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Original Research

Sigmoid Point Validation for Dosimetric Evaluation and Reporting of Accumulated Sigmoid Dose in Multifractionated Brachytherapy for Carcinoma Cervix

Ayesha Iqbal Maniyar M S Ramaiah Institute of Oncology, India.
Revathy P M S Ramaiah Institute of Oncology, India.
Janaki M G M S Ramaiah Institute of Oncology, India.
Arul Ponni T R M S Ramaiah Institute of Oncology, India.
Kirthi Koushik M S Ramaiah Institute of Oncology, India.
Mohan Kumar M S Ramaiah Institute of Oncology, India.
Lithika Lavanya M M S Ramaiah Institute of Oncology, India.
Shanmukhappa B Kaginelli M S Ramaiah Institute of Oncology, India.

Introduction: Carcinoma of the uterine cervix is the most common cancer in females. The mainstay of treatment is combined external beam radiotherapy (EBRT) and intracavitary brachytherapy (ICBT), especially in the advanced stages. Brachytherapy forms an integral part of radiation therapy and cornerstone for both the local control rates and toxicities. The doses received by organ at risks (OARs) are significantly associated with radiation-related toxicities. An accurate estimation of the cumulative irradiation dose for OARs is crucial. The sigmoid is an important organ at risk for gynecological brachytherapy (BT). However, the reliability of localization of high-dose regions during multi-fractionated treatment is limited. This work reports the methodological development of sigmoid points to summate multi-fractionated doses.

Materials and Methods: Fifty patients who were treated for locally advanced cervical cancer with radical chemoradiation and multifractionated high-dose rate (HDR) brachytherapy from April 2023 to December 2024 were evaluated. Sigmoid points 1 (SP1) and 2 (SP2) were assigned on the treated brachytherapy plans retrospectively. The correlation between SP1 and SP2 with sigmoid D0.1cc and D2cc doses were analyzed.

Results: The study involved 50 patients with a median age of 50 years, ranging from 35 to 70, all diagnosed with squamous cell carcinoma. The FIGO stages were: 6% in IIA, 40% in IIB, 12% in IIIB, 18% in IIICr1, 14% in IIICr2, and 10% in IVA. Treatment doses varied from 6 – 7.5Gy HDR in 2-4 fractions and inter-fraction time was 6-12 hours. The mean values for D0.1cc, D2cc, SP1, and SP2 were 4.12, 3.18, 3.82, and 15.20, respectively. Significant correlations were observed between D0.1cc and D2cc ($P = 0.000$), SP1 and SP2 ($P = 0.002$), D0.1cc and SP2 ($P = 0.003$), D2cc and SP1 ($P = 0.004$), and D2cc and SP2 ($P = 0.001$).

Conclusion: SP2 showed significant correlation with D0.1cc and D2cc sigmoid doses, suggesting preliminary utility as a surrogate for volumetric parameters in inter-fraction dose summation. However, further validation with clinical outcome correlation is warranted.

Introduction

Carcinoma of the uterine cervix is the most common cancer in females. The mainstay of treatment is combined external beam radiotherapy (EBRT) and intracavitary brachytherapy (ICBT), especially in the advanced stages. Brachytherapy forms an integral part of radiation therapy and cornerstone

for both the local control rates and toxicities.

The International Commission on Radiation Units and Measurement 38 (ICRU 38) recommendations have been followed universally by the oncology community for uniform reporting of ICBT. In the past, there have been many reports critically reviewing and challenging the International Commission on Radiation Units and Measurements (ICRU) 38 recommendations [1]. The advent of better imaging modalities and technological advances in the last two decades have paved the way for image-based brachytherapy, but logistics, conventional mindset and resource implications have been the major hurdles against its routine clinical application today.

In recent years, three-dimensional (3D) image-guided adaptive brachytherapy (IGABT) using magnetic resonance imaging (MRI) is being increasingly advocated as the gold standard in cervical cancers. Prospective image-guided studies including the recently published results from the IntErnational study on MRI-guided BRAchytherapy in CErvical cancer (EMBRACE-I) study group have demonstrated improved local control and favorable toxicity profile [2].

The doses received by organs at risk (OARs) are significantly associated with radiation-related toxicities. An accurate estimation of the cumulative irradiation dose for OARs is crucial. The sigmoid is an important organ at risk for gynecological brachytherapy (BT). However, the reliability of localization of high-dose regions during multi-fractionated treatment is limited. This work reports the methodological development of sigmoid points to summate multi-fractionated doses.

Materials and Methods

Study design and Participants

Fifty patients who were treated for locally advanced cervical cancer with radical chemoradiation and multifractionated high-dose rate (HDR) brachytherapy from April 2023 to December 2024 were evaluated. For correlation analysis, a minimum sample size of 47 is required to detect a moderate correlation coefficient ($r=0.4$) with 80% power and $\alpha=0.05$. Thus, our cohort of 50 patients was statistically adequate.

This retrospective study was approved by the Institutional Review Board (DRP ID: DRP/FAC-NF1582/2025), and the requirement for informed consent was waived owing to the retrospective nature of the analysis.

External Beam Radiotherapy

Patients underwent external beam radiation therapy (EBRT) with a total dose of 45 Gy delivered in 25 fractions, utilizing either three-dimensional conformal radiation therapy (3DCRT) or intensity-modulated radiation therapy (IMRT) on a 6 MV Elekta Agility Linear Accelerator. Concurrent weekly cisplatin chemotherapy was administered alongside the radiation treatment. Organs at risk (OARs) including the bladder, rectum, bowel, and bilateral femoral heads were carefully contoured, with the sigmoid colon delineated from the rectosigmoid flexure to two centimeters above the uterine fundus. The planning target volume (PTV) encompassed the entire uterus, bilateral parametria, and either the upper half or entire vagina depending on disease extent, in addition to bilateral common iliac, external iliac, internal iliac, obturator, and presacral lymph node groups up to the S2–S3 vertebral junction. Dose constraints for OARs were set to keep the volume receiving 45 Gy (V45 Gy) below 50% for both the bladder and rectum, while the bowel bag volume of 195 cc was limited to less than 45 Gy. The PTV coverage was planned to receive at least 95% of the prescribed dose.

Treatment planning was performed using the Monaco treatment planning system (TPS). For patients presenting with lymph nodes larger than one centimeter, a boost dose ranging from 5.4 to 9 Gy was delivered over 3 to 5 fractions, with the exact dose and technique tailored according to OAR tolerance and radiation delivery method.

Brachytherapy Procedure and Planning

Brachytherapy (BT) was initiated approximately 10 to 15 days following the completion of external beam radiation therapy (EBRT), based on clinical evaluation and treatment response. Intracavitary brachytherapy (ICBT) applicators, consisting of a uterine tandem with flange and two vaginal ovoids (Henske's or Fletcher's type), were inserted under spinal anesthesia or mild sedation, with the patient in the lithotomy position. [3] Adequate vaginal packing was performed to displace the bladder and rectum, thereby minimizing radiation dose to these critical organs. Following applicator placement, computed tomography (CT) simulation was conducted without intravenous contrast.

During CT simulation, the bladder was filled with 50 ml of normal saline and the rectum with 20 ml of rectal contrast. Axial CT slices with a thickness of 2.5 mm were acquired from the upper border of the third lumbar vertebra to the mid-shaft of the femur and transferred to the Sagiplan treatment planning system (Bebig, Eckert & Ziegler, Germany), which uses the Task Group 43 (TG-43) dosimetry algorithm. Organs at risk (OARs) including the bladder, rectum, and sigmoid colon as well as the high-risk clinical target volume (HRCTV) were contoured according to GEC-ESTRO guidelines [4]. The HRCTV included the residual gross tumor volume at the time of brachytherapy, the entire cervix, and any persistent parametrial or vaginal involvement. The intermediate-risk clinical target volume (IRCTV) was generated by expanding the HRCTV by 10 mm, excluding overlap with OARs, to encompass areas of initial disease spread. Applicators were digitized using the system library and verified with digitally reconstructed radiographs (DRRs) before dwell positions were activated. Surface control points were placed on the HRCTV, and dose was prescribed to this volume. Dose-volume histogram (DVH) parameters were evaluated, and the isodose reshaper tool was utilized to achieve optimal pear-shaped dose distribution, maximizing the D90 (dose received by 90% of HRCTV) while maintaining OAR doses within the acceptable limits. High-dose-rate (HDR) BT was delivered in 2 to 4 fractions of 6–7.5 Gy each, with inter-fraction intervals of 6–12 hours, using the SagiNova HDR afterloading unit (Eckert & Ziegler, Germany).

Figure 1 and 2 shows the sigmoid points (SP1 and SP2) according to Vanden Berk et al., with SP1 located 0.5 cm to the right (x-axis), 1.5 cm posterior (z-axis), and 2.5 cm cranial along the body axis (y-axis) from the cervical os; and SP2 defined as 0.5 cm anterior (z-axis) and 4.5 cm cranial (y-axis) from the cervical os. [5] These points were mapped on the treatment plans to correlate with the maximum dose, D0.1cc, D2cc, and D5cc received by the sigmoid colon.

Figure 1. Sagittal, Coronal and Axial Views Showing the SP1 Coordinates (white arrow head) corresponding along with isodose lines.

Figure 2. Sagittal, Coronal and Axial Views Showing the SP2 Coordinates (white arrow head) corresponding along with isodose lines.

The equivalent dose in 2 Gy per fraction (EQD2) was calculated for each dosimetric parameter using the formula EQD2 = BED / [1 + (2/α/β)], where BED = nd (1 + d/α/β), with 'n' representing the number of fractions, 'd' the dose per fraction, and α/β assumed as 3 for normal tissues and 10 for tumor tissue. The cumulative dose constraints, combining EBRT and BT, were set at D2cc

rectum < 75 Gy, D2cc sigmoid < 75 Gy, and D2cc bladder < 90 Gy EQD2 (α/β = 3), in accordance with ABS and GEC-ESTRO guidelines.

Statistical Analysis

All dosimetric and spatial data were tabulated and analyzed using SPSS software version 18.0 (IBM, Chicago, USA). One-way ANOVA was performed to compare dosimetric values across different groups, with p-values ≤ 0.05 considered statistically significant. Pearson correlation analysis was conducted to assess the linear relationships between the anatomical sigmoid points (SP1 and SP2) and dosimetric parameters such as D0.1cc and D2cc. Additionally, Bland-Altman plots were utilized to evaluate the agreement between D0.1cc and D2cc doses with those measured at SP2, providing a method to assess consistency and potential biases between these measurements.

Results

Table 1 summarizes the characteristics of the 50 patients included in our study. Based on the FIGO 2018 staging system, the majority of patients were diagnosed at intermediate to locally advanced stages.

Parameter	Details
Total no. of patients	50
Age (years)	
- Median	50
- Range	35-70
Histopathology	
- Squamous cell carcinoma	50 (100%)
FIGO stage	
- IIA	6%
- IIB	40%
- IIIB	12%
- IIICr1	18%
- IIICr2	14%
- IVA	10%
Dose/Fraction	
- 6Gy X 4FR	2
- 6.5Gy X 4FR	15
- 7Gy X 3FR	13
- 7.5Gy X 3FR	20

Table 1. Demographic Details.

Specifically, 6% of patients were in Stage IIA, representing the early phase of cervical cancer. The most common stage was Stage IIB, accounting for 40% of the cohort. Stage IIIB included 12% of patients, indicating further local advancement. Regional nodal involvement was observed in Stage IIICr1 and IIICr2, comprising 18% and 14% of patients, respectively. A smaller proportion, 10%, were diagnosed at Stage IVA, reflecting locally extensive disease. Overall, the data indicate that while some patients presented with early-stage disease, the majority were in intermediate or advanced stages at the time of diagnosis.

Among the 50 patients, Fletcher applicators were used in 27 patients, while Henschke applicators

were used in the remaining 23 patients. The median intrauterine (IU) length was 5 cm, with an interquartile range (IQR) of 3–7 cm and the ovoid sizes used were 1.5 cm and 2 cm.

As for the dose fractionation used for the study - least common regimen is 6 Gy x 4 fractions, two patients. The most common treatments are 6.5 Gy x 4 fractions, used for 15 patients, and 7 Gy x 3 fractions, used for 13 patients. The most frequent regimen is 7.5 Gy x 3 fractions, which is used for 20 patients. Overall, the majority of patients receive treatments with doses ranging from 6.5 Gy to 7.5 Gy per fraction.

As summarized in Table 2, the dataset includes 50 observations for each of six dosimetric parameters such as D0.1cc, D2cc, D5cc, maximum dose, SP1 and SP2. The median EQD2 dose of D0.1cc was 55.82 Gy, with an interquartile range (IQR) of 43.48–81.42 Gy).

Parameter	Median EQD2 (Gy)	Interquartile range	Correlation p value
D0.1cc	55.82	43.48-81.42	-
D2cc	52.28	43.16-71.71	-
D5cc	47.13	47.13-59.65	
Max dose	56.41	43.18-172.20	
SP1	56.66	43.57-84.39	-
SP2	68.73	43.39-983.54	-
D0.1cc vs D2cc	-	-	0
SP1 vs SP2	-	-	0.002
D0.1cc vs SP1	-	-	0.25
D0.1cc vs SP2	-	-	0.003
D2cc vs SP1	-	-	0.004
D2cc vs SP2	-	-	0.001

Table 2. Descriptive Analysis.

This table combines both descriptive and comparative analysis, presenting the number of observations (N), median with IQR (interquartile range), along with the p-values for the comparisons between parameters.

The D2cc and D5cc values had median doses of 52.28 Gy (IQR: 43.16–71.71 Gy) and 47.13 Gy (IQR: 43.13–59.65 Gy), respectively, The maximum dose recorded across the cohort had a median of 56.41 Gy, but with a wide IQR ranging from 43.18 to 172.20 Gy. For specific dose points, SP1 showed a median EQD2 of 56.66 Gy (IQR: 43.57–84.39 Gy), while SP2 exhibited a higher median of 68.73 Gy with a notably broad IQR of 43.39–983.54 Gy.

In the comparative analysis, SP2 correlated with D0.1cc (r=0.52, 95% CI 0.28–0.69, p=0.003) and D2cc (r=0.58, 95% CI 0.34–0.73, p=0.001). SP1 correlated with D2cc (r=0.42, 95% CI 0.15–0.62, p=0.004) but not with D0.1cc (r=0.18, 95% CI −0.12–0.44, p=0.25) (Table 3).

Comparison	Correlation coefficient (r)	95% CI	p value
D0.1cc vs D2cc	0.72	0.54–0.84	0
SP1 vs SP2	0.46	0.20–0.65	0.002
D0.1cc vs SP1	0.18	−0.12–0.44	0.25
D0.1cc vs SP2	0.52	0.28–0.69	0.003
D2cc vs SP1	0.42	0.15–0.62	0.004
D2cc vs SP2	0.58	0.34–0.73	0.001

Table 3. Correlation Analysis between Sigmoid Point Doses and Volumetric Parameters.

Figures 3 and 4 present the Bland-Altman plots assessing the agreement between D0.1cc and SP2, and D2cc and SP2, respectively.

Figure 3. Illustrates the Bland-Altman Plot Showing the Agreement between D0.1cc Values and SP2.

Figure 4. Represents the Bland-Altman Plot Illustrating the Agreement between D2cc and SP2.

Discussion

High-dose-rate brachytherapy (HDR-BT) remains a cornerstone in the management of cervical cancer, serving both as a definitive treatment and as a boost following external beam radiation therapy (EBRT). Due to the sharp dose gradients characteristic of HDR-BT, meticulous delineation of organs at risk (OARs) particularly the bladder, rectum, and sigmoid colon is critical. Among these, the sigmoid colon is especially vulnerable given its anatomical proximity to the cervix, placing it at risk of receiving high radiation doses during intracavitary applications. Accurate dose estimation to the sigmoid is, therefore, essential to prevent radiation-induced gastrointestinal toxicity while ensuring that therapeutic doses are delivered to the tumor.

Clinical studies have highlighted the association between excessive sigmoid dose and late gastrointestinal complications. Mehta et al. (2021) reported that when the sigmoid receives more than 80–90 Gy EQD2, there is a significantly increased risk of adverse events such as rectal bleeding, bowel perforation, obstruction, and fistula formation [6]. Based on these findings, dose constraints for the sigmoid colon in HDR brachytherapy are typically recommended to remain below 70–75 Gy EQD2, depending on the fractionation schedule. These dose constraints aim to maintain a balance between maximizing tumor control and minimizing treatment- related morbidity. However, achieving this precision in sigmoid dose reporting can be difficult due to anatomical variability and inter-fraction motion.

One of the main challenges in accurate sigmoid dosimetry is the positional variation of the sigmoid colon during and between fractions. As noted by Zhu et al. (2022), bowel peristalsis and variable filling patterns contribute to significant positional shifts, making it difficult to consistently define a static high-dose region within the sigmoid [7]. Li et al. (2021) further emphasized the impact of such anatomical changes on dosimetric evaluation, advocating for adaptive treatment planning and image-guided brachytherapy (IGBT) to account for these variations [8]. This variability complicates inter-fraction dose summation and makes cumulative dose assessments prone to error if surrogate markers or fixed points are not used consistently.

To address these challenges, Van den Bergh et al. (2023) introduced and validated two anatomical reference points within the sigmoid Sigmoid Point 1 (SP1) and Sigmoid Point 2 (SP2) as reproducible landmarks for dose assessment [5]. Defined using MRI imaging for enhanced soft tissue contrast, SP1 and SP2 provide coordinate-based localization of high-dose regions within the sigmoid colon. Their study demonstrated successful identification of SP1 and SP2 in 70% and 60% of patients, respectively, and showed strong correlations between these points and traditional DVH metrics such as D2cc. Importantly, the differences between doses at SP1/SP2 and D2cc were found to be clinically acceptable, supporting their use as surrogate markers for more complex volumetric dose measurements. In our study, we replicated the generation of SP1 and SP2 as per Van den Bergh et al.’s methodology and evaluated their correlation with dosimetric parameters D0.1cc and D2cc of the sigmoid colon. Statistically significant correlations were observed between SP2 and both D0.1cc and D2cc, as well as between SP1 and D2cc, indicating that these points can serve as reliable surrogates for volumetric dose estimates. Notably, the median SP2 dose was observed to

be 68.73 Gy, but with a wide interquartile range (IQR: 43.39–983.54 Gy), which we attribute to its fixed location 4.5 cm cranial and 0.5 cm anterior to the cervical os. In certain applicator geometries particularly with longer tandem lengths or anterior tandem angulation SP2 may fall within a high-dose region of the tandem/ovoid complex, leading to higher outliers.

To ensure accurate interpretation, we analyzed the cumulative EQD2 doses (α/β = 3 Gy) and found the median D2cc sigmoid dose to be 52.28 Gy (IQR: 43.16–71.71 Gy), safely within the recommended ABS/GEC-ESTRO constraint of <75 Gy. Our findings suggest that SP2, due to its reproducibility and significant correlation with high- dose regions, could serve as a surrogate for D0.1cc and D2cc estimation in clinical practice.

When contextualized within the broader clinical literature, our findings underscore the critical role of careful OAR dosimetry in cervical cancer radiotherapy. Ahmadloo et al. [9] demonstrated that induction chemotherapy followed by definitive chemoradiation is feasible and safe in patients with locally advanced disease, but they emphasized that toxicity remains a limiting factor in dose escalation. This highlights the importance of precise dosimetric monitoring to balance efficacy and safety. Similarly, Javadinia et al. [10] reported favorable local control and survival outcomes in patients treated with EBRT and HDR cobalt-60 intracavitary brachytherapy, reinforcing the principle that brachytherapy quality directly influences clinical outcomes. More recently, Homaei Shandiz et al. [11] investigated the addition of capecitabine to brachytherapy, showing potential improvements in efficacy, but again underscoring the necessity of stringent OAR dose monitoring to avoid exacerbating gastrointestinal complications. Together, these studies support our assertion that reproducible and reliable dosimetric methods such as the use of SP2 are essential to the continued advancement of cervical cancer treatment.

While this study was purely dosimetric and did not include clinical toxicity endpoints, future prospective studies incorporating CTCAE-graded gastrointestinal toxicity data will be essential to confirm the clinical relevance of these anatomical points, particularly SP2, in predicting and preventing radiation-induced sigmoid complications.

In conclusion, sigmoid point validation for dosimetric evaluation is a critical component of multifractionated brachytherapy in carcinoma cervix. The accurate reporting of accumulated sigmoid dose allows for effective treatment planning, reducing the risks of radiation-induced bowel toxicity while optimizing tumor control.

There is a need for further refinement in imaging and dosimetric validation methods, particularly in the context of managing organ motion and anatomical changes. Ongoing development of more advanced treatment planning systems that integrate real-time imaging will help enhance sigmoid point dosimetry and improve patient outcomes in cervical cancer brachytherapy. While the pilot work shows promising results, further validation and refinement are needed.

Acknowledgments

Statement of Transparency and Principals

• Author declares no conflict of interest

• Study was approved by Research Ethic Committee of author affiliated Institute.

• Study’s data is available upon a reasonable request.

• All authors have contributed to implementation of this research.

Originality Declaration for Figures

All figures included in this manuscript are original and have been created by the authors specifically for the purposes of this study. No previously published or copyrighted images have been used. The authors confirm that all graphical elements, illustrations, and visual materials were generated from the data obtained in the course of this research or designed uniquely for this manuscript.

Declaration on generative AI and AI-assisted technologies in the writing process

No generative AI and AI-assisted technologies were used in the writing process.

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