07%, respectively, ($P = 0.05$). The median NTC*P* value for rectum in Arm1, Arm2, and Arm3 was 4.73%, 4.35%, and 3.17%, respectively, ($P = 0.052$). The overall survival (OS) of 90%, 86%, and 84% was found for Arm1, Arm2, and Arm3, respectively, at 24 months of follow-up. **Conclusion:** TCP, NTCP, and OS rates were found higher in Arm1 as compared to the other two arms. The complications found in all arms were less, low grade, and manageable. Hence, Arm1, i.e., 9.5 Gy per fraction of two fractions can be concluded as the optimum fractionation regime in terms of radiobiological parameters as well as overall patient comfort.

Keywords: Brachytherapy, carcinoma uterine cervix, normal tissue complication probability, radiotherapy, tumor control probability

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Introduction

In developing countries, cervical cancer is a big public health problem in females. Cervical cancer is the fourth most common cancer among women globally, with an estimated 604,000 new cases and 342,000 deaths in 2020. In India, it is the third most common cancer with an incidence rate of 18.3% (123,907 cases) as per GLOBOCAN 2020. About 570,000 women had cervix cancer in 2018 and approximately 311,000 died because of this cancer.[1]

According to the Indian Council of Medical Research, carcinoma cervix is the third most common cancer with 123,907 cases accounting for an incidence of 18.3% in 2020.[2] According to Punjab Cancer Atlas 2012–2013, carcinoma cervix is the second most common cancer accounting for 13% after carcinoma breast accounting for 27.2% in Punjab.[3] In Punjab, according to National Cancer Registry Program 2018 data, the district which had a higher incidence of carcinoma cervix than the national average of 12.4% is: Bathinda has the highest percentage (17.5%), followed by Mansa (17.3%), Faridkot (14.6%), and Muktsar (12.7%).

In early-stage cervical cancer, treatment modalities available with equivalent results are surgery followed by radiotherapy. In the advanced stage, radiotherapy is the main modality of the treatment, consisting of external beam radiotherapy (EBRT) followed by brachytherapy.

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This study was based on image-guided brachytherapy in the framework of the current guidelines set by the American Brachytherapy Society (ABS) and in light of the recent European study on magnetic resonance imaging (MRI) guided brachytherapy in advanced cervical cancer collaborative results that support more rigorous dose recommendations.[4] The Groupe Europeen de Curietherapie and the European Society for Radiotherapy and Oncology (GEC ESTRO) have also introduced a novel target concept to facilitate image-guided brachytherapy.[5,6]

The concept of differential dose volume histogram (DVH), tumor control probability (TCP), normal tissue complication probability (NTCP), and its application has been used and an attempt has been made to provide a method to select the best treatment protocol for enhanced tumor cure and survival.

Materials and Methods

This was a prospective study performed on 150 patients treated for cervical cancer. The staging of the disease was done according to the International Federation of Gynecology and Obstetrics (FIGO) staging system. The patients with stage IIb and IIIb were included and patients with lymph node involvement were excluded from the study.

All the patients were treated through EBRT with prescribed dose of 46 Gy in 23 fractions to the central disease followed by 6 Gy in 3 fractions to parametrium involved with central shielding along with concurrent chemotherapy (3 weekly cycles) with cisplatin, followed by intracavitary brachytherapy (ICBT). The time between completion of EBRT and the first ICBT ranged from 5 to 7 days. In ICBT, patients were randomized into three different arms, i.e., 50 patients in each arm as follows, and computer-generated random numbers were used for allocating the patients into one of the three arms randomly.

- Two fractions of 9.5 Gy each (Arm1)
- Three fractions of 7.5 Gy each (Arm2)
- Four fractions of 6.0 Gy each (Arm3).

The patient, treatment, and tumor characteristics such as age, histopathology, FIGO stage, target volume, maximum tandem length, overall treatment time, and completion of chemotherapy cycles are shown in Table 1.

The ICBT was given by remote after loading micro-selectron high-dose-rate (HDR) V3 brachytherapy machine having an iridium 192 radioactive source. A computer tomography (CT) compatible Fletcher suit applicator was used for the ICBT application which consists of the uterine tandem with various angles (15°, 30°, and 45°) and a pair of ovoids with various 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. The target volume and organ at risk (OAR) on each CT slice were contoured in three-dimensional (3D) volumes. For target delineation, high-risk clinical target volume (HRCTV) was contoured which includes the whole cervix and presumed extra cervical tumor expansion area (if present) upon brachytherapy. The rectum and bladder were delineated on each CT slice. The dose prescription point was Manchester point A in each plan. The point of prescription in 3D planning was still point A due to the unavailability of MRI images and the target delineation was difficult.

In this study, radiobiological parameters, namely TCP and NTCP of the bladder and rectum were calculated. TCP for uniform dose distribution within the target volume is calculated according to the Linear Quadratic Model (LQ) model as:[7,8]

$$TCP = \exp\left[-\rho V \exp\left(-\alpha\, BED_t\right)\right] \quad (1)$$

where ρ, V, α, and biologically effective dose to the target (BED_t) are the clonogenic cell density, target volume, coefficient of lethal damage (radiosensitivity of lethal damage), and biologically effective dose to the target volume, respectively.

To calculate TCP for a nonuniform dose distribution within the tumor, the use of biologically effective equivalent uniform dose (BEEUD) is an appropriate term instead of BED which is obtained by dividing the target volume into four different regions. Each region has its own BED and for the present study, BED has been replaced by BEEUD as per the concept given by Than Kehwar *et al*. in 2008.[7]

$$BEEUD_t = -(1/\alpha)\ln[(1/V)\,\Sigma v_i \exp\{-\alpha\, BED_{ti}\}] \quad (2)$$

The BEEUD is a hypothetical biological dose that produces an equivalent biological effect to that of an absolutely uniform dose delivered to the entire target volume. With the use of BEEUD of each target volume region, the expression of TCP for each region was calculated as follows:[7]

$$TCP = \exp[-\rho TV_{Dref}\{[(1\text{-}CI)/CI]\exp(-\alpha BEEUD_1) + DHI \exp(-\alpha BEEUD_2) + (DNR-ODI)$$

$$\exp(-\alpha BEEUD_3) + ODI \exp(-\alpha BEEUD_4)\}] \quad (3)$$

where TV_{Dref}, coverage index (CI), dose homogeneity index (DHI), dose nonuniformity ratio (DNR), and overdose volume index (ODI) are the region/target volume that receives a reference dose, CI, DHI, DNR, and ODI, respectively.

Now, the assumption was made that for EBRT uniform dose has been delivered throughout the target volume for all the patients, so total TCP was calculated as follows:

$$\text{Total TCP} = \text{TCP (EBRT)} \times \text{TCP (ICBT)} \quad (4)$$

NTCP was calculated by the Niemierko model as:[9]

$$NTCP = \frac{1}{1 + [TD50 / EUD]^{4\gamma 50}} \quad (5)$$

where γ50 is the slope of the sigmoid dose-response curve of normal tissue at 50% complication probability, TD_{50} is the dose required to produce a toxic effect in 50% of the population. EUD is equivalent to the uniform dose which is calculated using equation (6) as proposed by Kutcher *et al*. in 1991.[10]

Table 1: Patient, treatment, and tumor characteristics

Characteristics	Arm1 (n=50)	Arm2 (n=50)	Arm3 (n=50)
Age (years), median	57.5	55.5	53
Histopathology			
Squamous cell carcinoma	50	50	50
Adenocarcinoma	0	0	0
FIGO stage			
IIB	20	18	25
IIIB	30	32	25
Target volume (cc), mean±SD	33.6±9.4	35.4±11.2	34.5±8.2
Maximum tandem length from external uterine orifice (cm)	6	6	6
Overall treatment time (days)	47±6.2	57±6.4	60±8
Completion of chemotherapy cycles (percentage of patients)	100	100	100

SD: Standard deviation, FIGO: Federation of Gynecology and Obstetrics

$$EUD = [\sum_{(i=1)}^{N} (Vi).(EQD2i)^{a}]^{1/a} \quad (6)$$

where EQD_{2i} = EQD_2 (EBRT) + EQD_2 (ICBT)

"a" is a parameter describing the response of the organ in relation to the irradiated volume; a > 0 for normal tissues (large and small positive value for small and large volume effect) where hotspots are undesirable. EQD_2 and (Vi) are the equivalent dose in 2 Gy fractions and the whole volume of the organ, respectively. Using equations (5) and (6), NTCP was calculated for the rectum and bladder in this study. Parameter values used for NTCP calculation of OARs according to the Niemierko model are shown in Table 2.

Follow-up

All the patients underwent follow-up evaluations for up to 24 months according to departmental protocol along with RTOG guidelines.[11] OAR complications were noted. All the patients were evaluated to estimate their response in terms of control and normal tissue complications for bladder and rectum at 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24 months intervals after the completion of EBRT and HDR ICBT.

Statistical analysis

All parameters of the target and OARs were examined statistically using the statistical package R-4.3.2. To analyze the difference among the three arms of the study, the Kruskal–Wallis test and moods median test was done as data was not normally distributed and have outliers. Overall survival (OS) was calculated using the Kaplan–Meier method. A $P < 0.05$ was considered significant.

Results

Tumor control probability and EQD_2 of target

To calculate TCP, the values of α/β = 10 Gy, α = 0.35 Gy^{-1}, and clonogenic cell density $\rho = 10^7$ cells/cc for cervical cancer patients were used.[12] The Kruskal–Wallis test was used to compare TCP values among three arm and the results are shown in Table 3 and Figure 1.

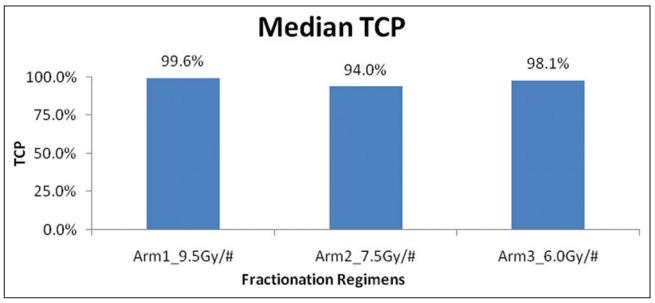

Figure 1: Tumor control probability values for all the arms in percentage. TCP: Tumor control probability

The median TCP value for Arm1 is 99.6%, for Arm2 is 94%, and for Arm3 is 98.1%. The P value for Chi-square is <0.01, which is significant. Hence, there is such evidence that shows a significant difference between the three arms.

EQD_2

The mean EQD_2 for Arm1 was 82.3 and the standard deviation (SD) was 4.6, for Arm2, it was 81.6 and SD was 5.1, and for Arm3, it was 83.8 and SD was 3.9 [Table 3 and Figure 2]. The ANOVA P = 0.05. EQD_2 values also demonstrated significant differences and represented variations in biologically effective doses across these arms.

Normal tissue complication probability and EQD_2 of bladder and rectum

The α/β value for rectum and bladder is 3 Gy in the present study.

For bladder

As shown in Table 4 and Figure 3, the median NTCP value for the bladder in Arm1 is 0.17, for Arm2 is 0.04, and for Arm3 is 0.07. According to the moods median test, the Chi-square value is 1.442 with a P = 0.486 that shows no association between the arms and NTCP of the bladder.

EQD_2: Mean EQD_2 for Arm1 was 86.2 and SD was 15.4, for Arm2, it was 79.1 and SD was 12.3, and for Arm3, it was 79.3 and SD was 10.5 [Table 4 and Figure 4]. ANOVA P = 0.01 and *post hoc* analysis revealed a significant difference between all the arms except Arm2 versus Arm3 (P = 0.91).

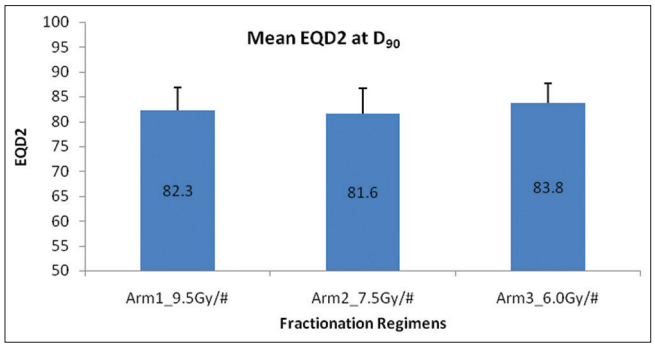

Figure 2: Mean EQD_2 at D_{90} of tumor

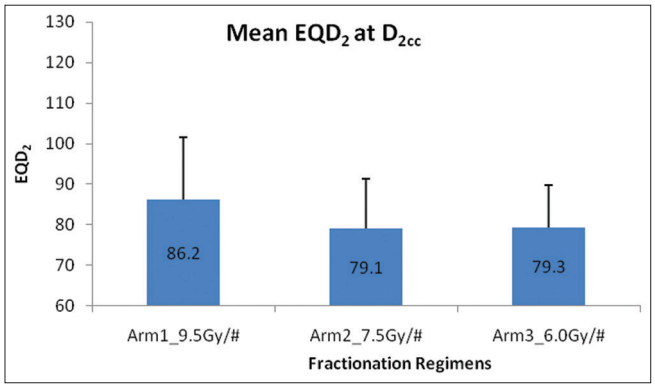

Figure 4: Mean EQD_2 for bladder at D_{2cc}

Table 2: Parameter values used for normal tissue complication probability calculations

OAR	*a*	γ50	TD_{50} (Gy)	Endpoint
Bladder	2	4	80	Bladder contracture/volume loss
Rectum	8.33	4	80	Severe proctitis/necrosis/ stenosis/fistula

OAR: Organ at risk

Table 3: Tumor control probability and equivalent dose in 2 Gy fractions values for all the arms in percentage

Arm	Median TCP (%)	EQD_2 at D_{90}
Arm1	99.6	82.3±4.6
Arm2	94	81.6±5.1
Arm3	98.1	83.8±3.9
P	<0.01	0.05

TCP: Tumor control probability, EQD_2: Equivalent dose in 2 Gy fractions

For rectum

The median NTCP value for the rectum in Arm1 is 4.73, for Arm2 are 4.35 and for Arm3 are 3.17 [Table 4 and Figure 5]. According to the moods median test, the Chi-square value is 5.920 with a $P = 0.052$. The *P* value is close to the commonly used significance level of 0.05, indicating that there may be some evidence to reject the null hypothesis for the association between the arms and the NTCP of the rectum.

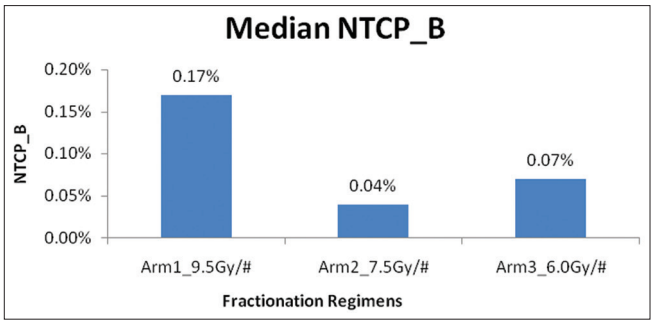

Figure 3: Normal tissue complication probability values of the bladder for all the arms in percentage. NTCP: Normal tissue complication probability

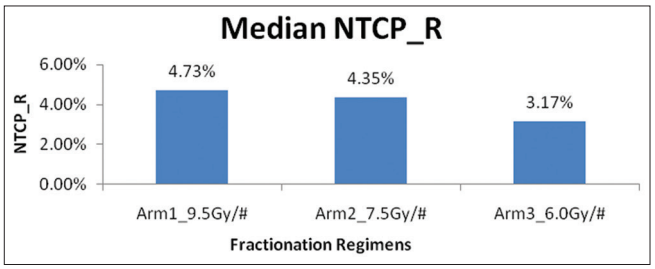

Figure 5: Normal tissue complication probability values of the rectum for all the arms in percentage. NTCP: Normal tissue complication probability

EQD_2

Mean EQD_2 for Arm1 was 81.1 and SD was 11.1, in Arm2, it was 75.9 and SD was 8.8, and for Arm3, it was 72.3 and SD was 6.8 [Table 4 and Figure 6]. ANOVA $P = 0.01$, *post hoc* analysis revealed a significant difference between Arm1 and Arm2 ($P = 0.01$), Arm1 and Arm3 ($P = 0.01$) and Arm2 and Arm3 ($P = 0.02$).

Toxicity analysis

Mainly gastrointestinal (GI) and genitourinary (GU) toxicities suffered by the patients irrespective of time in 2-year follow-ups were reported in this study.

Genitourinary toxicity

There were only 4% of patients having toxicity grade >2 and 96% of the patients having toxicity grade 0 and grade 1 in Arm1, 10% of patients having toxicity grade >2, and 90% of patients having toxicity grade 0 and grade 1 in Arm2, and 8% patients having toxicity grade >2 and 92% of the patients having toxicity grade 0 and grade 1 in Arm3. The Chi-square statistic was 1.37 and $P = 0.05$ which showed the insignificant difference between all the arms. Toxicity for the bladder is shown in Table 5.

Gastrointestinal toxicity

There were 14% of patients having toxicity grade >2 and 86% of the patients having toxicity grade zero and one in Arm1, 8% of patients having toxicity grade >2, and 92% of the patients having toxicity grade zero and one in Arm2, and only 2% patients having toxicity grade >2 and 98% of the patients having toxicity grade zero and one in Arm3. The Chi-square statistic was 4.89 and $P = 0.09$ which showed the insignificant

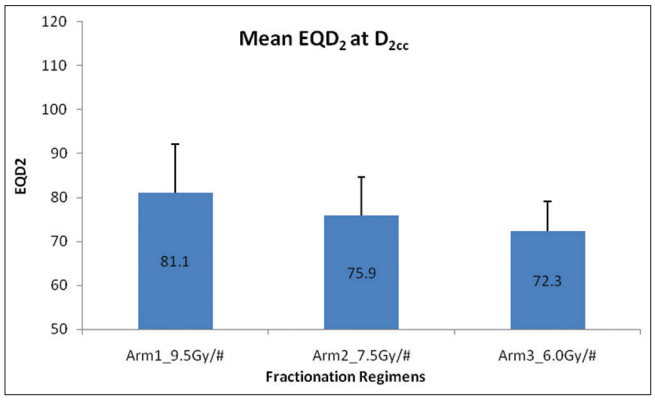

Figure 6: Mean EQD_2 for rectum at D_{2cc}

difference between all the arms. Toxicity for the rectum is shown in Table 6.

Overall survival

Two-year OS in Arm1 was 90% in Arm1, 86% in Arm2, and 84% in Arm 3. For the present data, the number of patient deaths that occurred was 5 (10%), 7 (14%), and 8 (16%) in Arm1, Arm2, and Arm3, respectively. The log rank test shows that there is no significant difference between the arms in terms of the distribution of time until the event occurs as the $P = 0.615$.

Discussion

According to ABS, and Indian Brachytherapy Society (IBS) guidelines[13,14] to respect the overall treatment time, total treatment should be completed within 56 days (EBRT + ICBT), and for a higher dose of up to 9 Gy can be used. In the present study, treatment was completed within 47 ± 6.2 days in Arm1, 57 ± 6.4 days in Arm2, and 60 ± 8 days in Arm3 so, Arm1 was meeting the criteria.

As described by Dale *et al*., the EQD_2 was often suggested as a better substitute of BED, but even the calculations of EQD_2 make use of the BED concept as a starting point.[15] The ABS/GEC-ESTRO and ICRU 89 recommend total EQD_2 dose including EBRT along with ICBT should be 80–90 Gy.[16] Furthermore, 75 Gy EQD_2 is a good dose when treatment is prescribed to point A (not to volume, i.e., HRCTV). Mean $EQD2_{10}$ (EBRT + ICBT) at D_{90} for HRCTV was 82.3 ± 4.6 Gy, 81.6 ± 5.1 Gy, and 83.8 ± 3.9 Gy in Arm1, Arm2, and Arm3, respectively, when prescription was done at point A. The result of the current study for the D_{90} dose parameter of HR-CTV was found in good agreement with ABS/GEC-ESTRO recommendations, Yadav *et al*.[17] study but not with Dimopoulos *et al*.[18] evaluations that concluded D_{90} (EQD_2) value for HR-CTV equal to or >87 Gy resulted in excellent (>95%) local control rates. This disagreement with Dimopoulos's results may be due to the point A prescription done in the present study.

The ABS/GEC-ESTRO and ICRU 89 recommend the total EQD_2 dose including EBRT and ICBT for bladder and rectum

Table 4: Normal tissue complication probability and equivalent dose in 2 Gy fractions for bladder and rectum

Arm	Bladder		Rectum	
	Median NTCP_B (%)	EQD_2 at D_{2cc}	Median NTCP_R (%)	EQD_2 at D_{2cc}
Arm1	0.17	86.2±15.4	4.73	81.1±11.1
Arm2	0.04	79.1±12.3	4.35	75.9±8.8
Arm3	0.07	79.3±10.5	3.17	72.3±6.8
χ^2	1.442	-	5.920	-
P	0.486	0.01	0.052	<0.01

EQD_2: Equivalent dose in 2 Gy fractions, NTCP: Normal tissue complication probability

Table 5: Genitourinary toxicity of the patients

Arm	G0–1, *n* (%)	G ≥2, *n* (%)	Mean time to develop, G ≥2 toxicity (months)	Mean EQD2 Gy (G ≥2 toxicity)
Arm1	48 (96)	2 (4)	13	132 Gy
Arm2	45 (90)	5 (10)	17.2	103 Gy
Arm3	46 (92)	4 (8)	15.5	103 Gy

EQD_2: Equivalent dose in 2 Gy fractions, GU: Genitourinary Toxicity

Table 6: Gastrointestinal toxicity of the patients

Arm	G0–1, *n* (%)	G ≥2, *n* (%)	Mean time to develop, G ≥2 toxicity (month)	Mean EQD2 Gy (G ≥2 toxicity)
Arm1	43 (86)	7 (14)	14.6	102 Gy
Arm2	46 (92)	4 (8)	14	95 Gy
Arm3	49 (98)	1 (2)	16	99 Gy

EQD_2: Equivalent dose in 2 Gy fractions

of D_{2cc} should be 90 Gy and 75 Gy, respectively. The present study reported that bladder mean EQD_2 (EBRT + ICBT) at D_{2cc} were 86.2 ± 15.4 Gy, 79.1 ± 12.3 Gy, and 79.3 ± 10.5 Gy, and for rectum, 81.1 ± 11.1 Gy, 76 ± 8.8 Gy, and 72.3 ± 6.8 Gy in Arm1, Arm2, and Arm3, respectively. For bladder, tolerance limits were acceptable as per ABS/GEC-ESTRO and ICRU 89 guidelines recommendation but in the case of rectum, limits were exceeding in Arm1 and Arm2 as observed in the study. Georg *et al*. in 2011,[19] correlated the DVH parameters along with late side effects of OARs (bladder, rectum, and sigmoid colon) in MRI-guided brachytherapy for cervical cancer and found that D_{2CC} and D_{1CC} were good analytical values for rectal toxicity. Yadav *et al*. in 2019,[17] also found that the total mean EQD_2 dose for the rectum and bladder was 63.74 ± 3.82 Gy and 68.89 ± 8.76 Gy, respectively, and it was less than the tolerance limit of ABS, GEC-ESTRO, and ICRU 89 recommendations. These studies had important differences in design, population, toxicity scoring, follow-up, and treatment method, but nonetheless, demonstrated a clear correlation between rectal D_{2cc} and toxicity.

The median TCP value for Arm1, Arm2, and Arm3 was 99.6%, 94%, and 98.1%, respectively. The *P* value for Chi-square is <0.01, which is significant. In the perspective of TCP values, Arm1 is recommended for the treatment

regime of cervix cancer, as it was found to have a high TCP value (goal of radiotherapy) among all the three regimens of the present study. A low NTCP in any regime will be preferable as per the aim of radiotherapy. In the present study, the median NTCP value for the bladder was 0.17%, 0.04%, and 0.07% in Arm1, Arm2, and Arm3, respectively. The *P* value for the Chi-square was 0.486. Arm 2 has the lowest NTCP followed by Arm3 and Arm1. As $P < 0.05$, there is no association between the dose regimens and NTCP of the bladder. Similarly, the median NTCP value for the rectum in Arm1 is 4.73%, for Arm2 is 4.35%, and for Arm3 is 3.17%. The *P* value for the Chi-square was 0.052. The *P* value is close to the commonly used significance level of 0.05, indicating that there may be some evidence for the association between the dose regimens and NTCP of Rectum. Thus, at the comparable level, no relationship was found between the Arms, i.e., different dose regimens and NTCP values of OARs. To maximize the therapeutic ratio, tumor control needs to increase while normal tissue complications need to decrease.

At 24 months of follow-up, the overall survival was 90%, 86%, and 84% in Arm1, Arm2, and Arm3, respectively, which is statistically insignificant. More survival in Arm1 may be associated with lesser overall treatment time in Arm1 and vice-versa in Arm3 (prolonged overall treatment time). Grade 2 and above GU toxicity was not statistically significant between the Arms. A total of 11 patients in all Arms developed bladder toxicity having an average EQD_2 113 Gy. Moreover, grade 2 and above GI toxicity was found slightly higher in Arm1 but the results were also not statistically significant. A total of 12 patients in all the Arms developed rectum toxicity having an average EQD_2 99 Gy. The patients who had complications were treated symptomatically. Thus, at a comparable level overall clinical toxicity found in each Arm was insignificant over 24 months.

The limitation of the present study was a small sample size, not have sufficient clinical follow-up, the use of a metallic applicator, and the utilization of CT imaging for treatment planning. Using metal artifact reduction algorithms while reconstructing images in CT will help to reduce the artifacts and result in better structure delineation.

Conclusion

Taking into account of increased hospital burden of cervical cancer patients from an Indian perspective, high dose with lesser number of fractions is preferable in terms of improving patient's comfort (limiting invasive procedures, financial burden, and hospitalization time) along with limited human resources (anesthesiologist, radiation oncologist, medical physicist, nurses, and hospitalization team) and material resources (imaging, implants, and catheters) used. It is concluded that Arm1, i.e., two fractions of 9.5 Gy per fraction each is the optimum solution for the objectives of the present study. A similar multi-institutional study with larger sample size and longer follow-up period is recommended to confirm the findings.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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