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Dosimetric Analysis of Computed Tomography-Based Brachytherapy Planning in Carcinoma Cervix

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Abstract

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Background The standard of care for locally advanced cervical cancer is concurrent chemoradiation followed by intracavitary brachytherapy (BT). BT forms an integral part of management as it improves local control and overall survival. In recent times, image-guided BT (IGBT) has been recommended as the standard of care. Computed tomography (CT) scan-based BT is a cost-effective and easily available modality for IGBT. The aim of the study was to do a dosimetric analysis of CT scan-based BT for patients with cervical cancer.

Methods This was a retrospective study and included patients with cervical cancer treated with radical chemoradiation followed by BT. CT scan was done before every fraction after applicator placement, and CT-based planning was done for all fractions. Clinical details were abstracted from the case records, and dosimetric details were collected from the treatment planning systems. Total equivalent dose in 2 Gy per fraction (EQD2) was calculated for external beam radiation therapy and BT target volumes and organs at risk (OARs).

Results This study included 50 patients. The mean age was 45 years. The majority of the cases were stage III. The mean high-risk clinical target volume (HRCTV) for the 1st, 2nd, and 3rd fraction was 53.1, 52.1, and 51.3 mL, respectively. Mean D90 HRCTV (dose received by 90% of the HRCTV) dose was 81.4 Gy (EQD2 10 Gy) and D2cc was 75.8 Gy (EQD2 3 Gy) for the rectum and sigmoid and 86.2 Gy (EQD2 3 Gy) for the bladder.

Conclusion CT-based BT is a reasonable option in high-volume and low-resource settings where the availability of magnetic resonance imaging is limited. CT-based BT at every fraction can ensure proper applicator placement and aid in optimizing the dose to the target volumes and OARs.

Keywords

- cervical cancer
- brachytherapy
- chemoradiation
- image-guided brachytherapy
- intracavitary brachytherapy

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Introduction

Cervical cancer accounts for nearly a fifth of the newly diagnosed cases in India. Cervical cancer-related mortality is high among women in low- and middle-income countries.[1] Eighty-five percent of all the locally advanced cases are seen in these countries.[2] The standard of care for locally advanced cervical carcinoma is concurrent chemoradiation followed by brachytherapy (BT).[3,4]

BT constitutes an integral part of management and is an independent factor in determining the outcomes of these cancers. It is associated with improvements in local control (LC) and overall survival.[4,5] Intracavitary BT (ICBT) is the standard procedure for cervical BT. ICBT with interstitial application can be performed in selected cases.[6] Historically, BT dose prescription was based on point A with planning done on postapplication orthogonal X- rays. High dose rate BT involves multiple fractions, which can lead to variations in the application geometry among fractions, which in turn can affect dose distribution to targets and organs at risk (OARs).[7,8] Advances in imaging and technology have led to the evolution of image-guided BT (IGBT). In contemporary practice, three-dimensional (3D) IGBT is becoming a standard part of treatment planning for cervical cancer.[9] IGBT aids in improving LC and reducing morbidity.[10]

Imaging modalities like ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography scans are being explored and are being used in recent times.[11–14] Although MRI is considered superior in visualization of the cervix and tumor volumes,[10,15] CT is more widely available and cost effective. Many institutes have dedicated CT simulators in their radiotherapy (RT) departments. Limitations of CT-based BT include difficulty in identifying the upper border of the cervix and differentiating gross tumor volume (GTV) from normal cervix. A comparison study between MRI and CT-based clinical target volume (CTV) contours showed a higher degree of agreement in CT-based contours. Consensus guidelines for CT- and MR-based target volumes have been published, and online contouring atlases are available.[16]

MRI-based contouring guidelines for BT have been given by the Groupe Européen de Curiethérapie and the European SocieTy for Radiotherapy and Oncology (GEC-ESTRO) group.[17–20] As CT scans are widely used for imaging, high-risk CTV (HRCTV) guidelines for standard CT-based contouring were developed.[21] Recommendations for a systematic, uniform, and universal approach for CT image-based contouring of target volumes in cervix BT have been published recently, including recommendations for delineating target volumes and OARs on CT in different clinico-radiologic scenarios.[22]

The aim of this study was to conduct a dosimetric analysis of target volumes and OARs in carcinoma cervix cases treated with CT-based BT.

Material and Methods

This was a retrospective study conducted in the department of radiation oncology at a tertiary cancer center. Patients with histopathologically diagnosed carcinoma cervix, International Federation of Gynecology and Obstetrics (FIGO) stages IB2 to IV A (2018 FIGO staging system for uterine cervical cancer), treated with external beam RT (EBRT) and chemotherapy followed by ICBT, were included in this retrospective analysis. Patients who received prior chemotherapy or surgery and those who failed to complete the prescribed radiation dose were excluded.

Demographics and disease-related data were abstracted from treatment records. Dosimetric details were extracted from the treatment planning system (Monaco Planning System Version 5.51.10).

Treatment

EBRT: Treatment volume without gross nodes was the whole pelvis, and the dose was 50 Gy in 25 fractions, one fraction per day, five fractions per week, for 5 weeks by three dimensional conformal radiotherapy (DCRT). Patients with enlarged nodes were treated with 45 Gy to the whole pelvis and a simultaneous integrated boost (SIB) up to 56.5 Gy by intensity-modulated RT to the gross nodal volume in 25 fractions. Patients followed bladder protocol during EBRT, and cone-beam CT was done on alternate days for setup verification. Central shielding was not done. A few patients did not receive chemotherapy in view of comorbidities and poor performance status.

Following the completion of EBRT, patients were assessed for suitability for ICBT. A clinical examination was done to document tumor regression and to choose the appropriate applicator size. First fraction of ICBT was planned for the next day.

ICBT: ICBT was done using modified Fletcher Suit applicators (tandem and ovoids) under local anesthesia and aseptic precautions. Applicators were placed, and adequate vaginal packing was done. The urinary bladder was catheterized prior to applicator insertion. Following insertion, it was filled with 50 mL of saline with radiopaque contrast. A planning CT scan of the pelvis was done after the applicator insertion. The BT planning CT scan was done for every fraction. If uterine perforation by the tandem was noted on the CT scan, removal and reinsertions were done (on the same day or the following day in a few cases). Contouring of the target volumes and OARs was done based on CT-based IGBT guidelines.[21] A pretreatment pelvic MRI was used as a reference, if available. Applicator reconstruction and treatment planning were done for every fraction. A dose of 7 Gy per fraction was prescribed to the HRCTV. Three fractions of ICBT were delivered using the ^{192}Ir after loading system (Flexitron 10 channel) by three separate insertions 1 week apart, for a total dose of 21 Gy.

Dosimetry

Treatment planning for the EBRT and ICBT was done on the Monaco Planning System (Version 5.51.10) and the Oncentra Planning System, respectively (►Fig. 1). The total EBRT dose, D90 (dose received by 90% of the target volume), D2cc (dose received by 2 cc volume) bladder, and D2cc (dose received by 2 cc volume) rectum were tabulated. The total BT dose, D90, D100 (dose received by 100% volume) for HRCTV, D2cc bladder, and D2cc rectum were tabulated for each fraction.

The total equivalent dose in 2 Gy per fraction (EQD2) was calculated for EBRT and BT target volumes and OARs. They

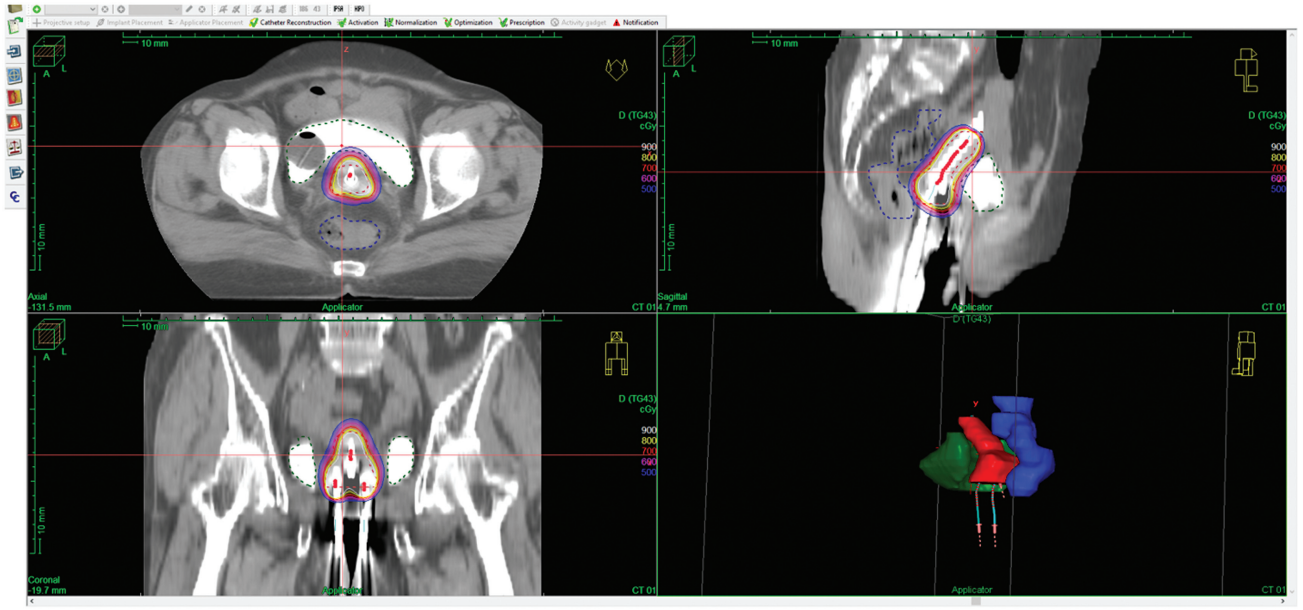

Fig. 1 Images from Oncentra Treatment Planning system showing prescription isodose coverage of target volumes and organs at risk (OARs).

were calculated as a cumulative linear quadratic equivalent dose (EQD2) using $\alpha/\beta = 10$ Gy for HRCTV and $\alpha/\beta = 3$ Gy for OARs. The total EQD2 dose was obtained by adding the EBRT and IGBT doses.

Descriptive analysis was done, and the categorical variables were summarized with percentages. An analysis of interfraction variation was done. A paired *t*-test was used to compare continuous variables. All reported *p*-values were two-sided. For all statistical tests, differences were considered significant at the 5% level. Statistical analysis was performed with IBM SPSS v20 software.

Results

Fifty patients treated over a period of 1 year were included in this study. The mean age was 45 years (range 38–68 years). Twenty-six (52%) had stage III disease, of which 3 (6%) were stage IIIA, 7 (14%) were stage IIIB, and 11 (22%) and 5 (1%) were stage IIIC1 and stage IIIC2, respectively. Eighteen patients (36%) were diagnosed with stage I and II cervical cancer and 6 (12%) with stage IVA.

Seventeen patients (34%) received a boost to the gross nodes to a dose of 56.5 Gy (SIB plan in 2.25 Gy per fraction to high-risk planning target volume) and 2 patients (4%) received boost dose up to 60 Gy (sequential plan in 2 Gy per fraction). Forty patients (80%) received concurrent chemotherapy with weekly cisplatin at 40 mg/m^2. The average number of chemotherapy cycles was 4.

Total number of BT applications for 50 patients were 150 (50 × 3). The mean HRCTV volumes for the 1st, 2nd, and 3rd fractions (weekly fractions) were 53.1, 52.1, and 51.3 mL, respectively. The mean D90 HRCTV dose was 81.4 Gy (EQD2 10 Gy) and D2cm^3 was 75.8 Gy (EQD2 3 Gy) for the rectum and sigmoid and 86.2 Gy (EQD2 3 Gy) for the bladder. Dosimetric data are tabulated in ►Tables 1 and 2.

Discussion

In this retrospective study, all the patients of cervical cancer received IGBT post-EBRT with or without chemotherapy. CT-based BT planning was done for every BT fraction. The same scanning protocol was followed for each fraction. The mean D90 for HRCTV was 81.4 Gy (EQD2 10 Gy) and D2cm^3 was

Table 1 Mean total doses to the target volumes and OARs

Dosimetric variables	Mean ± standard deviation (Gy) observed
Target	
EBRT dose (EQD2 10 Gy)	53.0 ± 3.9
BT dose (D90)	20.0 ± 4.4
BT dose (EQD2 10 Gy)	28.4 ± 1.8
Total dose (EQD2 10 Gy)	81.4 ± 3.9
Bladder	
EBRT dose (EQD2 3 Gy)	53.9 ± 2.7
BT dose (D2cc)	16.0 ± 1.7
BT dose (EQD2 3 Gy)	32.2 ± 3.7
Total dose (EQD2 3 Gy)	86.2 ± 5.2
Rectum	
EBRT dose (EQD2 3 Gy)	51.7 ± 1.5
BT dose (D2cc)	13.0 ± 1.8
BT dose (EQD2 3 Gy)	24.0 ± 3.9
Total dose (EQD2 3 Gy)	75.8 ± 4.0

Abbreviations: BT, brachytherapy; D2cc, dose received by 2 cc volume; D90, dose received by 90% treated volume; EBRT, external beam radiation therapy; EQD2, equivalent dose in 2 Gy per fraction; OARs, organs at risk.

Table 2 Mean doses to the target volumes and OARs at each fraction

Dosimetry	Mean ± standard deviation (Gy)
Target	
1st BT D90	6.6 ± 0.6
2nd BT D90	6.7 ± 0.5
3rd BT D90	6.6 ± 0.5
Bladder	
1st BT D2cc bladder	5.4 ± 0.7
2nd BT D2cc bladder	5.4 ± 0.6
3rd BT D2cc bladder	5.3 ± 0.6
Rectum	
1st BT D2cc rectum	4.3 ± 0.8
2nd BT D2cc rectum	4.4 ± 0.8
3rd BT D2cc rectum	4.2 ± 0.7
Volume of target	
HRCTV volume 1st BT	53.1 ± 19.6 mL
HRCTV volume 2nd BT	52.1 ± 17.6 mL
HRCTV volume 3rd BT	51.3 ± 17.1 mL

Abbreviations: BT, brachytherapy; D2cc, dose received by 2 cc volume; D90, dose received by 90% treated volume; EQD2, equivalent dose in 2 Gy per fraction; HRCTV, high-risk clinical target volume; OARs, organs at risk.

75.8 Gy (EQD2 3 Gy) for the rectum and 86.2 Gy (EQD2 3 Gy) for the bladder.

3D image guidance can aid in a personalized treatment approach through dose adaptation and escalation whenever necessary. It takes into account the tumor size at the time of diagnosis and also at the time of BT. It gives us the opportunity to limit doses to the OARs.[23,24] Detection of uterine perforation is also possible if imaging is done for every fraction. Uterine or bowel perforation due to improper placement of applicators can lead to complications, which might prolong the overall treatment time.[25] Disadvantages of IGBT include increased treatment time (acquisition of images, importing into the treatment planning system, contouring, and planning), uncertainty in applicator visualization, especially with MRI, and increased utilization of resources, cost, and additional training.[26]

BT for cervical cancer has considerably evolved over the last few decades since its introduction. ICBT, employing intrauterine and vaginal (tandem and ovoids) sources based on the Manchester system, has been widely used for many decades.[27] This system is based on point-dose prescriptions and measurement (i.e., two-dimensional) and uses orthogonal X-ray images for treatment planning. The guidelines for 3D image-based BT for cervical cancer have been framed by the GEC-ESTRO[23,24] and American Brachytherapy Society (ABS).[28] The GEC-ESTRO working group recommends using MRI for determining HRCTV and intermediate-risk CTV (IRCTV). These guidelines require a pretreatment pelvic MRI and an MRI at every BT fraction for target and OAR delineation.

MRI-based planning is considered the gold standard for intracavitary IGBT.[29] However, its applicability is limited in low-resource and high-volume centers, as it requires an advanced MRI simulator, MR-compatible applicators, additional training, and expertise.[30] The advantages of CT-based planning are wider availability, lower costs, and faster acquisition times. Studies suggest that the applicator reconstruction and OAR delineation using CT are comparable with MRI.[16] The disadvantages of CT-based planning are poor definition of GTVs, including detection of uterine corpus and parametrial invasion, poorer soft tissue contrast for target volumes, and OARs.[21] An American College of Radiology Imaging Network/Gynecologic Oncology Group study showed MRI is better than CT for visualization of tumor and detection of parametrial invasion.[31] Tumor regression following EBRT cannot be accurately quantified as CT cannot distinguish between normal tissue and residual disease.[32] A survey conducted in India among young radiation oncologists suggests that only 9% centers use MRI-based IGBT, whereas 50% of centers use CT-based IGBT.[33] As CT scan-based planning is more accessible and feasible, CT-based guidelines are essential. Viswanathan et al have developed guidelines for standard contouring of HRCTV based on CT images.[21]

A study by Beriwal et al used MRI-based planning for the first BT fraction, and subsequent fractions were contoured on CT images with MRI as a reference. This hybrid method was described, but the comparison with conventional plans or fully MRI-based plans was lacking.[34] Nesvacil et al[35] reported that a combination of MRI for the first fraction and CT for subsequent fractions is feasible as well as quick and easy.

CT- and MRI-based dose volume histograms (DVHs) were compared by Viswanathan et al using the GEC-ESTRO guidelines for contouring. They observed no difference in OAR DVH values between both modalities.[21] In another study of CT and MRI comparison by Viswanathan et al,[16] CT-generated CTV contours were more similar among physicians than MR-based contours. This indicates a higher degree of interobserver reliability and reproducibility for CT-based volumes. They observed discordance in cases with parametrial involvement. Delineation of target volumes and OARs is very important in BT owing to high doses with rapid fall off.[16] Ohno et al[36] published recommendations for CT-based contouring of high-risk CTV based on discussions with experts in the field using MRI obtained at diagnosis and pre-BT (without an applicator) as references. They emphasized the importance of clinical examination at diagnosis and before BT for target delineation. A retrospective study of patients with cervical cancer treated with in-room CT-based BT showed 5-year LC rates of 96, 91, and 94% for small-, medium-, and large-sized tumors, respectively.[37]

The EQD2 dose recommended by the ABS for HRCTV D90 is $\geq$ 85 Gy (EQD2), D2cc rectum and sigmoid $<$ 75 Gy, and D2cc bladder $<$ 90 Gy.[38] The GEC-ESTRO recommends reporting D90 and D100 of HRCTV and IRCTV and D0.1cc, D1cc, and D2cc for bladder, sigmoid, and rectum. Recommended

parameters for plan evaluation, HRCTV D90, and rectum, sigmoid, and bladder D2cc are similar to the ABS recommendations.[24]

IGBT improves LC and decreases treatment-related morbidity.[10] Published reports indicate that HRCTV D90 is one of the most important predictors of LC.[24,39–42] Dose escalation from 78 to 93 Gy to HRCTV D90 resulted in better LC according to the RetroEMBRACE study.[41] Dimopoulos et al, in their study of MRI-based BT for cervical cancer, reported that D90 for HRCTV > 87 Gy resulted in excellent LC.[43] Okazaki et al reported that D90 or D98 of the HRCTV should be 6.5 Gy (~9 Gy in EQD2) or 5.5 Gy (~7 Gy in EQD2) per fraction for favorable LC.[44]

A study was conducted to assess the role of CT-based contouring on survival in locally advanced carcinoma cervix.[30] Forty-eight patients underwent CT-based planning for the first and third fractions. Better locoregional control and progression-free survival (PFS) were reported in patients who received HRCTV D90 EQD2 doses greater than or equal to 79.75 Gy. Murakami et al reported that both LC and PFS were significantly better in patients receiving ≥ 60 Gy for HRCTV D90 in EQD2.[39]

CT-based contouring for OARs has a good correlation with MRI.[21,45] The ABS guidelines recommend that the D2cc dose constraints are 70 to 75 Gy for the rectum and sigmoid and approximately 90 Gy for the bladder.[38] Our study demonstrates that these are feasible in clinical practice.

Limitations

This study has the limitation of being a retrospective in design. There was no MRI comparator arm to establish the benefit of CT for every fraction of BT. Clinical and survival outcomes were not assessed.

Conclusion

CT-based BT is a reasonable option in high-volume and low-resource settings where the availability of MRI is limited. CT-based BT at every fraction can ensure proper applicator placement and aid in optimizing the dose to the target volumes and OARs.

Authors' Contributions

All authors contributed significantly for this work.

Funding

None.

Conflict of Interest

None declared.

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