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Calculation of Total Dose Delivered to Carcinoma Cervix Patients Treated with Volumetric Modulated Arc Therapy (VMAT) and Image-Guided Brachytherapy (IGBT)

Sana Naeem, Ayesha Anees, Ahmad Farooq, Tahir Sheikh, Rub Nawaz Maken

Abstract

Objective: To calculate the total radiation dose delivered to carcinoma cervix patients treated with Volumetric Modulated Arc Therapy (VMAT) and MRI-guided brachytherapy (IGBT), and to evaluate cumulative EQD2 to tumor and organs-at-risk.

Study Design and settings: This Descriptive, cross-sectional study was conducted at Department of Radiotherapy, INMOL Hospital, Lahore, from 1st August 2024 to 10th January 2025.

Methodology: Fifty patients with histologically confirmed carcinoma cervix, ECOG 0–II, aged 45–65 years, receiving VMAT-based external beam radiotherapy (45 Gy/25 fractions) followed by MRI-guided brachytherapy were included. EQD2 values for the high-risk target volume and organs-at-risk (bladder, rectum, sigmoid) were calculated using DVH parameters.

Results: The mean age of patients was 55.1 ± 5.8 years, with Stage IIIB being the most common stage (50%). A total of 64% received three brachytherapy insertions, while 36% required four. The mean cumulative tumor EQD2 was 84.9 ± 2.8 Gy. Mean bladder, rectum, and sigmoid EQD2 values were 78.1 ± 4.3 Gy, 67.3 ± 4.4 Gy, and 62.5 ± 4.2 Gy, respectively. More than 90% of patients met internationally recommended tumor and OAR dose constraints.

Conclusion: It is concluded that VMAT combined with MRI-guided brachytherapy delivers adequate cumulative tumor dose while maintaining organ-at-risk exposure within acceptable limits.

Keywords: Cervical cancer, patients, population, Radiotherapy, VMAT, MRI

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INTRODUCTION

Cervical cancer is the fourth most common cancer among women globally, with an estimated 601,000 new cases and 342,000 deaths in 2020.[1] In Pakistan, about 5,000 women in the country are diagnosed with cervical cancer every year and more than 3,000 of these women die (WHO).[1,2] The HPV infection is attributed to over 90 percent of the cases and other demographics that put individuals at risk are smoking, immunocompromised conditions, history of sexually transmitted diseases, young age at first intercourse, multiple sexual partners, and multiparty.[3] The patients may remain asymptomatic and be identified during screening, but the symptoms include, abnormal vaginal discharge, post-coital bleeding, dyspareunia, and pelvic pain. The workup involves a focused history, physical exam, and a gynecological examination of local and lymph node extension, smoking cessation counselling.[4] It also entails pertinent lab tests including complete blood count, full metabolic profile, pregnancy test, and HIV testing and diagnostic tests including colposcopy utilizing biopsy, cold-knife conization, and examination under anesthesia when necessary. PET-CT and pelvic MRI imaging studies determine the disease extent and fertility.[5]

Early-stage treatment consists of surgery, and the treatment of the locally advanced cervical cancer consists of concurrent chemo-radiotherapy (CCRT) and an external tumor boost with brachytherapy (BT). Image guided adaptive

Sana Naeem
Postgraduate Resident, Department of Oncology
INMOL Hospital, Lahore
Email: syedasananaeem@gmail.com

Ayesha Anees
Principal Medical Officer, Department of Oncology
INMOL Hospital, Lahore
Email:ayesha_anees@yahoo.com

Ahmad Farooq
Principal Medical Officer, Department of Oncology
INMOL Hospital, Lahore
Email:ahmadfarooq@gmail.com

Tahir Sheikh
Postgraduate Resident, Department of Oncology
INMOL Hospital, Lahore
Email: tahir.sheikh252@gmail.com

Rub Nawaz Maken
Deputy Chief Medical Officer, Department of Oncology
INMOL Hospital, Lahore
Email: rnmaken@gmail.com

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brachytherapy (IGABT) through MRI or CT imaging employs three-dimensional imaging which enhances the target area coverage through conformity, dose escalation, and reduction to the normal organs at risk (OARs). Main OARs of the greatest significance are the rectum and the bladder since there is a higher chance of radiation toxicity.[6] The constraints of dosage are necessary to prevent such complications as proctitis and cystitis. A 3-dimensional approach is obtained based on the 2cc volume on DVH (D2cc).[7] Dose higher than 80 Gy of rectum is known to cause rectovaginal fistula and higher than 2cc bladder volume causes 5-20% toxicity. The treatment methods such as IMRT and IGABT have facilitated compliance with these limitations.[8] IGABT and VMAT have been effective in enhancing the treatment of locally advanced cervical cancer, with the median dose of approximately 90.6 Gy to the area at risk being precisely delivered, and the dosage to the nearby organs is well controlled.[9] The multicenter study of Retro EMBRACE revealed the use of VMAT, IMRT and MRI-guided IGABT in patients with good long-term outcome. Mean dose of EBRT 46 +- 2.5 Gy, 77.4 percent underwent concurrent chemotherapy and mean total dose of IGBT-CTV was 87 ±15 Gy. The mean values of D2cc were bladder 81±22Gy, rectum 64±9Gy, sigmoid 66±10Gy, and bowel 64±9Gy (all EQD2). Cervical cancer is one of the big health issues that are experienced particularly in low- and middle-income countries where radiotherapy is a major treatment modality.[10] Such techniques as VMAT and IGABT can assist to obtain superior results as they provide functional, focused radiation with low toxicity. The correct dosage of delivered dose to the tumor and adjacent organs is an important factor in the successful treatment and reduction of complications.[11]

METHODOLOGY

This Descriptive, cross-sectional study was conducted at Department of Radiotherapy at INMOL Hospital, Lahore from 1st August 2024 to 10th January 2025. A total sample size of 50 patients was calculated with 95% confidence level, 5% margin of error, and expected response rate of 50%, ensuring adequate study power. A non-probability consecutive sampling technique was used to enroll eligible patients who fulfilled the inclusion criteria and consented to participate. Patients were eligible for inclusion if they had histologically confirmed carcinoma of the cervix and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–II. Only patients receiving external beam radiotherapy (EBRT) followed by MRI-guided brachytherapy were included in the study. Participants were required to be between 45 and 65 years of age and to have no history of contrast allergy to ensure safe administration of imaging protocols. Patients were excluded if they had a history of autoimmune disease or connective tissue disorders, severe comorbid conditions, or evidence of metastatic disease. Those who had previously received pelvic radiotherapy were also excluded. Additionally, patients who refused to provide informed consent or had contraindications to radiotherapy, such as psoriasis or xeroderma pigmentosum, were not considered eligible for participation. Approval from the ethical committee was obtained. Eligible patients who participated in the study after 2019 were identified and recruited. The baseline staging was conducted using MRI pelvis with contrast giving clear information on the extent of tumor before planning the treatment. The radiotherapy was applied as external beam radiotherapy based on CT-simulation without contrast, with regularized bladder-filling procedure and regular weekly image guidance to guarantee reliability and accuracy. VMAT to patients was administered at 45 Gy in 25 fractions, and then a boost as required by the institution. At the end of EBRT, MRI pelvis was repeated to determine tumor response. Depending on their response, patients underwent three insertions of the 7 Gy dose (of MRI-guided brachytherapy) in three locations (good responders) or four injections of the same dose (partial responders). On a case-by-case basis, the high-risk clinical target volume dose distribution, dose-volume histogram (DVH) parameters, and equivalent dose in 2 Gy fractions (EQD2) of the high-risk clinical target volume and the organs at risk, such as the bladder, rectum, and sigmoid colon, were calculated. Data were analyzed using SPSS version 20.0. Descriptive statistics were applied, with means and standard deviations calculated for quantitative variables such as age, tumor dose, and EQD2 parameters, while categorical variables such as stage and ECOG status were summarized as frequencies and percentages. Stratification by age and disease stage was performed to assess potential confounding effects. Post-stratification comparisons were carried out using independent sample t-tests for continuous variables and chi-square tests for categorical variables, with a p-value = 0.05 considered statistically significant.

RESULTS

Data were collected from 50 patients, with a mean age of 55.1 ± 5.8 years. Most patients presented with stage IIIB disease (50%), followed by stage IIIA (20%), while stage IIB and IVA accounted for 16% and 14% respectively. ECOG performance status was generally favorable, with 56% of patients having ECOG 1, 20% ECOG 0, and 24% ECOG 2. Regarding brachytherapy, 64% of patients required 3 insertions, whereas 36% required 4 insertions, reflecting differences in tumor response after external beam radiotherapy. Cumulative tumor dose delivery was consistent, with a mean tumor EQD2 of 84.9 ± 2.8 Gy, ranging from 80.1 to 89.9 Gy. Organ-at-risk doses stayed within acceptable tolerance limits: bladder EQD2 averaged 78.1 ± 4.3 Gy, rectum EQD2 averaged 67.3 ± 4.4 Gy, and sigmoid EQD2 averaged 62.5 ± 4.2 Gy. Patients receiving 3 insertions (n = 32) had a mean tumor EQD2 of 83.4 ± 2.1 Gy, whereas those receiving 4 insertions (n = 18) achieved a higher mean tumor EQD2 of 87.1 ± 1.8 Gy, with a p-value of <0.001 indicating statistical significance. Bladder EQD2 averaged

77.2 ± 4.4 Gy in the 3-insertion group and 79.7 ± 3.8 Gy in the 4-insertion group (p = 0.08). Rectum EQD2 averaged 66.4 ± 4.2 Gy in the 3-insertion group and 68.9 ± 4.5 Gy in the 4-insertion group (p = 0.09). Sigmoid EQD2 averaged 61.7 ± 4.1 Gy for 3 insertions and 63.9 ± 4.3 Gy for 4 insertions (p = 0.12). Patients with stage IIB (n = 8) received a mean tumor EQD2 of 83.6 ± 2.3 Gy, bladder EQD2 of 76.9 ± 4.2 Gy, rectum EQD2 of 66.2 ± 3.9 Gy, and sigmoid EQD2 of 61.1 ± 4.1 Gy. Stage IIIA patients (n = 10) had tumor EQD2 of 84.3 ± 2.6 Gy, bladder EQD2 of 77.5 ± 4.1 Gy, rectum EQD2 of 66.7 ± 4.5 Gy, and sigmoid EQD2 of 61.9 ± 4.0 Gy. Stage IIIB patients (n = 25) showed tumor EQD2 of 85.6 ± 2.7 Gy, bladder EQD2 of 78.9 ± 4.4 Gy, rectum EQD2 of 67.8 ± 4.3 Gy, and sigmoid EQD2 of 62.9 ± 4.3 Gy. Stage IVA patients (n = 7) had the highest doses, with tumor EQD2 of 86.2 ± 3.0 Gy, bladder EQD2 of 79.3 ± 4.0 Gy, rectum EQD2 of 68.4 ± 4.8 Gy, and sigmoid EQD2 of 63.4 ± 4.2 Gy. ECOG 0 patients (n = 10) received a mean tumor EQD2 of 84.1 ± 2.5 Gy, with 8 receiving 3 insertions and 2 receiving 4 insertions. ECOG 1 patients (n = 28) received a mean tumor EQD2 of 84.8 ± 2.9 Gy, with 20 receiving 3 insertions and 8 receiving 4 insertions. ECOG 2 patients (n = 12) received a mean tumor EQD2 of 85.6 ± 2.7 Gy, with 4 receiving 3 insertions and 8 receiving 4 insertions. The association between ECOG status and number of insertions was statistically significant (p = 0.04), reflecting the higher likelihood of requiring dose escalation in patients with poorer performance status.

Table 1. Baseline Demographic and Clinical Characteristics (N = 50)

Variable	Category	n (%) / Mean ± SD
Age (years)	—	**55.1 ± 5.8**
Stage	IIB	8 (16%)
	IIIA	10 (20%)
	IIIB	25 (50%)
	IVA	7 (14%)
ECOG Status	0	10 (20%)
	1	28 (56%)
	2	12 (24%)
IGBT Insertions	3 fractions	32 (64%)
	4 fractions	18 (36%)

Table 2. Treatment and Dosimetric Parameters

Parameter	Mean ± SD	Range
Tumor EQD2 (Gy)	**84.9 ± 2.8**	80.1 – 89.9
Bladder EQD2 (Gy)	78.1 ± 4.3	70.3 – 84.8
Rectum EQD2 (Gy)	67.3 ± 4.4	60.2 – 74.9
Sigmoid EQD2 (Gy)	62.5 ± 4.2	55.4 – 69.7

Table 3. Comparison of EQD2 by Number of IGBT Insertions

Variable	3 Insertions (n = 32) Mean ± SD	4 Insertions (n = 18) Mean ± SD	p-value
Tumor EQD2 (Gy)	83.4 ± 2.1	87.1 ± 1.8	**<0.001**
Bladder EQD2 (Gy)	77.2 ± 4.4	79.7 ± 3.8	0.08
Rectum EQD2 (Gy)	66.4 ± 4.2	68.9 ± 4.5	0.09
Sigmoid EQD2 (Gy)	61.7 ± 4.1	63.9 ± 4.3	0.12

Table 4. Stage-Wise EQD2 Distribution

Stage	Tumor EQD2 Mean ± SD	Bladder EQD2 Mean ± SD	Rectum EQD2 Mean ± SD	Sigmoid EQD2 Mean ± SD
IIB (n=8)	83.6 ± 2.3	76.9 ± 4.2	66.2 ± 3.9	61.1 ± 4.1
IIIA (n=10)	84.3 ± 2.6	77.5 ± 4.1	66.7 ± 4.5	61.9 ± 4.0
IIIB (n=25)	85.6 ± 2.7	78.9 ± 4.4	67.8 ± 4.3	62.9 ± 4.3
IVA (n=7)	86.2 ± 3.0	79.3 ± 4.0	68.4 ± 4.8	63.4 ± 4.2

Table 5. ECOG-wise Comparison of Treatment Parameters

ECOG	n	Tumor EQD2 Mean ± SD	IGBT Insertions (3/4)	p-value
0	10	84.1 ± 2.5	8 / 2	0.31
1	28	84.8 ± 2.9	20 / 8	0.28
2	12	85.6 ± 2.7	4 / 8	**0.04**

DISCUSSION

This study evaluated the cumulative radiation dose delivered to carcinoma cervix patients treated with VMAT followed by MRI-guided brachytherapy at a major oncology center in Pakistan. The results prove that the integrated treatment in the form of the combination therapy method attained the internationally recommended levels of the tumor dose and kept the organ-at-risk doses (OAR) within the reasonable tolerances of a considerable majority of patients. These findings underscore the usefulness of its contemporary radiotherapy methods in practice in the real world based on the purpose of modern radiotherapy, especially in limited resource areas where the lack of variation in the treatment, high patient load, and late-stage appearance is likely to make the delivery of the optimal dose a complicated affair. The average accumulated dose in the high-risk target volume up to 85 Gy was quite in line with GEC-ESTRO and ABS guidelines, which propose a minimum tumor dose of 80 Gy to ensure maximum local control.[12] Almost 80% of the patients had gone above the criterion mark of 84 Gy that has been linked to increased tumor response and reduced chances of local recurrence. The dose escalation in patients who are given four brachytherapy fractions is in line with international practice in that those patients with a suboptimal response of tumor may need extra fractions to counteract the remnant parametrial disease or the high-risk volumes of CTV. Notably, this escalation did not culminate into overdose of OAR, which supports the importance of MRI-based planning in the safe customization of fractions.[13]

The quality of the treatment delivery is also highlighted in the OAR dose distribution of this study. The average values of Bladder EQD2 were 78 Gy, and virtually no patient received a higher dose of 80-90 Gy which is the accepted

tolerance. Rectal and sigmoid doses were also well managed with a mean EQD2 of 67 Gy and 62 Gy respectively and a very low number of patients having an EQD2 of above 75 Gy- the level of EQD2 that is linked to more late gastrointestinal toxicity.[14] These results suggest that there is a standard aiding in the compliance to the accuracy of contours, the most adequate location of applicators and the correct utilization of volumetric optimization in the process of brachytherapy planning. They also point out the advantages of MRI guidance that can enable a better outline of the target and to define the dwell positions that would be more precise and would cause less exposure to the pelvic structures.[15] This distribution of stages in the Pakistani cohort of Stage III disease would represent the typical trend of late diagnosis in South Asians, which is usually ascribed to low levels of screening, socioeconomic, and cultural delaying health-seeking behavior. Regardless of this burden of advanced disease experience, cumulative doses met in this study were similar to that achieved in high-volume cancer centers in Europe and East Asia.[16] This confirms the use of VMAT with MRI-guided brachytherapy in the provision of high-quality radical therapy in even those population with larger tumors with larger parametrial involvement.

There is significant correlation between ECOG performance status and the risk of having to take up extra units of brachytherapy. Patients with ECOG 2 were more inclined to get four insertions and maybe there is some correlation between the poorer general health and slower tumor regression, or it may have been related to the tumor biology which responds differently to EBRT.[17] Nevertheless, OAR doses were employed even higher, but the effect was acceptable, which implied that a personalized planning ensured safety without affecting tumor coverage. The benefit of VMAT as the EBRT method of interest in cervical cancer is also highlighted by these findings. VMAT offers excellent conformity, shorter treatment time and dose distribution that is highly reproducible especially when minimization of bowel and bladder doses is required in treatment of the pelvis. When combined with MRI-guided brachytherapy, it constitutes a synergistic therapy, which increases the precision and therapeutic ratio.[18] One of the strong points of the given study is that it is a real-life clinical dosimetry study in Pakistan where the literature on much of the modern image-guided brachytherapy is scanty.[19,20]

Limitations: This research has a number of limitations that should be considered when analyzing the results. To begin with, it was carried out in only one tertiary care institution and the sample size of the study is very small (50 patients); thus, its results might not be applicable to the general population in Pakistan. Second, the study failed to correlate dosimetric adequacy with clinical outcomes, since cumulative values of EQD2 in the tumor and organs at risk had been well analyzed, but there were no clinical endpoints (e.g., local control rate, late toxicity, disease-free survival, and/or overall survival) to correlate the two. Thirdly, in all cases, MRI-guided brachytherapy was employed, which is a higher imaging level that is not evenly distributed across the regional centers; thus, dose distributions could vary in environments with CT-based or 2D brachytherapy planning. Fourth, the analysis was based on retrospective data retrieval that can induce documentation bias particularly in the treatment planning parameters. Also differences in applicator type, tumor regression patterns and individual anatomical differences may have an impact on dose distribution but were not stratified in this analysis. Lastly, there is no inter-observer variability assessment of contouring and planning, so there is no possibility of comparing reproducibility of clinicians. These limitations imply that bigger, multicenter projects that include clinical outcome measures and standardized planning protocols are necessary to verify these results and generalize them.

CONCLUSION

It is concluded that the combination of VMAT-based external beam radiotherapy and MRI-guided brachytherapy provides an effective and safe treatment approach for patients with carcinoma of the cervix. The cumulative EQD2 delivered to the high-risk target volume met internationally recommended dose thresholds in nearly all patients, ensuring adequate tumor coverage even in a population dominated by advanced-stage disease. Organs-at-risk, including the bladder, rectum, and sigmoid, consistently remained within acceptable tolerance limits, reflecting high-quality planning, accurate applicator placement, and the benefits of MRI-based optimization.

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Authors Contribution:
Sana Naeem: Conception, data collection, manuscript drafting
Ayesha Anees: Study supervision, critical review, approval of final draft
Ahmad Farooq: Methodology development, data validation, statistical support
Tahir Sheikh: Data acquisition, literature search, editing
Rub Nawaz Maken: Project administration, resource provision, final approval

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